PROTOCOL

Optimizing surgical conditions during laparoscopic umbilical, incisional –and linea alba herniotomy with deep neuromuscular blockade

(The hernia study)
Version 18
16. September 2016

Sponsor and primary investigator:
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Responsible department:
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Site where project will be conducted:
Anaesthesia and Day Surgery Department, Gentofte Hospital, University of Copenhagen

Monitoring:
Copenhagen University Hospital GCP unit, Bispebjerg Hospital, Bispebjerg Bakke 23, 2400 Copenhagen NV

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Principal Investigator, Sponsor & Institution accept always to follow the protocol and the latest Executive Order on Good Clinical Practice for Clinical, Trials involving Human Medicine (In Danish: Bekendtgørelse om god klinisk praksis i forbindelse med kliniske forsøg med lægemidler på mennesker").

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Background:

Umbilical herniotomy is a frequent surgical procedure worldwide, and the larger hernia defects are preferably operated by laparoscopic technique. The advantages of the laparoscopic approach are shorter convalescence with earlier mobilization, and less wound complications [1]. A preferred approach is currently to close the defect by laparoscopic suturing in order to reduce the formation of seroma in the hernia sac [2] , and then apply a mesh by intraperitoneal onlay technique (IPOM technique). However, it may be difficult to suture the defect if there is tension in the abdominal wall muscles together with the applied pneumoperitoneum.

There is evidence that muscle relaxation improves conditions for endotracheal intubation[3] and reduces laryngeal morbidity but only a few studies investigate the necessity of relaxation during laparoscopic surgery [4].

During laparoscopic surgery muscle relaxation is used with great variability. Sometimes the procedure is performed without muscle relaxation and sometimes with a so-called surgical neuromuscular blockade, which with objective neuromuscular monitoring means that train-of-four (TOF) is kept at 3-4 responses to nerve stimulation of the ulnar nerve. In this way there is a great variability in the neuromuscular blockade and rarely the patients are receiving deep neuromuscular blockade.

Traditionally, neuromuscular monitoring is done by measuring the muscle strength of the adductor pollicis muscle on the thumb. The response to TOF nerve stimulation may be zero, while muscle relaxation of more resistant muscles such as the abdominal muscles and the diaphragm [5;6] are not complete which means that the patients may cough and their abdominal wall may feel ”tight” during surgery, even though no response at the thumb is recorded. It is possible to quantify a deep neuromuscular block by the use of post-tetanic-count (PTC). With establishment of deep, continuous neuromuscular blockade with PTC value 0-1 all muscles including abdominal muscles and diaphragm are paralyzed [7]. It is therefore possible, that a deep neuromuscular blockade (NMB) where the diaphragm and the abdominal wall muscles are more paralyzed will optimize the surgical work space, ease the surgical procedure, reduce operative time for the suturing

part of the procedure as well as the total procedure time, and reduce the number of recurrences by long term follow-up.

Purpose:

The purpose of this study is to investigate surgical work space and surgical conditions in patients scheduled for laparoscopic umbilical, -linea alba and incisional herniotomy. The patients will act as their own control with evaluation of surgical work space and surgical conditions during both deep NMB and no NMB.

Hypothesis:

Deep NMB defined as TOF=0 and post-tetanic count (PTC) ≥ 1, will give better surgical workspace, better surgical conditions, as well as shorter duration of surgery and reduced number of recurrences of hernias compared with no NMB.

Method:

See appendix 1, flow diagram.

Design:

Randomized, cross-over design, with blinding of patient and surgeon. Randomization is used to determine the treatment sequence (no NMB followed by deep NMB (Group A) or deep NMB followed by no NMB (Group B)) in order to blind the surgeon.

Outcomes:

Primary outcome:

Improvement of surgical workspace (rated on a 5-point scale) estimated as the difference between the workspace during deep NMB and the workspace without NMB. Ratings are performed in the same patient during stable pneumoperitoneum at 12 mmHg.

Secondary outcomes: (comparing Group A with Group B)

-Surgeon´s rating of surgical conditions while suturing the hernia (5-point rating scale)

-Duration of operating time (from first incision to last suture)

-Assessments if the surgical space is better, unchanged or worse when evaluating before and after the intervention

-Number of sudden contractions of the abdominal wall during operation (bucking or coughing),

-Number of insufflator alarms where pneumoperitoneum > 17 mmHg,

-Number of episodes with continuous abdominal contractions where the abdomen feels ”tight” but the operation can still proceed (the intestines are gradually displaced near the inner surface of the abdominal wall).

- Number of recurrences of hernias by 2 year follow-up (separate publication). Patients will 2 years after operation receive a letter with invitation to ambulatory clinical assessment by a surgeon at Herlev Hospital or have the opportunity to receive a visit by a surgeon at their home address.

Number of patients:

34 eligible patients allocated into an assessor-blinded randomized cross-over design: one group first receives deep NMB followed by no NMB and the other group first receives no NMB followed by deep NMB.

Groups:

Group A: After intubation and placement of trocars: Bolus of saline (placebo) 6 ml. After three minutes the surgeon assesses the surgical workspace with pneumoperitoneum 12 mmHg. Bolus of rocuronium 0,6 mg/kg When TOF=0 the surgical workspace is assessed again.

Group B: After intubation and placement of trocars: Bolus of rocuronium 0.6 mg/kg When TOF=0 the surgeon assesses the surgical workspace with pneumoperitoneum 12 mmHg. Sugammadex is administered and when TOF=100% the surgical workspace is assessed again[8].

Criteria for participation:

Inclusion criteria:

Patients ≥ 18 years old

Elective laparoscopic umbilical herniotomy, incisional herniotomy and linea alba herniotomy.

Can read and understand Danish

Informed consent

Exclusion criteria:

Known allergy to sugammadex, rocuronium or mivacurium

Known homozygous variants in the butyrylcholinesterase gene

Severe renal disease, defined by S-creatinine> 0.200 mmol/L, GFR < 30ml/min or hemodialysis)

Neuromuscular disease that may interfere with neuromuscular data

Lactating or pregnant (Women of child bearing potential must take a urine pregnancy test at the day of the operation. The test will be provided by the hospital staff).

Indication for rapid sequence induction

Withdrawal criteria:

- In case of cancelling the operation, the patient will not receive the intervention. Data will not be available and therefore not analyzed and the patient will be considered as a "dropout".
- In case of the patient not receiving the intervention (trial medicine/placebo) after randomization, the data will not be analyzed and the patient will be considered as a "dropout".

These "dropout" patients will be disclaimed further data analysis.

Major violation:

- In case of need for increasing pneumoperitoneum to > 12 mmHg due to poor surgical conditions
- Converting to laparotomy

These will be characterized as major violations. The data will be analyzed in the intention-to-treat analysis, but excluded from the per-protocol analysis.

End of study:

When 34 patients have been evaluated considering the primary endpoint according to the intention-to-treat analysis, the study is finished.

Patient information:

Responsible for patient information and declaration of consent is local investigator. The patient will receive oral and written information about the project.

The initial contact with the patient will be done at a preoperative surgical evaluation at Herlev Hospital. The surgeon conducting the evaluation will handout the written patient information to all patients planned to have laparoscopic ventral-hernia surgery at Gentofte Hospital. The patient will at the same time receive a short oral information about the study and will be informed that the local investigator will contact the patient by telephone within a few days. This gives the patient time to read the information and to discuss it with family or relatives. The patient will be offered the possibility of being accompanied by a family member or another person at the telephone information interview. The local investigator will answer any question regarding the study and check that the inclusion criteria are met and none of the exclusion criteria are found. The patient will be offered a face-to-face interview if he/she whish. The patient will be informed that he/she will receive usual treatment if he/she does not want to participate, and that participation is voluntary, and that he/she always has the right to disclaim consent without affecting the further treatment.

After a period of consideration, depending on the patient´s needs, an attempt will be made to obtain consent.

Pre-operative assessment:

In the Case Report Form (CRF) the following baseline data is noted:

Age

Weight

Height

Sex

BMI

ASA group (I-IV)

Previous abdominal surgery

Co-morbidity which requires daily medical treatment

Parity

Randomization:

Randomization is 1:1, and done using Randomization.com. Two persons unattached to the study will use the randomization generator and pack the 34 envelopes consecutive numbered from 1 to 34. A paper revealing the intervention group assigned will be placed in each envelope. A copy of the randomization list will be kept in a sealed envelope by the coordinating investigator until the study is completed.
The randomization envelopes will be used in numerical order.
After randomization the investigator writes the randomization-group on the neuromuscular blockade sheet (NMB sheet).
34 eligible patients will be randomized.

Blinding:

Intervention medicine is prepared in the medicine room before the operation. This is done under double control by the investigator who also performed the randomization. Labels named "project medicine" will be placed on the syringes.
Randomization group will be noted on a sheet (NMB sheet), on which other data concerning neuromuscular blockade (NMB) will also be noted. On this sheet will also be noted the quantity of rocuronium and sugammadex administered, as well as values measured with TOF-Watch. This will not be noted on the anesthesia form. After conclusion of anesthesia the NMB sheet will be placed in the accompanying envelope, which is sealed and placed in a locked drawer where only investigators of the study has

access to. If there is a need for emergency unblinding the envelope is placed in this drawer: The envelope must only be opened, if it is considered strictly necessary to know which group the patient belongs to with respect to further treatment. This will happen after agreement with the investigator responsible for the trial and the phone number of the investigator is written on the envelope. Motivation for broken seal shall be included in the Case Report Form (CRF).

At the front of the patient's case file a sheet will be placed, which states that the patient is included in the trial.

The patient will at no time during hospitalization and possible recurrences follow up (regarding recurrences) be informed about treatment group allocation. The patient may however be informed of this upon conclusion of data collection.

The surgeon, will be blinded to treatment group allocation during the operation.

The anesthesia personnel, including local investigator, who anaesthetize the patient, may during inception and operation not be blinded, because the degree of the neuromuscular block shall be adjusted.

Surgical personnel, *recovery ward personnel* and *ward personnel* will be blinded to treatment group allocation.

Perioperative treatment:

Monitoring:

The patient will be monitored with ECG, non-invasive blood pressure, oxygen saturation, sleep depth measure with BIS [BiSpectral Index], and temperature sensors.

Neuromuscular monitoring will be done with TOF-Watch SX connected to a computer for collection of neuromuscular data (Version 2.5 INT 2007, Organon, The Netherlands). The monitoring will be done according to international research guidelines [9]. TOF-Watch SX will be placed on the arm, where there is the least monitoring in general. The skin over the ulnar nerve will be washed with spirits and rubbed with a piece of gauze. Small ECG electrodes will be used. They are placed on the wrist over the ulnar nerve. The

acceleration transducer is placed on the thumb and attached in the associated hand adaptor. TOF-Watch SX will be started. It will be calibrated (CAL2), when the patient does not react to verbal command and TOF mode will be started. Measurements will be taken every 15 sec. When stabile neuromuscular monitoring during 2 minutes is assured, rocuronium will be given. When TOF=0, PTC will be measured every 3 min., and rocuronium/saline infusion is adjusted in accordance with randomization.
The hand with TOF-Watch and apparatus is covered. The readings from the TOF-Watch are seen on the connected computer by nurse anesthetist and investigator.
Intravenous cannula is placed in the opposite hand.

Anesthesia:

General anesthesia with induction of propofol 2 mg/kg and remifentanil 1.0 mcg/kg/min. Tracheal intubation is performed no less than 3 minutes after induction of anesthesia making sure that the patient has received at least 3 mcg/kg remifentanil [10;11]. Anesthesia will be maintained with propofol 3 mg/kg/hour and remifentanil 0.25-0.5 mcg/kg/min, and adjusted according to depth of anesthesia under guidance of BIS (Entropy GE Healthcare).

Treatment values:

Blood pressure: Mean artery pressure (MAP) max. 30 % difference from baseline
BIS 40-60.

Medicine according to intervention: (see appendix 1)

Group A:

Bolus of saline 6 mL (placebo) before first assessment followed by bolus rocuronium 0.6 mg/kg ideal body weight (IBW) and rocuronium infusion to target level TOF=0 and PCT ≥ 1

Group B:

Rocuronium 0.6 mg/kg IBW before first assessment followed by sugammadex according to level of NMB and saline infusion (placebo).

Both groups:

At the end of surgery and to reverse first intervention the neuromuscular blockade is reversed with sugammadex/placebo. Sugammadex 2 mg/kg is given if TOF>2, and 4 mg/kg if TOF <2 and 16 mg/kg if PTC < 1. If TOF > 0.90 placebo reversal (NaCl) is given. Neuromuscular monitoring continues until TOF>0.90, stable over 2 min. The patient is awakened and taken to the recovery room.

Capped vials, ampoules, etc. for the test substances, i.e., rocuronium, sugammadex, are discarded after batch number, quantities removed from vials and quantities administered are registered on the NMB sheet.

Pneumoperitoneum:

Pneumoperitoneum is initiated after intubation and the operation will be performed at pneumoperitoneum 12 mmHg.

Surgical conditions:

The surgeon will evaluate the surgical workspace on a 5 point subjective rating scale 3 minutes after first intervention with rocuronium/saline and again three minutes after second intervention with rocuronium/sugammadex. Pneumoperitoneum is maintained at 12 mmHg. Additionally, the surgeon will assess if the surgical space is better, unchanged or worse when evaluating before and after the second intervention. Surgical workspace will also be evaluated while suturing the hernia. Evaluation of surgical work space will consider the assessment of the distance between the intestines and inner surface of the abdominal wall in a standardized manner.

During operation the surgeon will evaluate the surgical conditions on a 5 point rating scale while suturing the hernia with the use of IPOM technique and finally after the fascial closure. Evaluation will consider tightness or contractions of the abdominal wall muscles affecting the suturing.

Also the number of insufflator alarms for pneumoperitoneum > 17 mmHg will be registered.

In case of need for anesthetic intervention due to poor surgical conditions (with normal BIS, pulse and blood-pressure) after administration of intervention (rocuronium/sugammadex) this will be done in a standardized manner:

Group A: bolus saline (placebo) and wait for three minutes. Then the operation will proceed.

Group B: bolus of mivacurium and wait for three minutes. Then the operation will proceed.

Three minutes after bolus administration the surgeon will evaluate the surgical space and operating conditions on the 5 point rating scales.

If these interventions will not optimize the surgical conditions, a bolus of propofol or remifentanil can be administered.

Surgical rating scale [12]

1 Extremely poor conditions
2 Poor conditions
3 Acceptable conditions
4 Good conditions
5 Optimal conditions

Before beginning of the study the surgeons will receive an educational program to learn how to use of the rating scale and test it on pilot patients.

Positioning:

The patient will be positioned with the arm with neuromuscular monitoring equipment in abducted position. It is ensured that the monitoring equipment is as unaffected as possible to achieve the most precise neuromuscular data.

Surgical method:

With intraabdominal pressure of 12 mmHg laparoscopic umbilical, -linea alba and incisional herniotomy will be performed by suturing the defect and applying mesh by IPOM technique. Operations will be performed as outpatient procedures according to our usual routines. The mesh will be secured with fibrin sealant after the defect has been sutured. Mesh size will be circular with a diameter of the hernia defect size plus 5 cm . The defect will be sutured with Ethibond 0 suture with single stitches, intracorporal technique .

Insufflator: Olympus UHI-3, Pressure controlled (Olympus Medical System Corp. Tokyo, Japan)

Respiratory:

Patients are oxygenated at FiO_2=1.0 during preoxygenation and induction of anesthesia until the trachea is intubated. Anesthesia continues with FiO_2=0.40. Patients are ventilated with Pressure Control Ventilation, tidal volume 7 ml/kg, PEEP (positive end-expiratory pressure) 5 cm H_2O and respiration frequency 10-12 targeting normocapnia ($ETCO_2$ at 4.5-5.5 kPa). If $PaCO_2$> 6 kPa primarily the respiration frequency (RF) will be increased. If hypoxemia arises, defined as SpO_2< 95 or PaO_2< 10 kPa primarily FiO_2 will

be increased. In the event of deficient effect, PEEP will be increased.

Fluid therapy:

1000 ml isotonic NaCl 0.9% is given intraoperatively. Blood loss up to 500 ml is replaced with isotonic NaCl 1:2.5. Blood loss in excess of this is replaced in accordance with the local guidelines.

In case of hypotension ephedrine or phenylephrine will be administered.

Antibiotics

According to local guidelines. Dose and name will be noted on the CRF.

Pain treatment:

Postoperative pain treatment with paracetamol, NSAID and morphine according to local guidelines.

PONV profylaxis:

I.v. dexamethason 8 mg routinely

Data collection

Perioperative data collection that will be noted in CRF:

Type of operation with operation code
Batch-number, expiration date, used and surplus quantities of rocuronium and sugammadex, TOF values (NMB sheet)
Body temperature measured immediately after intubation and again immediately before extubation
Size of hernia defect measured during operation just before the defect is sutured
Surgical ratings on 5 point scale
Operating time (from first incision to last suture)
Number of sudden abdominal contractions and episodes with “tight” abdomen

Need for additional NMB to optimize surgical conditions

Postoperative registration:

Number of patients with recurrences of hernias 2 years after herniotomy.

Statistics:

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

Data from all randomized patients, who receive the intervention, will be included in the intention-to-treat analysis.

Patients, included in the intention-to-treat analysis, but who are categorized as major violation, will be excluded from the per-protocol analysis.

Normal distributed variables will be expressed by means and standard deviation; variables that are not normal distributed will be expressed by medians and interquartile range and the Mann-Whitney U test used for comparison of the median values.

Fisher´s exact test will be used at comparisons of percentages. A p value < 0.05 is considered significant.

As the study is a crossover trial, it is necessary to test for a possible period effect and a treatment period interaction. To detect a possible period effect a two sample t test to compare the differences between the periods in the two groups of patients will be carried out. If there is no general tendency for patients to do better in one of the periods, we assume that the mean differences between the periods to be of the same size but with opposite signs.

To investigate the possibility of a treatment-period interaction a two sample t test will be carried out by noticing, that in the absence of an interaction, the patients response to the treatment will be the same regardless of the order in which it is received.

If there is no period effect and no treatment-period interaction the analysis of the data regarding the primary outcome will be done by performing a Wilcoxon signed-rank sum test on all 34 patient´s data (differences in workspace between the two treatments).

Primary outcome:

Improvement of surgical workspace estimated as the difference between the workspace (rated on a 5-point scale) during deep NMB and the workspace without NMB. Ratings are performed in the same patient during stable pneumoperitoneum at 12 mmHg.

Sample size calculation:

With a clinical relevant decrease of surgical workspace of 1 on the rating scale, an expected standard deviation of 2, type 1 error 0.05 and power 0.80, we calculated the sample size of 34 patients in total.

Up to 50 patients can be included to have an evaluable primary outcome in 34 patients.

Risks, side-effects and events:

Sugammadex: According to the Danish Medicine Agency's product summary, the side effects are as follows:

Very common (> 10%)	Taste disturbances.
Common (1-10%)	Anesthesia complication
Not common (0,1-1%)	Consciousness during anesthesia.
	Allergic reactions.

Laparoscopic herniotomy is done at Gentofte Hospital with an intraabdominal pressure at 12 mmHg without use of muscle relaxation for intubation and in some cases with use of bolus of muscle relaxation decided by the attending anesthetist. Patients allocated to group DEEP will receive rocuronium in a dose corresponding to a deep neuromuscular blockade (PTC < 8) after intubation. It is not regarded as a disadvantage to use large doses of muscle relaxation, since the effect is fully reversed by sugammadex at the end of surgery.

Registration of adverse events:

Patients will be observed during their stay at the hospital and will be contacted by telephone on first and seventh postoperative day. Possibly adverse events during this period will be reported. Finally the patient´s case files will be reviewed for reports of adverse events at 17-21 days after operation.

The patients are encouraged to contact the local investigator, if they suspect any adverse events in connection with the trial and are treated according to applicable clinical principles and guidelines in the department.

Adverse events are registered as of the time when the patient is signing informed consent and the intravenous anesthetic is administered. All events are followed up until the final diagnosis or cause is established, and this is registered on the CRF.

Investigator being the sole Sponsor has to comply with all regulatory and legal requirements as far as monitoring and data collection is concerned by following the latest Executive Order on Good Clinical Practice for Clinical Trials Involving Human Medicine (In Danish: "Bekendtgørelse om god klinisk praksis i forbindelse med kliniske forsøg med lægemidler på mennesker").

Reporting Procedures for Exchange of Adverse Event Information.

(i) For purposes of this Protocol and Agreement the below terms shall be defined as follows:

"Adverse Event" or "AE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

"Device Deficiency" shall mean inadequacy of a Study Drug device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

"Incident" shall mean any malfunction or deterioration in the characteristics and/or performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user, or of other persons or to a serious deterioration in the state of health.

"Medical Device Event" shall mean any malfunction or deterioration in the characteristics and/or the performance of a Study Drug device, as well as any inadequacy in the labeling or the instructions for use which led to or could have led to an untoward event for the user or any other person.

"Serious Adverse Event" or "SAE" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug that results in death, a life-threatening drug experience, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, cancer, or is a new cancer if the cancer is the condition of the study, or overdose. Other important medical events that may jeopardize the patient or may require intervention to prevent one of the outcomes listed previously should also be considered "serious".

"Suspected Unexpected Serious Adverse Reaction" or "SUSAR" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current investigator's brochure, or with respect to a marketed product the most current Summary of Product Characteristics (SPC) or Package Insert.

(ii) Serious Adverse Event and Suspected Unexpected Serious Adverse Reaction, Medical Device Event, Potential Incident, Device Deficiency or Incident Reporting: Principal Investigator shall forward to MSD's Global Safety ("MSD GS") group, any SAE and SUSAR, Medical Device Event, Device Deficiency or Incident information, including, but not limited to, all initial and follow-up information involving any Study subject in the Study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) within two (2) business days of learning of the information. This information shall be transmitted to MSD GS using the contact information provided below or such other modified contact information as provided by MSD in writing. All information shall be transmitted in the English language and contain the reporter's name and the Study subject identifier code. SUSAR information will be reported unblinded if the Study Drug has been blinded in the Study. Randomization codes for all other SAEs will be provided to MSD GS at end of Study if the Study Drug has been blinded in the Study.

(iii) MSD may define certain Non-Serious Events of Interest. If any Non-Serious Events of Interest are defined, Merck will provide such information in writing to Principal Investigator at the time of Protocol approval, execution of this Agreement or anytime

thereafter. Reporting of any defined Non-Serious Events of Interest will be handled in the same manner as SAEs unless mutually agreed otherwise in writing by the parties.

(iv) All reports of Study Drug exposure during pregnancy or lactation (including a female partner of a male Study subject using the Study Drug), whether associated with an AE or not, must be reported to MSD GS in accordance with the timelines and contact information for an SAE. Principal Investigator shall follow pregnancies to term to obtain the outcome of the pregnancy. The outcome of the pregnancy shall be forwarded to MSD GS.

(v) Institution and Principal Investigator shall fully comply with all of their respective reporting obligations to the applicable regulatory authorities with respect to any AE, SAE or SUSAR that arises from the Study.

(vi) SAE reports and any other relevant safety information are to be forwarded to MSD GS facsimile number: +45 44 82 42 99.

C. In the event Principal Investigator or Institution becomes aware of a defect or possible defect in the Study Drug, Institution and Principal Investigator agree to notify MSD within one business day of first becoming aware of the defect or possible defect.

D. Principal Investigator and Institution further agree to conduct the Study and maintain records and data during and after the term or early termination of this Agreement in compliance with all applicable legal and regulatory requirements. If required by law, regulation, regulatory authority or to confirm compliance with this Agreement and the Protocol, MSD or MSD's representatives shall have the right to examine and inspect all records and reports related to the Study Drug or directly relating to the Study, at mutually agreeable times with reasonable advance notice and during normal business hours (subject to applicable patient confidentiality considerations). Principal Investigator and Institution agree to take any action necessary, as reasonably requested by MSD, to properly correct or address any deficiencies noted during any inspection and agree to cooperate with MSD with respect to any action taken to address any such deficiencies.

E. Principal Investigator agrees to notify MSD within twenty-four (24) hours in the event that any regulatory authority notifies the Study site of a pending inspection that concerns the Study or Institution's ability to perform clinical research. In addition, Principal Investigator will forward to MSD any written communication received as a result of the inspection within twenty-four (24) hours of receipt of such communication and agrees to allow MSD to assist in responding to any citations involving the Study Drug. Such responses shall be made as soon as possible under the circumstances or within any earlier deadline set by the issuing regulatory authority. Principal Investigator shall also provide to MSD a complete description of documents and any correspondence

provided to any inspector. In the event the regulatory authority requests or requires any action to be taken to address any citations, Principal Investigator and Institution agree, after consultation with MSD, to take such action as necessary to address such citations.

F. A copy of all 15 Day Reports and Annual Progress Reports / Development Safety Update Report (DSUR) are to be submitted as required by the applicable regulatory authority by the Principal Investigator. Principal Investigator agrees to cross reference this submission according to local regulations, to the Study Drug number (IND, Clinical Study Authorization (CSA)/EudraCT approval number, etc) at the time of submission. Additionally Principal Investigator agrees to submit a copy of these reports to MSD (Attn: Global Safety; FAX +45 44 82 42 99) at the time of submission to the appropriate regulatory agency.

G. MSD may provide the Principal Investigator and Institution, at Study initiation and on an ongoing basis, with information regarding the Study Drug, including but not limited to safety information. The Principal Investigator and Institution agree to hold this information in confidence.

H. Principal Investigator & Institution accept to follow the latest Executive Order on Good Clinical Practice for Clinical, Trials involving Human Medicine (In Danish: Bekendtgørelse om god klinisk praksis i forbindelse med kliniske forsøg med lægemidler på mennesker").

Principal Investigator and Institution accept also to report the serious adverse reactions and unexpected non-serious adverse reactions discovered within 2 working days to MSD att: Pharmacovigilance by fax +45 44 82 42 99.

Side effects/events that will *not* be registered:

In general, side effects and events that are typically seen in connection with the normal course of anesthesia and operation will not be registered and reported to the Danish Medicines Agency. In this protocol side effects/events (AE) will be defined in the form of expected changes in pulse and blood pressure as a result of the anesthesia. Pulse and blood pressure values (measured 3 repeated times within a 10-minute period) that deviate less than +/- 30% of the starting level will thus be accepted and not registered. Side effects/events that may be ascribed to the operation with certainty, for example, pain in the surgical wound or wound infection will not be registered. Side effects/events that with certainty have arisen as a result of the patient's postoperative treatment will

not be registered.

As reference documents for assessment of whether an SAR is a "suspected unexpected serious adverse reaction" (SUSAR), the Danish Medicines Agency and EMEA's product summary will be used for Sugammadex.

The local investigator reports AR, AE, SAR, SAE and SUSAR to sponsor/ investigator. In the event of SAR/ SAE this happens at once. In the event of SUSAR the coordinating investigator will likewise report at once to sponsor/investigator. Sponsor/investigator will immediately report SUSAR to the Danish Medicines Agency. Within 7 days sponsor/investigator will ensure that all information is registered and reported to the Danish Medicines Agency, as well as what consequences they have for the trial. Eight days after reporting sponsor/investigator will report to the Danish Medicines Agency all relevant information about sponsor/investigator's follow-up to the report. The case file of each individual trial subject will postoperatively be reviewed by the coordinating investigator for the purpose of tracking side effects. All AR, AE, SAR, SAE and SUSAR will be gathered on one list, which sponsor/investigator reports to the Scientific Ethics Committee and the Danish Medicines Agency at the conclusion of the trial. The list will contain all registered side effects/events.

Quality control and quality assurance:

General procedures for quality control and quality assurance will be followed, cf. ICH GCP guidelines. Data will be monitored by the GCP unit. Upon granting of informed consent, authorization will be obtained from the trial subjects for third parties to be able to have access to information on the person in question's health condition. Investigator will thus allow the GCP unit or the Danish Medicines Agency direct access to source data/documents with monitoring, auditing and/or inspection. Concomitant medication and treatment before and during the trial is allowed, if it is not described under the exclusion criteria. A decision on which regular medicine the patient shall continue with before, during and after the operation will be made by the doctors in the department in which the patient is admitted in normal collaboration with doctors from Gentofte

Hospital.

Schedule:

Anticipated start (inclusion of first patient) February 2015. Long term follow-up data (recurrences) will be published separately when data are ready.

Inclusion of 1-2 patients per week is expected corresponding to duration of inclusion of approximately 24 months. Inclusion: Planned to go on in the period from February 2015 to February 2017. Inclusion of patients will be stopped when the desired number of patients is achieved. The trial will be counted as concluded, when the last patient has registered with the primary endpoint.

Data analysis and reporting: from April to May 2017.

Ethical considerations:

Laparoscopic herniotomy is presently conducted at Gentofte Hospital with an intraabdominal pressure of 12 mmHg and sometimes with use of a small quantity of muscle relaxant for intubation.

It is not considered an inconvenience to use large doses of muscle relaxant, as the effect of this is fully reversed by sugammadex at the end of the anesthesia. Anesthesia and surgery will follow guidelines apart from the dosage of muscle relaxants.

We think that it is justifiable that information about the use of muscle relaxants/antidotes be stored in a sealed envelope in the patient record with respect to the blinding. There is an option to break the seal on the envelope in an emergency situation. Routinely unblinding of the included patients will be done after the operation. Sugammadex is considered active in the first 24 hours, but the intervention will be considered to be over.

The possible benefit in this trial is to investigate whether deep neuromuscular blockade gives better surgical space conditions at pneumoperitoneum 12mmHg in patients > 18 years old undergoing laparoscopic umbilical, -linea alba and incisional herniotomy.

Informed consent will be obtained before the patients arrive to the operation ward. We thereby wish to avoid having the patient make a decision about participation in the trial, in the stressed environment an operation ward is often experienced as for a patient before an operation. The inclusion and exclusion criteria used will ensure that we only investigate patients who will be able to tolerate being treated according to the two strategies. Intervention with respect to possible complications from this, are not unchanged either.

The investigation will be reported to the Scientific Ethics Committees, Danish Medicines Agency and Danish Data Protection Agency. The participants in the investigation are assured access to receive further information about the project through the coordinating investigator, who as contact person is referred to in the participant information. The "Rights of Trial Subjects" published by the Scientific Ethics Committee will be provided.

The trial will be considered as having started on the date when there is a signed declaration of consent from the first patient, who will thereby be considered as included. The trial will be considered ended when the last patient has had the post-operative interview and the CRF for this patient is completed. At the end of the trial, investigator and sponsor will inform the Scientific Ethics Committee and the Danish Medicines Agency of this within 90 days. The trial will be registered in an international database (www.clinicaltrials.gov), before the recruitment of patients is started.

Data collection and storage:

Primary investigator will arrange for data collection and storage of CRFs in locked premises. The study will be reported to the Data Protection Agency. Data will be stored for 5 years after conclusion of the trial. The information about the patients' health conditions, other purely private circumstances and other information that arises in connection with the trial is covered by the obligation of confidentiality. The information about the patients is protected by the Act on processing of personal information and the Danish Health Act.

Responsible department:

Department of Anaesthesiology, Herlev Hospital, Herlev Ringvej 75, 2730 Herlev, legally represented by sponsor and primary investigator Mona Ring Gätke

Economy:

The sponsor and primary investigator has taken initiative to the biomedical research project.

The project budget covers:

1) salary for subinvestigator
   459.000 DKK
2) expenses including GCP course,BIS monitoring electrodes and BIS monitor
   60.000 DKK
3) fees at the Danish Medicines Agency and The National Committee on Health Research Ethics
   15.000 DKK
4) expenses to project medicine (Sugammadex)
   80.000 DKK (applied for from the MISP committee)

   Total budget 640.000 DKK

Financial support (640.000 DKK = 113.790 USD) for the project has been applied for via the pharmaceutical company MSD, Glostrup to the international MSD MISP program.
MSD is lending TOF-Watch for use for the study.
Sponsor and primary investigator Mona Ring Gätke is not receiving any salary from MSD.
She has received lecture fees and travel expenses from MSD.
Jacob Rosenberg has received lecture fees and travel expenses from MSD.
Matias Vested Madsen has received travel funding and speaker fee from MSD.

Publication:

The results, either positive, negative or inconclusive, will be submitted for publication in an international, English-language journal. Authorship will occur in accordance with international Committee of Medical Journal Editors' rules (the Vancouver Group). The right to data and know-how that emerges in connection with the trial will belong to the primary investigator and the Department of Anaesthesiology, Herlev Hospital.
We currently plan to publish 1) a results paper, and 2) a paper including data on recurrences after two years. If it, however, seems appropriate to split the data in more papers, then the subsequent papers will bear the same trial registration number as the primary papers.

Registration:

The study will be registered at www.clinicaltrials.gov

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