Neuromuscular blockade for improvement of surgical conditions during laparotomy: protocol for a randomised study

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ABSTRACT

INTRODUCTION: During laparotomy, surgeons frequently experience difficult surgical conditions if the patient's abdominal wall or diaphragm is tense. This issue is particularly pertinent while closing the fascia and placing the intestines into the abdominal cavity. Establishment of a deep neuromuscular blockade (NMB), defined as a post-tetanic-count (PTC) of 0-1, paralyses the abdominal wall muscles and the diaphragm. We hypothesised that deep NMB (PTC 0-1) would improve surgical conditions during upper laparotomy as compared to standard NMB with bolus administration.

METHODS: This is an investigator-initiated, assessor- and patient-blinded, randomised study. A total of 128 patients scheduled for elective upper laparotomy will be included and randomised to either continuous deep NMB or standard NMB defined as bolus administrations. Surgical conditions are evaluated using a five-point rating scale every 30 min. Primary outcome is the average score for a patient's surgical condition. Secondary outcomes are, among others, surgical rating score during fascial closure, wound dehiscence, wound infection requiring surgical drainage and incisional hernia at the six-month follow-up.

CONCLUSIONS: This randomised, double-blinded study investigates potential effects of deep NMB on surgical conditions and patient outcomes during elective laparotomy.

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During laparotomy, surgeons frequently experience difficult surgical conditions if the patient's abdominal wall or diaphragm is tense [1]. This issue is particularly pertinent while closing the fascia and placing the intestines into the abdominal cavity [2, 3]. Moreover, tensions in the abdominal wall, which create tensions on the suture, may also influence patient outcomes such as wound dehiscence, wound infection and incisional hernia [4, 5].

Frequently, during open abdominal surgery, neuromuscular blockade (NMB) is administered as a bolus when the surgeon perceives tightness in the abdomen. Usually, such bolus establishes a moderate level of NMB, which with objective neuromuscular monitoring corresponds to a train-of-four (TOF) count of 1-4 responses to ulnar nerve stimulation. However, as the diaphragm and the abdominal wall muscles are among the most resistant to NMB [6], they have recovered 50-75% [7, 8] already at a TOF count of one. Even at a TOF count of zero, the patient is able to cough, and the abdomen may feel tight during surgery [9]. With establishment of deep, continuous NMB, defined as a post-tetanic-count (PTC) between zero and one, all muscles including the abdominal wall muscles and the diaphragm are paralysed [10].

A recent systematic review reported that use of deep NMB improves surgical conditions during laparoscopy [11]. Moreover, moderate NMB improved surgical conditions during laparotomy [1]. However, no previous studies have investigated the effect of deep NMB on surgical conditions during laparotomy. Accordingly, we aimed at investigating if deep NMB improves surgical conditions during open abdominal surgery. We hypothesise that deep NMB compared with standard NMB by bolus dosing improves surgical conditions evaluated on a subjective rating scale.

METHODS

Study design

This is a randomised, patient- and surgeon-blinded study.

Study population

Adult (> 18 years of age) patients scheduled for elective open upper abdominal surgery (Whipple, gastrectomy, gastric resection, liver resection and laparotomies due to bile obstruction, i.e. hepaticojejunostomy (not cholecystectomy)) are screened for inclusion. The exclusion criteria are listed in **Figure 1**.

Randomisation

Block randomisation (in blocks of four) using a computer-generated randomisation list with stratification for a body mass index (BMI) below or above 30 and for type of operation (liver resection or other laparotomy). Patients are assigned to either the DEEP group or to the STANDARD group (Figure 1).

PROTOCOL ARTICLE

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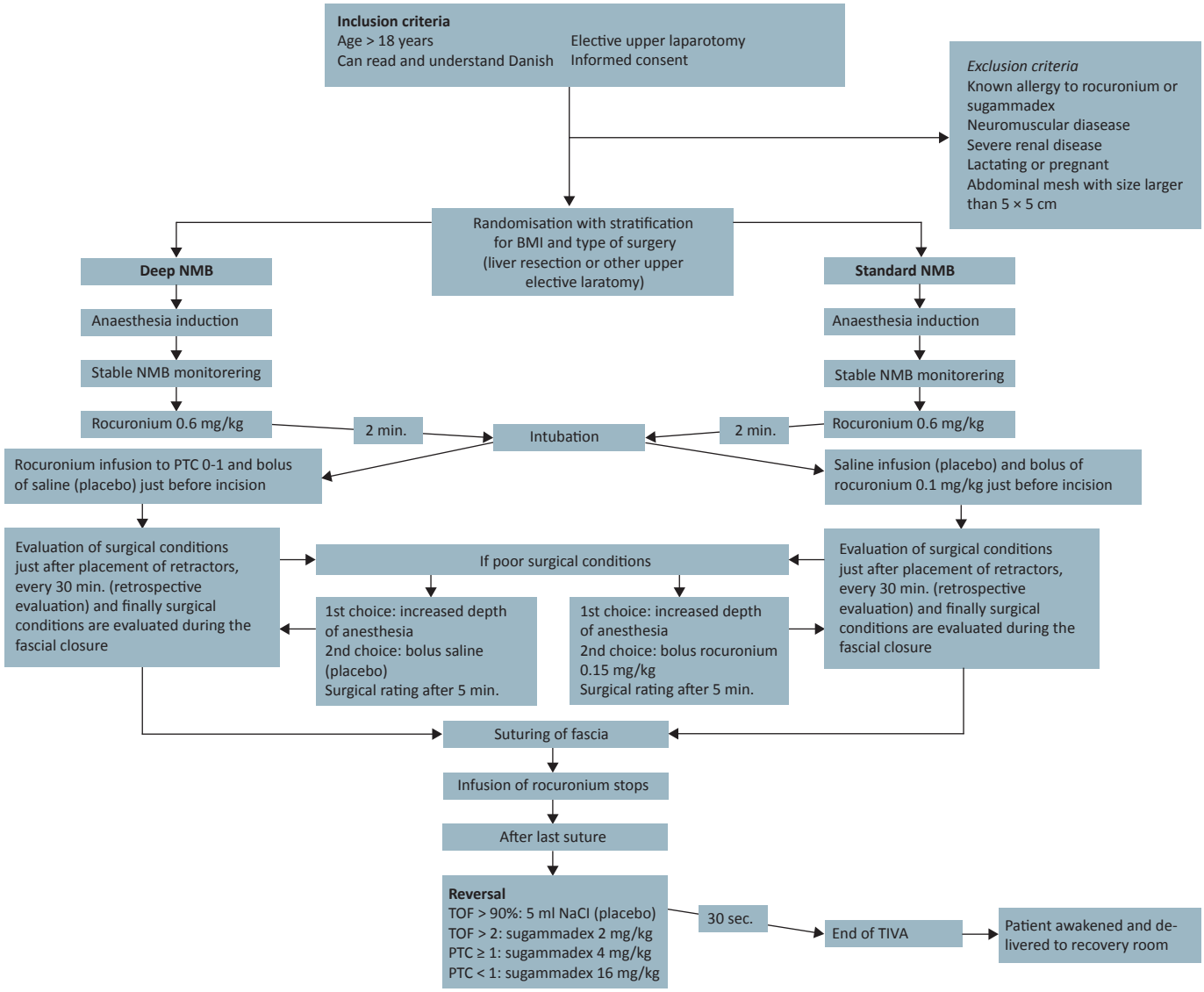
Anaesthesia

Induction of general anaesthesia by propofol 2 mg/kg and remifentanil 1.0 µg/kg/min. Tracheal intubation is performed with rocuronium 0.6 mg/kg. The DEEP group will subsequently receive rocuronium infusion with a target level of PTC 0-1 combined with bolus saline (placebo) mimicking the standard treatment. The STANDARD group will receive a saline infusion (placebo) and bolus rocuronium according to the standard treatment. Rocuronium 0.6 mg/kg is based on an ideal body weight and calculated as follows for men and women, respectively: height (cm) – 100 and height (cm) – 105. Anaesthesia will be maintained with propofol 0.5 mg/kg/h and remifentanil 0.25-0.5 µg/kg/min. and adjusted according to depth of anaesthesia under guidance of entropy 30-50. An epidural catheter will be placed preoperatively, and a test dose of 3 ml of lidocaine 20 mg/ml with adrenalin will be installed. No further medicine will be given in the epidural catheter until after closure of the abdominal wall.

In case of indication for rapid-sequence induction, the patient will receive succinylcholine 1 mg/kg for tracheal intubation. After tracheal intubation and full recovery from succinylcholine, the DEEP group will receive rocuronium 0.6 mg/kg and the STANDARD group will receive 5 ml of saline (placebo).

FIGURE 1

Flow chart.



BMI = body mass index; NMB = neuromuscular blockade; PTC = post-tetanic count; TOF = train-of-four; TIVA = total intravenous anaesthesia.

Sugammadex (a selective reversal agent) is administered at the end of anaesthesia in accordance with the product information from the European Medicines Agency (Figure 1). Neuromuscular monitoring continues until the train-of-four (TOF) ratio exceeds 0.90 and the value remains stable for a minimum of 2 min.

Neuromuscular monitoring will be performed in accordance with Good Clinical Research Practice [12] with a 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. TOF-Watch SX will be calibrated when the patient does not react to verbal command. Measurements will be taken every 15 sec. When stable neuromuscular monitoring is assured during 2 min., the first intervention will be administered.

Intervention

Surgical conditions are evaluated on a five-point subjective rating scale: after placement of retractors, every 30 min. (retrospectively from the previous assessment to the present) and after closure of the abdominal wall (**Table 1**) [13]. Applicability of the five-point rating scale was tested on five patients prior to inclusion. The surgeons, blinded to whether NMB was applied, practiced the use of the scale two at the time, and disagreements on its use were discussed and reconciled. Additionally, all surgeons received a written instruction of how to use the scale.

In the DEEP group: after intubation, patients receive a rocuronium infusion (2 mg/ml) with a target level of PTC 0-1. Just before incision, 1 ml of saline (placebo) will be administered.

In the STANDARD group: after intubation, patients receive a saline infusion (placebo). Just before incision, 0.1 mg/kg of rocuronium will be administered (Figure 1).

In case of need of an anaesthetic intervention due to poor surgical conditions, the first choice is to increase the depth of anaesthesia with propofol or opioids at the discretion of the attending anaesthetist. If a need for anaesthetic intervention remains, this is achieved in a standardised manner. In the STANDARD group: a bolus of rocuronium, 10 mg if weight between 50-90 kg will be given. If weight is below 50 kg or above 90 kg, we will administer 0.15 mg/kg. In the DEEP group: a 1 ml bolus of saline (placebo) will be given. If there is a need for an anaesthetic intervention, this will be given the score 1 in the corresponding 30-min. time interval. Moreover, surgical conditions are rated 5 min. after the anaesthetic intervention.

Closing of the abdominal wall will be done in a standardised manner with continuous suture of both the peritoneum and the fascia in one layer [14]. Skin will be closed with clips. A list of perioperative care is presented in **Table 2**.

TABLE 1

Surgical rating scale [15].

Rating	Conditions	Evaluation
1	Extremely poor	The surgeon is unable to work due to coughing, sudden abdominal contractions or inadequate muscle relaxation Additional neuromuscular blocking agent must be administered or the depth of anaesthesia must be increased
2	Poor	The surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions with the hazard of tissue damage The surgeon considers asking for administration of neuromuscular blocking agent or increased depth of anaesthesia
3	Acceptable	Increased tonus in the abdominal wall muscles or the diaphragm occurs regularly causing some interference with the surgeon's work
4	Good	Conditions are not optimal due to minor episodes of increased tonus in the abdominal wall muscles or the diaphragm
5	Optimal	The surgeon does not experience any episodes of increased tonus in the abdominal wall or the diaphragm

Blinding

Intervention medicine is prepared in the operating room before surgery under double control by a nurse anaesthetist and by the investigator who performs the randomisation. The randomisation group will be noted on a sheet (the 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 any surgical personnel are blinded to the patients' 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 sealed envelope and placed in a locked drawer to which only the investigator has access. A case will only be un-blinded if this is needed for emergency treatment.

Data collection

A list of the data recorded are presented in **Table 3**.

Data collection is completed six months after surgery.

Outcome measures

Primary outcome is the final score for the surgical conditions of a patient defined as the average of all scores provided during the surgical procedure.

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

- The surgical rating score during fascial closure
- Number of patients with need for intervention (increased depth of anaesthesia or NMB/saline (placebo)) during fascial closure
- Number of patients with need for intervention (increased depth of anaesthesia or NMB/saline (placebo)) to optimise surgical conditions
- Frequencies of surgical rating scores of 1 or 2 in each patient
- Number of patients with need to increase the initial incision
- Number of patients with sudden retractions during the procedure (bucking or coughing)
- Operating time (total and during abdominal wall closure)
- Wound dehiscence (up to three weeks after operation)
- Wound infection, which requires surgical drainage (up to three weeks after operation)
- Incisional hernia (six-month follow-up).

Adverse events and reactions

An investigator contacts the patients between the seventh and 28th post-operative day. The patient's file is screened in the same period. The sponsor decides whether or not there is a relationship between an adverse event and the intervention. The discrimination between an expected and un-expected adverse event is based on the product resume for rocuronium and sugammadex and the expected natural course after an elective laparotomy.

Side effects and events categorised as typically seen in connection with anaesthesia and surgery will not be recorded. The following events are found to belong to

TABLE 2

Perioperative care.

Protocol element	Description
Preoperative	
Fasting guidelines	Allowed to drink clear fluids until 2 h prior to anaesthesia Allowed to eat until 6 h prior to anaesthesia
Analgesics	Paracetamol 1 g and ibuprofen 400 mg
Antiemetics	Not as standard of care
Central and arterial lines	Arterial line in left a. radialis and central line in v. jugularis interna
Intraoperative	
General anaesthesia	Induction with propofol 2 mg/kg and remifentanil 1.0 µg/kg/min. Maintenance with propofol 0.5 mg/kg/h and remifentanil 0.25-0.5 µg/kg/min. adjusted according to depth of anaesthesia under guidance of entropy 30-50 Change to sevoflurane is allowed when assessed necessary by the attending anaesthetist
Respiratory	During induction oxygenation with FiO_2 1.0 until the trachea is intubated Ventilation with pressure control and FiO_2 0.50, tidal volume 7 ml/kg and PEEP 5 cmH_2O
Neuromuscular monitoring	Objective neuromuscular monitoring using TOF-Watch SX according to research guidelines [12]
Positioning	Supine position
Surgical technique	Kocher incision for hepatic and bile procedures Upper midline incision for gastric procedures Upper transverse incision for pancreatic procedures Thompson Retractor used for all procedures Closing of the abdominal wall will be done in a standardised manner with continuous sutures of both peritoneum and fascia in 1 layer Skin will be closed with clips
Fluid therapy	Peroperatively: basic fluid losses replaced with Ringer lactate or Ringer acetate 2 ml/kg/h Blood-loss up to 500 ml is replaced by isotonic NaCl 1:1.5 (maximum 3,000 ml NaCl)
Temperature control	Core temperature is measured in the bladder aiming at 36-37 °C
Analgesics	Fentanyl 0.2 µg/kg 15 min. before last suture
Antiemetics	If risk of PONV: dexamethasone 4 mg and ondansetron 4 mg
Antibiotics	Cefuroxim 1,500 mg
Post-operative	
Analgesics	Epidural catheter infusion (bupivacaine, 1 mg/ml + fentanyl 2 µg/kg + adrenalin 2 µg/kg) 4-18 ml/h after closure of abdominal wall Paracetamol 1 g × 4 As needed, IV morphine 0.05-0.1 mg/kg at NRS 4-6 As needed, IV fentanyl 0.5-1.0 µg/kg at NRS 7-10
Post-operative stay	1-3 days stay at intensive care unit

FiO_2 = fraction of inspired oxygen; IV = intravenously; NRS = numerical rating scale; PEEP = positive end expiratory pressure; PONV = post-operative nausea and vomiting; TOF = train-of-four.

this category: changes in blood pressure or heart rate not exceeding ± 30% of the preoperative value, events that may be ascribed to the surgery with certainty, for example pain or infection in the surgical wound (except for those requiring drainage within the first three post-operative weeks). Serious adverse events will be recorded and the relevant authorities will be contacted.

Major protocol violation

The intention-to-treat analysis will include all patients randomised to and treated within the framework of the intervention.

If the patient has prolonged duration of action of succinylcholine that frustrates the calibration and stabilisation of neuromuscular monitoring, this is considered a major protocol violation.

In operations with less than two surgical rating scores, the patient will be considered a dropout. "Dropout" patients will be excluded from further data analysis.

Trial conduct and monitoring

The study is conducted in accordance with the International Conference on Harmonisation (ICH)/Good Clinical Practise (GCP) guidelines [15] and supervised by an independent inspector from the GCP unit of Aalborg and Aarhus University Hospital, Denmark.

Statistics

Eligible patients and excluded patients will be registered on a screening list.

Data from all randomised patients who receive the intervention will be included in the intention-to-treat analysis. Patients included in the intention-to-treat analysis but categorised as major violations (due to a prolonged effect of succinylcholine) will be excluded from the per-protocol analysis.

Normally distributed variables will be expressed by means and standard deviations; variables that are not normally distributed will be expressed by medians and interquartile ranges. Student's t-test will be used to compare normally distributed variables and the Mann-Whitney test will be used to compare ordinal or continuous variables that are not normally distributed. Likewise, the chi-squared test or Fisher's exact test will be used for comparison of frequencies. A p-value < 0.05 is considered significant.

Sample size

The sample size is based on the overall surgical condition scores.

One single-surgeon study comparing surgical conditions estimated on a five-point rating scale during laparoscopic prostatectomy and partial nephrectomy reported a significant difference between treatments with a mean rating of 4.0 during moderate NMB (TOF 1-2) and 4.7 during deep NMB (PTC 1-2) [13].

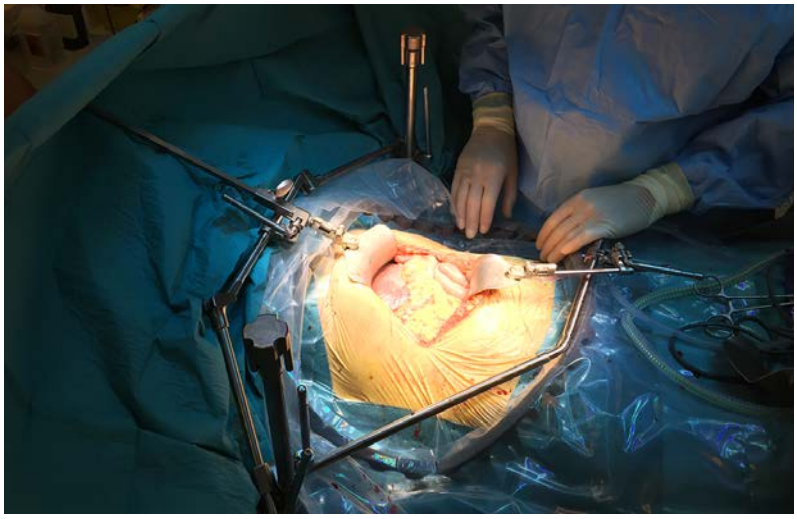
In our study which, however, embraces a wider array of surgical procedures and surgeons, a somewhat higher level of variability is anticipated as well as somewhat lower differences between treatments. In our study, an effect size of half a standard deviation is,

TABLE 3

Data collection.

Protocol element	Description
Preoperative	Sex (male/female)
	Age
	Weight
	Height
	BMI
	Previous abdominal surgery
	Smoking (current smoker, ex-smoker or never been smoking)
	Co-morbidities:
	Diabetes
	Coronary heart disease
	Other cardiovascular disease (hypertension, high cholesterol or valvular disease)
	COPD or asthma
	Parity
	ASA-score I-IV
Intraoperative	Duration of anaesthesia (min.)
	Core temperature (°C, immediately after intubation and before extubation)
	Duration of surgery (time in min. from 1st incision to last suture)
	Duration for closing the abdominal fascia (min.)
	Surgical ratings on a 5-point scale every 30 min.:
	1st evaluation immediately after opening of the abdominal cavity
	Final evaluation immediately after closing of the abdominal fascia
	When need of anaesthetic intervention to optimise surgical conditions, the following values are noted:
	Time
	TOF-ratio, TOF-count or PTC-value
	Entropy (RE and SE)
	Pulse
	Blood pressure
	Whether 1st or 2nd choice of intervention was used
	Surgical rating 5 min. after intervention (5-point scale)
	Number of sudden retractions
	Need of increasing primary incision (yes/no)
Post-operative	Surgeon's guess of patients' allocation (to evaluate blinding)
	Type of operation
	Blood loss
	Fluid administration
	Patient's experience of side effects at 7-28th day post-operatively
	Incidence of wound dehiscence within the 1st 3 post-operative weeks
	Incidence of wound infection requiring drainage within the 1st 3 post-operative weeks
	Incisional hernia 0-6 months after surgery

ASA = American Society of Anesthesiologists; BMI = body mass index; COPD = chronic obstructive pulmonary disease; PTC = post-tetanic-count; RE = response entropy; SE = state entropy; TOF = train-of-four.



Laparotomy.

nevertheless, considered feasible and of clinical relevance [16]. At a significance level of 0.05 (two-sided), a sample size of 64 patients in each group will yield 80% power.

Ethics, approvals and registration

All patients give their signed and written consent before surgery. The study was approved by the Research Ethics Committee of Copenhagen (Protocol No. H-2-2014-048), the Danish Health and Medicines Authority (EudraCT No. 2014-001155-22), the Danish Data Protection Agency (Protocol No. HEH-2014-040) and is registered with Clinicaltrials.gov (NCT02140593).

DISCUSSION

Surgeons' perception of a continuous and deep NMB throughout open abdominal surgery has not been investigated. We aim to capture any changes in surgical conditions. Accordingly, surgeons will evaluate the surgical conditions on a five-point rating scale retrospectively every 30 min.

Our study has important methodological strengths including blinding of the surgeon and randomisation with stratification for BMI and type of surgery. Additionally, we compare the intervention with standard practice, namely single bolus administration of rocuronium just before incision. Moreover, we have involved six very experienced surgeons in the assessments of surgical conditions, and our results therefore rely on more than just a single surgeon's perception [13].

A possible weakness, however, is the involvement of more than one surgeon, which may blur an effect. Nevertheless, all involved surgeons get to practice and receive instructions about the use of the numerical rating scale prior to enrolment. The five-point rating scale has been used in a laparoscopic study and the usefulness of the scale has been reported, though not formally validated [13]. We believe, however, that this tool is the best available at present.

Finally, this study may generate hypotheses about the influence of NMB on fascial rupture and wound infections requiring drainage and incisional hernias. We believe that our study will contribute with relevant results to the present investigations on the use of NMB for improvement of surgical conditions and patient outcomes.

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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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