Protocol

PROTOCOL nr: P17.049
Date: November 1, 2017
Version: 2.0
CCMO nr NL60821.058.17

Title: Effect of deep *versus* moderate neuromuscular block during sevoflurane anesthesia on intraoperative surgical conditions, hemodynamics and postoperative pain in patients undergoing laparoscopic (donor) nephrectomies **– The BLISS 4 trial**

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List of abbreviations and definitions

AE: Adverse event. Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product and or the experimental treatment.

CCMO: (Centrale commissie mensgebonden onderzoek) Central Human Ethics Committee

CRF: Case record form.

DNB: Deep neuromuscular block

GCP: Good clinical practice

ICH: International conference on harmonisation

LOAA/S: Leiden Observer's Assessment of Alertness/Sedation

LUMC: Leiden University Medical Center

METC: (Medisch Ethische Commissie) Medical Ethics Committee

NMBA: non-depolarizing neuromuscular blocking agent

VAS: Visual analogue score. Pain score measured on a 11-point scale from 0 (= no pain) to 10 (worst pain imaginable).

Train of four (TOF). Four supramaximal stimuli of 2 Hz are provided to the ulnar nerve via the skin at the wrist. The effect of the stimuli can be measured at upper arm (in our study with the TOF CUFF) as muscle contractions. With increasing muscle blockade a fade (*i.e.,* the amplitude decreases) appears followed by the disappearance of muscle contractions. The reverse is true when the muscle blockade disappears. Under conditions of deep or profound neuromuscular blockade (with absence of any twitches) the TOF is of limited use.

Train of four ratio (TOF ratio). The ratio of the amplitude of the last twitch of the TOF relative to the first twitch (*i.e,* T4/T1). The lower this ratio, the greater the extent (depth) of muscle relaxation.

Post Tetanic Count (PTC). In contrast to TOF stimulation, PTC can be used to determine the degree of neuromuscular blockade under conditions of a deep neuromuscular block. A 50 Hz stimulus, given for 5 seconds, is applied at the skin over the ulnar nerve. Three seconds after this stimulus, muscle contraction is counted in response to single 1 Hz stimulation. In an intense neuromuscular block, no PTC response may be observed.

Summary

Rationale: A deep neuromuscular block (DNM) is often associated with improved surgical conditions especially in laparoscopic surgery. However, a deep block comes at the expense of a variety of items that may conflict with the use of a deep surgical muscle blockade including a long recovery phase, the need for muscle reversal, postoperative ventilation, impaired postoperative breathing. With the introduction of sugammadex there is now the possibility to reverse an even deep surgical block. This may overcome most if not all of the issues mentioned. We previously showed that DNM is superior to a moderate NMB under propofol anesthesia. However, this may not apply to sevoflurane anesthesia and sevoflurane by itself produces some degree of muscle relaxation.

Objective: To assess whether a deep neuromuscular block provides better surgical conditions than a moderately deep block as derived from a surgical rating score during sevoflurane anesthesia.

Study design: Single center, double-blind randomized controlled trial.

Study population: 100 ASA I-III patients scheduled for laparoscopic renal surgery, i.e. (donor) nephrectomies.

Intervention: Fifty patients will receive a deep NMB with a continuous infusion of rocuronium causing a TOF score of 0 and PTC of 1-2. Fifty other patients will receive a moderate NMB using bolus administrations of rocuronium causing a TOF score of 1-2. Anesthesia induction is with propofol, while anesthesia maintenance is with sevoflurane 1.5% end-tidal (ET) concentration.

Main study parameters/endpoints: To study the surgical conditions in patients undergoing laparoscopic renal surgery during deep versus less deep neuromuscular block as assessed by the surgical rating score.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Compared to current practice there will be no additional risk.

1. Ethics

Ethics Committees. The protocol, possible protocol amendments, the patient information form, informed consent form and any other study related information or documents will be reviewed and approved by the LUMC ethics committee (METC) before subjects are screened for study entry. The Investigator will submit periodic reports and inform the METC of any reportable adverse events (AEs) per ICH guidelines and local ethical committee standards of practice.

Ethical Conduct of the Study. This study will be conducted in accordance with LUMC standard operating practices, which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

- Declaration of Helsinki, version 2013 ("WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects").

- ICH Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonization of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).

- European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.

- GCP Directive 2005/28/EC.

This study will be conducted in accordance with national and local laws.

Subject Information and Consent. All subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. Each subject will be given a copy of the informed consent and written information. The subject will be asked to sign an informed consent form prior to any study-specific procedures being performed.

2. Investigators and study personnel

Qualified Investigators under the sponsorship of the Leiden University Medical Center will conduct this study. The names of the investigators, independent physician and contact person are given on page 1 of this protocol. The Principle Investigator is BROK certified.

3. Introduction

In two independent studies we previously showed that deep NMB produces superior surgical rating scores compared to a moderate NMB [1,2]. In retroperitoneal surgery, for example, we showed that during propofol anesthesia deep NMB was associated with a mean surgical rating scale (SRS) of 4.7 (on a 5-point scale) compared to a score of 4.0 during moderate NMB. This difference was considered highly significant by the surgeon. Since both studies were performed during general anesthesia with the intravenous anesthetic propofol, it remains unknown what the influence is of the anesthesia type on the SRS scores. Therefore we will now study the effect of deep *versus* moderate NMB on SRS scores during sevoflurane in retroperitoneal surgery. We expect a difference in SRS scores albeit of smaller magnitude than in our first two studies since sevoflurane has neuromuscular relaxing properties.

The main end-point of the study is the effect of the deep block on surgical conditions during sevoflurane anesthesia. To that end-the surgical team will be asked to rate the quality of the surgical field at 15-min intervals using the 5-point Leiden-Surgical Rating Scale (L-SRS), a scale that was previously developed at LUMC and recently validated [1,2].

Secondary end-points of the study are hemodynamics (blood pressure and heart rate) and Nociception Level (NoL [3]) during anesthesia, and pain and sedation scores following surgery.

4. Objectives and hypothesis

Main objective

To study the surgical conditions in patients undergoing laparoscopic renal surgery: (donor) nephrectomies during deep *versus* moderate neuromuscular block as assessed by the Leiden Surgical Rating Scale during sevoflurane anesthesia.

Minor objectives

1. To study the hemodynamic conditions during deep *versus* moderate neuromuscular block.

2. To study the nociception level during deep *versus* moderate neuromuscular block.

3. To assess the effect of deep *versus* moderate NMB on pain, sedation and nausea/vomiting in the recovery room (PACU).

Hypotheses

1. Deep neuromuscular block leads to excellent surgical condition in patients undergoing laparoscopic renal surgery.

2. The difference in surgical conditions between deep or moderate neuromuscular block is absent during sevoflurane anesthesia;

3. Deep neuromuscular block leads to favorable hemodynamic conditions;

4. Deep NMB is associated with less postoperative pain.

5. Study design

The study will be a randomized control trial (RCT) performed in 100 patients that will undergo elective laparoscopic surgery for (donor) nephrectomy. The trial starts after the medical ethical committee has approved the study protocol and will have a maximum duration of 2 years.

Patients will be randomized to either receive a continuous infusion with rocuronium aimed at a deep block (TOF 0 twitches, PTC 1-2 twitches), or receive muscle relaxation aimed at a moderately deep neuromuscular block (TOF 1-2)

Deep block is obtained with continuous rocuronium infusion: loading dose of 1.0 mg/kg, followed by 0.3-0.6 mg/kg per h.

Moderate block is obtained with a bolus-dose rocuronium technique: loading dose of 0.5 mg/kg followed by bolus doses of 5-10 mg when the TOF exceeds 2-3.

Both the surgeon and the research team will be blinded to the muscle relaxant used and the level of muscle relaxation. The attending anesthesiologist will be made responsible for both the administration of the muscle relaxant and degree of NMB. He or she will not correspond about the NMB with the surgeon or the research team.

Anesthesia induction is by propofol/sufentanil followed by sevoflurane maintenance (approx. 1.5% end-tidal concentration) and sufentanil for analgesia. Reversal is by sugammadex 4 mg/kg following a deep NMB and 2 mg/kg following a moderate NMB. Patients will be extubated when TOF ratio becomes 0.9 or larger.

Note that both NMB techniques are standard-of-care at LUMC.

6. Patients and patient requirements/procedures

A total of 100 patients will be included in this study.

6.1 Patient inclusion criteria

(i) Patients that will undergo an elective laparoscopic (donor) nephrectomy;

(ii) ASA class I-III

(iii) > 18 years of age;

(iv) Ability to give oral and written informed consent.

6.2 Patient exclusion criteria

(i) Known or suspected neuromuscular disorders impairing neuromuscular function;

(ii) Allergies to muscle relaxants, anesthetics or narcotics;

(iii) A (family) history of malignant hyperthermia;

(iv) Women who are or may be pregnant or are currently breast feeding;

(v) Renal insufficiency, as defined by serum creatinine x 2 of normal, or urine output < 0.5 ml/kg/h for at least 6 h. When available, other indices will be taken into account as well such as glomerular filtration rate < 60 ml/h and proteinuria (a ratio of 30 mg albumin to 1 g of creatinine).

(vi) Previous retroperitoneal surgery at the site of the current surgery.

(vii) Body mass index > 35 kg/m^2

6.3 Preoperative procedures. Eligible patients who are scheduled to undergo a (donor) nephrectomy will be informed about the study and asked to participate and complete the informed consent. General preoperative examination and testing will be done as usual at the preoperative outpatient department.

6.4 Recruitment. Subjects will be recruited after approval of the study protocol by the medical ethics committee of the LUMC. Eligible subjects will be informed and recruited at the preoperative outpatient department by an anesthesiologist.

6.5 Informed consent. Patients will receive verbal and written information about the study. A written informed consent must be completed for a subject to enter the study.

6.6 Medical examination. Full medical examination and relevant blood laboratory tests will be completed at the preoperative outpatient department.

6.7 Pre-study requirements. Pre study requirements will be no different compared to patients undergoing surgery under general anesthesia. This includes refraining from eating six hours before surgery and refraining from drinking two hours before surgery.

6.8 Withdrawal of an individual subject. Subjects can decide to leave the study at any time, for any reason if they wish to do so, without any consequences. The responsible investigator can also decide to exclude a subject if by continuing participation the subject's wellbeing is harmed in any way. Subjects can also be excluded in case of protocol violations and non-compliance.

In case of dropping out from the study at the subject's own request, the subject is asked permission for using the data already collected. The subject is allowed to decline this request, without giving any reason, and again without any consequences. When permission is not granted to use already available data, this specific data is deleted from the database and any paperwork will be disposed of.

In case of withdrawal the subject will be replaced by another patient.

7. Anesthesia

Anesthesia. Induction and maintenance of anesthesia is by propofol combined with bolus doses of an opioid (sufentanil).

Propofol will be given as bolus of 2-2.5 mg/kg, followed the administration of sevoflurane for the duration of surgery. The target end-tidal sevoflurane concentration = 1.5%

The opioid use will be at the discretion of the attending anesthesiologist. Sufentanil will be administered in single bolus infusions of 0.25 to 0.6 μg/kg.

The dosage and moment of drug administrations will be collected on the CRF.

Use of neuromuscular blocking agents and reversal agents is given in section 5.

After the neuromuscular block has been given, the trachea of the patient will be intubated with an oro-tracheal tube. At the end of the case, after reversal of the NMB the patient will be extubated when the TOF ratio > 0.9.

Teams in the operating room during the study. During the procedure there will be three teams present in the operating room:

(1) The surgical team. They will be blinded to the patient treatment.

(2) The anesthesia team (an attending anesthesiologist and anesthesia nurse). They will have knowledge on the treatment allocation of the subject. They will deliver the treatment to the patient and they will monitor the depth of the neuromuscular block with the TOF CUFF.

(3) Some of the investigators. The junior investigator will be present and will monitor the case. He is blinded to the treatment and will not communicate with the anesthesiology team regarding the treatment allocation.

8. Measurements

8.1 Pre-study parameters/variables

Patient characteristics including age, gender, weight, height, ASA class, medication, comorbidity.

8.2 Measurements/variables/images obtained during anesthesia

A. Surgical rating. During the procedure, the surgical condition will be scored by the surgeon using a 5-point surgical rating scale. In order to reduce variability in the surgical rating all surgeries will be performed the surgical team. All members of the team are well trained in using the L-SRS. The rating scale will be a 5-point ordinal scale ranging from 1 = poor condition to 5 = optimal surgical conditions (see Table 1, below). The surgeon will score the condition at 15 minute intervals. In case of a sudden change in surgical conditions additional scores will be added to the CRF. If conditions are poor (score 1 or 2), muscle relaxation will be increased, a score of 1 will be used.

The surgical rating score

1 Extremely poor conditions

2 Poor conditions

3 Acceptable conditions

4 Good conditions

5 Optimal conditions

In case of scorings 1 or 2 additional doses of rocuronium will be administered.

C. Neuromuscular monitoring. For neuromuscular function monitoring the TOF CUFF will be applied at 15 min intervals. When no twitches are present the PTC will be assessed. Neuromuscular data will be collected via an arm cuff system. The data will be collected on the CRF.

D. Haemodynamic monitoring. Blood pressure, heart rate and NoL will be measured using the monitoring devices available in the operating room.

E. Intra abdominal pressure. Intra abdominal pressure will be measured every 15 minutes from the retroperitoneal CO_2 insufflation device.

F. Additionally the following variables are included:

- duration of surgery;
- drug dosages (propofol, sevoflurane ET conc. opioid, muscle relaxant, reversal agent, any other agents used during anesthesia);
- duration from reversal to extubation

8.3 Measurements/variables obtained during recovery and on the ward

A. Pain. Pain will be measured directly by asking for a visual analogue score (VAS) at 15 min intervals. Additionally opioid consumption will be collected.

B. Sedation/Alertness. The level of sedation/alertness will be assessed in the recovery room using the validated Leiden Observer's Assessment of Alertness/Sedation (LOAA/S) scale at 15 min intervals.

The LOOA/S

0 = normal alertness, eyes open, responds normal to command

1 = drowsy with open eyes, closed and opened on command

2 = drowsy with closed eyes, opened in response to light auditory stimulus

3 = eyes closed, opened in response to rubbing the shoulder or a loud auditory stimulus

4 = eyes closed and opened only briefly in response to touching the subject

5 = eyes closed, unarousable by touching the subject, aroused by a painful stimulus

6 = unarousable by a painful stimulus

C. Occurrence of nausea/vomiting. The occurrence of nausea (yes/no) and vomiting (yes/no) will be scored at 15 min intervals.

9. Safety

9.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including placebo, and which does not necessarily have to have a causal relationship with treatment. An AE can be:

- Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study medication, whether or not considered related to the study medication.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in protocol-required or non-protocol-required measurements of laboratory value or other clinical tests (e.g. ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study medication.
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline.

Subjects with AEs that are ongoing at the subject's completion/discontinuation visit (last treatment visit) will be followed up for *7* days and the follow up information will be recorded in the CRF. New AEs that are reported in the *7* days following the subject's completion/ discontinuation visit will be recorded in the AE section of the CRF. Any AE that is still ongoing 7 days after the completion/discontinuation visit will have an end date of 'ongoing' in the CRF, however the investigator will continue to follow up ongoing AEs and record information in the source documents. SAEs will be followed until the event resolves or the event or sequels stabilize and this information will be reported to the Sponsor using the SAE Data Form.

9.2 Reporting of Adverse Events

For subjects who receive study medication, all AEs (learned through spontaneous reports, subject interview) starting from providing informed consent for study participation through the period beyond study completion will be collected on the AE pages of the CRF. In addition, a note should be made in the source documentation of the subject.

For each AE on the AE pages of CRF, the following information will be recorded: AE (e.g. headache), start date, start time, stop time, severity, study medication action taken, other action taken, relationship to study medication, outcome, seriousness. A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g. fever, elevated WBC, cough, abnormal chest x-ray, etc. can all be reported as “pneumonia.”).

9.3 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he/she may judge the true nature and severity of the AE. Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

Mild: Awareness of sign, symptom, or event, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

The criteria for assessing severity are different to those used for seriousness (see below for the definition of an SAE).

9.4 Criteria for Assessing Causality

The question of the relationship of an AE to study medication should be determined by the Investigator after thorough consideration of all facts that are available. Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations. The causal relationship of an AE to study medication will be assessed according to the following criteria (based on World Health Organisation definitions):

Not related: Temporal relationship to study medication administration is missing or implausible, or there is an evident other cause.

Related

Unlikely to be related: Temporal relationship to study medication administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Possibly related: Reasonable time sequence to administration of study drug, but event could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probably related: Reasonable time sequence to administration of study drug, but unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

Definitely related: Plausible time relationship to study medication administration; event cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

9.5 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e. the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study medication);

- Is a medically important event or reaction (see below).

Other important medical events that may not be immediately life-threatening or result in death or hospitalisation but may, based on appropriate medical judgment, jeopardize the subject or require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias or seizures that do not result in hospitalisation, or development of drug dependency or drug abuse. These events may be considered to need rapid reporting by the Sponsor to competent authorities.

All SAEs, including those occurring up to 7 days following the subject's completion/ discontinuation visit (subject's last treatment visit), will be recorded on the AE pages of the CRF. In addition, SAEs must be reported to the Sponsor using the SAE Data Form. Subjects with SAEs must be followed until the event resolves or the event or sequels stabilize.

9.6 Reporting of SAEs

All SAEs must be reported to the Sponsor within one business day of first knowledge of the SAE using the SAE Data Form. In the initial report, all of the information requested that is available should be provided. The SAE Data Form must be signed by the Investigator prior to submission to the Sponsor. Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor as it becomes available using the SAE Data Form. SAE Data Forms must contain the following information, at a minimum: the reportable event, the study medication (if known), the protocol number, the subject number, and the Investigator name.

9.7 Expedited Reporting

Adverse Reaction. Any untoward and unintended responses to an investigational medicinal product related to any dose administered. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression “reasonable causal relationship” means to convey in general that there is evidence or argument to suggest a causal relationship (i.e. causality is at least “unlikely”).

Unexpected Adverse Reaction. An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator' Brochure for an unregistered investigational product or summary of product characteristics for a registered product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Suspected Unexpected Serious Adverse Reaction (SUSAR). A SUSAR is an adverse drug reaction, which is both serious and unexpected. If an SAE was assessed to be a SUSAR by the Sponsor, the Competent Authorities, ECs and Investigators must be informed as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. If the SUSAR was immediately life-threatening or fatal, it must be reported as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Relevant follow-up information should be communicated to the competent authority and the Ethics Committee within an additional 8 calendar days. The Sponsor is responsible for expedited reporting of SUSARs and other reportable events and safety issues to the Competent Authorities, according to local legislations. Investigators will be informed by the Sponsor. The Investigator or Sponsor, depending on local regulations, must inform the EC/IRB about SUSARs and other reportable events and safety issues in accordance with ICH guidelines and the practices of the governing ECs.

9.8 Data Monitory Committee (DMC)

The DMC will receive the filled in CRF’s of the research team, make a copy of that data set and give the originals back to the research team (part of which is blinded).

The DMC will consist of three members of the Department of Anesthesiology not involved in the study (members are: Dr. E. Sarton, chair; Dr. J. Vuyk, member, and E. Olofsen MSc, statistician). The primary concern of the DMC is patient safety. If AEs or SAEs do occur they will advise the Investigator on the continuation of the study. Reporting to the DMC is independent of the reporting to sponsor, METC and CCMO.

10. Sample size, randomization, blinding and statistical analysis

10.1 Sample size calculation. The sample size was based on the expectations of the clinical experts on a 5 point overall score of the surgical procedures. The *a priori* estimated mean difference between the treatment groups is 0.5 point on the 5-point L-SRS scale. Assuming a standard deviation of 0.75, a sample size of 47 subjects per group would provide at least 90% power to observe the expected difference at alpha = 0.05. A sample size of 50 per group was chosen to take into account any margin of uncertainty around the effect size and SD.

10.2 Randomization, blinding and treatment allocation

Randomization will be performed by an independent person not involved in the study or its analysis. An envelope with the randomization code (deep or moderate) will be made available to the attending anesthesiologist. He or she will apply NMBs and reversal agents according to the instructions as dictated by the current protocol. Only the attending anesthesiology team will know the allocation and degree of muscle relaxation as measured by TOF CUFF. All others involved in the study (anesthesia research team and surgical team) will be blinded to the allocated treatment of the patient.

After the patient has been sent to the recovery room all relevant syringes will be discarded by the anesthesiology team according to local protocol.

The information regarding drug doses, TOF levels, and other items that may un-blind the allocation of the patient will be put on a separate sheet (part of the CRF) by the anesthesiology team and will be kept in a blinded envelope marked with the patient's study number. It will be kept blinded in a separate CRF binder until the end of the study under supervision of by the DMC.

10.3 Statistical Analysis

Linear mixed effects model with ARMA1 (autoregressive moving average covariance structure) correction will be used to compare the L-SRS data. To estimate the variability (95% confidence interval) bootstrap analyses were performed. Comparisons of scores at fixed times points were done with Mann-Whitney-U tests. Statistical analysis will be performed using the SPSS statistical software package (version 23.0; SPSS Inc., Chicago, IL). P-values < 0.05 were considered significant.

11. References

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2. Torensma B, Martini C, Boon M, Olofsen E, in 't Veld B, Liem RSL, Knook MTT, Swank DJ, Dahan A. **Deep neuromuscular block improves surgical conditions during bariatric surgery and reduces postoperative pain: a randomized double blind controlled trial**. PLoS ONE 2016; 11: 20167907

3. Martini C, Boon M, Broens SJL, Hekkelman EF, Oudhoff LA, Buddeke AW, Dahan A. **Ability of the Nociception Level, a multiparameter composite of autonomic signals, to detect noxious stimuli during propofol-remifentanil anesthesia.** Anesthesiology 2015; 123: 524-534.