Optimized surgical space during low-pressure laparoscopy with deep neuromuscular blockade

Anne K. Staehr-Rye[1], Lars S. Rasmussen[2], Jacob Rosenberg[3], Poul Juul[4] & Mona R. Gätke[1]

ABSTRACT

INTRODUCTION: Laparoscopic cholecystectomy (LC) can be performed using low intra-abdominal pressure (< 12 mmHg), but surgical conditions may not be optimal. The present study aims at comparing surgical space conditions using either deep, continuous muscle relaxation or moderate blockade during low-pressure (8 mmHg) LC. We hypothesise that a deep neuromuscular block will be associated with a higher proportion of optimal surgical space conditions.

MATERIAL AND METHODS: This is an investigator-initiated, patient- and assessor-blinded study. Up to 72 patients scheduled for elective LC are randomised to either deep neuromuscular blockade (post-tetanic count 0-1) or moderate neuromuscular blockade, where at least one response to train-of-four nerve stimulation is present. The primary outcome is surgical space conditions at the time during surgery when conditions are worst. The secondary outcomes include the proportion of procedures completed at pneumoperitoneum 8 mmHg, post-operative pain, and incidence of nausea and vomiting.

CONCLUSION: This study is the first randomised study to assess the association between depth of neuromuscular blockade and surgical space conditions during low-pressure LC. The study findings may be applicable to a general surgical population undergoing LC.

FUNDING: The University of Copenhagen, Denmark and Sophus Johansens Foundation of 1981, Denmark funds this study, which is also financed by a research grant from the Investigator Initiated Studies Program of Merck Sharp & Dohme Corp.

TRIAL REGISTRATION: NCT 01523886.

The number of laparoscopic procedures is increasing and laparoscopic cholecystectomy (LC) is commonly performed. LC has previously been carried out at an intra-abdominal pressure of 12-15 mmHg, but a pneumoperitoneum below 12 mmHg is associated with significantly less post-operative pain intensity [1]. It is not well established if this low pressure impairs surgical conditions and thereby increases the duration of surgery or the risk of complications [2].

Neuromuscular blocking agents are often used during surgery to improve surgical conditions, but only few studies have focused on the need for muscle relaxation, and the depth of blockade was not accurately reported [3-7]. The determination of the contraction of the adductor pollicis muscle is the gold standard for neuromuscular monitoring [8]. This muscle, however, may be completely paralysed, while other muscles – including the diaphragm and muscles in the abdominal wall – have recovered partly from a neuromuscular blockade [9-11]. This means that muscle relaxation in the surgical field may be inadequate. With the establishment of a deep, continuous neuromuscular blockade, defined as a post-tetanic-count (PTC) of 0-1, all muscles, including the diaphragm, will be paralyzed [12].

We designed this study to assess the effect of a deep, continuous neuromuscular blockade during low-pressure LC on surgical space conditions. We hypothesise that a deep neuromuscular block is associated with a higher proportion of optimal surgical conditions.

MATERIAL AND METHODS

Study design

This on-going investigator-initiated study was launched 6 March 2012 and is a randomised, patient-and assessor-blinded study.

Study population

All adult (> 18 years of age) patients scheduled for elective LC at Aleris-Hamlet Hospital, Soeborg, Denmark during the study period are screened for inclusion (**Figure 1**). Inclusion of patients ends when the primary outcome has been assessed by per-protocol in 48 patients.

The exclusion criteria are given in Figure 1.

Randomization

A computer-generated randomisation is used with stratification for body mass index (BMI), BMI < 30 kg/m^2 or ≥ 30 kg/m^2. Patients are assigned to either deep, continuous neuromuscular blockade (The D-Group) or moderate neuromuscular blockade (The M-Group). This is done immediately before arrival to the operating room.

Anaesthesia

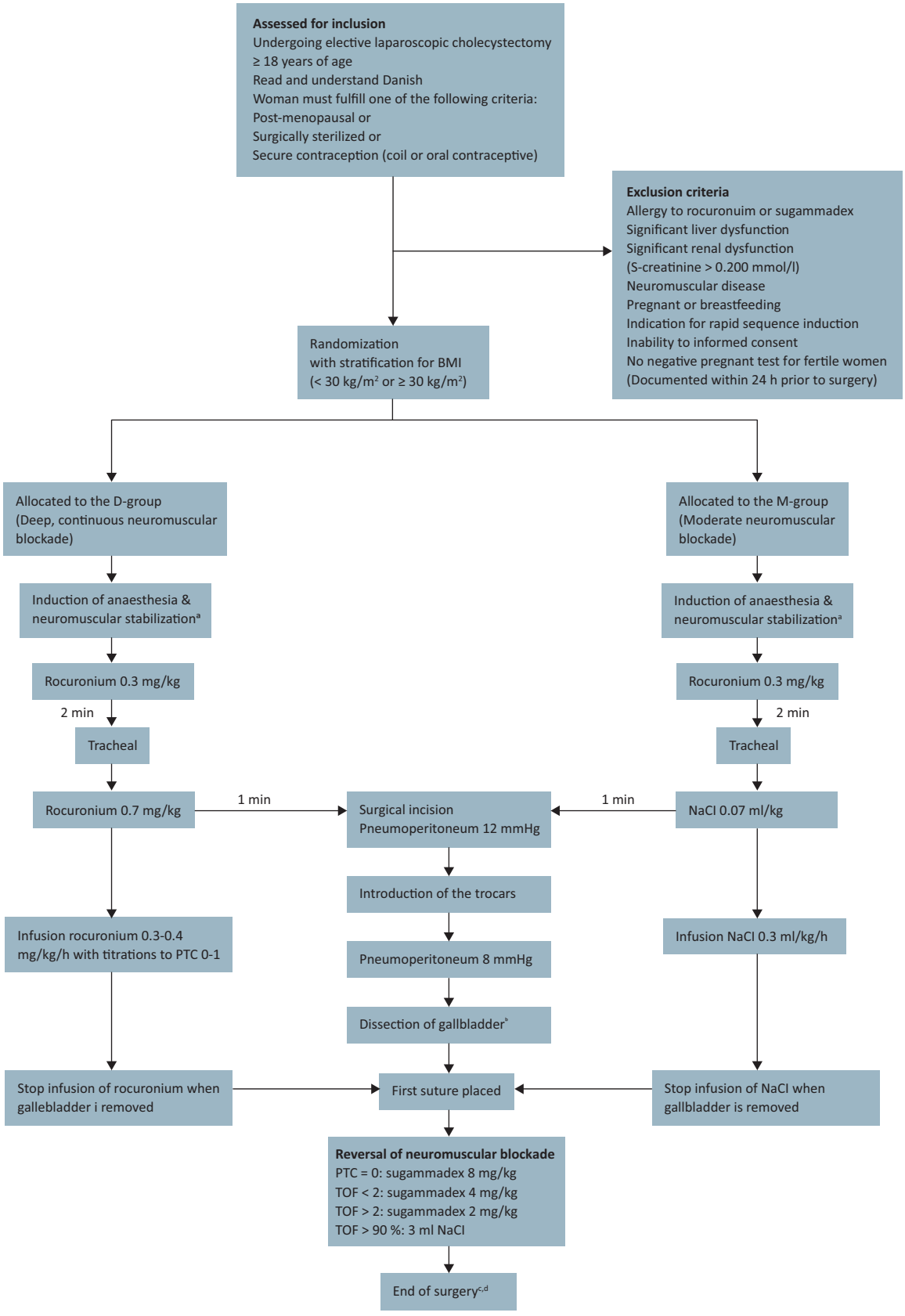
Anaesthesia is induced with propofol 2 mg/kg and remifentanil 0.5 µg/kg/min. Tracheal intubation is facilitated with rocuronium 0.3 mg/kg in both groups. Anaesthesia is maintained with propofol and remifenta-

PROTOCOL ARTICLE

1) Department of Anaesthesiology, Herlev Hospital
2) Department of Anaesthesia, Centre of Head and Orthopaedics, Rigshospitalet
3) Department of Surgery, Herlev Hospital
4) Department of Surgery, Aleris-Hamlet Hospital

Dan Med J 2013;60(2):A4579

FIGURE 1



Flow chart of patients undergoing elective laparoscopic cholecystectomy.
BMI = body mass index.
PTC = post-tetanic-count
TOF = train-of-four ratio.
a) Neuromuscular monitoring is performed with acceleromyography in accordance with Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents II [8].
b) Assesment of surgical space conditions during dissection of the gallbladder.
c) Assesment of surgical space conditions when they were worst.
d) Assessment of overall surgical space condititions.

TABLE 1

Trial protocol for perioperative care of 48 patients undergoing laparoscopic cholecystectomy.

Protocol element	Description
Preoperative	
Fasting guideline	Allowed to drink clear fluids until 2 h prior to anaesthesia
Analgesics	Paracetamol 1 g orally
Antiemetics	Dexamethasone 8 mg orally
Intraoperative	
General anaesthesia	Induction with propofol 2 mg/kg and remifentanil 0.5 µg/kg/min
	Maintenance with propofol 3 mg/kg/h and remifentanil 0.25-0.5 µg/kg/min
Respiratory	FiO_2 1.0 until tracheal intubation and immediately prior to extubation During surgery FiO_2 0.4, PEEP 5 cmH_2O
	Patients are ventilated to ensure normocapnia with PCV-VG
Neuromuscular monitoring	Neuromuscular monitoring is accomplished in a standardized fashion according to the international recommendations [8]
Positioning	After induction and intubation the patient is positioned in 20° anti-Trendelenburg verified by angle measurement
Surgical technique	Standard 4-hole incision
	A nasogastric tube is used for intra-operative gastric decompression and removed before extubation
Pneumoperitoneum	Initiated with 12 mmHg
	Reduced to 8 mmHg when all trocars are inserted
	At the end of surgery intra-abdominal CO_2 is removed by lung recruitment manoeuvre (five times pulmonary inflation with a pressure of 40 cmH_2O) and manual compression of the abdomen while keeping trocars open
Fluid therapy	No preoperative fluid loading
	Perioperatively up to 1,000 ml NaCl 0.9%
	Blood-loss up to 500 ml is replaced by isotonic NaCl 1:2.5
Temperature control	Core temperature is measured continuously, aiming at 36-37°C
Analgesics	Start of surgery: infiltration with local analgesic (20 ml bupivacaine 0.5%)
	15 min before end of surgery: sufentanil 0.2 mg/kg IV
	Immediately before last suture: ketorolac 15 mg IV
Antiemetics	Droperidol 0.626 mg IV
	Ondansetron 2 mg IV if indicated at the discretion of the attending anaesthetist
Antibiotics	Gentamicin 240 mg IV
Post-operative	
Analgesics	Paracetamol 4 g and ibuprofen 1,200 mg orally for the 3 subsequent days
	Oxycodone 2.5-5 mg IV in case of breakthrough pain (VAS 30 at rest or 50 during mobilization)

FiO_2 = inspired oxygen fraction; PCV-VG = pressure controlled ventilation-volume guaranteed; PEEP = positive end expiratory pressure; IV = intravenous; VAS = visual analogue scale.

nil and adjusted under guidance of entropy (Entropy Sensor, GE Healthcare, Hillerød, Denmark) and blood pressure (**Table 1**).

Neuromuscular monitoring is performed with accelermyography (TOF-Watch SX, MSD, Ballerup, Denmark) connected to a computer using the software TOF-Watch SX (Version 2.5 INT 2007, Organon, Netherlands) in accordance with Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents II [8]. The study arm is immobilized and a preload is placed on the thumb for monitoring acceleration (Hand Adapter, MSD, Ballerup, Denmark).

Sugammadex 2-8 mg/kg is given at the end of surgery if the train-of-four (TOF) ratio is below 0.90 (Figure 1). Patients are not extubated before they are fully awake and the TOF ratio has reached a plateau above 0.90 that is maintained for a minimum of 2 min.

Intervention

The dosage of rocuronium is based on ideal body weight in kg, which is calculated as follows: height (cm)-105 for women and height (cm)-100 for men.

In patients allocated to the D-group, a bolus of rocuronium (0.7 mg/kg) is given immediately before tracheal intubation (Figure 1). An infusion with rocuronium 3-4 mg/kg/h is started when the Post Tetanic Count (PTC) > 0, with titration towards PTC 0-1. PTC is measured every 3-4 min. In patients allocated to the M-group, no additional rocuronium is given immediately before intubation, but a similar volume of saline is given, and an infusion of NaCl 0.9% (0.3 ml/kg/h) is started approximately 20-30 min later. PTC measurement is imitated every 3-4 min and TOF measurement is made every 15 seconds.

Pneumoperitoneum is obtained with insufflation of CO_2 through a Verres needle to 12 mmHg, but reduced

TABLE 2

Description of the four-step scale and the numeric rating scale used to assess surgical space conditions in 48 patients undergoing laparoscopic cholecystectomy.

Scale	Description
4-step	
1 (optimal)	Optimal surgical space conditions
2 (good)	Surgical space conditions not optimal, but the surgeon does not consider any intervention
3 (acceptable)	The surgeon considers an intervention to optimize surgical space conditions
4 (poor)	An intervention is necessary in order to ensure acceptable surgical space conditions
NRS	
0	Optimal surgical space conditions
100	Extremely poor surgical space conditions and an intervention is needed

NRS = numeric rating scale.

to 8 mmHg after the introduction of the trocars. The following three-step procedure is used in both groups in case of inadequate surgical conditions:

1) Increase of pre-set intra-abdominal pressure to 12 mmHg.
2) If still not adequate, patients in the M-group are given a bolus of rocuronium 0.6 mg/kg. Patients in the D-group are given an equivalent amount of 0.9% NaCl.
3) If still not adequate, the surgeon will decide according to usual clinical practice.

If any of these interventions are needed, surgical space conditions will automatically be rated as four (four-step scale) and 100 (Numeric Rating Scale (NRS) 0-100) at the time of surgery when they were worst (**Table 2**).

Blinding

In a separate room, the primary investigator prepares syringes containing rocuronium, sugammadex and NaCl, and only the anaesthesia personnel will know the group allocation.

The patient's hand with the neuromuscular monitoring equipment and the connecting neuromuscular monitor are covered in order to keep the surgical team blinded to group allocation.

Information about group allocation, administered doses of rocuronium and sugammadex and neuromuscular data are recorded on a separate form and placed in a sealed opaque envelope when the patient is leaving the operating room.

This will keep the personnel in the post-anaesthesia care unit and the investigator collecting post-operative data blinded to group allocation.

Data collection

After inclusion, all patients are carefully instructed by the same investigator in how to use a visual analogue scale (VAS). Pain is evaluated as abdominal pain, incisional pain, shoulder pain and overall pain using VAS (VAS 0 = no pain; 100 = worst possible pain). Each assessment is done at rest and during mobilisation moving from a lying to a sitting position, using the abdominal muscles (**Table 3**). Patients are discharged on the day of surgery. A questionnaire is given to the patients to be filled out after discharge from hospital. An investigator blinded to group allocation contacts the patient on the first post-operative day and again one week after surgery to make sure that post-operative pain assessment is made and to assess any discomfort.

Outcome measures

The primary outcome is optimal surgical space conditions at the time of surgery when they were worst (rated as 1 on the four-step scale; Table 2).

The secondary outcomes are as follows:

- Surgical space conditions at the time of surgery when they were worst (NRS 0-100; Table 2).
- Surgical space conditions upon dissection of the gallbladder (four-step scale and NRS 0-100) – rated during surgery.
- Overall surgical space conditions as an average of the entire procedure (4-step scale and NRS 0-100).
- Proportion of laparoscopies performed with an intra-abdominal pressure of 8 mmHg.
- Pain expressed as the area under the curve from the first post-operative assessment to one week after surgery.
- Pain (abdominal, incision, shoulder and overall pain) at arrival in the Postanaesthesia Care Unit, two hours after surgery and one day after surgery.
- Number of days after surgery before resumption of normal activity.
- Duration of surgery.
- Post-operative consumption of analgesics up to 24 hours after surgery.
- Post-operative consumption of antiemetics up to 24 hours after surgery.
- Incidence of post-operative nausea and/or vomiting up to 24 hours after surgery.

Adverse events and reactions

We use a 21-day follow-up period regarding adverse events or reactions. Whether an adverse event or reaction is related to the intervention is decided by the sponsor. The product summaries for rocuronium and sugammadex will be used to evaluate if an adverse event or reaction is expected or unexpected.

The following adverse events are considered so frequent during and after surgery that they are not recorded: Perioperative changes in pulse and blood pressure which deviate less than 30% from baseline measurements, entropy values below 30 or above 50, and postoperative constipation requiring laxatives. The following adverse events are considered to be complications due to the surgical procedure and are not recorded: blood loss below 500 ml, surgical site infection and wound dehiscence.

However, if any of these adverse events or incidents are considered serious adverse events, they will be recorded.

Major protocol violation

All patients receiving the intervention will be included in the intention-to-treat analysis.

Patients with missed rating of surgical space conditions or conversion to open surgery due to other reasons than poor exposure of surgical space will not be include in the per-protocol analysis.

Trial conduct and monitoring

Data are collected on printed case report forms. The study is monitored by an independent inspector from the department of Good Clinical Practice, Bispebjerg, Denmark and conducted according to the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guidelines [13]. Case report forms are checked for validity and internal consistency through visits where source data are inspected.

Statistics

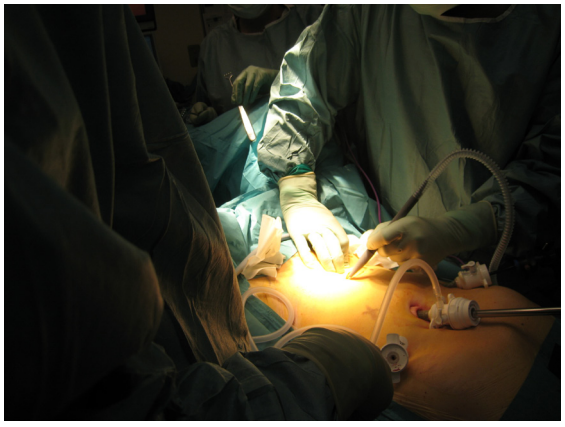
Students' t-test will be used to compare normally distributed variables, and Mann-Whitney U test will be used to compare not-normally distributed continuous data. Categorical variables will be compared with the χ^2-test. P-values < 0.05 will be considered statistically significant.

TABLE 3

Trial protocol for data collection in 48 patients undergoing laparoscopic cholecystectomy.

	Description
Preoperative	
Demographic	Gender, age, height, ASA Physical Health status
History	History of intra-abdominal surgery or pancreatitis
	Presence of acute or chronic cholecystitis
Pain	Presence and severity of abdominal pain, shoulder pain, other pain and overall pain[a, b]
	Current use of analgesics
Intraoperative	
Surgical conditions	Surgical space conditions (4-step scale and NRS, Table 2): during dissection of the gallbladder, at the worst time during surgery, overall (mean value for whole procedure)
	Any change in intra-abdominal pressure or body positioning
	Any surgical difficulties or complications
	Duration of surgery
Anaesthesia	Neuromuscular measurements every 15 sec.[c] Administration of rocuronium, sugammadex and any vasopressors Body core temperature after intubation and before extubation Estimated blood loss and administered volumes of crystalloids and colloids
	Duration of anaesthesia
Post-operative	
Pain	Presence and severity of abdominal pain, shoulder pain, other pain and overall pain[a]:
	Upon arrival to the post-anaesthesia care unit[b] 1 h, 2 h and 4 h after end of surgery[b]
	Immediately before discharge from hospital[b] 8 h after end of surgery[d]
	Daily in the morning until pain-free or 14 days after surgery[d]
Medication	Analgesics and antiemetics during hospitalisation
	Daily administration of analgesics until 14 days post-operatively
Discomfort	Nausea and/or vomiting during the first 24 h after surgery
	Any incidents or discomfort until 14 days post-operatively
Normal activity	Resumption of work
	Resumption of domestic activities

ASA = American Society of Anesthesiologists; NRS = numeric rating scale.
a) Assessed as visual analogue scale (0 = no pain; 100 = worst possible pain) at rest and during mobilisation; b) Assessed by use of a mechanic visual analogue scale ruler; c) If the train-of-four ratio is 0, post-tetanic count is measured every 3-4 m;
d) Recorded as a vertical stroke on a visual analogue scale 0-100 ruler.



Laparoscopic cholecystectomy.

Sample size

A difference in the proportion of adequate surgical space conditions of 28% was previously found between no neuromuscular blockade (72%) and neuromuscular blockade (100%) in laparoscopic surgery [7]. We calculated that a sample size of 48 patients would allow us to detect a difference between 72% and 100% in the proportion of optimal surgical conditions with a power of 80% and a type 1 error risk of 5%.

Ethics

The study is conducted in compliance with the Helsinki Declaration and approved by the Research Ethics Committee of Copenhagen (Protocol No. H-2-2011-146), the Danish Medicines Agency (EudraCT No. 2011-005502-29) and the Danish Data Protection Agency (Protocol No. 2012-41-0041). The study is registered at clinicaltrials.gov (NCT 01523886). All included patients sign written informed consent before arrival in the operation room.

DISCUSSION

The benefits of a deep, continuous muscle relaxation on surgical conditions during low pressure LC may be substantial, but have never been investigated. Focusing on surgical space conditions during laparoscopic surgery with accurate assessment of neuromuscular block, this study will compare a deep, continuous muscle relaxation with moderate relaxation.

A main strength of the present study is the mandatory nature of monitoring according to the ICH-GCP standards, which includes monitoring of adverse events.

Computer-randomisation with stratification for BMI is used to avoid a skewed distribution of important risk factors for poor surgical conditions. The abdominal circumference may have been a more accurate measurement, but BMI is easy to measure and often used scientifically and clinically, which makes comparison with patient populations easier.

All laparoscopies are performed by only two surgeons, each with more than ten years of surgical experience and more than 1,000 performed LCs, which will reduce variability in the assessment of surgical space conditions. Moreover, only one investigator instructs the patients regarding the use of VAS and the assessment of pain. This investigator also collects all the pre-and post-operative in-hospitalization data and contacts each patient on the first and seventh post-operative day.

There are some potential limitations of the study. Firstly, the power calculation is based on results from the only currently available study evaluating the effect of neuromuscular blockade on surgical conditions during laparoscopy [7]. This study found a 28% difference in adequacy of pneumoperitoneum (12 mmHg), but no difference in the quality of surgical view between a group receiving muscle relaxants and a non-relaxed group. It may raise some uncertainty that the power calculation is based on another outcome. However, we believe that the calculation is realistic.

Secondly, it may be necessary to increase the intra-abdominal pressure and to give an additional dose of rocuronium to patients in the control group (the M-group) to ensure optimal surgical conditions. This is in accordance with clinical practice and we believe such a pragmatic nature of the intervention is important. Any of these interventions will be recorded and the patient will be included in the per-protocol analysis with the primary outcome indicated as four (four-step scale). All patients receive a small dose of rocuronuim to facilitate intubation, which is in accordance with clinical practice in our institution. Completely omitting rocuronuim in the M-group could allow a better separation regarding the primary outcome, but this could impair tracheal intubation conditions.

Thirdly, the employed rating scales (four-step scale and NRS 0-100) have not been validated for assessment of surgical space. In addition, it may be difficult for the surgeons to distinguish between surgical space conditions and surgical conditions in general. Moreover, other factors than neuromuscular blockade or intra-abdominal pressure may influence surgical space conditions or surgical conditions in general and they may be different between the groups. Many of these factors are not known prior to surgery as they are only experienced intra-operatively.

We therefore report any surgical difficulties as well as operating time.

The study may be applicable to a general surgical population undergoing LC. However, we do not anticipate the results of this study to be generalizable to other laparoscopic procedures or other forms of anaesthesia.

CORRESPONDENCE: *Anne Kathrine Staehr-Rye,* Anæstesiologisk Afdeling, Herlev Hospital, 2730 Herlev, Denmark.
E-mail: anne.kathrine.staehr@regionh.dk

ACCEPTED: 5 December 2012

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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