Deep neuromuscular blockade and neuromuscular reversal : applications and implications

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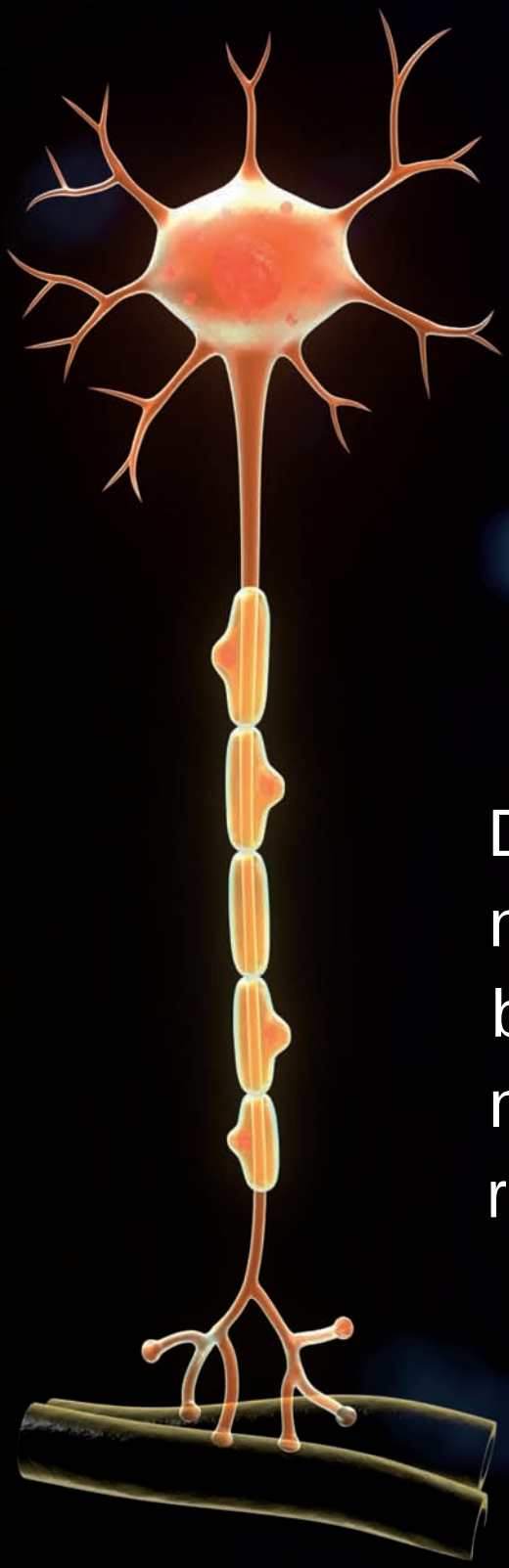

Martijn Boon

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Colofon
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Deep neuromuscular blockade and neuromuscular reversal applications and implications

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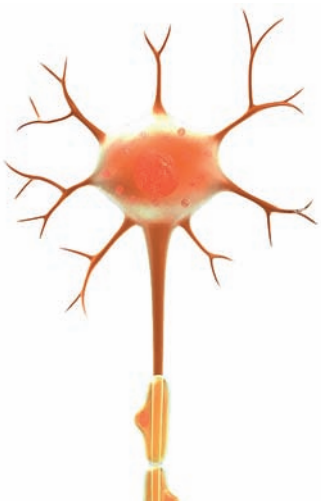
Chapter 1

Introduction and thesis outline



EVOLUTION OF NEUROMUSCULAR BLOCKADE IN ANAESTHESIA: FROM CURARE TO SUGAMMADEX

General anaesthesia is a pharmacologically induced state of the body that is characterized by unconsciousness (hypnosis), pain relief (analgesia) and muscle relaxation (paralysis). It allows patients to endure invasive surgical procedures without cognition and pain perception. Every pharmacologic component of anaesthesia is essential for success. Hypnosis and analgesia are induced by agents that depress the central nervous system at various levels. They prevent somatic and cognitive arousal and suppress the sympathetic response to painful (surgical) stimuli. The combination of both agents is sufficient to induce and maintain general anaesthesia; however they do not fully depress all motor reflexes in every circumstance.[1, 2] For example, even during adequate general anaesthesia, high intensity (surgical) stimuli can trigger reflexes that result in sudden movement of a patient. The addition of muscle relaxants to general anaesthesia prevents these sudden movements and ensures an immobile patient throughout a procedure.

The use of muscle relaxation as a routine part of general anaesthesia has historically not been an easy matter of course. The first muscle relaxing agents were direct derivatives of an agent called *curare*. Curare is naturally present in the jungle plants of the *Chondodendron* and *Strychnos* genus. Curare's deadly characteristics were long known by jungle tribes, who used it as a poison on their hunting arrows. Curare induces a flaccid paralysis of all skeletal muscles by blocking the signal transmission from the nerve-end to the muscle at the neuromuscular junction. This eventually causes death by respiratory arrest. Curare only exerts its muscle relaxing properties when it directly enters the bloodstream and is harmless when it is ingested by mouth. Hunted animals were therefore safe for consumption. Colonial expansion eventually brought curare to the attention of western scientists.[3] Experiments with curare began in the mid-1800 and were led by important discoveries on neuromuscular transmission by Claude Bernard and others.[4] Interestingly, these experiments took place at the same time ether and nitrous oxide inhalation anaesthesia became known.[5, 6] However, in contrast to the rapid adoption of these hypnotic agents, it would take nearly a 100 years longer for muscle relaxants to become a part of anaesthesia.

In 1942, Harold Griffith and Enid Johnson were the first to use a muscle relaxant (Intocostrin) during general anaesthesia.[7] They sought a way to provide optimal surgical working conditions during abdominal surgery by ensuring an immobile patient. At that time, the only way to ensure an immobile patient during surgery was to use high doses of anaesthetic agents to maintain a deep level of general anaesthesia. Deep anaesthesia,

although applicable, comes with a variety of disadvantages, most notably prolonged recovery times and hemodynamic collapse. Muscle relaxation allowed for a reduction in the depth of general anaesthesia, whilst maintaining an immobile patient and ensuring good surgical working conditions. Four main purposes for the use of muscle relaxants during general anaesthesia were recognized by that time[8]:

To provide muscular relaxation required for abdominal surgery
To facilitate respiratory control during thoracic procedures
To ensure freedom of laryngospasm
To reduce the amount of anaesthetic agents in whilst achieving the previous

The pioneering work of dr. T.C. Gray and others further shaped the technique of "light anaesthesia" with muscle relaxation and the control of respiration. This laid the basis of the well-known Liverpool anaesthetic technique.[9, 10] However, the increasing use of muscle relaxants soon unfolded major concerns. In 1954, Beecher and co-workers reported a six fold increase in anaesthesia related mortality in cases were muscle relaxants were used.[11] This association was noted in the period *after* anaesthesia and surgery had ended (*i.e.* the postoperative period). Incomplete recovery of neuromuscular block (NMB) after anaesthesia has ended (known as *postoperative residual curarization*) causes persistent general muscle weakness in the early postoperative period. This condition interferes with normal breathing and is strongly associated with adverse respiratory events in the recovery ward.[12] Postoperative residual curarization remains a common problem, even in the present day. Despite the availability of neuromuscular monitoring devices and reversal agents, incidences of 40-60% have been reported consistently in the literature over the last decades.[13]

From a pharmacological view, the potential for postoperative residual curarization to occur is evident. The paralyzing effect of muscle relaxants last much longer than the effects of the hypnotic agents. For instance, an induction dose of rocuronium, a commonly used muscle relaxant with an intermediate duration, has an average recovery time of 50-60 minutes.[14] In contrast, the time for a patient to awake after termination of a propofol and remifentanil infusion (a commonly used hypnotic and analgesic agent respectively) is less than 10 minutes.[15] In addition, the recovery time of muscle relaxants is unpredictable and displays a large variation between patients.[16] The use of muscle relaxants always bears a risk of incomplete recovery and the only way to fully preclude residual curarization is objective measurement of the level of neuromuscular block at the end of anaesthesia.

Neuromuscular monitoring is one of the corner stones to prevent residual curarization. Currently, multiple commercially available neuromuscular monitoring devices are avail-

able. In this thesis, *acceleromyography* of the adductor pollicis muscle (device: TOF watch SX, Organon, the Netherlands) or *compressomyography* of the biceps muscle (device: TOF cuff, RGB medical devices, Spain) were used. All these devices work by the same principle: a peripheral nerve is stimulated by a low voltage current, which evokes a contraction in a nearby muscle (see fig. 1 for schematic setup of the TOF watch). The magnitude of the evoked muscle contraction reflects the level of neuromuscular blockade. Several distinct stimulation modes exist, of which *train-of-four* and *post-tetanic-count* are the most common.[17, 18] *Train-of-four* (TOF) stimulation is used to assess shallow and moderate levels of neuromuscular bock. A train-of-four consists of four short electrical stimuli which evoke four short muscle contractions (*twitches*). With increasing level of neuromuscular block, the twitches will first reduce in strength and will eventually disappear.[18] In addition, the ratio of the fourth twitch relative to the first twitch (*TOF ratio*) has to be recovered to at least 0.9 or 90% before the end of anaesthesia, to ensure that muscle strength is adequate. . Any TOF ratio below 0.9 is called residual curarization by definition and poses patients at risk for postoperative respiratory complications.[19-21]

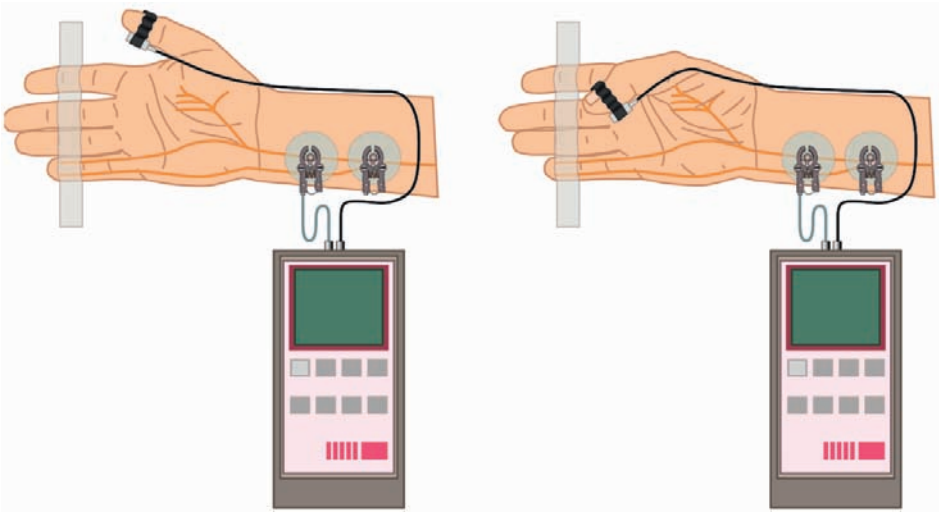


Figure 1: Schematic setup of the TOF watch at the adductor pollicis muscle. Two electrodes are placed adjacent to the ulnar nerve. A current of 30-60 mA administered at the ulnar nerve will evoke a muscle contraction of the adductor pollicis muscle at the base of the thumb. A piezoelectric sensor placed at the distal end of the thumb records the acceleration of the thumb that is caused by the muscle contraction. The magnitude of the acceleration is a reflection of the level of neuromuscular block.

During a deep neuromuscular block, the train-of-four will not yield any muscle responses (*i.e.* TOF = 0 twitches). In this instance, the *post-tetanic-count* (PTC) method can be used to determine the exact depth of neuromuscular block. The post-tetanic-count method differs from the train-of-four method in that this stimulation mode begins with

a prolonged current on the nerve (tetanic stimulus, 50Hz for 5 seconds). This results in a massive pre-synaptic release of acetylcholine in the neuromuscular junction. Acetylcholine is the neurotransmitter that is primarily responsible for signal transmission between a nerve end and a muscle fiber. The acetylcholine excess will exist for a short period of time, before it is broken down by the enzyme acetylcholinesterase. During this period, neuromuscular signal transmission is temporarily enhanced, so that 10 to 20 short stimuli following the tetanic stimulus may evoke muscle responses during a deep neuromuscular block. The number of detectable twitches add up to form the *post-tetanic-count*.[17] In this thesis, a deep neuromuscular block is defined as a *post-tetanic-count* of 1 to 2 twitches; a moderate neuromuscular block is defined as a *train-of-four count* of 1 to 3 twitches (see fig. 2). Further reading about depth of neuromuscular block can be found in chapter 7.

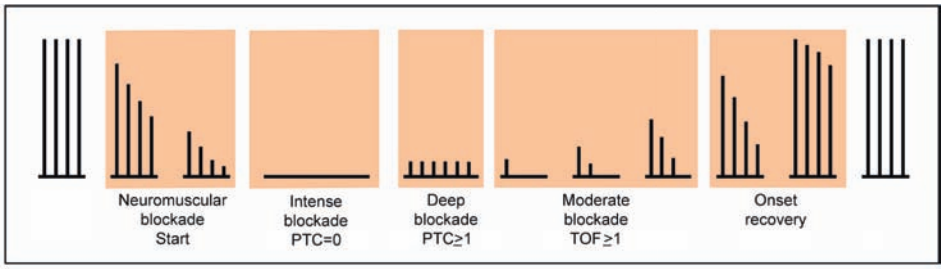


Figure 2: Schematic illustration of depths of neuromuscular block. The vertical bars represent the twitches of the thumb evoked by either TOF or PTC stimulation. The figure shows, from left to right, the typical course neuromuscular block (NMB) after a single administration of muscle relaxant. In the first orange square, the twitches of the train-of-four disappear after the administration of a muscle relaxant. As the NMB deepens in the first minutes after administration, all twitches of the TOF and PTC disappear (second square), leading to an intense NMB. When the muscle relaxant starts to wear off, the twitches return, first in the PTC (third square) and later on in the TOF (fourth and fifth square). Eventually, as the NMB has completely recovered, the twitches in the train-of-four will again have equal strength. TOF= train-of-four; PTC = post-tetanic-count.

Neuromuscular monitoring has proven to be essential in reducing the incidence of postoperative residual curarization,[22-24] but other strategies exist. One of these strategies is to *reverse* any residual neuromuscular block before the end of anaesthesia. Neuromuscular reversal may be of equal importance as neuromuscular monitoring and in practice these strategies go hand in hand. Reversal techniques are aimed to significantly speed up the recovery of neuromuscular block. Traditionally, this is achieved with the use of an acetylcholinesterase inhibitor (*e.g.* neostigmine). These agents reduce the breakdown of acetylcholine in the neuromuscular junction, resulting in enhanced neuromuscular signal transmission and competitive antagonism with the neuromuscular blocking agent.[25] However, acetylcholinesterase inhibitors have important intrinsic limitations. Reversal with these agents is often lengthy or incomplete and they cannot be used for reversal

of deep neuromuscular block.[26] Consequently, acetylcholinesterase inhibitors should be dosed well in anticipation of surgery-end and exclusively for reversal of shallow levels of neuromuscular block.[27] Inappropriate use of acetylcholinesterase inhibitors still yields a high incidence of residual curarization and the associated respiratory complications.[28]

To reduce the risk for residual curarization, the depth of the neuromuscular block *during* anaesthesia is often maintained at a shallow or moderate level to ensure prompt spontaneous recovery or easy reversal with an acetylcholinesterase inhibitor. In addition, a moderate depth of neuromuscular block is generally considered to be sufficient for abdominal muscle relaxation, ensuring good operating conditions (*i.e.* a *"surgical block")*. However, due to the evolution of surgical procedures from open to minimal invasive (laparoscopic) approaches, a moderate NMB may not be sufficient to maintain good surgical working conditions. To understand this, two things are important to realize. First, in laparoscopic surgery, space is often limited and muscle contractions can severely hamper the surgeon. Second, these muscle contractions can happen during a moderate NMB because the abdominal muscles and diaphragm are more resistant to muscle relaxants than other muscles in the body and require a larger dose to become fully paralyzed.[29-31] In practice, this means that a deep NMB must be applied to fully relax all these muscles.[1, 2, 30] Until recently, the application of a deep NMB was very unpractical for routine use. As a deep NMB cannot be reversed with acetylcholinesterase inhibitors, it came with very long recovery times and a high risk of postoperative residual curarization. The introduction of sugammadex, a novel, selective reversal agent, took away these disadvantages.

Sugammadex reversal is based on a new reversal principle, which substantially differs to the reversal principle of acetylcholinesterase inhibitors. Sugammadex is a modified, cyclic sugar molecule (y-cyclodextrin), which is able to *encapsulate* molecules of neuromuscular blocking agents with a steroidal structure (rocuronium, vecuronium and pancuronium).[32] Encapsulation renders the muscle relaxant molecules unable to exert their effect and quickly terminates the muscle relaxing effect. The encapsulation process takes place in the plasma, happens on a 1 to 1 basis (*i.e.* 1 molecule sugammadex encapsulates 1 molecule rocuronium) and is irreversible (see fig. 3). Unlike acetylcholinesterase inhibitors, sugammadex is able to completely reverse a deep neuromuscular block in a very short period of time.[33-35]

Sugammadex has opened the door for clinical application of deep neuromuscular block during general anaesthesia. The use of deep neuromuscular blockade may improve surgical working conditions over a standard (moderate) neuromuscular block during laparoscopic procedures. Especially in laparoscopic retroperitoneal prostatic and renal surgery, where space is very limited, surgical working conditions may largely depend

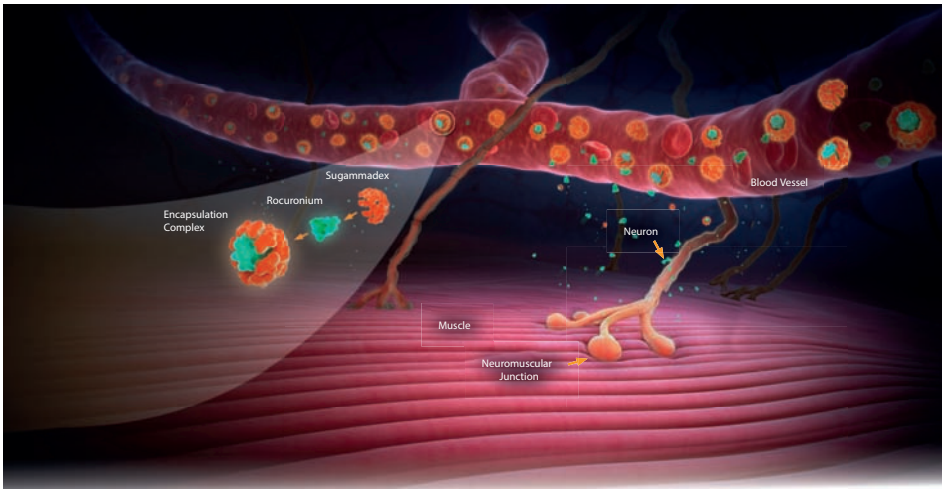


Figure 3. Schematic illustration of neuromuscular transmission at the neuromuscular junction and the encapsulation of rocuronium by sugammadex in the blood plasma. Courtesy of MSD, not authorized for reproduction.

on a deep neuromuscular block. In addition, the intensity of sugammadex reversal compared to neostigmine reversal may reduce the occurrence of postoperative residual curarization. In this thesis, these two hypotheses were tested. Additionally, the effect of deep neuromuscular block and reversal of neuromuscular block with sugammadex on postoperative outcomes was assessed.

THESIS OUTLINE

This thesis is divided in four subsections.
Section 1 presents two prospective studies about the effect of deep neuromuscular block on surgical conditions during laparoscopic retroperitoneal surgery (chapters 2 and 3).

The effect of deep neuromuscular block and of sugammadex reversal on postoperative outcome is presented in *section 2* (chapters 4 and 5).

The methods and use of surgical rating scales in laparoscopic surgery are discussed in *section 3* (chapter 6).

Section 4 presents an overview of recent literature and places the results of this thesis in perspective (chapter 7). Finally, conclusions and applications and implications of the results of this thesis are presented in chapter 8.

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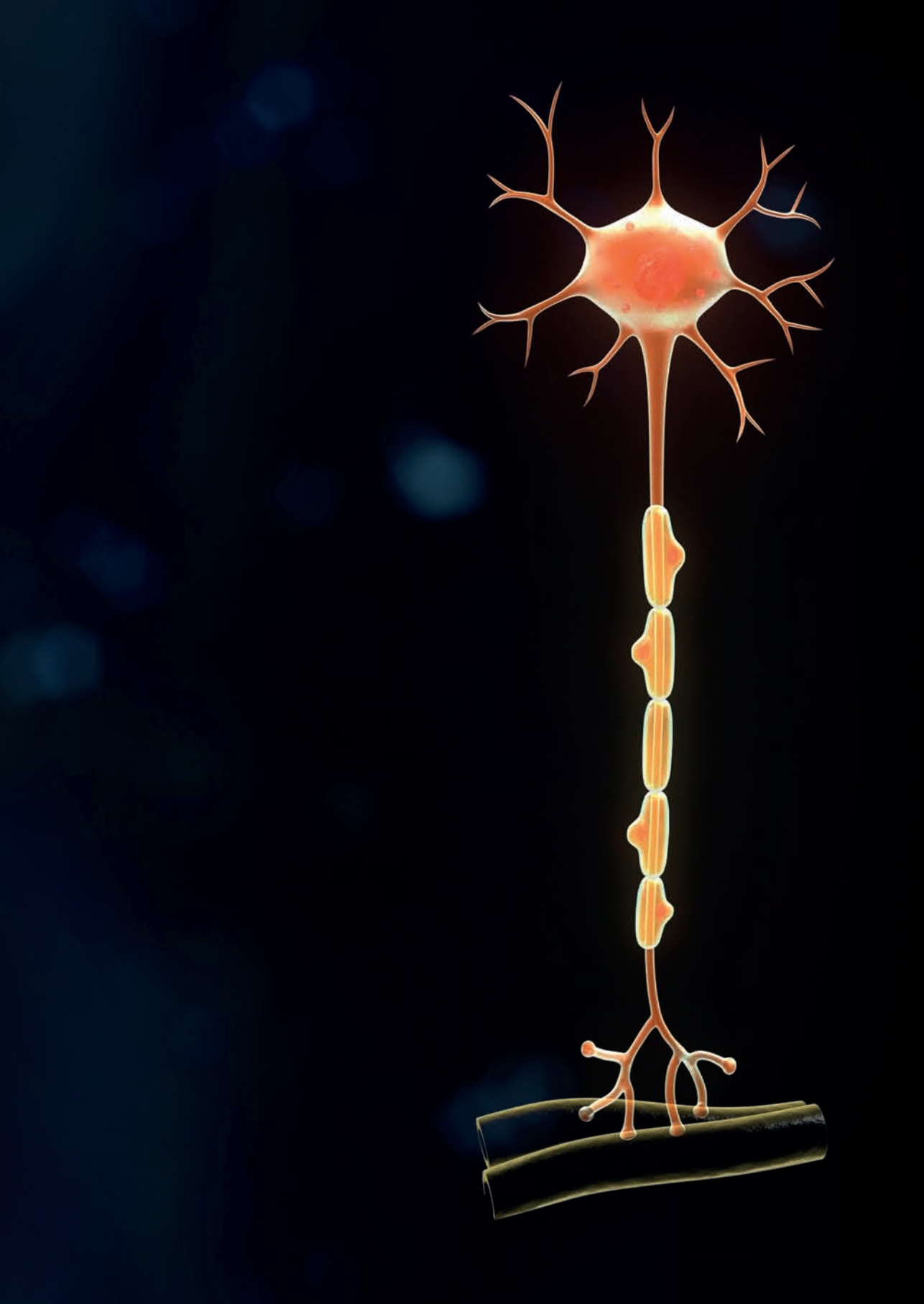
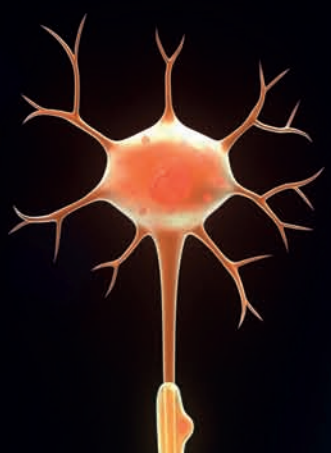


Section 1

Surgical conditions



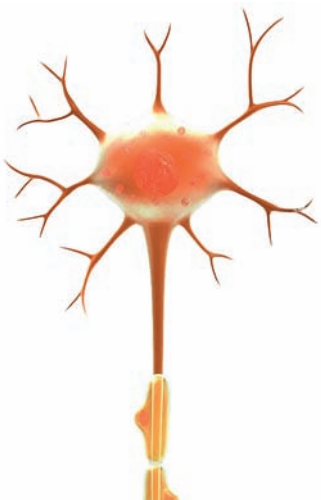
Chapter 2

Evaluation of surgical conditions during laparoscopic surgery in patients with moderate *versus* deep neuromuscular blockade

Martijn Boon,* Christian Martini,* Rob Bevers, Leon Aarts, Albert Dahan

British Journal of Anaesthesia 2014; 112(3): 498-505

* Authors contributed equally



ABSTRACT

Background

The routine use of neuromuscular blocking agents reduces the occurrence of unacceptable surgical conditions. In some surgeries, such as retroperitoneal laparoscopies, deep neuromuscular block (NMB) may further improve surgical conditions compared to a moderate NMB. In this study, the effect of deep NMB on surgical conditions was assessed.

Methods

Twenty-four patients undergoing elective laparoscopic surgery for prostatectomy or nephrectomy were randomized to receive moderate NMB (train-of-four 1–2 twitches, induced by atracurium and mivacurium) or deep NMB (post-tetanic count 1–2 twitches, induced by a high dose rocuronium). After surgery, NMB was reversed with neostigmine (moderate NMB), or sugammadex (deep NMB). During all surgeries, one surgeon scored the quality of surgical conditions using the five-point Leiden - surgical rating scale (L-SRS) ranging from 1 (extremely poor conditions) to 5 (optimal conditions). Video images were obtained and 12 anaesthetists rated a random selection of images.

Results

Mean (SD) SRS was 4.0 (0.4) during moderate and 4.7 (0.4) during deep NMB ($p < 0.001$). Moderate NMB resulted in 18% of scores at the low end of the scale (scores 1–3); deep block resulted in 99% of scores at the high end of the scale (scores 4 and 5). Cardiorespiratory conditions were similar during and after surgery in both groups. Between anaesthetists and surgeon, there was poor agreement between scores of individual images (average k statistic 0.05).

Conclusions

Deep NMB results in an improved quality of surgical conditions compared with moderate block in retroperitoneal laparoscopies, without compromise to the patients' peri- and postoperative cardiorespiratory conditions.

INTRODUCTION

Administration of muscle relaxation is essential in a variety of procedures since it causes an improvement of surgical conditions. For example, King *et al.* demonstrated that the routine use of muscle relaxants reduced the frequency of unacceptable surgical conditions in radical prostatectomies.[1] Improvement of surgical conditions may be even more important when the surgeon has to work in a narrow space surrounded by muscles such as in case of retroperitoneal laparoscopic surgery. It may be argued that in retroperitoneal laparoscopic surgery, a deep neuromuscular block (NMB), with train-of-four (TOF) values of 0 and a post-tetanic-count (PTC) of 1-2, would further improve working conditions. However, the use of deep NMB may come with complications including long-reversal times, incomplete recovery of neuromuscular function compromising respiratory and upper airway function, or the return of NMB following a period of seemingly normal neuromuscular function (re-curarization).[1-3]

The development of sugammadex enables rapid reversal of deep NMB. Sugammadex is a modified γ-cyclodextrin, especially created to bind the free plasma molecules of the muscle relaxant rocuronium to which is has high affinity.[4] Recent studies demonstrate that sugammadex produces rapid reversal of deep NMB following administration of high dose rocuronium.[5] Theoretically, the combination of rocuronium and sugammadex makes it possible to achieve deep NMB and consequently further improve surgical conditions in retroperitoneal laparoscopic surgery without the fear for prolonged reversal times or incomplete recovery of neuromuscular function. However, the association between the depth of NMB and surgical conditions has not been evaluated as yet.

In the current study we investigated the effect of a deep neuromuscular block (TOF count 0, PTC 1-2 twitches) against a moderate block (TOF count 1-2 twitches) on surgical conditions in patients undergoing retroperitoneal laparoscopic surgery for a prostatectomy or (partial) resection of a kidney. Surgical conditions were rated using a 5-point surgical rating scale (SRS) by one dedicated surgeon with ample experience in such surgery (RB). We hypothesize that deep NMB is associated with improved ratings by the surgeon. Secondary end-points of our study included the assessment of the level of agreement between anaesthetists (the providers of the NMB agents and consequently responsible for a significant part of surgical conditions) and surgeon in terms of their rating of the surgical conditions. To that end, 30-s video images of the surgical field, obtained at the time of scoring by the surgeon, were rated by the anaesthetists.

METHODS

The study (acronym BLISS study: effect of deep BLock on Intraoperative Surgical conditions, perioperative hemodynamic status and respiratory parameters following reversal with Sugammadex in patients undergoing laparoscopic renal and prostate surgery. was carried out between November 2012 and February 2013 at the Leiden University Medical Centre (Leiden, the Netherlands) and was performed according to guidelines of Good Clinical Practice and Good Research Practice. Approval of the protocol was obtained from the institutional review board (Commissie Medische Ethiek, Leiden, the Netherlands). Patients scheduled to undergo an elective laparoscopic prostatectomy or nephrectomy (partial or total), were approached 2 weeks prior to surgery and received oral and written information about the study. All patients who were willing to participate gave written informed consent before enrolment. The study was registered at clinicaltrials.gov (NCT01361149); the protocol was published earlier online.[6] The design of the study was randomized (deep neuromuscular block against standard or moderate block) and blinded (the surgical team, the research team and the anaesthetists that scored the video were all blinded to the treatment); the attending anaesthetist was not blinded. Randomisation was performed using a computer-generated randomisation code. The code was presented to the attending anaesthetist who prepared the medication and took care of patient dosing during anaesthesia.

Patients enrolled in the study had prostate or renal disease and were all eligible for surgical resection by laparoscopic approach. All procedures were performed by one surgeon (RB). Excluded from participation were patients with ASA class > III, age < 18 years, inability to give informed consent, known or suspected neuromuscular disease, allergy to medication to be used during anaesthesia, a (family) history of malignant hyperthermia, renal insufficiency (serum creatinine > 2 times normal or urine output < 0.5 $mL.kg^{-1}.h^{-1}$ or glomerular filtration rate < 60 $mL.h^{-1}$, or proteinuria), previous retroperitoneal surgery, and a body mass index of 35 $kg.m^{-2}$ or greater.

Perioperative protocol

All patients received total intravenous anaesthesia with propofol and sufentanil. During the procedure routine monitoring was applied: electrocardiography, blood pressure, heart rate, electroencephalographic monitoring using a bi-spectral index (BIS) module (*Philips*, Eindhoven, the Netherlands). Propofol dosing was such that BIS values remained within the range of 40 to 50. Additionally, the cardiac output was measured non-invasively using an inflatable finger cuff attached to the Nexfin haemodynamic monitor (*bmeye*, Amsterdam, the Netherlands).

With respect to neuromuscular blockade the patients were randomly assigned to one of two treatment groups:

Group 1: Moderate neuromuscular block, in which the goal was to realize a moderate neuromuscular block (train-of-four 1-2 twitches). Neuromuscular blockade was induced with a bolus dose of atracurium 0.5 mg.kg^{-1}, followed by a continuous infusion of mivacurium 0.5 mg.kg^{-1}.h^{-1}. In case of deviations from the target train-of-four values, the pump speed could be increased or decreased, or a bolus dose could be given. This was left to the discretion of the attending anaesthetist. We used atracurium/mivacurium in Group 1 rather than low-dose rocuronium, as this combination is the current standard of care in our hospital. This approach enables us to compare our current local practice against a new paradigm, which is deep NMB for the chosen surgical procedures.

Group 2: Deep neuromuscular block, in which the goal was to realize a block of zero twitches in the train-of-four but 1-2 twitches in the post-tetanic-count. To that end, patients received a loading dose of rocuronium 1.0 mg.kg^{-1} followed by a continuous infusion of 0.6 mg.kg^{-1}.h^{-1}. In case of deviations from the target train-of-four and post-tetanic-count, the pump speed could be increased or decreased, or a bolus dose could be given. This was left to the discretion of the attending anaesthetist.

In case of poor or extreme poor surgical conditions (as scored by the surgeon, see below), mivacurium or rocuronium infusion rates were increased by 20% after the administration of a bolus dose of 15 mg.

At the end of surgery all patients received a reversal agent: neostigmine following a moderate NMB block (neostigmine 1-2 mg combined with atropine 0.5-1 mg) and sugammadex (4 mg.kg^{-1}) following a deep NMB block. Extubation occurred when the train-of-four ratio > 0.9.

Administration of all drugs was performed by the attending anaesthetists and not corresponded to the surgical team or the anaesthesia research team.

Monitoring

Neuromuscular function using an acceleromyograph was measured at the wrist (TOF-watch-SX, *MSD* BV, Oss, the Netherlands). The TOF-watch delivers an electrical stimulus to the ulnar nerve and measures contractions of the adductor pollicis muscle (causing adduction of the thumb) through a sensor attached to the tip of the thumb. The thumb was placed in a flexible adaptor that applied a constant preload to the thumb. Before administration of any NMB agent the device was calibrated according the specifications of the manufacturer. To that end, before administration of any neuromuscular blocking agent, but after induction of general anaesthesia, the following procedures were conducted to standardize the neuromuscular monitoring: (1) application of a tetanic ulnar nerve stimulation (50 Hz for 5 seconds); (2) calibration of the TOF watch; and (3) performing a series of TOF measurements ensuring that the TOF ratio differs by less than 5% between measurements. If the TOF ratio differed by more than 5% the TOF watch was recalibrated. The TOF ratio was normalised to the baseline values obtained during the

calibration procedure. After these steps the neuromuscular blocking agent was administered according to protocol. The number of thumb twitches upon electrical stimulation of the ulnar nerve was measured and recorded. At 15-min intervals the train-of-four was measured and in case of TOF count = 0, this was followed by the post-tetanic-count. In our study a TOF count of 1-2 twitches reflects a standard block and a PTC of 1-2 twitches reflects a deep NMB. Finally, when a TOF count of 4 twitches was present, the ratio of the fourth to the first twitch was determined (the TOF ratio).

Leiden - Surgical Rating Scale (L-SRS)

During the laparoscopic procedure the surgeon scored the surgical working conditions at 15 min intervals according to a 5-point ordinal scale ranging from 1 (extremely poor conditions) to 5 (optimal conditions); Table 1. Extremely poor (score 1) indicates that the surgeon is unable to work due to coughing or due to the inability to obtain a visible field because of inadequate muscle relaxation; poor (score 2) indicates that there is a visible field but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions and/or movements; acceptable (scores 3) indicates that the there is a wide visible field but muscle contractions and/or movements occur regularly; good (score 4) indicates a wide working field with sporadic muscle contractions and/or movements; and optimal (score 5) indicates a wide visible working field without any movement or contractions. In case of a sudden deterioration of conditions additional measurements could be added. The feasibility of this method of scoring was

Table 1. The Leiden- surgical rating scale (L - SRS)

1	**Extremely poor conditions:** The surgeon is unable to work due to coughing or due to the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional muscle relaxants must be given.
2	**Poor conditions:** There is a visible laparoscopic field but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions and/or movements with the hazard of tissue damage. Additional muscle relaxants must be given.
3	**Acceptable conditions:** There is a wide visible laparoscopic field but muscle contractions and/or movements occur regularly causing some interference with the surgeon's work. There is the need for additional muscle relaxants to prevent deterioration.
4	**Good conditions:** There is a wide laparoscopic working field with sporadic muscle contractions and/or movements. There is no immediate need for additional muscle relaxants unless there is the fear for deterioration.
5	**Optimal conditions:** There is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional muscle relaxants.

investigated during 5 surgical procedures not included in the study.

Video Images

Each time the surgeon rated the surgical conditions a video image of 30 seconds was captured using a camera connected to the endoscopic probe placed in the retroperitoneal surgical space. The procedure was such that the images collected give a visual indication of the surgical condition at the time of scoring. A randomized subset of these images (n = 10) was presented to twelve anaesthetists with ample experience in giving anaesthesia for urological laparoscopic procedures. They were asked to give a rating to the surgical condition using the same 5-point scale as used by the surgeon. These anaesthesia experts were blinded to the level of neuromuscular blockade and goals of the study.

Data Acquisition

The following clinical variables were collected on the case record form for further analysis: anaesthesia-related parameters (drug dosages, bi-spectral index, time from reversal to optimal extubation conditions (TOF ratio > 0.9)), haemodynamic parameters (blood pressure, heart rate, cardiac output, cardiac index), ventilatory parameters (tidal volume, breathing rate, breathing pressure), surgical parameters (L-SRS, intra-abdominal pressure, duration of surgery) and post-anaesthesia care-related parameters (time spent in the post-anaesthesia care unit, respiratory rate, oxygen saturation, pain score (on an 11-point numerical rating scale from 0, no pain, to 10, most severe pain imaginable), occurrence of nausea/vomiting and sedation (on a 5-point scale ranging from 0, normal alertness to 5, not aroused by a painful stimulus)). Recurrent observations were made at 15-min intervals both during anaesthesia and in the post-anaesthesia care unit.

Sample Size and Statistical Analysis

The sample size was based on the expectation of the surgeon for the distribution of the surgical ratings between the two treatment conditions: rating during the moderate block = 5 occurs in 10% of cases, 4 in 20%, 3 in 55% 2 in 10% and 1 in 5%; rating during the deep block = 5 in 70% of cases, 4 in 20%, 3 in 10%, 2 in 0% and 1 in 0%. These anticipated frequencies result in an odds ratio of 21 for optimal conditions (SRS 5) *versus* non-optimal conditions (SRS < 5). Ten-thousand simulations were performed to obtain the power for a given sample size with moderate block as a fixed distribution and a simulated distribution of the deep block condition assuming proportionality of the odds ratio with an odds ratio of 21 and analysing the results with a proportional odds model using the score test. The power ranged from 82% at a sample size of 14 (7 in each group) to 97% (n = 12/group). A sample size of 24 was chosen to take into account any margin of uncertainty around the effect size.

The data analysis was based on the intent-to-treat approach. The primary end-point of the study was the influence of the depth of the neuromuscular block on the surgical rating scale. For each patient the final score was the average of all 15-min SRS values.

The treatment effect on the final score was tested using a *t*-test (SigmaPlot version 12.5, Systat Software Inc., San Jose, CA, USA). Secondary end-points were (1) the assessment of the level of agreement between anaesthetists and surgeon in terms of their rating of the surgical conditions; and (2) the effects of level of neuromuscular block on haemodynamic variables during surgery, time to TOF > 0.9, and relevant variables in the post-anaesthesia care unit (pain rating, sedation levels, cardiorespiratory variables). All variables were averaged over time to get an indication of their mean value. Treatment effects were evaluated on the average data by *t*-test.

The scores of each of the 12 anaesthetists were compared with that of the surgeon's score using the kappa statistic (also known as Cohen's kappa) and population Bland Altman analysis.[7-9] The kappa statistic calculates the agreement between a pair of scores over and above what is expected from chance, where kappa = [P(A) – P(E)]/[1 – P(E)], P(A) is the proportion of scores that agree and P(E) the proportion of scores that would agree by chance.[7, 9] Kappa values between 0 and 0.2 are indicative of poor to slight agreement, values between 0.2 and 0.4 indicate fair agreement, 0.4 to 0.6 moderate agreement, 0.6 to 0.8 substantial agreement, and 0.8 to 1 near complete to complete agreement.[10] Bland Altman plots give the difference between paired measurements (scores) against the mean of the values, which results in values for bias and limits of agreement to describe how closely measurements from two sources are related.[8]

All values presented are mean ± SD unless otherwise stated. *p*-values < 0.05 were considered significant.

RESULTS

A total of thirty patients were screened. In four patients one or more exclusion criteria were met. The others were randomized. Two patients withdrew consent before treatment; two others replaced them. See Fig. 1 for the flow chart of the study. Patient characteristics are given in Table 2 showing that the two treatment groups were similar in physical characteristics, gender, types of surgery and haemodynamic variables. Duration of surgery was similar between treatment groups and ranged from 80 to 240 min with average surgical times of 141 and 144 min for standard care and deep NMB, respectively (Table 3).

Anaesthesia

Depth of anaesthesia, as measured by the bi-spectral index of the electroencephalogram (BIS), was similar between treatment groups (moderate block 42 (5) *vs.* deep block 44 (6)). Neuromuscular block in patients receiving a standard treatment was moderate with an average TOF count of 2.2 (0.9) twitches during surgery. Patients receiving a deep neuromuscular block had zero twitches in the TOF and 1.6 (1.5) twitches in the post-

tetanic count. During surgery the dosages of the anaesthetic (propofol) or analgesic (sufentanil), the intra-abdominal pressure and haemodynamic variables were similar between treatments (Table 3).

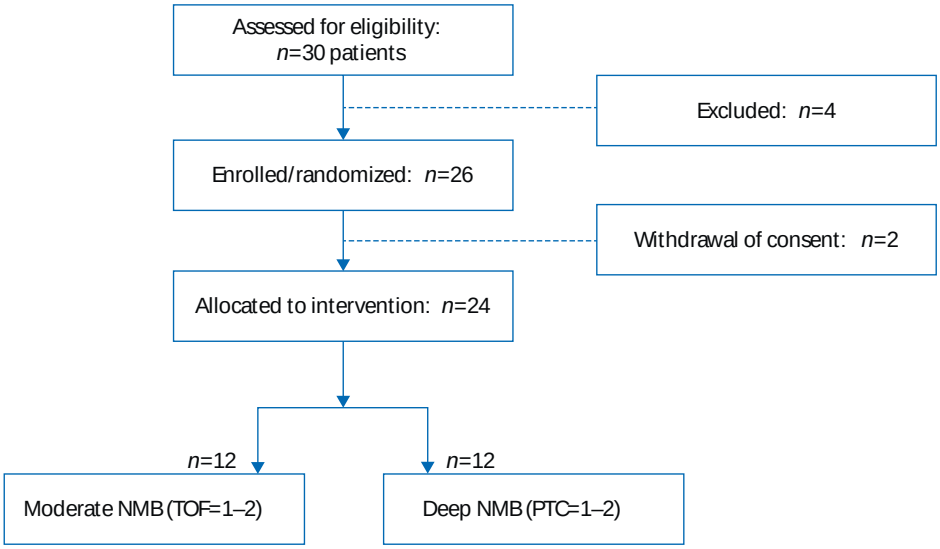


Figure 1. Study flow chart.

Table 2. Patient characteristics and screening measurements

	Moderate NMB (*n* = 12)	**Deep NMB** (*n* = 12)
Prostate surgery (*n*)	7	7
Renal surgery (*n*)	5	5
Gender (M/F)	10/2	10/2
Age (median, range)	59 (28-74)	60 (24-70)
Weight (kg)	83 (14)	83 (10)
Height (cm)	180 (10)	180 (9)
BMI ($kg.m^{-2}$)	25.8 (3.2)	25.9 (3.9)
BP systolic (kPa)	19.6 (2.1)	18.9 (1.5)
BP systolic (mm Hg)	147 (16)	142 (11)
BP diastolic (kPa)	11.2 (2.2)	11.5 (1.6)
BP diastolic (mmHg)	84 (15)	86 (12)
HR (min^{-1})	71 (12)	73 (15)
CO ($L.min^{-1}$)	5.9 (1.6)	5.8 (2.4)
CI ($L.min^{-1}.m^{-2}$)	3.0 (0.8)	3.1 (1.0)

BMI is body mass index, BP: blood pressure, HR: heart rate, CO: cardiac output and CI: cardiac index. Haemodynamic measurements were obtained prior to induction of anaesthesia. Values are mean (SD) unless stated otherwise.

Table 3. Measurements during surgery

	Moderate NMB	Deep NMB
Duration of surgery (min, range)	141 (80-240)	144 (90-195)
BIS	42 (5)	44 (6)
Propofol (g)	1.6 (0.8)	1.6 (0.4)
Sufentanil (µg)	73 (30)	78 (22)
Rocuronium (mg)	-	223 (81)
Atracurium (mg)	37 (10)	-
Mivacurium (mg)	41 (24)	-
Train-of-four count	2.2 (0.9)	0
Post-tetanic-count	-	1.6 (1.5)
Leiden – surgical rating scale	4.0 (0.4)	4.7 (0.4) *
Retroperitoneal pressure (kPa)	1.5 (0.5)	1.4 (0.2)
BP systolic (kPa)	15.3 (2.6)	15.4 (1.7)
BP systolic (mmHg)	115 (20)	116 (13)
BP diastolic (kPa)	9.1 (0.9)	9.2 (1.2)
BP diastolic (mmHg)	68 (7)	69 (9)
HR (min^{-1})	67 (10)	69 (13)
CO ($L.min^{-1}$)	4.9 (1.4)	5.6 (2.0)
CI ($L.min^{-1}.m^{-2}$)	2.5 (0.8)	2.8 (0.9)

* $p < 0.001$ *vs.* moderate NMB.
NMB: neuromuscular block, BIS: bi-spectral index, TOF: train-of-four, PTC: post-tetanic-count, L-SRS: 5-point Leiden - surgical rating scale, BP: blood pressure, HR: heart rate, CO: cardiac output and CI: cardiac index. Values are mean (SD) unless stated otherwise.

Rating of surgical conditions during laparoscopic surgery

The rating of the surgical field was significantly different between treatments with a mean rating of 4.0 ± 0.4 (range 3.5 to 4.5, median 3.9) during a moderate NMB with TOF count of 1-2 twitches and 4.7 ± 0.4 (range 4.0 to 5.0, median 4.9) during a deep block with PTC of 1-2 twitches ($p < 0.001$, Figure 2). The distribution of all ratings taken during surgery is given in Figure 3. From these data the significant difference between the moderate (TOF count 1-2 twitches) and deep (PTC 1-2 twitches) blocks is apparent from the fact that 18% of scorings during moderate block was in the SRS range of 1-3 (scores rated as less than good), while 99% of scoring in the deep block was in the SRS range 4-5 (good and excellent scores). Variability in the individual ratings was higher for a block with TOF count = 1-2 twitches (mean coefficient of variation of ratings of surgical sessions 26%) compared to block with TOF = 0 and PTC = 1-2 (5%).

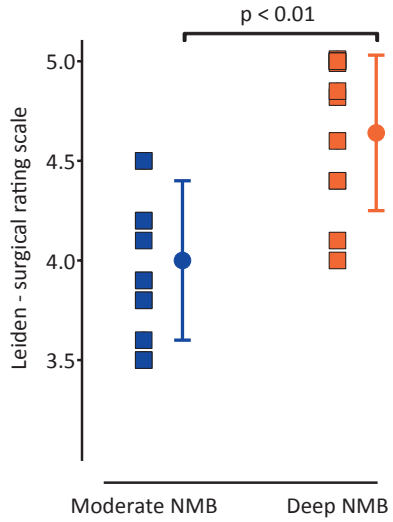


Figure 2. Surgical ratings by the surgeon during laparoscopic surgeries using the 5-point Leiden - surgical rating scale (see Table 1). Squares denote the individual mean ratings obtained during surgery. Circles are the mean of the means ± SD. NMB: neuromuscular block

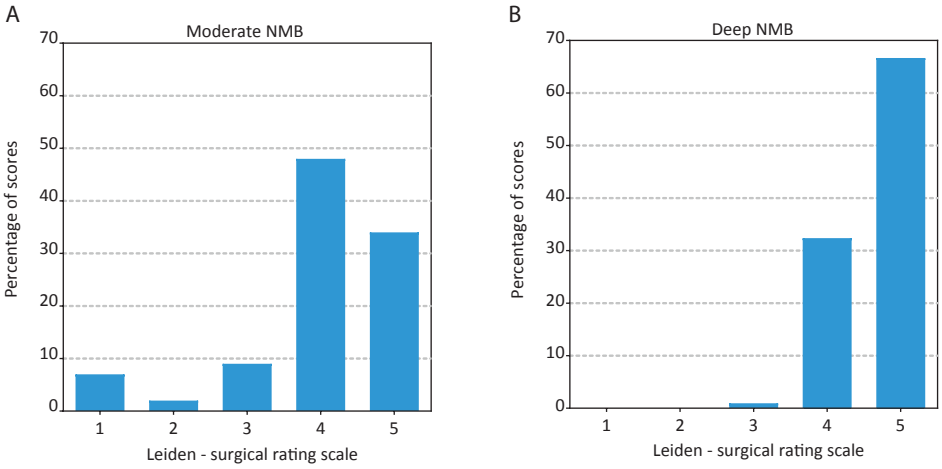


Figure 3. Distribution of the surgical ratings obtained during standard of care (**A**) and during deep neuromuscular block (**B**). NMB is neuromuscular block.

Measurements following surgery

Reversal of the neuromuscular block in patients with a deep block with sugammadex resulted in acceptable extubation conditions (TOF ratio > 0.9) after 5.1 (2.4) min. In contrast, similar extubation conditions were obtained after 10.9 (4.9) min ($p < 0.01$) in patients with a TOF count of 1-2 twitches and reversal with neostigmine. In the post-anaesthesia care unit, no differences were observed in respiration, pain and sedation levels (Table 4).

Table 4. Measurement following surgery

	Moderate NMB	Deep NMB
Sugammadex (mg)	-	380 (101)
Neostigmine (mg)	1 (0)	-
Time to TOF ratio > 0.9 (min)	10.9 (4.9)	5.1 (2.4)
Time in PACU (min)	86 (19)	86 (25)
SpO_2 (%)	98.6 (1.8)	98.2 (1.4)
Breathing rate (min^{-1})	14.5 (2.2)	14.5 (2.2)
Pain score (11-point scale)	2.6 (1.6)	2.1 (2.2)
Sedation score (5-point scale)	2.0 (0.6)	1.3 (1.0)

TOF is train-of-four count, PACU: post-anaesthesia care unit and SpO_2: arterial haemoglobin oxygen saturation. Values are mean (SD).

Rating of surgical condition by anaesthetists

A random set of 10 video images was scored by 12 anaesthetists. The distribution of the surgeon's ratings of these 10 images is given in Figure 4A; the corresponding distribution of ratings of the anaesthetists is given in Figure 4B. Compared to the surgeon their ratings were skewed to the right and agreement with the surgeon's ratings was poor (agreement between scores ranged from 0 to 40%). The kappa statistic was 0.05 (range -0.25 to 0.25). The Bland Altman analysis resulted in a significant bias of -0.43 (0.21; p = 0.03) and large limits of agreement of 2.87 and –3.72, and a between-subject variance of 0.25 (Figure 4C).

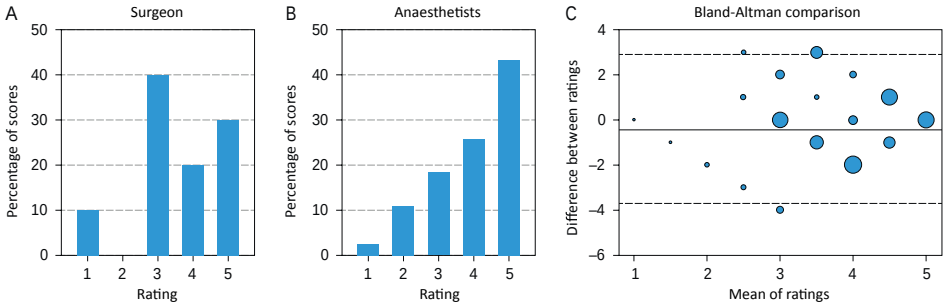


Figure 4. A. Distribution of scorings obtained from a random sample of 10 video snippets scored by the surgeon. **B.** Distribution of scorings obtained from a random sample of 10 video snippets scored by the surgeon and a group of 12 anaesthetists. **C.** Population Bland Altman analysis of the scorings from anaesthetists and surgeon. The continuous horizontal line is the bias; the dotted line the limits of agreement. The size of the dots represents the number of (overlapping) data points, which range from 1 for the smallest dots (1,0) and (1.5,-0.5), to 16 for the largest dot (4,-2).

DISCUSSION

This is the first study to assess the impact of a deep neuromuscular block (PTC 1-2 twitches) on surgical working conditions. The main results of our study are: (1) A deep neuromuscular block (TOF count = 0 and PTC 1-2 twitches) is associated with higher (*i.e.* improved) ratings from the surgeon compared to a moderate neuromuscular block (TOF count of 1-2 twitches) during laparoscopic prostatectomies and nephrectomies, indicating a significant improvement of surgical conditions; (2) Ratings from anaesthetists and surgeon of video images of the surgical field showed little agreement. In the current study, we chose to study retroperitoneal laparoscopic surgeries for two urological procedures (prostatectomy and (partial) nephrectomy) as these procedures are confined to a narrow working space where adequate (deep) muscle relaxation is of high importance and an effect of less optimal muscle relaxation on the quality of the surgical field is rapidly apparent.

The Leiden - surgical rating scale

The 5-point rating scale used in our study was developed in close cooperation with the surgeon involved in our project, who has ample experience in the performed procedures. It was decided that, while the scoring system should integrate all qualitative aspects that are important to the surgeon when judging the surgical working field, it should remain as simple as possible. A scoring system with more than 5 points was initially considered, such as an 11-point numerical quantitative scale (for example, numerical rating or visual analogue scales from 0 to 10, *cf.* Ref. 9), however, it was decided to rank the surgical field qualitatively from extremely poor, *via* poor, acceptable, good to optimal conditions (see Table 1 for an explanation of the different ratings). Further, to reduce variability in scoring between assessors just one surgeon was requested to score the surgical field in our study. Our system is similar to other scoring systems. For example, the Clinical Global Impression (CGI) rating scale is a 7-point qualitative scale in which physicians rate the severity of a patient's mental illness relative to the physician's past experience.[11] The GCI and our scoring systems are subjective but in our case the ample experience of the surgeon gives credibility to the procedure. Indeed the results of our study indicate that the surgeon was able to discriminate between a moderate and a deep neuromuscular block. The difference of 0.7 points (a difference of 18%) was regarded as important and clinically significant by the surgical team. We argue that the ability of our scoring system to discriminate between two distinct anaesthetic regimes indicates the validity of the 5-point surgical rating scale we developed.

Our study should be considered a proof-of-concept trial and further validation of the surgical rating scale is mandatory. Therefore, one should be cautious in extrapolation of our results to other procedures and other surgeons. Other surgeons may rate the surgi-

cal condition differently and other procedures may require a different anaesthetic and/or surgical approach. In an attempt to get an indication of the ability of other surgeons with ample experience in laparoscopic surgery to apply the scoring system, we invited eight surgeons, specialized in laparoscopic surgery for gastroenterological procedures, to score the 10 videos earlier presented to the anaesthetists. Their kappa statistic was on average 0.50 indicative of moderate agreement. As expected this agreement is substantially greater than that between surgeon and anaesthetists. It further shows that different surgeons (in this case with a different subspecialty) rate the surgical field differently. The current study was specifically aimed at scoring urological procedures performed in narrow retroperitoneal space. The results show a clinically relevant benefit of deep neuromuscular block for the surgeon involved in this study. Whether this benefit will also be relevant to other surgeons performing similar surgeries and possibly even for other laparoscopic procedures, such as for bariatric laparoscopic surgery is the topic of further research.

Deep neuromuscular block

Our *a priori* estimation of SRS distributions was satisfactory for the deep neuromuscular block but was underestimated for the moderate block. Good and optimal conditions were achieved during standard care (good 48% and optimal 34%) although at a lower frequency than during deep NMB (good 32% and optimal 67%). This indicates that in 82% of measurements during standard care and in 99% during deep NMB conditions were good to optimal. However, variability in ratings was high for moderate NMB compared to deep NMB: 26%, *versus* 5%. Also, in the deep NMB group, the range of scores (mean ranged from 4 to 5) was considered high and is still open for improvement. Further improvement may be obtained by (more) strictly controlling anaesthetic depth, analgesic state and arterial carbon dioxide concentrations. In the current study respirator settings were such that end-tidal carbon dioxide concentrations were between 4.4 and 6 kPa (33 and 56 mmHg). High arterial carbon dioxide concentrations stimulate the respiratory neuronal pool in the brainstem, which activates the phrenic nerve.[12] As a consequence, diaphragm contractions may persist despite a deep NMB. The neuromuscular block at the diaphragm is less intense than at the adductor pollicis muscle.[13, 14] Indeed, some of the video images showed movement related to diaphragm contraction unrelated to the ventilator-induced inspiration-expiration sequence or cardiac contractions despite train-of-four values of zero. The surgeon scored such conditions at the low end of the L - SRS. In laparoscopic bariatric surgery the working space volume and visibility increased in response to neuromuscular blockade.[15] In the current study, the retroperitoneal pressure was kept constant to 1.3-1.5 kPa (9-11 mmHg) in both groups and it may be assumed that the working space volume was greater in the deep NMB group. However, the scoring by the surgeon is only in part based on the perceived volume of the retro-

peritoneal space. Other factors similarly influence the surgeon's working conditions and consequently play an additional role in his scoring. For example, muscle contractions (including the diaphragm) and resultant movement of other structures are important as well. Further studies should address these issues.

We tested deep *versus* moderate block using two different drug regimens. The reason for this was that this approach enabled us to compare our current practice with atracurium and mivacurium with an approach that not only allows us to induce a deep neuromuscular block but also allows rapid reversal of that deep block. Since our end-point was to compare the depth of the neuromuscular block irrespective of the drugs used to induce that state, we do not believe that this influenced our outcome significantly. We observed that full reversal after deep NMB occurred after 5 min. It is importantto realise that measurements were made at 5-min intervals and full reversal with TOF ratio's > 0.9 may have occurred earlier (for sugammadex reversal to TOF ratio > 0.9 is expected after 2-3 min).

Scoring by anaesthetists of the surgical field

An important finding in our study is that the agreement of scores between the anaesthetists and surgeon was poor. This indicates that the anaesthetists are less well able to measure the quality of surgical conditions from the video images and hence derive insufficient information from these images regarding the working conditions of the surgeon. It may be argued that in our study observing a 30-s video image does not provide sufficient input to assess the quality of surgical condition in non-surgically skilled personnel. This may be true, but in our study, and possibly also in clinical practice, the anaesthetists base their impression of the surgical field primarily on the volume of the working space and the visibility of retroperitoneal tissues (most importantly related to the absence or presence of blood in the image obscuring relevant structures) without addressing muscle contractions and other movements visible on the video image. In our hospital, life video images of the laparoscopic field are available to the anaesthetists during each case and these, together with his/her clinical experience and interaction with the surgeon, form the basis of the anaesthetic regimen, including the additional use of muscle relaxants when surgical conditions are deemed poor. Some anaesthetists may not be willing to induce a deep neuromuscular block. This may be related to their inability to adequately judge the operating field from the video screen or to their fear for suboptimal post-surgical conditions. This may be the cause of some discussion in the operating room. To prevent such situations, we suggest that surgeons and anaesthetists communicate their wishes and intentions prior to the procedure (*e.g.* during preoperative *time-out*) and closely cooperate in obtaining optimal working conditions. Here we show that providing a deep neuromuscular block improves surgical conditions.

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Chapter 3

Influence of variations in arterial pCO_2 on evaluation of surgical conditions during laparoscopic surgery

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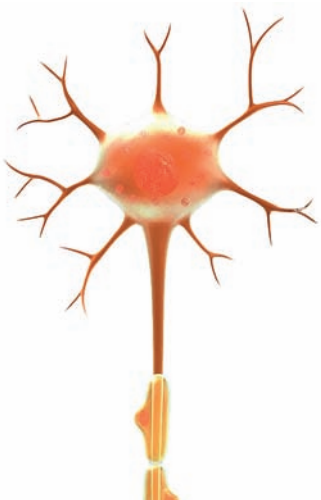

ABSTRACT

Background

Although deep neuromuscular block (post-tetanic-count 1-2 twitches) improves surgical conditions during laparoscopic retroperitoneal surgery compared to a standard block (train-of-four 1-2 twitches), the quality of surgical conditions varies widely, possibly related to diaphragmatic contractions. Hypocapnia may improve surgical conditions by silencing the diaphragm. In this study we assessed the effect of changes in arterial carbon dioxide concentrations on surgical conditions in patients undergoing laparoscopic surgery under general anaesthesia and deep neuromuscular block.

Methods

Forty patients undergoing elective laparoscopic surgery for prostatectomy or nephrectomy received propofol/ remifentanil anaesthesia and a deep neuromuscular block with rocuronium. Patients were randomized to surgery under hypocapnic or hypercapnic conditions. During surgery, the surgical conditions were evaluated using the 5-point Leiden- surgical rating scale (L-SRS) ranging from 1 (extremely poor conditions) to 5 (optimal conditions) by the surgeon, who was blinded for the randomization allocation.

Results

Mean (SD) arterial carbon dioxide concentrations were 4.5 (0.6) kPa under hypocapnic and 6.9 (0.6) kPa under hypercapnic conditions. The L-SRS did not differ between groups: 4.84 (0.4) in hypocapnia and 4.77 (0.4) in hypercapnia. Ninety-nine percent of ratings were good or optimal irrespective of the treatment.

Conclusions

Deep neuromuscular block provides good to optimal surgical conditions in laparoscopic retroperitoneal urological surgery, independent of the level of arterial pCO_2.

INTRODUCTION

Anaesthetists play an essential role in optimizing surgical conditions. This is especially true for procedures which are performed in a narrow space, such as laparoscopic retroperitoneal surgery and robot-assisted laparoscopic surgery.[1, 2] We recently showed that application of a deep neuromuscular block (deep NMB, 1-2 twitches post- tetanic- count) significantly improves surgical conditions in laparoscopic retroperitoneal prostatectomies and nephrectomies and greatly reduces the incidence of unacceptable conditions.[1] Similar observations were made by others for laparoscopic gynaecological procedures and laryngeal microsurgery.[3, 4] Despite the improvement of surgical conditions at deep muscle relaxation, the variation in surgical conditions is still high (>20%), indicating that there is still room for improvement.[1] Also other studies show that that during deep NMB suboptimal surgical conditions may persist. For example, Fernando et al. showed that at deep NMB (PTC values 1-2 twitches) diaphragmatic contractions still occur.[5] Causes of such diaphragmatic contractions include resistance to muscle relaxants (diaphragm relaxation is often less intense compared to relaxation of the adductor pollicis longus muscle) as well as efferent activation from brainstem respiratory centres due to high arterial CO_2 levels. The latter item is relevant as CO_2-insufflation with high intra-abdominal pressures during laparoscopic surgery coincides with high arterial CO_2 concentrations even when end-tidal concentrations suggest values in the normal range.

One possible method to reduce high CO_2-related diaphragm contractions is to hyperventilate the patient to (sub)normal arterial pCO_2 levels. Application of this technique has been used before to reduce the dose of anaesthetics and to improve surgical conditions when standard relaxation is applied (TOF 1-2 twitches).[6-8] Here we study the effect of hyperventilation to assess whether we can further improve surgical conditions during deep neuromuscular relaxation. We hypothesize that the induction of hypocapnia during laparoscopic surgery improves surgical conditions compared to hypercapnia.

METHODS

The study with acronym BLISS2 was carried out at Leiden University Medical Centre between February 2013 and September 2015 after approval was obtained of the protocol (protocol number P13.127) by the local medical ethics committee (Commissie Medische Ethiek). The protocol was registered at clinicaltrials.gov under number NCT01968447. The study was conducted in accordance with Good Clinical Practice and Good Research Practice guidelines. Eligible patients were approached in advance by one of the investigators and received oral and written information about the study. If a patient was willing

and able to participate, oral and written informed consent was obtained. The study had a randomized (hypocapnia against hypercapnia), double-blinded design (the surgical team and the investigators were blinded to treatment allocation; the attending anaesthetist was not blinded). Randomisation was performed using a computer-generated randomization list obtained from www.randomization.com. The attending anaesthetist, who received the randomization code just prior to induction of anaesthesia, was responsible for setting the desired tidal volume and respiratory rate on the anaesthesia ventilator (Primus, *Dräger Medical Netherlands BV,* Zoetermeer, the Netherlands).

American Society of Anesthesiologists (ASA) class I-III patients were included if they had prostatic or renal disease requiring elective laparoscopic retroperitoneal surgery. Patients were excluded if they were < 18 years of age, ASA class > III, had a known or suspected neuromuscular disorder, allergies to medication to be used during anaesthesia, a (family) history of malignant hyperthermia, renal insufficiency (as defined by glomerular filtration rate of < 30 $mL.h^{-1}$), previous retroperitoneal surgery at the site of the current surgery, a body mass index > 35 $kg.m^{-2}$ or chronic obstructive pulmonary disease GOLD 2 or higher.

Perioperative protocol

All patients received total intravenous anaesthesia with propofol, remifentanil and rocuronium; the patients inhaled 40% oxygen in nitrogen. Monitoring was according to local practice and consisted of ECG, blood pressure and EEG monitoring (BIS module, *Philips,* Eindhoven, the Netherlands). Throughout surgery BIS values were kept between 45-55. A 22-gauge arterial cannula was placed in the radial artery of the left or right wrist and connected to a Vigileo advanced minimally invasive monitoring system (*Edwards Lifesciences*, USA) for hemodynamic monitoring. The arterial cannula was further used to obtain blood samples for arterial pCO_2 measurements at 15 min intervals.

Neuromuscular monitoring was performed using the TOF cuff device (*RGB Medical Devices,* SA, Madrid, Spain).[9] The TOF cuff is an upper arm cuff that was applied contralateral to the blood pressure cuff. The cuff incorporates two electrodes that stimulate the ulnar nerve. The evoked neuromuscular activity is recorded by measuring the pressure change induced by the muscular activity from stimulation. In comparison with mechanomyography (gold standard), the TOF cuff has an acceptable bias and limits of agreement, which compares to acceleromyography.[9] In a few patients we compared the TOF cuff with the TOF watch and observed similar results. Hence, we contend that using the TOF cuff resulted in a reliable assessment of neuromuscular function during anaesthesia. The TOF cuff is easier to use in patients in the lateral position or when the arm is hidden below the surgical drapes.

The TOF cuff was calibrated after induction but before administration of rocuronium. Thereafter, rocuronium 1.0 $mg.kg^{-1}$ was given and a continuous rocuronium infusion was started at 0.2-0.6 $mg.kg^{-1}.h^{-1}$. The depth of neuromuscular block was closely monitored and aimed at 1-2 twitches post-tetanic count (PTC; *i.e.* a deep NMB). At the end of surgery, the deep NMB was reversed with a bolus dose of sugammadex 4 $mg.kg^{-1}$. The patient was extubated when the TOF ratio was > 0.9 and the patient was breathing spontaneously and opened his/her eyes on request. For postoperative pain relief, morphine 0.15-0.2 $mg.kg^{-1}$ was given at least 45 min before surgical closure.

All patients were randomized before induction of anaesthesia and the "time out" procedure. Allocation to treatment was performed just prior to intra-abdominal insufflation of carbon dioxide. Patients were randomly assigned to one of two treatment groups. *Group 1:* hypocapnia during surgery (arterial pCO_2 range 3.5 to 4.5 kPa or 26 to 34 mmHg). The tidal volume of the ventilator was set at 7 $mL.kg^{-1}$ and the respiratory rate at 16 min^{-1}; *Group 2:* hypercapnia during surgery (arterial pCO_2 range 6.5 to 7.5 kPa or 49 to 53 mmHg). The tidal volume of the ventilator was set at 7 $mL.kg^{-1}$ and the respiratory rate at 11 min^{-1}. Insufflation rates were adjusted such that the target arterial pCO_2 was maintained throughout the laparoscopic procedure. However, the attending anaesthetist could deviate from the protocol at his/her discretion. In both treatment groups PEEP values were kept constant during anaesthesia at 5 mmHg.

The Leiden - Surgical Rating Scale (L-SRS)

During the laparoscopic procedure, the surgical field was rated by one surgeon (RB), with ample experience in laparoscopic retroperitoneal renal and prostatic surgery, using the Leiden - surgical rating scale (L-SRS).[1] The L-SRS is a five-point scale, which covers the quality of the surgical field from extremely poor to optimal conditions (see Table 1 in Ref. 1 for a detailed description of the L-SRS). If the rating was 3 or lower, the surgeon and anaesthesia team would negotiate ways to improve the surgical working field. For example, a bolus of rocuronium 15 mg could be given in case of suboptimal neuromuscular block and the infusion rate increased by 20% or propofol 30 mg in case of high BIS values. The L-SRS is currently used in multiple studies to assess the influence of anaesthesia on the surgical field in retroperitoneal, laparoscopic, thoraco-laparoscopic and microlaryngeal surgeries.[1, 2, 10, 11]

Sample size calculation

The primary end-point of this study is the L-SRS. Our previous study yielded a mean surgical rating score of 4.7 during deep NMB. [1] However, in that study, arterial pCO_2 was not controlled resulting in hypo- or hypercapnic conditions in some patients. Also, depth of anaesthesia was not controlled, possibly resulting in deep levels of anaesthesia (BIS <

40), which may have confounded the study outcome to some extent. A realistic *a priori* estimation of the L-SRS in the current study was 4.1-4.3 in the hypercapnic group and 4.8-4.9 in the hypocapnia group. The estimated mean difference between the treatment groups was therefore conservatively estimated to be 0.5. Assuming a standard deviation of 0.45, a sample size of at least 19 subjects would provide at least 90% power to observe the expected difference at alpha = 0.05.

Data and statistical analysis

The following clinical variables were collected on the case record form: surgical variables (L-SRS, retroperitoneal pressure), anaesthesia variables (BIS, TOF or PTC, drug dosages), hemodynamic variables (arterial blood pressure, heart rate, cardiac index) and respiratory variables (arterial and end-tidal pCO_2, tidal volume, respiratory rate, inspiratory pressure, PEEP). Repeated measurements were made at 15 min intervals.

Data analysis was based on an intent-to-treat basis. A linear mixed model with an autoregressive covariance structure was used to determine the effect of hypocapnia against hypercapnia on the primary end-point, L-SRS. Secondary end-points were the effect of hypocapnia against hypercapnia on cardiorespiratory variables. These variables were averaged over time to get an indication of their mean value. Treatment effects were evaluated on the average data by *t*-test. The data were analyzed with SPSS (v. 22; *IBM corporation*, Armonk, NY, USA0). All data are presented as mean ± SD unless otherwise stated. p-values < 0.05 were considered significant.

RESULTS

The flow chart of the study is given in Figure 1. After randomization, three randomized patients were not studied due to inability to insert an arterial line (n = 2) and a decision to perform open surgery at the pre-surgical "time-out". These three patients were replaced. In total 40 patients in both groups received the allocated treatment and were analyzed. Patient characteristics and data obtained at screening did not differ between groups (Table 1).

Anaesthesia, pCO_2 and neuromuscular blockade

The use of anaesthetics and opioids did not differ between groups. Also, post-tetanic-count values were comparable (3.2 - 3.8), indicative of a similar deep NMB in both treatment groups (Table 2). Figs. 2A and B show the individual profiles of the end-tidal pCO_2 over time for the two study groups and the individual mean end-tidal and arterial pCO_2 values. The end-tidal pCO_2 differed by 2.3 kPa between treatments: hypocapnia 3.4 (0.2)

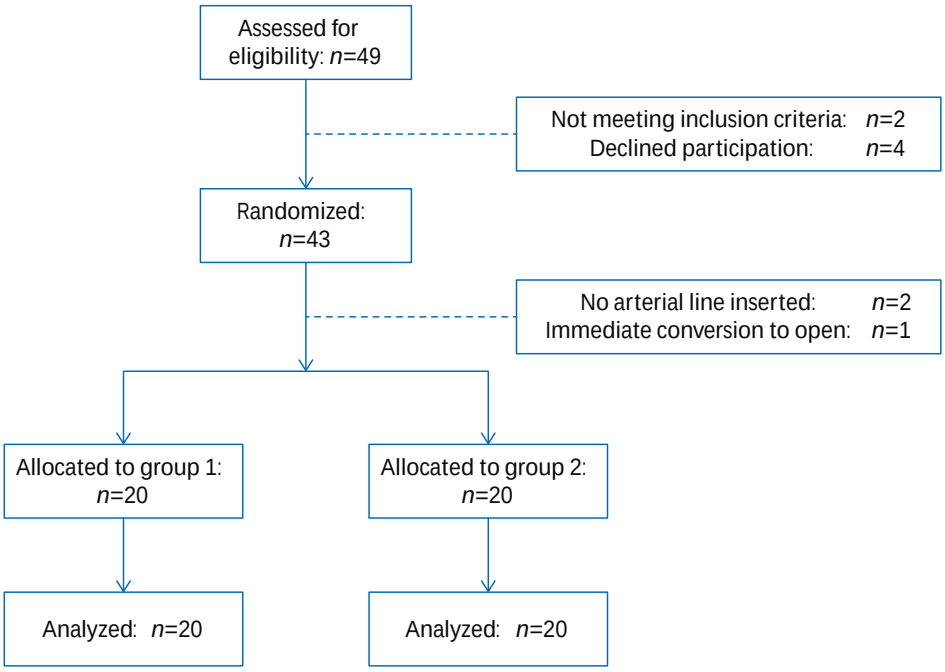

Figure 1. Study flow chart

Table 1. Patient characteristics and data obtained at screening.

	Hypocapnia ***(n=20)***	**Hypercapnia** ***(n=20)***
Prostate surgery (*n*)	13	11
Renal surgery (*n*)	7	9
ASA class I (*n*)	8	3
ASA class II (*n*)	12	17
Gender M/F (*n/n*)	17/3	14/6
Age (years; median, range)	65 (22-80)	62 (25-72)
Weight (kg)	81 (12)	81 (17)
Height (cm)	176 (10)	175 (9)
BMI ($kg.m^{-2}$)	26,1 (3.4)	26.3 (4.3)
BP systolic (mmHg)	137 (15)	139 (16)
BP diastolic (mmHg)	81 (11)	85 (12)
Heart rate (min^{-1})	77 (16)	74 (14)

Data are presented as mean (SD) unless stated otherwise.

Table 2. Measurements during anaesthesia and surgery.

	Hypocapnia	Hypercapnia
Duration (min)	184 (43)	170 (50)
BIS	41 (3)	43 (5)
Propofol (g)	1.7 (0.4)	1.5 (0.5)
Remifentanil ($\mu g.kg^{-1}.min^{-1}$)	0.21 (0.06)	0.19 (0.08)
Rocuronium (mg)	223 (65)	201 (94)
Sugammadex (mg)	317 (77)	334 (96)
Post-tetanic-count	3.2 (2.4)	3.8 (3.3)
Retroperitoneal pressure (mmHg)	11 (1)	11 (1)
Leiden – surgical rating scale	4.84 (0.4)	4.77 (0.4)*
Mean arterial pressure (mmHg)	85 (10)	81 (9)
Heartrate (min^{-1})	68 (11)	69 (9)
Cardiac output ($L.min^{-1}$)	3.9 (1.1)	4.4 (1.3)
Arterial pCO_2 (kPa)	4.5 (0.6)	6.9 (0.6)**
Arterial pCO_2 range (kPa)	3.8-5.6	6.1-8.1
End tidal CO_2 (kPa)	3.4 (0.2)	5.7 (0.5)**
Minute volume ($L.min^{-1}$)	12.5 (2.1)	7.1 (1.3)**
Respiratory rate (min^{-1})	20.3 (3.0)	12.7 (1.6)**
Inspiratory pressure (cm H_20)	25 (4)	22 (2)*
Peep (cm H_20)	5 (0.6)	5 (0.3)

Values are mean (SD). * p>0.05, **p<0.001

kPa with a range of 3.0 to 3.7 kPa and hypercapnia 5.7 (0.5) kPa with a range of 4.9 to 6.8 kPa. Similarly, arterial pCO_2 differed by 2.4 kPa between treatments: hypocapnia 4.5 (0.6) kPa (range 3.8-5.6 kPa) and hypercapnia 6.9 (0.6) kPa (range 6.1 – 8.1 kPa). A clear difference between arterial and end-tidal pCO_2 was present during both hypocapnia and hypercapnia and averaged to 1.2 (0.1) kPa (Fig. 2). As is visible in panels C and D of Figure 2, the difference tended to slowly increase over time.

Rating of surgical conditions

We obtained 9 to 12 scores per patient. In Figure 3A, the mean scores over time are given for the two treatment groups. The scores did not differ between groups (p = 0.59). The mean of the mean L-SRS scores were: hypocapnia group 4.84 (0.4) against hypercapnia group 4.77 (0.4) (Fig. 3B). The distribution of the individual L-SRS scores is given in Figure 3C, showing that 99% of all scores were good or optimal, irrespective of the arterial pCO_2 conditions. There was no correlation between end-tidal pCO_2 and L-SRS (Fig. 3D, Pearson r = 0.02, p = 0.9) or between arterial pCO_2 and L-SRS (r = -0.08, p = 0.67).

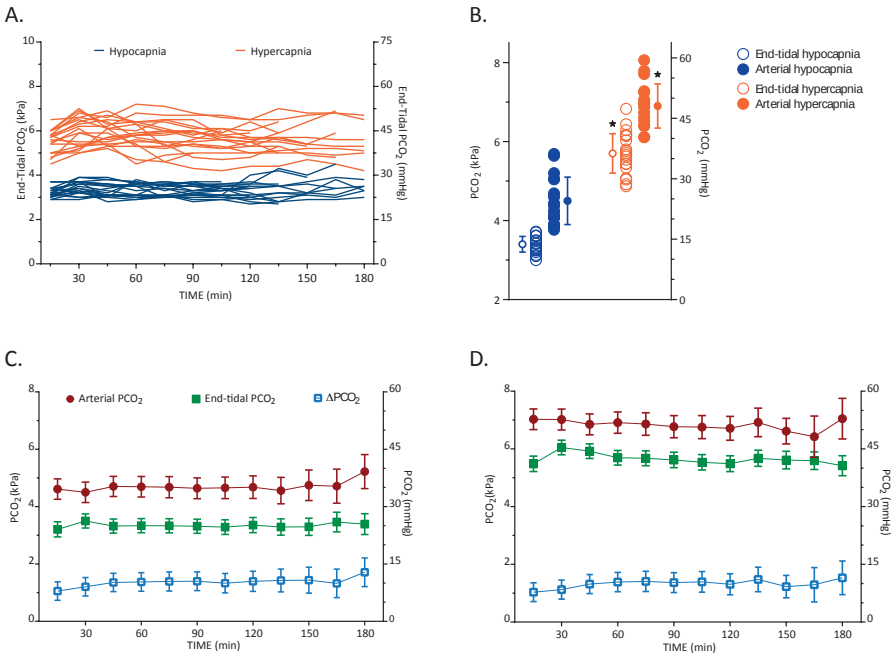

Figure 2. A. Individual end-tidal pCO$_2$ values over time. Blue lines hypocapnia, orange lines hypercapnia. **B.** Individual mean end-tidal and arterial pCO$_2$ values and mean of the means (SD). * $p < 0.001$. **C** and **D.** Profiles of the arterial pCO$_2$, end-tidal pCO$_2$ and difference between arterial and end-tidal pCO$_2$ (ΔpCO$_2$) under hypocapnic (**C**) and hypercapnic conditions (**D**). Data are mean ± 95% confidence interval.

Measurements following surgery

NMB reversal was by sugammadex 4 mg.kg^{-1} and resulted in optimal extubation conditions (train-of-four ratio > 0.9) within 3 min in all patients. Postoperative pain scores were similar between groups (data not shown).

DISCUSSION

We tested the hypothesis that hypocapnia would improve surgical conditions during retroperitoneal laparoscopic surgery and deep muscle relaxation, as rated by the Leiden-surgical rating scale To emphasize any difference between the treatment groups, we compared hypocapnic conditions against hypercapnic (rather than normocapnic) conditions induced by differences in respiratory rate. We cannot reject the null-hypothesis as no differences were observed in L-SRS (mean L-SRS hypocapnia 4.84, hypercapnia 4.77; Figs. 3A-D) between the two CO$_2$ conditions.

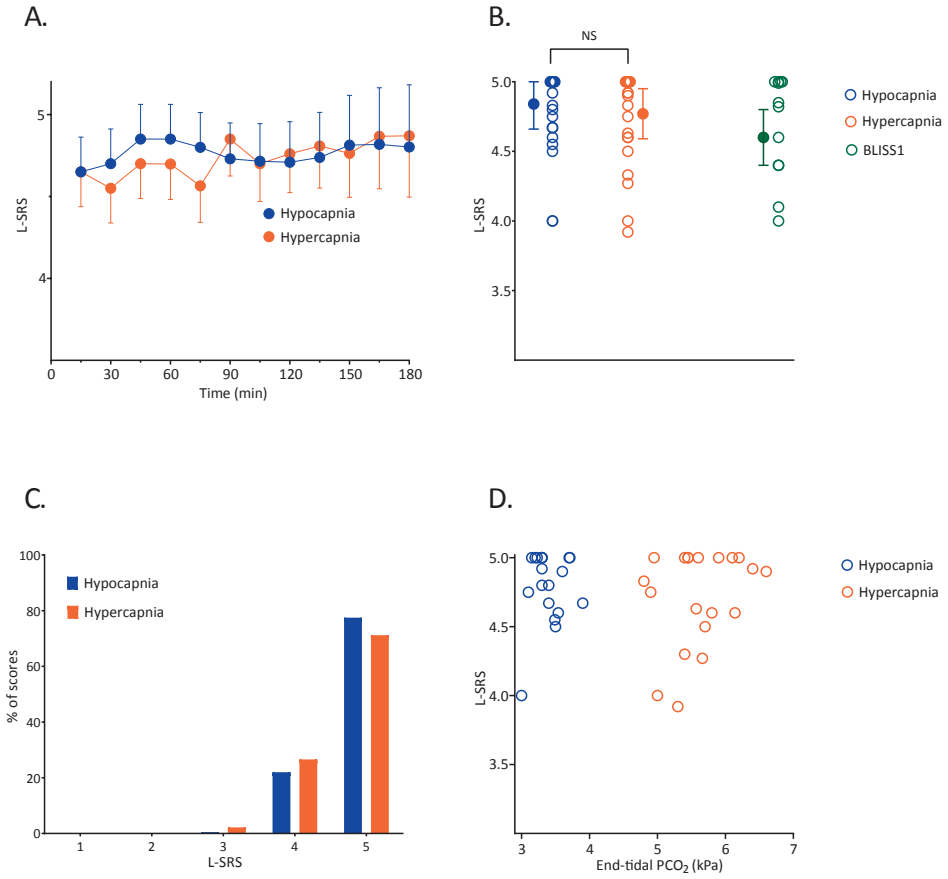

Figure 3. A. Mean (95% confidence interval) Leiden - surgical rating scale (L - SRS) scores *versus* time under hypocapnic (blue symbols) and hypercapnic conditions (orange symbols). **B.** Individual mean L - SRS scores (each symbol is the mean L - SRS of one patient) and mean of the means (SD). In green the results of the patients that had recieved a deep NMB (under normocapnic conditions) in the BLISS 1 study. **C.** Distribution of the surgical ratings under hypocapnic (blue bars) and hypercapnic (orange bars) conditions. **D**. Individual mean L - SRS scores *versus* mean individual end-tidal pCO_2 values in subjects treated with hypocapnia (blue symbol) and hypercapnia (orange symbol). Pearson r = 0.02, p = 0.9.

There are many physiological and pharmacological effects of hypocapnia that made us believe that lowered arterial CO_2 concentrations would improve surgical conditions. These effects include deepening of the anaesthetic state, enhanced muscle relaxation, inhibition of and abdominal muscle reflexes and a reduced efferent output from the brainstem to the diaphragm.[6-8, 12] Our inability to detect a significant difference between L-SRS scores does not imply that any of these effects of hypocapnia did not occur. It simply indicates that hypocapnia, irrespective of the physiological changes it causes, was without effect on the quality of the surgical field. We infer from our data that in case

of suboptimal surgical conditions, increasing ventilation is without effect and additional relaxation may be required.

We induced hypocapnia by increasing respiratory rates rather than increasing tidal volume. We did not allow high tidal volumes to prevent any pressure-related damage to the lungs.[13] Despite the relative high insufflation rates in hypocapnia peak inspiratory pressures were considered acceptable (Table 2) and none of the patients experienced any harm from the hypocapnic treatment.

Two recent studies from outside our institute have been published that use the L-SRS to assess the quality of the surgical field in deep NMB. Yoo and colleagues[2] observed a mean score of 4 (range 3-5) during deep NMB against a mean score of 3 (range 2-5) during a moderate block in robotic laparoscopic prostate surgery. Kim and colleagues[4] showed improved conditions during deep block compared to a moderate block in micro laryngeal surgery with 92% of patients with scores 4 or 5 at PTC 1-2 and 78% at TOF 1-2. Furthermore, just 3% of patients at deep NMB exhibited vocal cord movement during surgery compared to 39% of patients at moderate NMB. These studies indicate not only that a deep NMB is associated with superior surgical conditions in various complex surgeries but also show the practical usefulness of the L-SRS in scoring the quality of surgical field in different surgeries. Screening the various public clinical trial registries showed that additional studies that assess surgical conditions during anaesthesia using the L-SRS are underway, including one study on the effect of deep NMB in bariatric surgery (clinicaltrials.gov identifier NCT02553629). Apart from the 5-point L-SRS that we developed, other scoring systems were used in clinical studies, such as a 4-point scale by Dubois et al.[3] with similar end-points to those we used, a 4-point scale to assess the surgical space conditions by Staehr-Rye et al.[14] (only the worst score per case is reported), and a 100-point visual analogue scale by Blobner et al.[15] While we do not feel that one scoring system is superior to the other, we do express the need for a uniform scoring system that allows comparison between studies.

There are some limitations to our study. (1) The target pCO_2 at hypocapnia was not reached in all patients. Hyperventilation to relatively low levels of pCO_2 is more difficult in laparoscopic surgeries with continuous intracorporal CO_2 insufflation than in open surgeries. Greater ventilatory frequencies than applied would have been required to reach the target values. Since these high rates often hindered the surgeon we accept these deviations from target. (2) Scoring in our current and previous study was performed by one surgeon (RB), with large experience in the tested surgeries. This eliminates inter-observer variability but other surgeons may rate the surgical field differently, especially surgeons with less experience or surgeons trained in other subspecialties. This is illustrated by our previous observation that there was just moderate agreement between the ratings of our expert surgeon and eight other laparoscopy-skilled surgeons who rated video images of the surgical procedure.[1] Further validation of the L-SRS in

other specialties is therefore necessary. (3) The ability to effectively reverse a deep NMB in an acceptable time frame is essential in clinical practice. Sugammadex is currently the only reversal agent that allows rapid and safe recovery from a deep block without consequences such as residual curarization. However, the restricted use or availability of sugammadex in some hospitals makes application of a deep NMB not always practical.

In conclusion, our study shows that deep NMB provides good to optimal surgical conditions in laparoscopic retroperitoneal urological surgery, which were independent of the level of arterial pCO_2.

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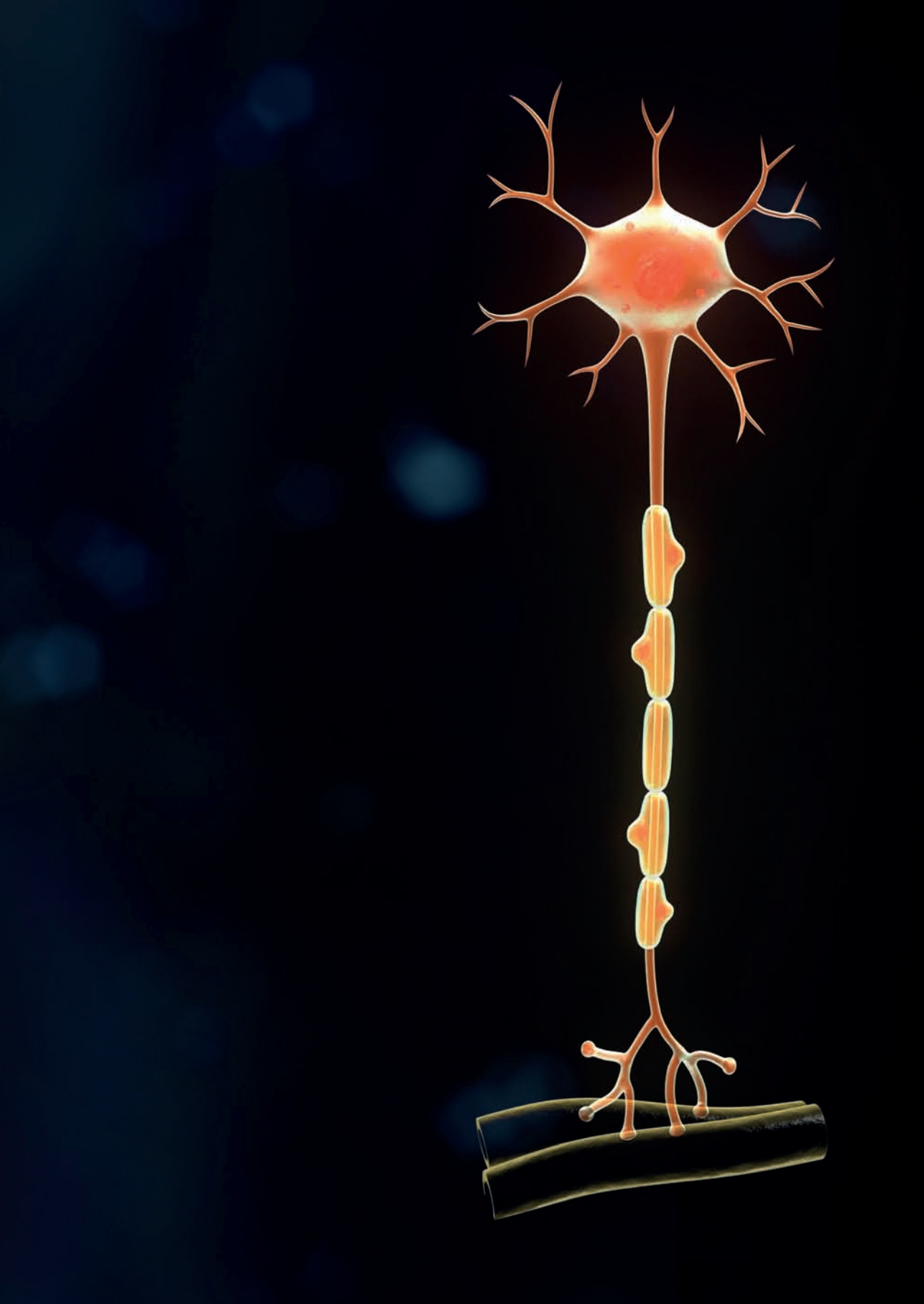
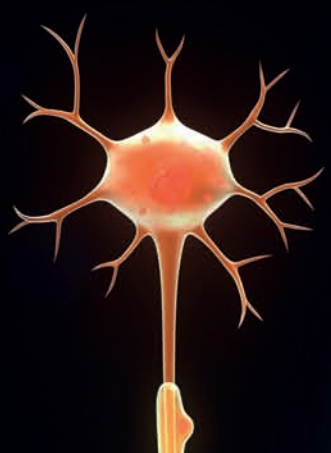


Section 2

Outcome



Chapter 4

Impact of high- *versus* low-dose neuromuscular blocking agent administration on unplanned 30-day readmission rates in retroperitoneal laparoscopic surgery

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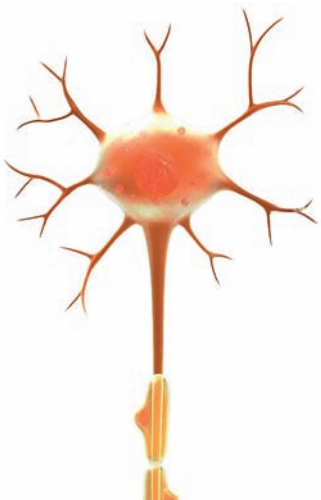
*Authors contributed equally



ABSTRACT

Background

Recent data shows that a neuromuscular block (NMB) induced by administration of high doses of rocuronium improves surgical conditions in certain procedures. However, there are limited data on the effect of such practices on postoperative outcomes.

Methods

A retrospective analysis was conducted to compare unplanned postoperative 30-day readmissions in patients that received high-dose *versus* low-dose rocuronium administration during general anaesthesia for laparoscopic retroperitoneal surgery. Charts of patients receiving anaesthesia between January 2014 and December 2016 were searched for surgical cases receiving high-dose rocuronium and matched with respect to procedure, age, sex and ASA classification to patients receiving low-dose rocuronium. The primary postoperative outcome was the unplanned 30-day readmission rate.

Results

Each cohort contained 130 patients. Patients in the high-dose and low-dose rocuronium cohorts received 217 ± 49 *versus* 37 ± 5 mg rocuronium, respectively. All patients receiving high-dose rocuronium were reversed with sugammadex, while just 33% of matched patients were reversed with sugammadex and 20% with neostigmine; the remaining patients were not reversed. Unplanned 30-day readmission rate was significantly lower in the high-dose compared to the low-dose rocuronium cohort (3.8% *vs.* 12.7%; p = 0.03; odds ratio = 0.33, 95% C.I. 0.12-0.95).

Conclusion

This small retrospective study demonstrates a lower incidence of unplanned readmissions within 30-days following laparoscopic retroperitoneal surgery with high-dose relaxant anaesthesia and sugammadex reversal in comparison to low-dose relaxant anaesthesia. Further prospective studies are needed in larger samples to corroborate our findings and additionally assess the pharmaco-economics of high-dose relaxant anaesthesia taking into account the benefits (reduced readmissions) and harm (costs of relaxants and reversal agents) of such practice.

INTRODUCTION

Typically, general anaesthesia is induced by administration of a hypnotic agent to provide loss of consciousness, an opioid analgesic to blunt hemodynamic and stress responses and a muscle relaxant to facilitate tracheal intubation and improve surgical conditions.[1, 2] Recently we showed that a neuromuscular block (NMB) induced by the administration of high-dose rocuronium, produces superior surgical conditions compared to the traditionally used NMB induced by low-dose rocuronium in laparoscopic retroperitoneal urologic and bariatric surgery.[3, 4] This has been replicated by others in various abdominal and non-abdominal procedures.[5-9] Moreover, a high-dose rocuronium NMB effectively precludes unexpected deterioration of the surgical field at any time.[3-9] Prevention of sudden patient movements is important during critical procedures, such as ophthalmic and neuro-radiologic intervention procedures. Additionally, recent data suggest that high-dose rocuronium NMB may improve pain scores after laparoscopic surgery,[4] although this is not a consistent finding.[3, 10]

Although tightly controlled randomized trials have shown improved subjective scores of surgical conditions when using high-dose rocuronium NMB, there is little evidence that the use of a high-dose rocuronium NMB improves outcome such as reduced postoperative pain scores or less postoperative surgical complications. In addition, the use of muscle relaxants during anaesthesia is associated with postoperative residual neuromuscular blockade and respiratory complications.[11, 12] Therefore, the intraoperative benefits of high-dose rocuronium NMB during surgery must be weighed against possible postoperative complications. Currently, one possible strategy to prevent residual NMB induced by high-dose rocuronium NMB is reversal with sugammadex, a rocuronium- and vecuronium-specific reversal agent that has been associated in previous studies with a reduction in the incidence of postoperative respiratory complications.[13, 14] However, the cost of sugammadex is a consideration and the cost benefit of high-dose rocuronium NMB has therefore been questioned due to its uncertain effect on outcomes and the high cost of reversal.[15]

Given the results of the majority of studies showing improved surgical conditions during high-dose rocuronium NMB, we have routinely applied such a NMB in close coordination with our surgical colleagues since July 2015. The high-dose rocuronium NMB is now a part of our clinical practice in a variety of surgical procedures including laparoscopic abdominal procedures, eye surgery and neuro-radiological interventions. To understand the utility of high-dose rocuronium anaesthesia under "real world" conditions and to address the above-mentioned gap in the evidence on outcomes, we performed a retrospective analysis of chart data to compare high-dose *versus* low-dose rocuronium

administration in patients undergoing laparoscopic retroperitoneal surgery. In the analysis we focused on unplanned 30-day readmission rates. Unplanned 30-day readmission is a quality measure of patient care and is costly.[16-18] Previous studies showed that an important factor associated with unplanned readmission is surgical complexity, with infectious complications being the most common indication for readmission.[16, 19-21] We hypothesized that the intraoperative advantage created by high-dose rocuronium (*i.e.* high-dose rocuronium NMB) may ultimately translate into fewer unplanned readmissions within the 30 days following the elective surgical procedures. The choice of focusing on laparoscopic retroperitoneal surgery is based on the fact that in our institution the majority of general anaesthetics with high-dose relaxant is applied for these procedures as they benefit the most from high-dose rocuronium NMB compared to other laparoscopic procedures.[3]

METHODS

High-dose rocuronium NMB was applied using a standard operating procedure that was introduced in July 2015 in our hospital for a series of procedures unless contraindicated (*e.g.* allergies to rocuronium or sugammadex, an estimated glomerular filtration rate < 30 mL.kg-1). High-dose rocuronium NMB is induced by an induction dose of rocuronium (1 $mg.kg^{-1}$), followed by a continuous infusion (range 20-50 $mg.h^{-1}$) aimed at a post-tetanic count of 1-2 twitches as measured by the TOF cuff monitor system (*RGB medical devices*, Madrid, Spain). After approval of the protocol by the local institutional ethical-board (Commissie Medische Ethiek, Leiden University Medical Center, 2300 RC Leiden, the Netherlands) and registration at clinicaltrials.gov (NCT03174223), fully anonymized data of patients that received anaesthesia from January 2014 to December 2016 were retrieved from two electronic medical record databases (Healthcare Information X-change (HIX) and Patient Data Management System (PDMS) both from Chipsoft, the Netherlands). The electronic databases were searched for cases that received general anaesthesia with high-dose rocuronium by continuous infusion for any type of elective procedure by using HIX and PDMS specific queries. High-dose rocuronium was defined by a 1 $mg.kg^{-1}$ bolus dose at induction followed by a continuous infusion. Next, we identified cases that received high-dose rocuronium from July 2015 to December 2016 were matched (one-on-one) for type of surgery, sex, age and American Society of Anesthesiologists (ASA) physical status classification to a case that had received general anaesthesia with low-dose rocuronium from January 2014 to July 2015. Low-dose rocuronium was defined by a 0.6 $mg.kg^{-1}$ bolus dose at induction and absence of a continuous infusion during the surgical procedure. The matching was performed on type of surgery, sex, age (ages could differ by a maximum of 4 years) and ASA status (ASA

class 1 and 2 were combined into one group). The research team checked and validated the data manually for consistency and accuracy.

The following data were compared between patients that had received high- and low dose rocuronium NMB: (1) patient-related data, including age, sex, weight, body mass index (BMI) and ASA physical status classification; (2) data related to anaesthesia and surgery, including surgery type, hemodynamics (blood pressure and heart rate; average of values collected during surgery), depth of anaesthesia as measured by bi-spectral index monitoring (average of values collected during surgery), drugs administered and their dose, duration of surgery, duration of anaesthesia, postoperative pain scores (measured on an 11-point verbal rating scale (VRS) from 0, no pain to 10, worst imaginable pain); (3) immediate respiratory complications as defined by hypoxemic events in the PACU (SpO_2 < 90%), bronchospasm, pneumonia during hospital stay; (4) admissions to intensive or intermediate care departments during hospital stay; (4) 30-day unplanned readmission data (cause of readmission, duration of readmission and relevant patient data of readmitted cases); (5) cost of relaxation and reversal. Pain scores were obtained in the post-anaesthesia care unit (PACU) at 15 min intervals and on the ward three-times daily. The pain data were averaged for location (*i.e.* average pain data obtained at the PACU and on the ward).

Data were analyzed comparing high-dose relaxant *versus* low-dose relaxant groups by paired-*t*-test, Mann-Whitney U test or χ^2 test, depending on the type of data and data distribution. Data are presented as mean ± SD or median with interquartile range (IQR); p-values < 0.05 were considered significant. Data analysis was performed using GraphPad Prism version 7.00 for MAC OS X (*GraphPad Software,* La Jolla, CA).

The primary outcome of our study was the incidence of unplanned readmission within 30-days of the elective surgical procedure; secondary outcome was cost of relaxation and reversal in the high- and low-dose rocuronium cohorts. Additionally, we compared duration of surgery and anaesthesia, and postoperative pain between cohorts.

RESULTS

Patients and procedures

During the search period 51,000 anaesthetics were administered for various procedures at Leiden University Medical Center. The initial selection procedure resulted in 537 cases that were considered eligible for inclusion in the analysis. High-dose rocuronium anaesthesia was administered most frequently to patients undergoing urological

procedures, ophthalmologic surgery or surgical renal procedures. During the manual validation process 407 cases were excluded for the following reasons: age < 18 years, lack of surgical procedure code, multiple patient inputs, missing time stamps, absence of reversal dosing information, or procedures other than elective laparoscopic retroperitoneal surgeries (these procedures included open eye surgeries (n = 77), gastrointestinal surgery (n = 14), organ transplantations (n = 15), neurosurgical procedures (n = 4) and gynaecological procedures (n = 1)). The final data set consisted of 130 cases that received high-dose rocuronium in patients undergoing elective laparoscopic retroperitoneal surgery. Matching was successful in 100% of cases, yielding a total of 130 cases that on average received 217 ± 49 mg rocuronium and 130 matched cases that received 37 ± 5 mg rocuronium. Patient characteristics and surgical procedures are given in Table 1. Patients in the two cohorts had similar age, ASA classification, weight and body mass index. Due to the predominance of urology in our cohort, males were in the majority (in each cohort 98 men and 32 women). Glomerular filtration rate was above 30 mL.min^{-1}

Table 1. Patient and procedural characteristics.

	High-dose rocuronium	**Low-dose rocuronium**	**P-value**
Patient characteristics			
Number of patients (*n*)	130	130	
Men/women (*n*/*n*)	98/32	98/32	
Age (years; mean, 95% CI)	60 (58-63)	59 (56-61)	0.46
Weight (kg; median, IQR)	81 (73-92)	80 (72-93)	0.65
BMI (kg.m^{-2}; median, IQR)	26 (24-29)	25 (23-29)	0.21
ASA score 1	34%	32%	
ASA score 2	60%	62%	
ASA score 3	6%	6%	
ASA score 4	0%	0%	
ASA score 5	0%	0%	
CKD stage 1-3 (*n*)	130	125	
CKD stage 4 and 5 (*n*)	0	5	
Laparoscopic retroperitoneal procedures (*n*)			
Nephrectomy (partial + complete)	56	56	
Retroperitoneal lymph node resection	36	36	
Prostatectomy	24	24	
Pyelumplasty	14	14	

CKD = chronic kidney disease. CKD stage 1-3: glomerular filtration rate ≥ 30 mL/min; CKD stage 4 and 5; glomerular filtration rate < 30 mL/min. Values are numbers (n), percentages or mean and 95% confidence interval (95% CI) or median and interquartile range (IQR).

in all patients receiving high-dose rocuronium and in 125 patients receiving low-dose rocuronium.

Anaesthesia and surgery

The two study cohorts differed by a factor of 6 in the amount of rocuronium that was administered (Table 2; Supplemental Figure 1). For induction and maintenance all patients received propofol combined with remifentanil, sufentanil or both. More patients in the high-dose relaxant group received remifentanil (65% *vs.* 33%) with on average a 20% higher dose compared to patients in the low-dose relaxant group (p = 0.015, Table 2). Similarly, patients that received sufentanil in the high-dose relaxant groups received on average a 14% higher dose than patients in the low-dose relaxant group (p = 0.025, Table 2).

Table 2. Medication administered during anaesthesia.

	High-dose rocuronium	Low-dose rocuronium	P-value
Total intravenous anaesthesia (*n*)	130	130	
Propofol dose (mg.kg^{-1}.min^{-1})	0.13 (0.06)	0.13 (0.05)	0.62
Remifentanil (*n*)	71	33	
Remifentanil dose (µg.kg^{-1}.min^{-1})	0.16 (0.05)	0.13 (0.04)	< 0.001
Sufentanil (*n*)	87	108	
Sufentanil dose (µg.kg^{-1})	1.5 (0.8)	1.3 (0.6)	0.025
Rocuronium dose (mg)	217 (49)	37 (5)	< 0.001
Sugammadex (*n*)	130	44	
Sugammadex dose (mg)	267 (101)	212 (55)	< 0.001
Neostigmine (*n*)	-	26	
Neostigmine dose (mg)	-	1.4 (0.6)	
Atropine (*n*)	-	26	
Atropine dose (mg)	-	0.6 (0.2)	

Values are number of patients (n) or mean (SD).

All patients in the study received rocuronium as muscle relaxant. Patients that received high-dose rocuronium were all reversed with sugammadex (dose 267 ± 101 mg), while patients in the low-dose rocuronium group were either not reversed (46%), received sugammadex (34%, dose 212 ± 55 mg, p < 0.001 *vs.* high-dose relaxant group) or received neostigmine (20%, dose 1.4 ± 0.6 mg). Duration of anaesthesia, duration of surgery and heart rate values did not differ between cohorts. A small difference in bi-spectral index (BIS) values was observed with a deeper anaesthesia level in patients receiving high-dose than low-dose rocuronium. However, the difference was small (mean difference = 1.5 with 95% confidence interval 0.1-3.0, p = 0.03). Similarly, a small difference in mean

Table 3. Measurements during anaesthesia.

	High-dose rocuronium	Low-dose rocuronium	P-value
Duration of surgery (hours; median, IQR)	2.4 (1.7-3.1)	2.3 (1.7-3.1)	0.77
Duration of anaesthesia (hours; median, IQR)	3.1 (2.4-4.1)	3.1 (2.4-4.1)	0.88
Stay in PACU (hours; median, IQR)	1.9 (1.4-2.2)	1.7 (1.2-2.2)	0.16
Mean arterial pressure (mmHg)	85 (10)	80 (11)	< 0.01
Heart rate (beats.min^{-1})	68 (11)	69 (11)	0.48
Bi-spectral Index	42 (5)	44 (6)	0.03
Oxygen saturation (%)	99 (1)	99 (1)	0.95
Length of hospital stay (days; median, IQR)	2.2 (1.7-3.2)	2.2 (1.3-3.3)	0.52

PACU = post-anaesthesia care unit; IQR = interquartile range. Values are mean (SD) unless otherwise stated

arterial pressure was observed between groups (mean difference 5.5 mmHg with 95% confidence interval 3-8 mmHg, $p < 0.01$). See Tables 2 and 3.

There were no differences in postoperative pain between the two groups in the PACU (median verbal rating scale high-dose relaxant: 3.0, IQR 1.0-4.7 *vs*. low-dose relaxant: 2.7, IQR 1.0-4.0; $p = 0.19$) and the ward (median VRS high-dose relaxant: 2.0, IQR 1.0-3.3 *vs*. low-dose relaxant: 2.0, IQR 1.1-3.1 $p = 0.89$). Length of hospital stay did not differ between the two cohorts: high-dose rocuronium median duration 2.2 (IQR 1.7-3.1) days *vs.* low-dose rocuronium 2.2 (1.3-3.3) days ($p = 0.52$). In both cohorts there were no immediate postoperative respiratory complications or inadvertent admissions to intensive or intermediate care departments.

Readmission rates

In the two cohorts, 26 patients were readmitted within 30 days. In 7 patients, readmission was pre-planned (reasons for readmission: chemotherapy, learning how to catheterize, screening for kidney transplantation, reassessment of renal function, bisphosphonate treatment) occurring in both cohorts. In 19 (7.3%) patients readmissions was unplanned: 5 (3.8%) in patients receiving high-dose rocuronium and 14 (10.8%) in patients receiving low-dose rocuronium ($\chi^2 = 4.6$, $p = 0.03$; odds ratio = 0.33, 95% C.I. 0.12-0.95). In Table 4 the reasons for readmission are given. None of the patients died during readmission. See Table 4 for a specification of the data. In total 8 readmissions were related to an infection at the surgical site (1 in patients receiving high-dose rocuronium, 7 in patients receiving low-dose rocuronium).

Cost

Combined cost of relaxation and reversal was on average $131 (95% confidence interval $115-$147) per patient in the high-dose rocuronium cohort *vs.* $34 (95% confidence interval $26-$42) in the low-dose cohort. All of these costs were paid by the hospital. Total

Table 4. 30-day unplanned readmission.

	High-dose rocuronium	Low-dose rocuronium	P-value
Unplanned readmissions (95% confidence interval)	3.8% (1.3-8.8%)	12.7% (6.0-17.4%)	0.03
Male/female (*n*/*n*)	4/1	13/1	
Age (years; median, range)	56 (27-69)	63 (43-75)	0.29
ASA classification (*n*)			
1	2	7	
2	3	7	
3	0	0	
CKD stage 1-3	5	13	
CKD stage 4 and 5	0	1	
Reasons for readmission	- Abscess in renal bed - Brain metastasis - Enteritis - Lymphocele (n = 2)	- Collapse/hypotension - Enteritis and transient ischemic attack - Intra-abdominal urinary leak - Complicated urinary tract infection (n = 7) - Urinary retention - Lymphocele - Urethra/bladder anastomosis leak - Worsening of renal function (CKD stage 2 to 3)	

CKD chronic kidney disease. CKD = stage 1-3: glomerular filtration rate ≥ 30 mL/min; CKD stage 4 and 5: glomerular filtration rate < 30 mL/min.

reimbursement from reimbursement agencies for readmissions (at the benefit of the hospital) was $116,000 for the 14 patients in the low-dose rocuronium cohort against $42,000 for the 5 patients in the high-dose rocuronium cohort (average reimbursement per patient was similar between the 2 cohorts at approx. $8,300 per patient).

DISCUSSION

This retrospective matched cohort study presents data of the everyday clinical use of high-dose rocuronium neuromuscular block for elective laparoscopic retroperitoneal surgery in a single tertiary academic hospital in the Netherlands. A total of 130 patients who received high-dose rocuronium anaesthesia (and reversal with sugammadex) were compared to 130 matched patients that received low-dose rocuronium anaesthesia (to induce a moderate NMB). The main finding of this study is that the administration of high-dose rocuronium is associated with reduced unplanned readmission rates in the 30 days following elective surgery (3.8% *vs*. 12.7%). Furthermore, the application of high-dose rocuronium anaesthesia was without inadvertent admissions to intensive or intermediate care departments.

Neuromuscular blocking agents are routinely used in anaesthesia to facilitate endotracheal intubation and improve surgical conditions.[1, 2] A recent meta-analysis of 12 randomized controlled trials concluded that high-dose rocuronium NMB (intended to achieve deep NMB with PTC 1-3 twitches) improves surgical conditions in a variety of procedures as determined by the scoring of the surgical space conditions by the attending surgeon.[22] In most studies included in this review, the applied scoring systems combine the impression of visibility, surgical space, muscle contractions, handling tactics and patient movement into one numerical rating score. In all studies, the effect of the high-dose rocuronium NMB on the score is modest (on average the score improves by about 20%) but considered highly clinically significant by the surgical team.[3, 4] Still, the risk of postoperative complications from residual NMB has historically precluded the use of high doses of muscle relaxants for many years.[11, 12] With the introduction of sugammadex, quick and safe reversal of high-dose rocuronium NMB became possible.[14] In our institute we now provide high-dose rocuronium anaesthesia upon request of the surgeons to allow a stable and qualitatively superior surgical space conditions in a variety of procedures.

Our current analysis shows that the both cohorts did not differ in hemodynamics, duration of surgery and anaesthesia or immediate postoperative conditions, including postoperative pain. A small difference in depth of anaesthesia and mean arterial pressure was observed although we do not consider these differences clinically relevant. We previously identified a small positive effect of high-dose rocuronium NMB on postoperative pain scores following bariatric surgery but not following retroperitoneal urologic procedures.[3, 4] The above mentioned meta-analysis of 12 studies also revealed a small advantage of high-dose rocuronium NMB over standard or low-dose rocuronium NMB with an improvement in postoperative numerical pain scores of 0.5 on an 11-point scale.[22] These data suggest that the effect of high-dose rocuronium NMB on pain scores is small. Different procedures may activate specific pathophysiologic pain pathways that interact differently with the high-dose rocuronium NMB. In the current analysis we focus on retroperitoneal surgeries. These procedures are associated with relatively low pain scores and little effect of high-dose rocuronium NMB.[3] Hence, our analysis does not allow definite conclusions regarding the influence of high-dose rocuronium NMB on postoperative pain.

We encountered a reduction in unplanned readmission rates from 12.7% in the low-dose to 3.8% in the high-dose rocuronium cohort (Table 4). Readmissions after surgery are relatively common, with rates ranging from 4-16% after major urologic surgery and 9-20% after colorectal surgery.[23, 24] Readmission after surgery represents a major cost for

the health care system. For instance, readmission after colorectal surgery costs $9000 per readmission; this annually accounts for $300 million in the US alone.[25] To address and reduce costs, readmission is increasingly being used as a hospital quality indicator by reimbursement agencies. In the US, as a part of the Hospital Readmission Reduction Program, reimbursements may be denied in case of excessive readmission rates.[26] The cost of readmission to reimbursement agencies in our institute is approximately $8,300 per patient. Given the reduction in readmissions observed in patients receiving high-dose rocuronium anaesthesia (combined with sugammadex reversal) compared to patients receiving low-dose rocuronium anaesthesia, there is a potential financial benefit to the healthcare system that could offset the costs associated with high doses of rocuronium and sugammadex made by the hospital. As this retrospective data may be biased due to changes in surgical and/or anaesthesia practice over time, possible inaccuracies in the dataset or its retrieval from HIX or PDMS or other relevant limitations (see below), a prospective randomized pharma-coeconomic trial should be considered to definitely capture relevant cost data.

Known risk factors for readmission include older age, comorbid conditions, length of procedure, surgery complexity and intra- and postoperative complications.[16-20, 27] Due to matching, in our study all relevant factors were comparable at baseline (Tables 1 and 2). We therefore account the application of high-dose rocuronium anaesthesia as the most important factor associated with the lower readmission rates. Although our study does not answer the question why better chemical relaxation results in improved surgical outcome, we believe that it is important to discuss possible mechanisms. All procedures were performed in the retroperitoneal space, where working space is very limited. As previously shown, high-dose rocuronium NMB leads to superior scoring of the surgical space conditions in these retroperitoneal surgeries.[3, 22] Possibly, the improved surgical conditions in the narrow space of retroperitoneal laparoscopic surgery during high-dose rocuronium NMB contribute to superior technical performance of the surgeon and less trauma to tissue. A recent review supports this hypothesis by concluding that superior technical performance positively affects patient outcome.[28] An important reason for readmission was an infectious complication of the urinary tract (complicated urinary tract infection including pyelonephritis and urosepsis). We hypothesize that urinary tract tissue is particularly susceptible to infection when surgical space conditions are less optimal and/or urinary tract tissue is more frequently or more intensely manipulated (causing micro trauma). Additionally, it is important to realize that NMB agents possess anti-inflammatory properties through actions at the nicotinic acetylcholine receptor α1.[29] The high-dose rocuronium infusion may therefore have had some tissue protective effect leading to less postoperative complications. Reduced glomerular filtration rate (chronic kidney disease, CKD, stage 4 and 5 with a glomerular filtration rate

< 30 mL.min^{-1}) affects rocuronium clearance. This may be a cause of residual NMB and postoperative complications, especially in those patients that are not or inadequately monitored. However in patients with complications that required readmission just 1 patient receiving low-dose rocuronium and none receiving high-dose rocuronium had CKD stage 5 (Table 4). The reason for readmission in this one particular patient was severe enteritis and a transient ischemic attack. Consequently, we do not think that renal function influenced the outcome of our study. Finally, in other surgery types such as ophthalmology, we did not observe a difference in readmission rates (data not shown). This suggests that the improved outcome in our study is most importantly related to the type and site of surgery.

Our study has various limitations that need to be considered:

(1) Since the use of high-dose rocuronium anaesthesia is relatively new to our clinical practice, we were able to just include a small number of patients in our analysis. This small sample precluded the analysis of underlying contributing risk factors as a cause of readmission.
(2) We remain unaware whether the results of our study are related to the high-dose rocuronium infusion, the reversal with sugammadex or to both. The number of patients that received sugammadex in the low-dose rocuronium cohort was too small to perform a separate analysis.
(3) This is a single-center study and generalizability to other centers is likely to be limited. For example, the use of a rocuronium infusion (and reversal with sugammadex) is not standard care in other hospitals in Europe or the US.
(4) This is a non-randomized study with a non-contemporaneous control group. We cannot exclude that temporal changes in anaesthesia or surgical care may have contributed to the study outcome.
(5) More subjects in the high-dose rocuronium group received the opioid remifentanil and irrespective of the type of opioid, the opioid dose was higher in the high-dose rocuronium group. This is a surprising observation that so far remains unexplained. We do not perceive a role for the difference in opioid dose in our study outcome, although it might explain the slightly deeper levels of anaesthesia in the high-dose rocuronium cohort (Table 3).
(6) Our dataset lacks complete TOF data, as TOF measurements are not automatically recorded in our electronic patient database system. Although neuromuscular monitoring devices are available in all our operating rooms and monitoring is mandatory by local protocols, it cannot be ruled out that part of the patients were in fact inadequately or not monitored, especially in the low-dose rocuronium group. This may be a source of residual confounding, however to what extent this influenced our study remains unclear.

Evidently, further prospective randomized controlled trials (with appropriate monitoring) in larger populations are required to determine causal inferences between the relaxant dose and patient outcome and a possible role for the reversal agent on patient outcome.

In conclusion, this small retrospective study presents the first real world data of the effect of a high-dose rocuronium/sugammadex anaesthetic technique on postoperative outcome. Our data indicate that the use of a high-dose rocuronium/sugammadex technique is associated with reduced readmission rates in the 30 days following elective laparoscopic retroperitoneal surgery compared to low-dose rocuronium infusions. Given the study limitations, future prospective randomized studies in larger samples are needed to further investigate the benefit of high-dose relaxants on patient outcome. Additionally, the prospective study of the pharmaco-economic effect of such practice taking into account benefit (reduced readmission rates) and harm (cost of relaxants and reversal agents) is needed.

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Chapter 5

Improved postoperative oxygenation following reversal of moderate neuromuscular block with sugammadex compared to neostigmine

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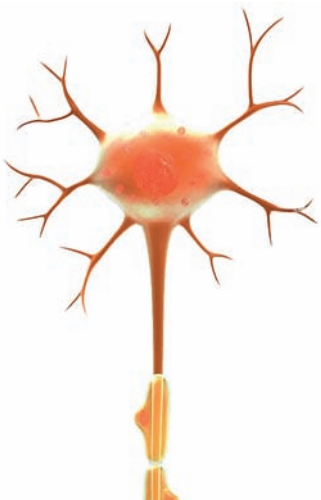

ABSTRACT

Background

Incomplete recovery of neuromuscular block (NMB) at the end of surgery is one of the leading causes of postoperative adverse events, most importantly hypoxaemia. Adequate reversal of NMB may overcome these complications. This study was designed to compare reversal with neostigmine and sugammadex on postoperative oxygenation during the first 45 minutes postoperatively.

Methods

In this randomized controlled, double-blind trial, 100 patients received propofol/sufentanil/rocuronium anaesthesia and were randomized to NMB reversal at 1-2 twitches in the train of four (TOF) with sugammadex 2 $mg.kg^{-1}$ or neostigmine 2.5 mg. Extubation was based on clinical signs of adequate muscle strength. Postoperative use of supplemental oxygen was not allowed unless saturation dropped to values below 94%.

Results

Mean (SD) TOF ratio at extubation was 0.74 (0.22) in patients reversed with neostigmine; 70% of these patients had a TOF ratio < 0.9. In contrast, patients reversed with sugammadex had a TOF ratio of 0.99 (0.3) ($p < 0.0001$ *vs.* neostigmine); 4% of these patients had a TOF ratio < 0.9. Postoperatively, the lowest oxygen saturation was 96.8 (2.2)% against 93.3 (3.9)% in sugammadex and neostigmine groups, respectively ($p < 0.0001$). The combination of TOF ratio > 0.90 and oxygen saturation levels ≥ 94% occurred in 90% of patient reversed with sugammadex compared to 16% of patients reversed with neostigmine.

Conclusions

Compared to reversal with neostigmine, reversal of a moderate neuromuscular block with sugammadex resulted in improved muscle function at extubation with less postoperative hypoxaemia in patients not receiving supplemental oxygen.

INTRODUCTION

Neuromuscular blocking agents are routinely used during general anaesthesia to optimize intubation and improve surgical conditions. For example, we recently showed that a deep neuromuscular block (NMB) improves the quality of the surgical field in retroperitoneal laparoscopic surgery.[1] The persistence of some level of NMB (residual relaxation defined by a train-of-four (TOF) ratio < 0.9) is an independent risk factor for postoperative pulmonary complications, with hypoxaemia as most frequent event.[2,3] We relate the relatively high incidence of residual relaxation following general anaesthesia to the lack of adequate quantitative monitoring (but instead subjective monitoring based on clinical signs of recovery) and the impatience of the anaesthetist (not realizing that reversal with some agents is relatively slow). For example, even when the NMB is reversed with the acetylcholinesterase inhibitor neostigmine residual relaxation is a frequent observation in the PACU, independent of the use of monitoring.[4] We previously showed that more than 30% of patients experience frequent hypoxic events in their 45 min stay in the PACU following isoflurane/fentanyl-based anaesthesia with spontaneous recovery or reversal with neostigmine of a moderate NMB.[5] The link between residual relaxation and hypoxaemia in the PACU is that persistence of even low levels of acetylcholine receptor blockade cause inadequate pulmonary and upper airway muscle function as well as reduced carotid body activity.[6-8] Consequently, alveolar hypoventilation combined with loss of upper airway patency and a reduced ventilatory response to hypoxaemia facilitates frequent hypoxic events in the PACU.

A relatively new reversal agent is the γ-cyclodextrin sugammadex, which encapsulates rocuronium (and vecuronium) in plasma and consequently causes the diffusion of the NMB agent from the neuromuscular junction.[9] While several studies show that sugammadex causes rapid and complete reversal of moderate and deep NMB,[10-13] a recent study showed that even following sugammadex reversal residual relaxation (defined by a train-of-four (TOF) ratio < 0.9) occurred in 4% of patients.[14] No data are available on the incidence of hypoxaemia in the PACU following reversal with sugammadex or the association between TOF ratio at extubation following sugammadex reversal and oxygen saturation levels in the PACU.

We conducted a double-blind randomized controlled trial comparing the effect of reversal of a moderate NMB (TOF 1-2 twitches) with sugammadex 2 $mg.kg^{-1}$ and neostigmine 2.5 mg on oxygen saturation levels in the PACU. The use of supplemental oxygen in the PACU was not allowed unless arterial oxygen saturation dropped to values below 94%. We hypothesize that, compared to neostigmine, reversal with sugammadex is associated with less hypoxaemia in postoperative patients that do not receive supplemental oxygen.

METHODS

The study with acronym Neuropa was conducted between February 2015 and February 2016 at two medical centres in the Netherlands, Leiden University Medical Centre in Leiden and Haga Ziekenhuis in The Hague. Ethics approval of the protocol was obtained from the ethics committees of both institutions; the protocol was registered at clinicaltrials.gov under number NCT02243943. The study was conducted in accordance with Good Clinical Practice and Good Research Practice guidelines. Eligible patients were approached in advance by one of the investigators and received oral and written information about the study. If a patient was willing and able to participate, written informed consent was obtained.

Patients and randomization

Patients were eligible to participate in the study if they fulfilled the following criteria: 18 years or older, ASA class I-III, body mass index <35 $kg.m^{-2}$, scheduled for elective surgery with a planned duration of at least 60 minutes and requiring general anaesthesia with the use of muscle relaxants. Exclusion criteria included known or suspected neuromuscular disorder, allergy to muscle relaxants or reversal agents, a (family) history of malignant hyperthermia, (suspected) pregnancy or current breast feeding, contraindications for neostigmine use, planned regional or neuraxial anaesthesia, pulmonary disease and renal insufficiency (glomerular filtration rate < 30 $mL.min^{-1}$).

All patients were randomized to receive either sugammadex or neostigmine as reversal agent at the end of surgery. Randomization was performed before induction of anaesthesia and the 'time out" procedure. Randomization was performed using a computer-generated randomization list (obtained from www.randomization.org). Allocation to treatment was at the end of surgery. The patient and researchers were fully blinded, but the attending anaesthetist was not and he or she administered the drugs at a train-of-four (TOF) count of 1 (T1) or 2 (T2) twitches. Thereafter the anaesthetist was blinded to the TOF count and TOF ratio and his or her decision to extubate the patient was based on clinical grounds.

Anaesthesia and neuromuscular management

Premedication consisted of oral midazolam 3.75 to 7.5 mg and rectal paracetamol 1000 mg one hour before surgery. All patients received total intravenous anaesthesia with sufentanil, propofol and rocuronium and inhaled a 50/50 mixture of oxygen and nitrogen. Monitoring was according to local practice and included electroencephalogram monitoring using the Philips BIS module (*Philips,* Eindhoven, the Netherlands). Target BIS values in this study were values between 45 and 55. Relaxation was measured using

the TOF cuff device (*RGB Medical Devices,* SA, Madrid, Spain), which was applied around the left or right upper arm, contralateral to the blood pressure cuff. The TOF cuff was calibrated after induction but before administration of rocuronium. The TOF cuff is equally reliable to acceleromyography and has been used in our previous studies on NMB.[15] In our opinion, the TOF cuff is easier to use in daily practice than the TOF watch and is less prone to error. One hour before the end of surgery, morphine 0.1 $mg.kg^{-1}$ was given.

The target level of neuromuscular relaxation was T1 or T2 throughout the procedure until reversal. If measurement indicated a TOF of 3 twitches or higher during surgery, an incremental dose of rocuronium 10 mg was administered. At the end of the procedure, neuromuscular block was reversed with sugammadex 2 $mg.kg^{-1}$ or neostigmine 2.5 mg (combined with atropine), according to randomization. Upon the discretion of the attending anaesthetist additional doses could be given. At reversal, the inhaled oxygen concentration was set at 100%; lung recruitment manoeuvres were not allowed unless deemed necessary by the attending anaesthetist.

Extubation was performed by the attending anaesthetist based on clinical signs as is commonly practiced in both medical centres. These signs include adequate level of spontaneous ventilation, eye opening, hand grip strength, 5s. head lift and tongue protrusion. A blinded research nurse collected TOF data at 1-minute intervals from the time of reversal.

After extubation and transport to the PACU oxygen saturation (SpO_2) was continuously monitored and recorded at 2-minutes intervals. Supplemental oxygen was only allowed when SpO_2 dropped below 94%. The SpO_2 was collected on the case record form and the lowest value observed in the PACU was used for analysis. Additionally, the following variables were recorded on the case record form at 15-minutes intervals: blood pressure, heart rate, pain (using an 11-point numerical rating scale from 0 to 10) and sedation (using a 5-point scale ranging from 0, normal alertness to 5, not aroused by a painful stimulus). After 45 minutes in the PACU the study ended.

Sample size and statistics

We judged that a difference in SpO_2 between treatment groups of at least 2% is clinically relevant. Assuming a SD of 3.0%, a sample size of 49 patients per group would provide at least 90% power to detect the observed difference at $\alpha = 0.05$.

The primary outcome was the lowest SpO_2 as measured during the first 45 minutes in the PACU. Data analysis was based on an intent-to-treat basis. A significant difference between treatment groups was tested by two-tailed Student *t*-test. Secondary outcomes were time to a TOF ratio > 0.9, time from reversal to extubation, postoperative pain level

and sedation scores in the PACU. Student *t*-tests and Mann Whitney U tests were used as appropriate. The data were analyzed with SPSS (version 22; *IBM corporation*, Armonk, NY, USA). All data are presented as mean (SD) or mean (95% confidence interval) unless otherwise stated. p-values < 0.05 were considered significant.

RESULTS

Figure 1 shows the flow diagram of the study. A total of 126 patients were contacted of whom 16 refused consent, 4 did not meet inclusion criteria and 6 patients could not enter the study due to logistic reasons (e.*g.* rescheduling of surgery). One-hundred patients were randomized between the treatment groups. No patients were lost to follow-up and postoperative data of all patients were used in the final analysis.

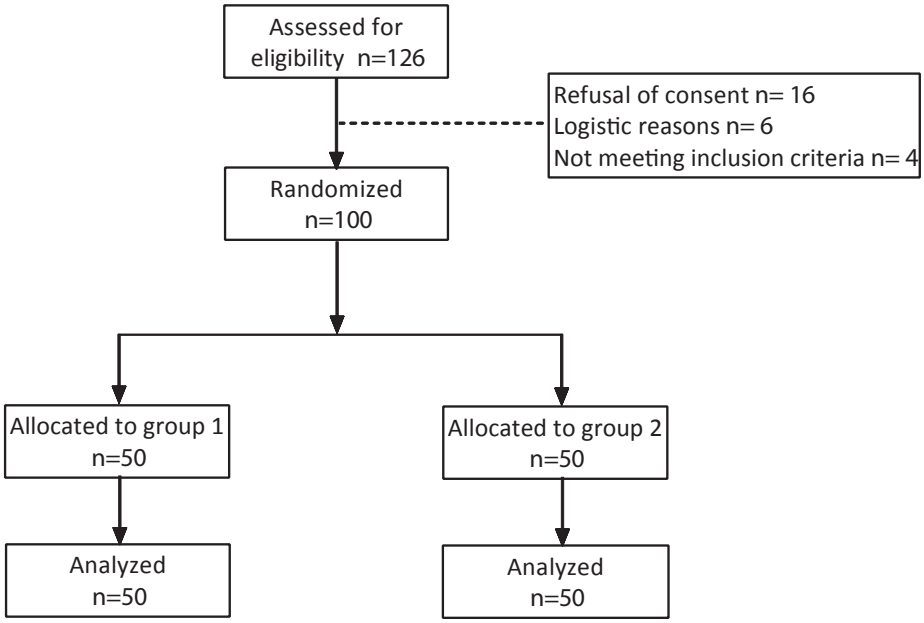

Figure 1. Study flow chart.

Reversal

Table 1 gives the baseline characteristics and perioperative measurements. No significant differences were present between both groups. In addition, no significant differences in duration of surgery and anaesthetic medication were present. At the end of surgery, relaxation was reversed at a mean TOF count of 1.4 (1.1-1.7) and 1.6 (1.2-1.9) twitches in sugammadex and neostigmine groups respectively (p > 0.05). Patients in

Table 1. Baseline characteristics and perioperative data.

	Sugammadex N=50	**Neostigmine** N=50	P-value
BASELINE CHARACTERISTICS			
Age (years; median, range)	55 (27-72)	55 (19-94)	NS
Male (n, %)	27 (53%)	24 (44%)	NS
Weight (kg)	79 (75-83)	75 (71-79)	NS
BMI ($kg.m^{-2}$)	26 (25-27)	25 (24-26)	NS
ASA (n, %)			NS
1	18 (35%)	32 (59%)	
2	32 (63%)	22 (41%)	
3	1 (2%)	-	
Preoperative saturation (%)	99 (98-99	99 (98-99)	NS
SURGERY			
Duration of surgery (min)	107 (91-123)	90 (77-105)	NS
Propofol dose (mg)	1114 (972-1256)	951 (803-1098)	NS
Sufentanil dose (µg)	52 (45-58)	43 (38-49)	NS
REVERSAL			
Sugammadex dose (mg)	170 (156-184)	-	
Neostigmine dose (mg)	-	2.5 (2.4-2.6)	
Atropine dose (mg)	-	1.08 (1.03-1.13)	
BIS at reversal	46 (44-49)	44 (42-46)	NS
TOF count at reversal	1.4 (1.1-1.7)	1.6 (1.2-1.9)	NS
Time to TOF ratio 0.9 (min)	2.5 (2.1-2.8)	10.0 (7.6-12.3)	< 0.0001
EXTUBATION			
TOF ratio at extubation	0.99 (0.98-1.00)*	0.74 (0.68-0.80)	< 0.0001
TOF ratio below 0.90 at extubation	-	0.60 (0.55-0.67)**	
Time to extubation from reversal (min)	8.0 (6.9-9.1)	11.7 (9.9-13.4)	0.01
Time to extubation from TOF 0.9 (min)	5.8 (4.7-6.8)	3.8 (2.1-5.4)#	NS
BIS at extubation	79 (76-82)	77 (74-80)	NS
POST ANAESTHESIA CARE			
Lowest Saturation in PACU (%)	96.8 (96.1-97.4)	93.3 (91.9-94.7)	< 0.0001
Morphine dose (mg)	11 (10-12)	11 (9-12)	NS
Pain score (NRS)	3.0 (2.4-3.7)	3.2 (2.4-3.0)	NS
Sedation score	1.4 (1.2-1.6)	1.4 (1.2-1.6)	NS

Values are mean (95% confidence interval) unless otherwise stated; *n= 48; ** n = 35; # n = 20

the neostigmine group received a mean of 2.5 (2.4-2.6) mg of the reversal agent. Eight patients (16%) required one additional neostigmine dose of 1 mg; three others (6%) received a dose of sugammadex after their initial neostigmine dose. Patients in the sugammadex group received 170 (156-184) mg; none received an additional dose of sugammadex or neostigmine.

Extubation

In 2 patients, TOF values could not be measured following sugammadex reversal due to patient movement and rapid extubation. Thirty-five patients (70%) treated with neostigmine had a TOF ratio < 0.9 upon extubation against 2 (4%) patients treated with sugammadex (Fig. 2). The TOF ratio at extubation was 0.74 (0.71-0.83; *n* = 50) in the neostigmine group and 0.99 (0.98-1.00; *n* = 48) in sugammadex group (p < 0.0001). In the 35 patients reversed with neostigmine that had a TOF ratio < 0.9 their average ratio was 0.60 (0.55-0.67); the two patients reversed with sugammadex that had a ratio < 0.9 had ratios of 0.88 and 0.82. In those subjects that reached a TOF ratio of 0.9 or greater, the time from reversal to a TOF ratio > 0.9 was significantly shorter in the sugammadex group, 2.5 (2.1-2.8; *n* = 48) minutes, compared to the neostigmine group, 10.0 (7.6-12.3; *n* = 15) minutes (p < 0.001). The time from reversal to extubation was shorter for sugammadex, 8.0 (6.9-9.1; *n* = 50) minutes, compared to neostigmine, 11.7 (9.9-13.4; *n* = 50) minutes (p = 0.01).

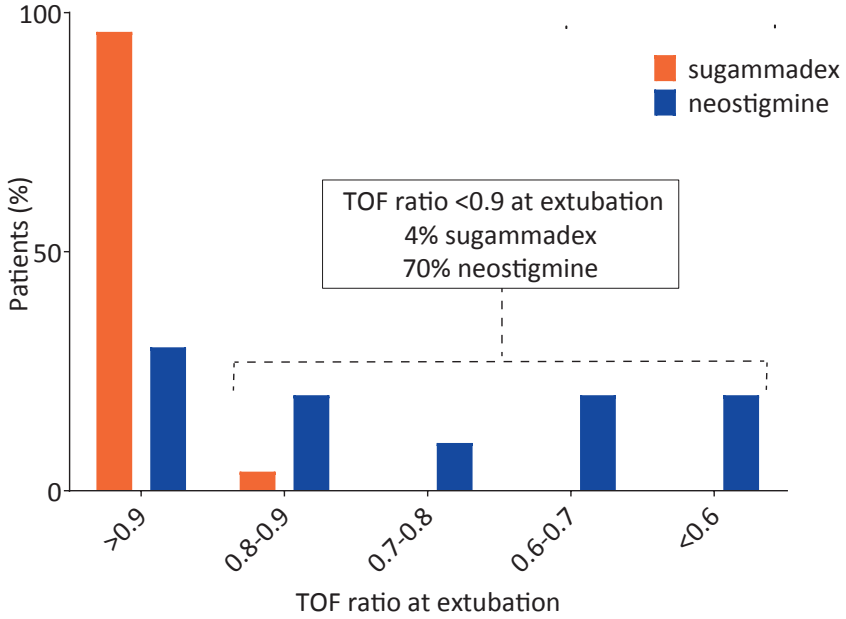

Figure 2. Train-of-four ratio at extubation following reversal with sugammadex or neostigmine .

Post-anaesthesia care

The main outcome, lowest SpO_2 in the 45 minutes following reversal, was 3.5% lower in patients treated with neostigmine compared to patients treated with sugammadex: 93.3 (91.9-94.7)% against 96.8 (96.1-97.4)% ($p < 0.0001$). Figures 3A and 3B show the distribution of the lowest SpO_2 per group and highlight the difference in SpO_2 distribution for the two treatments. Figure 4 shows the individual lowest saturation values in the PACU in relation to TOF ratio at extubation. In the sugammadex group, 90% of the patients were in the upper right quadrant of the graph (TOF ratio of > 0.9 combined with lowest saturation ≥ 94%), while for neostigmine treated patients just 16% of patients were in the upper-right quadrant.

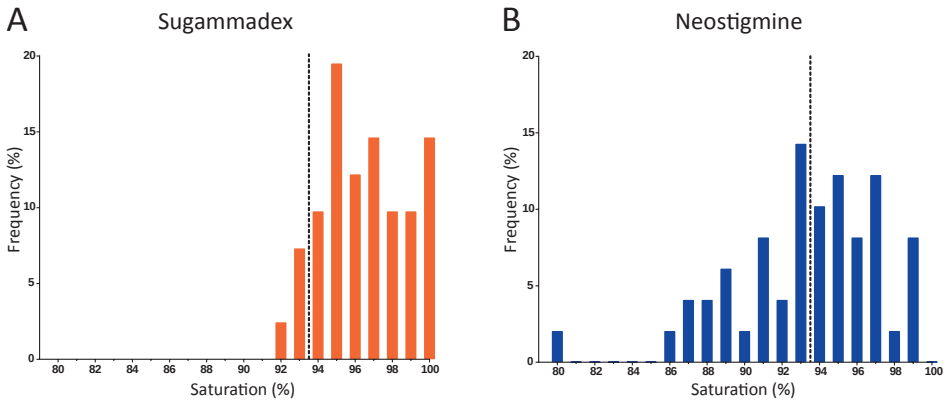

Figure 3. Frequency distribution of the lowest oxygen saturation values measured in the PACU following reversal with sugammadex (**A**) and neostigmine (**B**).

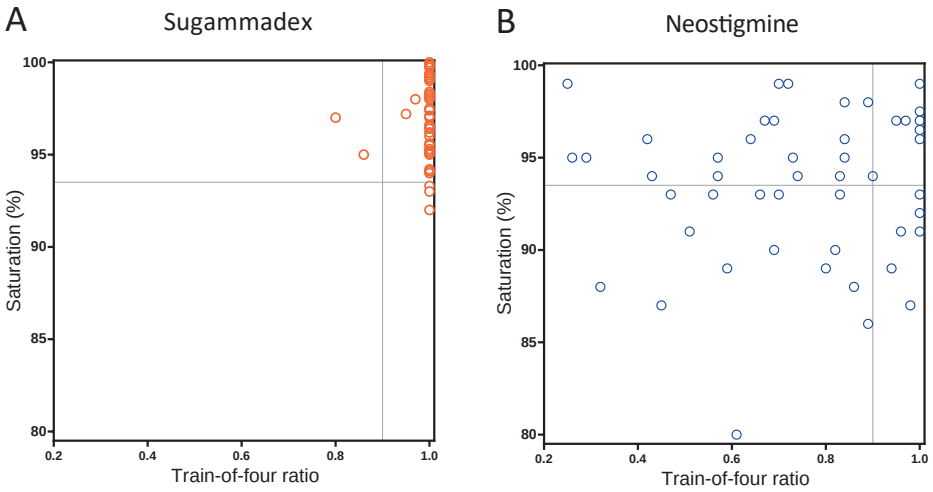

Figure 4. Lowest saturation values measured in the PACU *versus* train-of-four ratio's at extubation for sugammadex (**A**) and neostigmine (**B**).

In the PACU, no significant differences in sedation and pain scores were observed. No adverse events occurred.

DISCUSSION

This double-blind, randomized, controlled trial compared the effect of reversal of a moderate neuromuscular block (NMB) with sugammadex and neostigmine on oxygen saturation levels in postoperative patients. The main results are that NMB reversal with sugammadex resulted in less patients with postoperative hypoxaemia (defined by SpO_2 levels < 94%) compared to neostigmine in patients not receiving supplemental oxygen.

Low SpO_2 levels are not uncommon in the PACU and are related to multiple factors, including residual effects of opioids and anaesthetics, type of surgery, patient characteristics, underlying disease, the use of recruitment manoeuvres and the inhaled oxygen concentration during anaesthesia and recovery. Since these factors were either evenly distributed between the two treatment groups or tightly controlled according to protocol, we hold the intervention (sugammadex *versus* neostigmine) responsible for the large difference in SpO_2 distribution in the PACU (Figs. 3 and 4). Reversal of the NMB with neostigmine resulted in SpO_2 levels < 94% in 47% of patients compared to 8% of patients after reversal with sugammadex. On average SpO_2 levels (*i.e.* lowest measured SpO_2) were 3.5% lower after neostigmine (neostigmine 93.3% *vs.* sugammadex 96.8%). Our data support the growing body of evidence showing that neostigmine reversal is associated with an increased risk of postoperative respiratory complications such as hypoxaemia,[10, 16-18] and additionally show the beneficial effect of sugammadex with significantly less risk of postoperative hypoxaemia. These are important results and indicate that the choice of reversal agent has a significant effect on postoperative conditions.

This is the first study that measured residual NMB at extubation in conjunction with postoperative SpO_2 levels in patients that did not receive supplemental oxygen. By initially restricting the use of oxygen in the PACU, the masking effect of supplemental oxygen on the measured SpO_2 levels was absent and hypoxaemia related to hypoventilation either from reduced respiratory drive or from persistent muscle weakness (or hypoxaemia from any other cause) was now readily detected.[19, 20] Consequently, we were able to identify a significant difference in postoperative oxygenation between treatments in a relatively healthy population. The difference between treatments was however relatively small (3.5%) since we administered supplemental oxygen by mask or nasal cannula when SpO_2 dropped below 94%. Evidently, this was done to prevent any harm to the patient. It is highly probable, however, that in a more susceptible population the difference in SpO_2 would have been more pronounced. Such populations include

patients with pulmonary disease, muscle weakness, heart failure, elderly patients and ASA class 3-4 patients.

Neostigmine is commonly used upon spontaneous recovery of muscle relaxation (*i.e.* T > 0). In the current study we administered neostigmine 2.5 mg at T1 or T2. The use of neostigmine at T1 or T2 is not unusual, although in most studies the dose is higher than used by us.[21, 22] In the two institutions in which the study was performed, neostigmine is generally used at T > 0 in doses of 1 to 2.5 mg, irrespective of the patient's weight and without proper NMB monitoring. Our current data indicate that this practice is associated with slow recovery, residual curarization at extubation (in 70% of patients) and hypoxic events in the PACU (in 47% of patients). In Figure 4, we associate the TOF ratio at extubation with the lowest SpO_2 in the PACU and observed that 90% of patients had a TOF ratio of > 0.9 combined with saturation levels of 94% or above following sugammadex (upper-right quadrant of Fig. 4), compared to 16% after neostigmine reversal. Possibly higher neostigmine doses might have improved either of these outcomes,[22] however, it is our experience that higher neostigmine doses come at the expense of uncomfortable cholinergic side effects such as nausea, vomiting, abdominal cramps and blurred vision. Given the results of our current study we changed our practice and now routinely reverse a moderate NMB with sugammadex 2 $mg.kg^{-1}$.

We observed a TOF ratio < 0.9 at extubation in 70% of patients after neostigmine and 4% after sugammadex reversal. The incidence of residual block varies widely among studies, with incidences ranging from 2% to 64%, depending on definition, clinical circumstances, agents used and timing of measurements.[4] For example, Murphy et al.[23] and Fortier et al.[24] observed residual curarization in 63% to 88% of patients at extubation following predominantly neostigmine reversal; in agreement with our study, the anaesthetists were blinded to NMB monitoring. Brueckmann et al.[10] performed measurements in the PACU and detected TOF ratio values < 0.9 in 43% and 0% following neostigmine and sugammadex treatment, respectively.[10] We contend that similar values may have occurred in our patients in the PACU. We did not measure TOF ratio's in the PACU to prevent possible respiratory stimulation from TOF measurements. An important observation was made by Kotake et al. who studied sugammadex reversal and detected an incidence of residual NMB of 4% in a setting where no monitoring was used.[14] These findings are in agreement with our results and emphasize the importance of neuromuscular monitoring.

In our current study extubation was performed under "blinded" conditions (*i.e.* the anaesthetist was unaware of the number of twitches and TOF ratio). This practice is very similar to standard of practice in many institutions. The use of monitoring at extubation might have reduced the incidence of residual curarization in both groups and possibly might have improved oxygenation in the PACU. The effect of reversal with neostigmine

versus sugammadex on SpO_2 levels in the PACU in a monitored setting should be assessed in future studies.

In conclusion, we show that the selection of reversal agent controls not only the speed and intensity of recovery of the neuromuscular block, but additionally has a significant effect on postoperative respiratory conditions. Both the TOF ratio at extubation and the oxygen saturation levels in the PACU differ significantly in patients reversed with neostigmine and sugammadex with favorable conditions for both end-points in 90% of patients after sugammadex *versus* just 16% of patients after neostigmine reversal.

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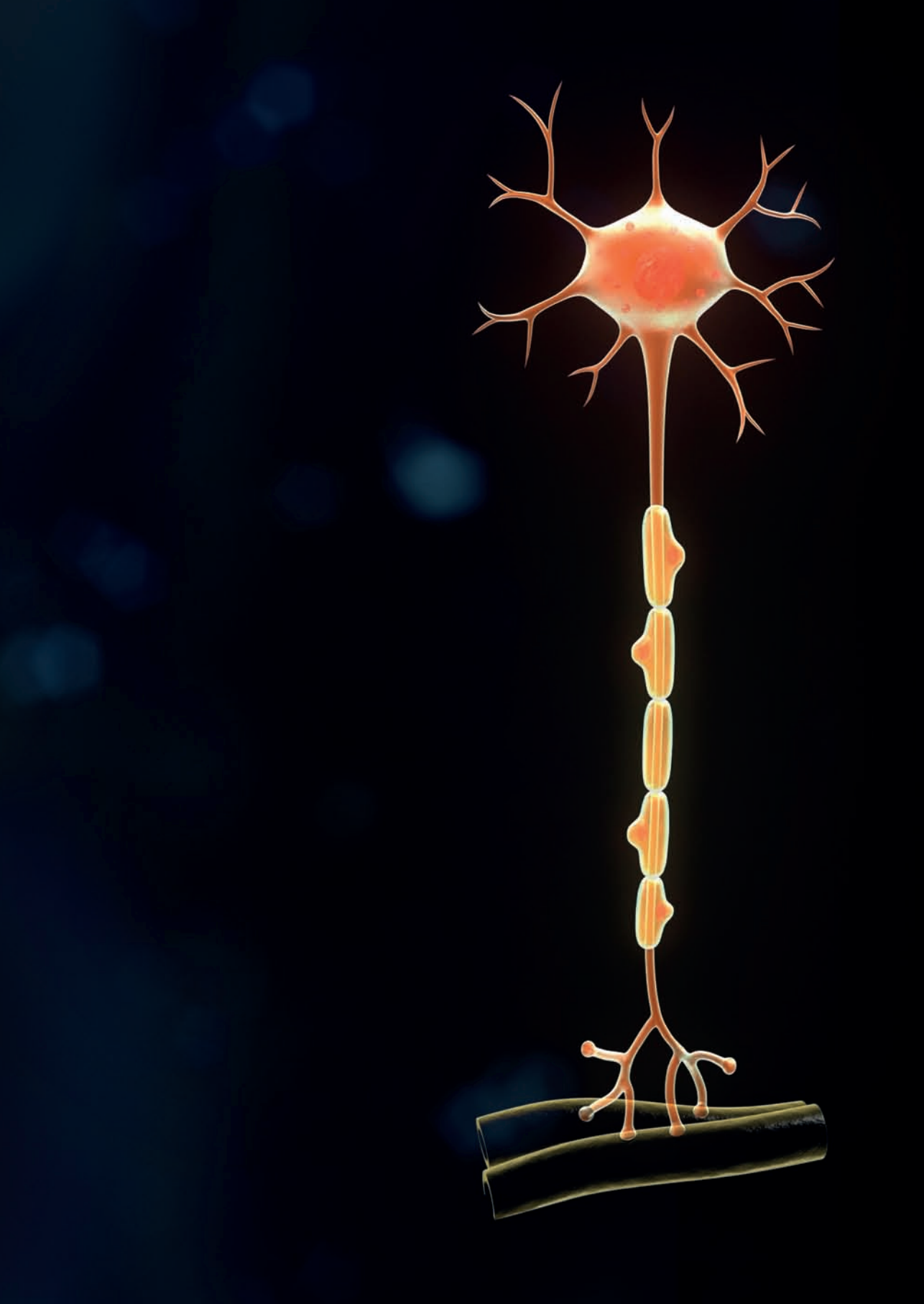
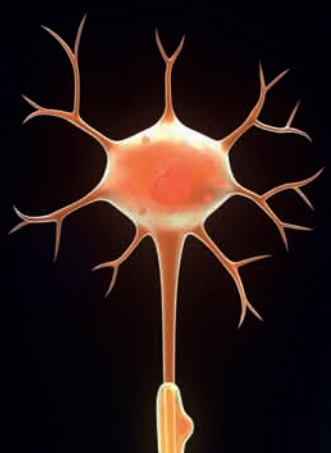


Section 3

Surgical rating scales



Chapter 6

The use of surgical rating scales for the evaluation of surgical working conditions during laparoscopic surgery. A scoping review

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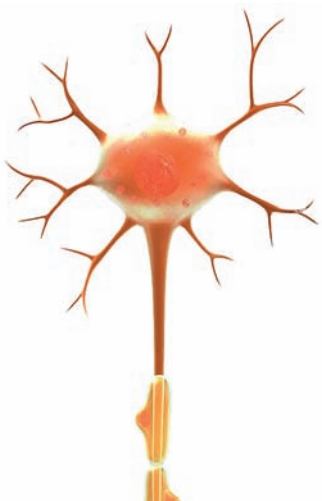

ABSTRACT

Introduction

Surgical ratings scales (SRS) enable the surgeon to uniformly quantify surgical working conditions. They are increasingly used as a primary outcome in studies evaluating the effect of anaesthesia or surgery related interventions on the quality of the surgical work field. SRS are especially used in laparoscopic surgery due to a renewed interest in deep neuromuscular block. There are however no guidelines regarding the uniform use of SRS and the uniform reporting of results.

Methods

A systematic search was conducted in the databases of PubMed, Web of Science and Embase for studies that reported the use of an SRS to evaluate surgical conditions in laparoscopic surgery. Only original human research in English language with full text availability through the Leiden university library were considered for this review. The full texts of eligible abstracts were independently reviewed by the first and second author. The quality of SRSs and methodology of rating were systematically reviewed.

Results

The search yielded 2830 reports, of which 17 were identified using a surgical rating scale in laparoscopic surgery. Ten of these reports used a unique SRS, these were systematically appraised for their quality. The overall quality of the SRSs was low: the majority of the scales were poorly described and lacked assessment of inter- and intra rater reliability. In addition, considerable differences exists in the methodology of rating and the reporting of results.

Conclusion

There is substantial inconsistency in SRS quality, methodology and results reporting. The uniform use of high quality surgical rating scales is needed to improve the quality and reproducibility of future research.

INTRODUCTION

Surgical rating scales (SRS) are increasingly used to rate the quality of surgical working conditions. A SRS enables the surgeon to translate his or her experienced but subjective impression of the quality of the operative conditions into a standardised rating. The use of SRSs has potential benefits in daily practice and research. First, it offers a uniform platform for the surgeon to negotiate with the anaesthetist whether or not to improve or consolidate surgical working conditions induced by the anaesthetic. Second, surgical rating scales may be used in research to evaluate interventions and new techniques aimed at improving the surgical working / operating conditions. Recent developments in the reversal of neuromuscular block by sugammadex has renewed the interest in the effect of deeper levels of neuromuscular block (NMB) on surgical working conditions in laparoscopic surgery. In these studies, surgical rating scales are often used as primary outcome.[1-8] However, guidelines on the use of surgical rating scales do not exist as yet. This systematic review gives an overview of the use of SRSs in laparoscopic surgery and proposes guidance for future research.

METHODS

The first author conducted a literature search assisted by the librarian of the Leiden University Medical Centre. The following query was used to search the pubmed database: ("rating scale"[tw] OR "rating scales"[tw] OR "Visual Analog Scale"[Mesh] OR Visual Analogue Scale*[tw] OR Visual Analog Scale*[tw] OR "scale"[tw] OR "scales"[tw] OR scaling*[tw] OR rating*[tw] OR scoring*[tw] OR "score"[tw] OR "scores"[tw] OR "scored"[tw] OR "grading"[tw] OR "grade"[tw] OR "graded"[tw]) AND ("surgical conditions"[tw] OR "surgical condition"[tw] OR "operating conditions"[tw] OR "operating condition"[tw] OR "surgical quality"[tw] OR "surgery quality"[tw] OR "surgical field"[tw]). Embase and Web of Science were searched with a similar query containing the following terms: "rating scale" "visual analogue scale"(included Mesh term), "scale", "rating", "scoring", "score", "grading", "surgical conditions", "operating conditions", "surgical quality", "surgical field". The databases were searched on the 20th may 2017, without date range limit. The results were screened on title and abstract by the first author. Relevant full text articles were retrieved and the reference lists of these articles were screened for any additional missed papers (snow ball method). After this first selection, the full texts of the selected articles were reviewed by the first and second author for inclusion in the review.

Study inclusion criteria

Studies included in this systematic review were limited to original randomized controlled trials, English language and full text availability through the Leiden University full text access service. Articles were included if the study: (1) described a method to evaluate a surgical working condition or operating field or (2) applied a surgical rating scale or evaluation of surgical conditions in (3) laparoscopic surgery. Included publications were assessed for the following items: type of rating scale, description of the scale items, number of raters, scoring moments, validation methods, and reporting of results.

Exclusion criteria

Reports that did not score surgical conditions as a whole, but only specific subparts such as "satisfaction of the surgeon", were excluded.

Quality assessment of the rating scales

In general, the quality of a measurement instrument is critically dependent on its construct validity and reliability.[9, 10] Construct validity refers to the quality of the data based on the scores from a measurement instrument and whether it adequately represents the underlying construct (*i.e.* the surgical working conditions).[9] For construct validity the following domains are considered important: scale content, internal structure, response process, correlation to other variables and clinical consequences.[9-11] These domains reflect both the internal quality of the rating instrument (scale content, internal structure, correlation to other variables) and how the rating instrument is used in practice (scoring methodology; response/rating process). To uniformly assess the quality of the identified SRSs in this review, an appraisal score was constructed. We are not aware of any pre-existing scores for the appraisal of surgical rating scales. In the appraisal score, relevant previous mentioned domains were translated into the following psychometric items: (1) scale length, (2) description of the scale items, (3) test-retest reliability and (4) correlation with other variables (see table 1). The appraisal score only assesses internal SRS quality; the scoring methodology is discussed separately. All SRSs were independently reviewed by the first and second author with the use of the appraisal score. Discrepancies were resolved by consensus. We will briefly explain the separate items of the appraisal score.

Length of the SRS. An SRS length of 5-7 items is considered optimal. Test-retest reliability, internal consistency and discriminating power of scales with 5-7 items are generally superior to short scales (2-4 item points) or very large scales (>10 item points).[12, 13] In our appraisal score, scales with a length of 5-7 items received one point. Scales that contained less than 5 or more than 7 items were not granted any points.

Description of scale items. In a well-described scale, each item in the scale has a grade (*i.e.* moderate or excellent) *plus* a detailed description of the specific aspects of the

surgical working field for that grade. An example of an SRS with an adequate scale item description is the Leiden- surgical rating scale. This scale is presented in table 2.[14] Scales that have an adequate description of the scale items were granted one point in the appraisal score. Inadequate, or absence of detailed description of the scale items, resulted in 0 points in the appraisal score.

Table 1. Appraisal score

Length of the scale	Points
< 5 items	0
5-7 items	1
>7 items	0
Scale Item description	
Inadequate	0
Adequate	1
Reliability assessment	
None	0
Inter rater reliability	1
Intra rater reliability	1
Both	2
Correlation with other variables	
No	0
Yes	1

Table 2. The Leiden- Surgical Rating Scale (L-SRS)

1	**Extremely poor conditions:** The surgeon is unable to work due to coughing or due to the inability to obtain a visible laparoscopic field because of inadequate muscle relaxation. Additional muscle relaxants must be given.
2	**Poor conditions:** There is a visible laparoscopic field but the surgeon is severely hampered by inadequate muscle relaxation with continuous muscle contractions and/or movements with the hazard of tissue damage. Additional muscle relaxants must be given.
3	**Acceptable conditions:** There is a wide visible laparoscopic field but muscle contractions and/or movements occur regularly causing some interference with the surgeon's work. There is the need for additional muscle relaxants to prevent deterioration.
4	**Good conditions:** There is a wide laparoscopic working field with sporadic muscle contractions and/or movements. There is no immediate need for additional muscle relaxants unless there is the fear for deterioration.
5	**Optimal conditions:** There is a wide visible laparoscopic working field without any movement or contractions. There is no need for additional muscle relaxants.

Test-retest reliability. Test-retest reliability assesses the reproducibility of ratings by one rater (intra-observer reliability) or between two (or more) raters (inter-observer reliability). At best, an SRS was assessed for both. The appraisal score grants 1 point for

intra-observer and one point for and inter-observer reliability verification. Hence, the maximum score in the appraisal score for this domain was 2 points.

Correlation with other variables. According to the domains of construct validity, a measurement instrument should be compared to another measurement instrument or variable that reflects the same underlying construct. In the appraisal score, if an SRS was compared with another scoring instrument or variable, it received one point. Absence of such a comparison would result in 0 points.

The appraisal scoring system is given in Table 1. The maximum score that an SRS could receive was 5 points (excellent quality) and the lowest score was 0 points (very poor quality).

RESULTS

Included articles

The initial search yielded 2,830 publications. After removing duplicates, non-English language and non-human research, we screened 873 abstracts of which 763 non-relevant publications were discarded. The full texts of 110 reports were reviewed. The snowball method yielded 14 additional relevant studies. After full text review of 124 selected articles, 15 reports were excluded because (1) the SRS was not used for assessment of surgical conditions, or (2) surgical conditions were not scored. Another 92 reports were excluded because of non-laparoscopic surgery (3). In total, 17 publications were included in this review. Figure 1 outlines the selection process. The unique SRSs were systematically judged for their quality with the use of the appraisal score. Overall, the quality of the majority of the SRSs was low. (see table 3)

Table 3. Quality score per surgical rating scale.

Author	Year	Specialty	Scale length	Item description	Reliability assessment	Correlation with other variables	Total
Martini[14]	2013	Urology	1	1	2	1	5
Caldwell[25]	1985	Gynaecology	0	1	0	0	1
Madsen[17]	2015	Gynaecology	1	0	0	1	2
Williams[23]	2003	Gynaecology	1	0	0	1	2
Dubois[2]	2014	Gynaecology	0	0	0	0	0
Blobner[3]	2014	General Surgery	0	0	0	1	1
Koo[19]	2016	General Surgery	1	0	0	1	2
Kim[6]	2016	General Surgery	1	0	0	0	1
Rosenberg[22]	2017	General Surgery	0	0	0	1	1
Taylor[16]	1992	General Surgery	1	0	0	1	2

0 = very poor quality; 5= excellent quality

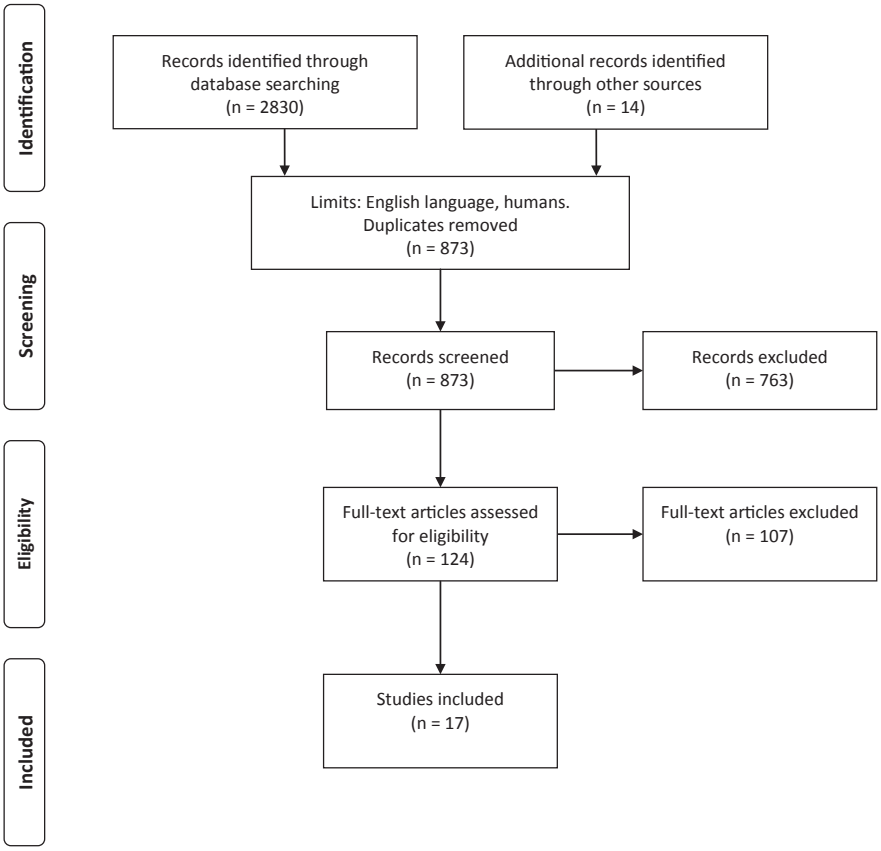

Figure 1. Study flow chart.

Surgical rating scales used in laparoscopic surgery

Seventeen studies used a SRS for evaluation of surgical conditions in laparoscopic surgery. [1-7, 15-24] The length of the individual scales varied between 3-, 4-, 5- ,6-, 11- and 100 points. Most surgical rating scales were 4- or 5-point scales (see table 4).

Four point scales are commonly used for evaluation of surgical conditions, predominantly laparoscopic gynaecologic surgery.[2, 15, 17, 23] However, in the quality appraisal, these 4-point scales were rated as poor quality scales as the length of 4-point scales was considered suboptimal (<5 items) and all lacked test-retest reliability assessment.

Taylor et al. used a 5-point SRS to assess surgical conditions during cholecystectomy in relation to bowel distension and the use of nitrous oxide.[16] This scale also lacked test-retest reliability assessment. Martini et al. developed their 5-point Leiden - surgical rating scale (L-SRS) for use in laparoscopic retroperitoneal urologic surgery (see table 2).[14] The scale was later successfully used in bariatric surgery.[4] The scale items are well described and incorporate visibility of critical structures, working space, and muscle contractions

Table 4. The use of surgical rating scales in laparoscopic surgery.

Author	Year	Specialty	Comparison	Scale	Scale description	Raters (n)	Interval	Outcome
Martini[14]	2014	Urology	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	1	15 minutes	Mean SRS, % subopt./opt. cond
Yoo[18]	2015	Urology	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	1	end of surgery	Mean SRS
Boon[7]	2016	Urology	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	1	15 minutes	Mean SRS, % subopt./opt. cond
Torensma[4]	2016	Bariatric surgery	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	3	10 minutes	Mean SRS, % subopt./opt. cond
Baete[5]	2017	Bariatric surgery	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	1	end of surgery	Mean SRS
Caldwell[24]	1985	Gynaecology	NMB	3 point	1 (good) – 3 (inadequate)	unknown	unknown	SRS distrubution
Williams[23]	2003	Gynaecology	Moderate vs. no NMB	4 point	1 (poor) – 4 (excellent)	unknown	unknown	SRS distrubution
Dubois[2]	2014	Gynaecology	Deep vs. moderate NMB	4 point	1 (optimal) – 4 (unacceptable)	1	10 minutes	Mean SRS, SRS distribution
Madsen[17]	2015	Gynaecology	Deep vs. no NMB	4 point	1 (optimal) – 4 (bad)	2	fascia closure	Mean SRS, Intra-abdominal space (cm)
Taylor[16]	1992	General Surgery	Nitrous oxide	5 point	1 (extremely poor) – 5 (very good)	1	15 minutes	SRS, bowel distention
Staer Rye[15]	2014	General Surgery	Deep vs. moderate NMB	4 point	1 (optimal) – 4 (unacceptable)	2	multiple	% subopt./opt.cond, completion IAP 8 mmHg
Blobner[3]	2014	General Surgery	Deep vs. no NMB	101 point	0 (not acceptable) – 100 (excellent)	unknown	end of surgery	% subopt./opt. cond
Koo[19]	2016	General Surgery	Deep vs. moderate NMB	4 point	1 (excellent) – 4 (poor)	unknown	end of surgery	% subopt./opt. cond., increase IAP (n)
Kim[26]	2016	General Surgery	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	unknown	end of surgery	SRS, titrated IAP
Rosenberg[22]	2017	General Surgery	Deep vs. moderate NMB	11 point	0 (poor) – 10 (excellent)	unknown	end of surgery	Mean SRS, SRS distribution
Ozdemir[20]	2017	General Surgery	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	unknown	15 minutes	Mean SRS, SRS distribution
Ozdemir[21]	2017	General Surgery	Deep vs. moderate NMB	5 point*	1 (extremely poor) – 5 (optimal)	unknown	15 minutes	Mean SRS, SRS distribution

SRS: surgical rating scale; % subopt./opt. Cond.: percentage of suboptimal/optimal conditions; NMB: neuromuscular block; IAP: intra-abdominal pressure; * Leiden - surgical rating scale

as determinants of the surgical working field.[14] The 5-point L-SRS was assessed for inter-rater reliability by the original research group.[4, 14] In addition, Nervil et al. assessed both inter and intra-rater reliability of a modified version of the 5-point L-SRS and an 11-point SRS. [13] Both the 5-point and 11-point SRS showed excellent intra-rater reliability and fair inter-rater reliability. Due to the lower inter rater variability, the 5-point scale was considered superior. [13]

The L-SRS scale is used by other research groups, including the use in laparoscopic donor nephrectomy. [5, 18, 20, 21]. This endorses the utility of this scale. In laparoscopic donor nephrectomy, the L-SRS is used to titrate insufflation pressures to the lowest possible, whilst maintaining good operating conditions.

Methodology and results reporting

Most studies reported a mean SRS score and a distribution of the scores (see table 4). Some only reported the percentages of unacceptable surgical conditions, which was generally the frequency of scores on the lower half of the SRS.[3, 15, 19] In addition, the number and moments of scoring differed considerably, with some studies scoring every 10- or 15-minutes,[2, 4, 7, 14-16] while others scored one overall score at the end of surgery.[3, 5, 8, 17-19, 22] Some reports do no mention a scoring interval at all.[23, 24] In addition to the SRS, some have assessed other outcomes as well such as intra-abdominal space and the effect on insufflation pressures (see table 4).[6, 15, 17, 19]

Table 5. Guideline for future research

Surgical rating scale	
I.	Researches should only use pre-existing, validated scales available in their field of research, *or (if unavailable)*
II.	Validate a pre-existing, high quality, non-validated scale in the field of interest (*ie.* assessment of inter- and intra-observer reliability), *or*
III.	Develop and validate a new surgical rating scale with respect to the domains in the appraisal score
Use of the rating scale	
I.	Rating at multiple predefined moments during a procedure (instead of one rating at the end)
II.	Report number and experience of scoring surgeons - raters
Reporting of results	
I.	Mean and/or median overall score
II.	Mean/median score at every rating moment during a procedure
III.	Distribution of the scores
IV.	Clearly define (un)acceptable conditions (if applicable)
V.	Compare SRS with other important variables.

DISCUSSION

Surgical rating scales (SRS) are increasingly used in clinical research. These scales are used to translate the subjective perception of the surgical field by the surgeon into a more objective and reproducible integer on a fixed scale. Surgical rating scales are a useful tool to investigate the effect of surgery- or anaesthesia-related interventions on surgical working conditions. To get an indication on the variety of SRSs in use and their quality, we retrieved 17 relevant studies from the literature and identified 10 unique scales that are used in laparoscopic surgery. Since the introduction of sugammadex (a novel selective neuromuscular reversal agent), there has been a renewed interest in the application of deep neuromuscular block (NMB) in these types of surgery. This type of research relies heavily on the use of a SRS.

Based on our results, it is evident that the large number of rating scales in literature comes with significant heterogeneity. There is ample difference in the quality of the rating scales and second, there is no uniformity in the method of rating and reporting of the results. In general, the quality of the rating scales was low. Most encountered problems were: absence of test- retest reliability assessment, absence of a comparison with a different scoring instrument and poor definition of the scale items. Only the Leiden - surgical rating scale received the highest quality score. (see table 3)

The methods of rating (rating methodology) and the reporting of the results of each study were also reviewed and revealed significant differences (see table 4). For example, the moment of rating (at fixed time points vs. at the end of surgery) and the number or raters (one vs. multiple) differed per study or was not detailed in the methods section. This methodologic heterogeneity may impact results considerably. For instance, a surgical rating that is obtained at fixed time points during a procedure, *i.e.* every 15 minutes, may give a different result compared to one "overall rating" rating at the end of a procedure.[4, 5] Furthermore, the reporting of the SRS results varied considerably, with some reporting means or medians of the SRS, and others only the distribution of the SRS.

In this review, we aimed to uniformly appraise the quality of the identified SRS. To be useful instruments, SRSs should display good psychometric properties, such as reliability and validity, and also be easy to use.[9-11] To this end, we created an appraisal score that was used to review these aspects of each SRS (see table 1). The appraisal score allowed us to uniformly assess the quality of each SRS. Note however, that the appraisal score is not evidence for validity of the results obtained with the SRS. Both validity and reliability are not inherent properties of the rating instrument, but they rather reflect the interaction of the scale with the measure being tested. We are aware that our appraisal score may possess shortcomings and lacks formal validation. Therefore, others may judge the quality of the SRS differently. Finally, it is important to realise that only English

language literature was searched and that useful, high quality rating scales may exist in non-English literature. In addition, high quality SRSs may exist in non-laparoscopic surgery, however this is beyond the scope of this review.

The use of poor quality SRSs combined with poor rating methodology for research is undesirable, and reduces the validity of the results. While we do not intent to recommend a preferred SRS for specific procedures, we do propose some guidance in the use of SRSs. If a good quality SRS in the field of interest is available, researchers should strongly consider using that scale. The use of existing SRSs increases the comparability of research. If validated SRSs are unavailable for specific surgical procedures, investigators can either choose to validate a pre-existing non-validated scale, or develop and validate a new scale. Any new developed scale should be of high quality. The items mentioned in the appraisal score can act as a guideline for this. The validation procedure should assess both inter- and intra-rater reliability of a scale. In addition, the scale should be compared with other variables to increase its validity. See table 5 for an overview of recommendations.

Finally, ratings should be obtained at predefined moments and researches should report the following in their methods and results: number of individuals involved in the scoring and their surgical experience, time-stamp of scoring, mean and/or median SRS values, mean/median scorings at each time-stamp, and the distribution of the scorings. Uniformity of these aspects, will improve comparability and reproducibility of this type of research.

In conclusion, this review found that multiple surgical rating scales have been used in laparoscopic surgery to assess the quality of the surgical field. The majority of the scales are of low quality and the method of rating and reporting of results differed considerably. The uniform use of high quality surgical rating scales is needed to improve the quality and reproducibility of future research.

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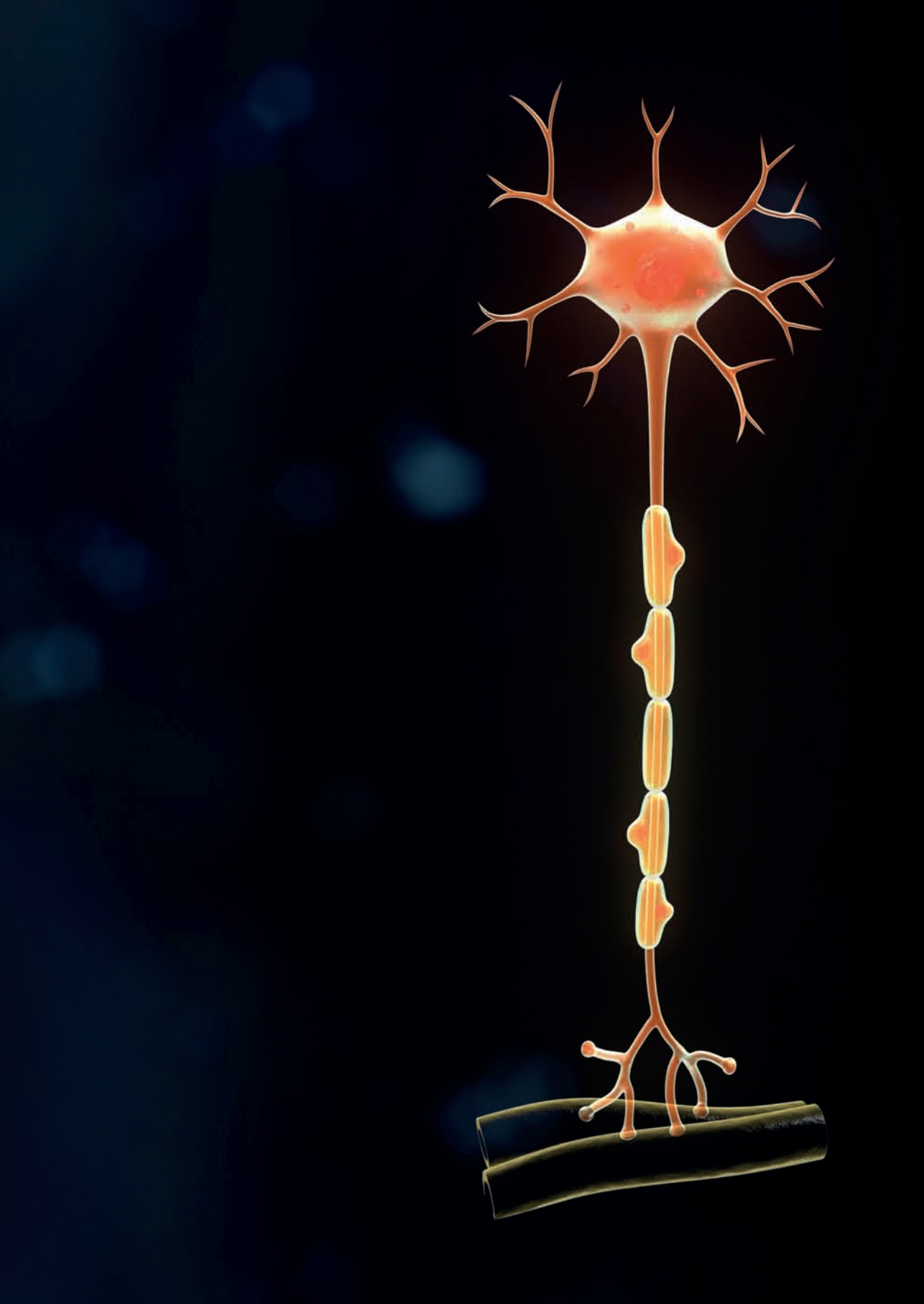
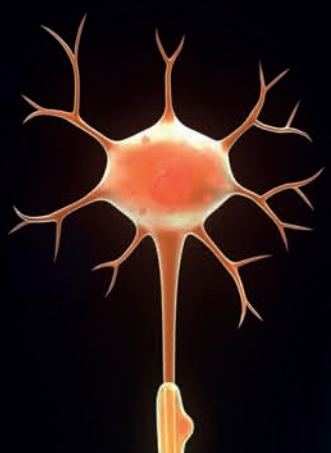


Section 4

Perspectives



Chapter 7

Recent advances in neuromuscular blocking during anaesthesia

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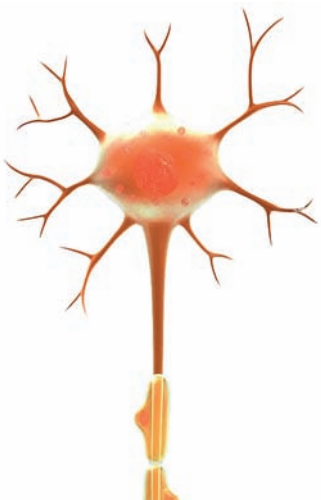
F1000Research 2018, 7:167



ABSTRACT

Muscle relaxation is a routine part of anaesthesia and has important advantages. However, the lingering effects of muscle relaxants in the postoperative period have historically been associated with postoperative adverse events. Neuromuscular reversal, together with neuromuscular monitoring, is a recognized strategy to reduce the rate of postoperative residual relaxation but has only marginally improved outcome in the past decades.

Sugammadex, a novel reversal agent with unique encapsulating properties, has changed the landscape of neuromuscular reversal and opened new opportunities to improve patient care. By quickly and completely reversing any depth of neuromuscular block it may reduce the rate of residual relaxation and improve respiratory recovery. In addition, sugammadex has made the use of deep neuromuscular block possible during surgery. Deep neuromuscular block may improve surgical working conditions and allow for a reduction in insufflation pressures during selected laparoscopic procedures. Whether and how this may impact outcomes is not well established.

INTRODUCTION

Muscle relaxants or neuromuscular blocking agents (NMBAs), introduced in 1942 by Griffith and Johnson, revolutionized the practice of anaesthesiology.[1] NMBAs block neuromuscular transmission at the neuromuscular junction by binding to the postsynaptic nicotinic acetylcholine receptor. This renders these receptors unavailable for acetylcholine-mediated neuromuscular signal transmission (see Fig. 1). In practice, NMBAs enable anaesthetists to temporarily paralyze patients during anaesthesia. The introduction of NMBAs in anaesthesia meant that optimal surgical conditions (*i.e.* by ensuring an immobile patient) could be achieved with lower doses of volatile or intravenous anaesthetics, improving hemodynamic stability. Consequently, induction of muscle relaxation became an established part of the classic anaesthesia triad, alongside unconsciousness (hypnosis) and pain relief.[2] However, like most medication, NMBAs are not devoid of disadvantages. Lingering effects of NMBAs in the postoperative period, also known as *postoperative residual curarization* (PORC), may cause life-threatening respiratory complications in the first hours after surgery.[3] In 1954, Beecher et al. were the first to note a six fold increase in anaesthesia-related mortality when NMBAs were used.[4] Despite the development of short-acting agents and neuromuscular monitoring techniques, NMBAs continue to be associated with severe adverse events after anaesthesia, even today.[5, 6]

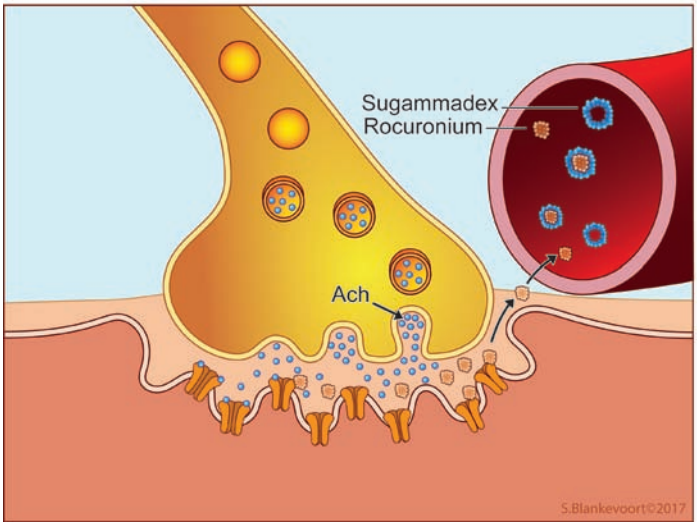


Figure 1. This figure shows the connection between the end of a motor neuron and a muscle fiber membrane (also called neuromuscular junction). Signal transmission occurs by the release of acetylcholine (Ach, blue dots) from the neuron. Ach is able to open an ion-channel on the post synaptic muscle membrane, causing post synaptic membrane depolarization. Rocuronium is able to block signal transmission by inhibiting Ach to bind to the post synaptic ion-channel. The effect of rocuronium can be terminated by sugammadex, which encapsulates rocuronium in the blood plasma.

Reversal of neuromuscular block

Currently two concepts of neuromuscular reversal exist. A moderate neuromuscular block (moderate NMB; see below) is traditionally reversed with an acetylcholinesterase inhibitor such as neostigmine. These drugs increase the amount of acetylcholine in the neuromuscular junction by inhibiting the enzyme acetylcholinesterase. The increased levels of acetylcholine compete with the NMBA molecules for the postsynaptic nicotine receptors (*i.e.* competitive antagonism) and tip the balance towards enhanced signal transmission. Encapsulation of NMBA molecules by sugammadex represents a novel reversal strategy. Sugammadex is a modified y-cyclodextrin, which is able to selectively bind free plasma NMBA molecules (Fig. 1).[7] Encapsulation by sugammadex immediately inactivates these NMBA molecules, rendering them permanently unavailable for redistribution to the neuromuscular junction.[8] Sugammadex produces rapid and safe reversal of the commonly used non-depolarizing NMBAs rocuronium and vecuronium.[9, 10] It encapsulates and consequently inactivates these NMBA molecules on a one-to-one basis and is able to reverse both moderate and deep or even intense levels of NMB.[11-13] Importantly, sugammadex reversal is much faster and more intense than reversal with acetylcholinesterase inhibitors.[14] For example, the average time for reversal of a moderately deep neuromuscular block is 2.7 min after administration of sugammadex 2 mg kg^{-1}, compared to 17.9 min after administration of neostigmine 50 $\mu g.kg^{-1}$.[15] In addition, sugammadex is well tolerated by patients and is devoid of cholinergic side effects.[14, 16] Sugammadex has been available in Europe since 2008 and has been approved by the FDA for use in the USA in 2015.

Although the introduction of sugammadex represents a great improvement in reversal of the neuromuscular block, there are some important aspects that deserve consideration. First, only NMB-induced by rocuronium, vecuronium and pancuronium can be reversed with sugammadex, leaving acetylcholinesterase inhibitors the only choice for reversal of the other NMBAs, such as cisatracurium. In the future, new broad spectrum encapsulating agents may become available for all NMBAs.[17] Second, the cost of sugammadex is significant (in the Netherlands one ampoule of 200 mg costs 78 euro). It is unclear whether sugammadex reversal leads to an improved postoperative outcome that justifies its cost. The same holds true for another emerging area of interest made possible by sugammadex, which is the application of a deep neuromuscular block during anaesthesia. With the introduction of sugammadex the use of a deep NMB during surgery is now possible without having to fear for prolonged recovery times. Deep NMB may improve surgical working conditions for some procedures and allows for a reduction in insufflation pressures during laparoscopic surgeries.[18-21] However, the impact of deep NMB on patient outcome is still unclear.

Monitoring depth of neuromuscular block

Neuromuscular monitoring during anaesthesia is most commonly performed using the *train- of-four* (TOF) method.[22] Train-of-four peripheral nerve monitors (such as the TOF-Watch™ monitor) are usually applied at the distal fore arm to stimulate the ulnar nerve. Here, four consecutive supramaximal electrical stimuli (a *train-of-four*) will evoke contractions (*twitches*) at the m. adductor pollicis of the thumb. Under normal conditions, the amplitude of all 4 motor responses will be equal. With an increasing degree of NMB (induced by non-depolarizing NMBAs), the amplitude of the latter twitches decreases, relative to the first twitches; a phenomenon called *fade*. Eventually, as NMB increases, all twitches will become absent (see figure 2). Thus, the number of detectable thumb twitches and the degree of fading corresponds with the intensity of the NMB. The degree of fading can be further expressed as a ratio, by dividing the motor response of the fourth twitch (T4) to the first twitch (T1), *i.e.* the T4/T1 ratio or the so-called *TOF ratio*. Available evidence indicates that the NMB has to be recovered to a TOF ratio of 0.9 or greater to allow for safe extubation of the patient.[23-27]

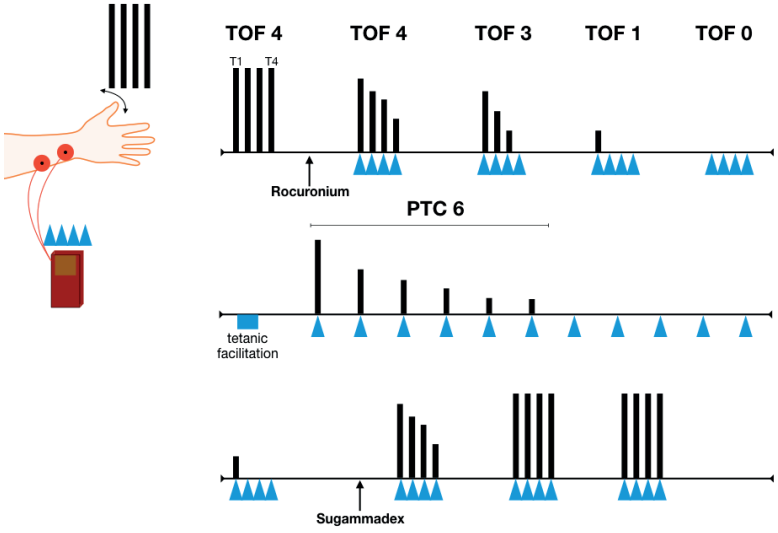


Figure 2. Neuromuscular monitoring. The figure shows, from top to bottom, the typical course neuromuscular block after a single administration of muscle relaxant (*i.e.* rocuronium). The above line shows the disappearance of train-of-four twitches after rocuronium administration. The middle part shows the decline in post-tetanic-count twitches as neuromuscular block deepens in the first minutes. The bottom line shows the return of train-of-four twitches after administration of the reversal agent sugammadex. TOF: train-of-four; PTC: post-tetanic-count. Blue arrows resemble electrical stimuli

When high doses of NMBAs are given, train-of-four measurement at the ulnar nerve will show zero thumb twitches (TOF = 0). To measure the degree of NMB in this instance, a tetanic stimulus of 50Hz for 5 seconds is applied to the ulnar nerve. The tetanic stimulus

causes a large amount of acetylcholine to be released in the neuromuscular junction. This *tetanic facilitation* is subsequently followed by 10 - 15 single electrical stimuli delivered at 1-s intervals. The number of measured thumb twitches make up the *post-tetanic-count* (PTC).[28] For example, when 6 thumb twitches are observed following the tetanic facilitation, the PTC equals 6 (see figure 2). With TOF and PTC measurements, the depth of the NMB can be classified as follows: (1) moderate NMB: TOF count 1-3 out of 4 twitches; (2) deep NMB: TOF count 0 twitches and PTC > 0 twitches; and (3) intense NMB: TOF count 0 twitches and PTC = 0 twitches.

Postoperative residual curarization

Full recovery of NMB at the end of anaesthesia is essential for the return of adequate respiration and upper airway muscle function.[3, 29, 30] By definition, PORC is present when some level of NMB (TOF ratio < 0.9) persists after extubation. This can readily occur as most NMBAs have much longer recovery times than the often-short acting opioids and hypnotics used during general anaesthesia. Incidences of PORC range between 20 and 60% of patients in the post-anaesthesia care unit (PACU).[30-32] Residual curarization negatively affects pulmonary and upper airway muscle function. It promotes upper airway collapse and ventilatory compromise. This is relevant, as even a small degree of residual curarization (*e.g.* TOF ratio between 0.6-0.9) is associated with increased upper airway collapsibility and dysfunction of pharyngeal and upper oesophageal sphincter muscles.[23, 27] Additionally, NMBAs directly block the hypoxic ventilatory response due to blocking of nicotinic acetylcholine receptors at the carotid bodies.[24] Inhibition of the hypoxic ventilatory response renders patients at increased risk for hypoxia. Due to these effects, PORC is highly associated with postoperative respiratory complications.[3, 29] Use of a neuromuscular monitor and adequate reversal of NMB are essential strategies that will reduce the incidence of PORC.

Prevention of postoperative residual curarization

With the use of neostigmine and other acetylcholinesterase inhibitors, a variable degree of residual NMB often persists.[33] It is therefore not surprising that the effect of NMB-reversal with neostigmine on postoperative respiratory complications and outcome is at best ambiguous. Increasing evidence shows that NMB-reversal with neostigmine (without the guidance of a TOF watch) does not improve postoperative respiratory safety[34] and may even be associated with increased rates of atelectasis,[35] hypoxemia[36] and consequently reintubation[37]. There are several explanations for these findings. Timely administration and exclusive reversal of a moderate NMB are important for successful reversal. Evidently, this requires adequate neuromuscular monitoring. In addition, time to full reversal following neostigmine treatment displays wide between-patient variations and is unpredictable. Sugammadex has the potential to do better in both respects,

as it allows for fast, complete and predictable reversal of both moderate and deep NMB.[15, 16, 38, 39] Emerging evidence shows that NMB-reversal with sugammadex reduces the rate of postoperative residual curarization compared to reversal with neostigmine (see table 1).[33, 36, 40] A recent investigation reported a 0% PORC rate in patients reversed with sugammadex, *versus* 46% in those who received neostigmine.[40] These results are promising, however, in an unmonitored setting PORC after sugammadex reversal still occurs in 4% of patients.[33, 36, 41] This highlights the need for adequate neuromuscular monitoring in any setting where NMBAs are used, regardless the type of reversal agent.

Table 1. Studies comparing sugammadex and neostigmine on incidence of postoperative residual curarization and pulmonary outcome.

Author	Year	Design	Comparison	Monitoring	PORC	Pulmonary outcome
Kotake[41]	2013	Prospective observational	Sugammadex vs. neostigmine	No	4.3% vs. 23.9%**	UA
Ledowski[44]	2014	Retrospective cohort	Sugammadex vs. neostigmine	Available	UA	Reduced pulmonary outcome score in ASA 3-4 patients**
Brueckmann[40]	2015	RCT	Sugammadex vs. neostigmine	Available	0% vs. 43.3%**	Respiratory disorders 1.4% vs. 6.5% # hypoxemia 1.4% vs. 2.6%#
Boon[36]	2016	RCT	Sugammadex vs. neostigmine	No	4% vs. 70%**	Lowest O_2 saturation 93.3 vs. 96.8%**
Nemes[33]	2017	RCT	Sugammadex vs. neostigmine	No	3.7% vs. 15.4%#	UA

RCT: randomized controlled trial; UA: unavailable; PORC: postoperative residual curarization (TOF ratio <0.9 after extubation). *p<0.05, **p<0.001, #p>0.05

We argue that NMB reversal with sugammadex will decrease the incidence of postoperative pulmonary complications by causing complete recovery of ventilatory muscle strength. This was shown in two studies in healthy volunteers. Sugammadex-reversal led to a higher degree of diaphragmatic and intercostal muscle activation and higher arterial pO_2 values compared to neostigmine reversal.[42, 43] In addition, it is likely that sugammadex will allow for a better return of the hypoxic ventilatory drive, which is attenuated at very low levels of residual neuromuscular block.[24] Especially in vulnerable patients such as the obese and elderly, full recovery of the ventilatory muscles and hypoxic ventilatory reflex are crucial to prevent pulmonary complications. Initial evidence from a retrospective study shows that sugammadex reversal was associated with reduced incidence of

pulmonary complications in elderly ASA 3 and 4 patients compared to reversal with neostigmine.[44] In a small prospective study, sugammadex-reversal was associated with less hypoxemic events in the PACU compared to neostigmine-reversal.[36] The current evidence is far from complete and future prospective studies should determine the exact value of sugammadex in improving post anaesthesia pulmonary outcome.

Deep neuromuscular block: prevention of diaphragmatic contractions and optimized surgical conditions

Most important advantages of a deep NMB over a moderate block are the loss of (sudden) diaphragmatic contractions and significant improvement in surgical conditions especially of procedures confined to a narrow space, such as laparoscopic surgery. Various studies show that the diaphragm has a high resistance to NMBAs in comparison to other muscles.[45-47] For example, Fernando and colleagues showed that an intense NMB is required to silence the diaphragm in response to stimulation of the carina.[45] Similarly, Werba and colleagues showed that diaphragmatic responses evoked by tracheal suctioning lead to coughing, bucking and elevated intracranial pressures in neurosurgical patients, unless deep NMB was applied.[46] In addition, during laparoscopic surgery, efferent activation of the diaphragm from brainstem chemo-sensitive respiratory centres may occur as a result of elevated arterial pCO_2 levels (due to CO_2 insufflation). Only with deep NMB are these diaphragmatic contractions effectively prevented.

Martini et al. assessed the effect of deep *versus* moderate NMB on surgical conditions during laparoscopic retroperitoneal urologic surgery.[19] They developed the validated 5-point Leiden - surgical rating scale (L-SRS, 0-5; extremely poor to optimal working conditions) to objectively qualify the quality of the surgical field as experienced by the surgeon at various points during the procedure.[19, 20, 48] The study showed an improvement of 0.7 L-SRS points (mean L-SRS 4.0 vs. 4.7) when deep NMB was applied, an improvement deemed clinically significant by the surgical team.[19] In many other procedures, a similar effect of deep NMB was found,[18, 20, 21, 49-51] but it is important to acknowledge that some studies found no effect of deep NMB on surgical conditions (see table 2).[52] A recent meta-analysis confirmed the positive effect of a deep NMB on surgical conditions and reduced postoperative pain scores, however significant heterogeneity between the included studies reduces the overall quality of evidence.[53] It is important to realize that other factors such as deep anaesthesia may positively affect surgical working conditions. However, deep anaesthesia, although applicable, is associated with less hemodynamic stability and prolonged recovery times.

Adversaries of deep NMB claim that the gains in surgical conditions with deep NMB are modest at best and are not worth the extra effort and cost of the reversal agents (su-

Table 2. Studies assessing deep NMB on surgical conditions during open and laparoscopic surgery (normal pressure pneumoperitoneum).

Author	Specialty	Control	Intervention	Scale	Mean score	% Unacceptable surgical conditions
Martini[19]	Urology (laparoscopy)	Moderate NMB	Deep NMB	L-SRS	4.0 vs 4.7**	18% vs 1%
Yoo[21]	Urology (laparoscopy)	Moderate NMB	Deep NMB	L-SRS	3,0 vs 4,0**	UA
Boon[49]	Urology (laparoscopy)	Deep NMB + hypercapnia	Deep NMB + hypocapnia	L-SRS	4.84 vs 4.77#	1 vs 1%
Torensma[20]	Bariatric surgery (laparoscopy)	Moderate NMB	Deep NMB	L-SRS	4.2 vs.4.8**	UA
Baete[60]	Bariatric surgery (laparoscopy)	Moderate NMB	Deep NMB	L-SRS	4.1 vs 3.9#	UA
Madsen[59]	Gynaecology (laparoscopy)	No NMB	Deep NMB	1 (optimal) - 4 (unacceptable)	1.7 vs. 1.0*	UA
Blobner[18]	General surgery (laparoscopy)	No NMB	Deep NMB	0 (not acceptable) - 100 (excellent)	UA	0 vs 28%*
Rosenberg[51]	General surgery (laparoscopy)	Moderate NMB	Deep NMB	0 (poor) - 10 (excellent)	6,8 vs. 7,9*,	UA
Madsen[50]	General surgery (laparotomy)	Moderate NMB	Deep NMB	L-SRS	4.0 vs. 4.75**	17 vs. 49%**

NMB: neuromuscular block; UA: unavailable; L-SRS: Leiden- surgical rating scale: 1 (extremely poor) – 5 (optimal)[19]. *p<0.05, **p<0.001, #p>0.05

gammadex).[54, 55] We argue that the observed differences in L-SRS are clinically relevant, the incidence of suboptimal conditions is greatly reduced during deep NMB (especially the occurrence of sudden diaphragmatic contractions)[18-20, 49], and most important, deep NMB is associated with less postoperative pain and a reduced incidence of unplanned 30-day readmission.[20, 56]

Finally, there are indications that a deep NMB allows for lower intra-abdominal pressure during laparoscopic surgery. Reduced insufflation pressure is associated with less postoperative pain.[57] Deep NMB might cause an increase in abdominal wall compliance and consequently an increase in intra-abdominal space.[58, 59] However, while various studies indeed show that deep NMB allows titration to lower intra-abdominal pressures with still acceptable surgical conditions, the gain in intra-abdominal space may be marginal [59], and the incidence of unacceptable surgical conditions remained substantial higher than under standard pressures. The feasibility of low-pressure pneumoperitoneum hence needs further investigation.

CONCLUSIONS

Neuromuscular blocking agents have important advantages but also serious disadvantages. Postoperative residual curarization is an important threat, especially in patients that are not adequately reversed or monitored. An important new development is the introduction of the reversal agent sugammadex. Sugammadex may help reduce the incidence of postoperative residual curarization and improve postoperative respiratory recovery. In addition, sugammadex enables the use of a deep NMB during general anaesthesia. While the deep NMB has been shown to improve surgical conditions and reduce postoperative pain in a variety of procedures, its place in anaesthesia is not yet fully determined.

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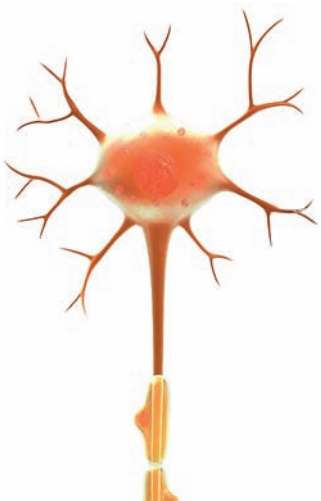
Chapter 8

Summary and conclusions



The introduction of sugammadex brought new opportunities in perioperative neuromuscular management. Sugammadex enables the application of deep neuromuscular block (NMB) and may help to reduce the incidence of postoperative residual curarization (PORC). This thesis investigated the effect of deep NMB on surgical conditions in laparoscopic retroperitoneal surgery using the Leiden - surgical rating scale. In addition, outcome data of neuromuscular reversal with sugammadex *versus* neostigmine and of everyday use of deep NMB is presented.

In *Section 1*, two randomized controlled trials are presented that investigated the effect of deep neuromuscular block on surgical working conditions in laparoscopic urologic surgery. **Chapter 2** presents data of a randomized controlled trial, which assessed the effect of moderate (train-of-four count of 1-2 twitches) vs. deep NMB (post-tetanic-count of 1-2 twitches) on surgical conditions during laparoscopic retroperitoneal prostatic and kidney surgery. These procedures take place in a limited space and it was hypothesized that surgical conditions in especially in these procedures may largely depend on adequate muscle relaxation. The primary outcome was the quality of the surgical working conditions as rated by the surgeon. For this purpose, the five-point Leiden - surgical rating scale was developed (L-SRS: 1. *extremely poor conditions* to 5. *optimal conditions*). Surgical conditions were rated by the surgeon every 15 minutes after installation of the pneumoperitoneum. The main finding of this study was that a deep NMB resulted in a higher L-SRS than a moderate NMB (mean L-SRS 4.0 vs. 4.7, $p<0.001$). In addition, L-SRS scores of 3 or lower occurred in 1% in deep NMB vs. 18% in the moderate NMB group. This indicates that deep NMB produced superior surgical conditions and significantly reduced the incidence of sudden deterioration of the surgical working field.

Although a deep NMB improved surgical conditions over a moderate NMB, the quality of the surgical working field varied considerably (*e.g.* L-SRS scores <5 were noted even during a deep NMB). It was hypothesized that variation this could be due to involuntary diaphragmic contractions that are triggered by elevated arterial CO_2 levels (*i.e.* hypercapnia) induced by CO_2 pneumoperitoneum. **Chapter 3** presents a study that investigated the effect of arterial CO_2 levels on surgical conditions in laparoscopic retroperitoneal surgery during deep NMB. In this study, patients were randomized to have arterial CO_2 levels maintained at a low level (hypocapnia, pCO_2 3.5 – 4.5 kPa) or at a high level (hypercapnia, pCO_2 6.5 – 7.5 kPa). Primary outcome parameter was the quality of surgical field rated on the L-SRS at 15 minutes intervals. The mean L-SRS scores during hypo- and hypercapnia were 4.84 vs. 4.77 respectively ($p >0.05$). Again, 99% of the ratings were good (L-SRS score 4) or excellent (L-SRS score 5), irrespective of the randomisation. This study confirmed the results of the previous study that deep NMB overall yields good surgical working conditions, but the hypothesis suggesting an influence of arterial CO_2 levels on surgical conditions during deep NMB was rejected.

In *Section 2,* two outcome studies are presented. **Chapter 4** presents retrospective data about the everyday use of deep neuromuscular block in laparoscopic retroperitoneal surgery. Electronic charts of patients who had received general anaesthesia between January 2014 and December 2016 were searched for anaesthetics with the use of high dose rocuronium to achieve deep NMB. These cases were matched with respect to sex, age and ASA class to patients that had received anaesthesia with low dose rocuronium. The primary postoperative outcome was 30-day readmission rate; secondary outcomes included duration of surgery and anaesthesia, and postoperative pain. 130 Patients were included in each cohort. All patients of the high dose of rocuronium cohort were reversed with sugammadex (mean) 267 mg at the end of anaesthesia. In the low dose rocuronium cohort 33% of the patients were reversed with sugammadex 212 mg, 20% were reversed with neostigmine 1.6 mg. The remainder of the patients were not reversed. Postoperative respiratory and pain outcomes, as well as hospital length of stay did not differ between the two groups. Unplanned readmission rate was significantly lower in the high dose rocuronium cohort compared to the low dose cohort (3.8% *vs.* 12.7%, OR = 0.33, p =0.03). This was primarily due to fewer infectious complications at the site of surgery in patients who had received a high dose rocuronium. Prospective studies are needed to confirm these findings and to study the effects of a high dose rocuronium/ sugammadex reversal anaesthetic technique on the pharmaco-economic variables.

In **Chapter 5**, the effect of sugammadex vs. neostigmine reversal on postoperative oxygenation was studied. In this randomized controlled trial, 100 patients were randomized for reversal of a moderate NMB with sugammadex 2 $mg.kg^{-1}$ or neostigmine 2.5 mg. To mimic real world conditions, neuromuscular monitoring was not allowed. Instead, timing of extubation was based on clinical signs of adequate muscle strength. In the recovery ward, the use of supplemental oxygen was not allowed unless saturation dropped to values below 94%. Patients who had received sugammadex had a mean (95% confidence interval) Train-of-four (TOF) ratio at extubation of 0.99 (0.98-1.00) compared to a TOF ratio of 0.74 (0.68-0.80) for patients who had received neostigmine. This translated to a mean lowest arterial oxygen saturation of 96.8% (96.1 – 97.4) vs. 93.3% (91.9-94.7) in the recovery ward for sugammadex and neostigmine reversed patients respectively. Following reversal with sugammadex, 90% of patients had a TOF ratio of > 0.9 at extubation *and* a lowest saturation > 94% at the PACU, compared to 16% of neostigmine reversed patients. It was concluded that, in a setting were neuromuscular monitoring is not used, reversal of a moderate NMB with sugammadex leads to less postoperative residual curarization (TOF ratio <0.9) and less postoperative hypoxemia.

In *Section 3,* **Chapter 6** presents a systematic review of the use of surgical rating scales in laparoscopic surgery. After a systematic search in Pubmed, Embase and Web of Science, 17 reports were eligible for inclusion. A total of 10 unique surgical rating scales were identified. These scales were judged for their quality with the use of a quality

score. This score delivered points for optimal length of the scale, description of the scale items, validation procedures and correlation with other variables. The overall score of the rating scales was low and most scales lacked a validation procedure. In addition, the methodology of rating and the reporting of the results differed significantly between studies. The only fully validated surgical rating scale for laparoscopic surgery was the Leiden - surgical rating scale. A guideline about the construction and use of surgical rating scales, as well as for methodology and results reporting was proposed for future research.

In the final section, **Chapter 7** gives a broad overview about current management of neuromuscular relaxation during surgery. Literature was systematically reviewed for the latest evidence concerning the effect of sugammadex reversal and the use of deep neuromuscular block during surgery on outcome. Increasing evidence shows beneficial effects of reversal of NMB with sugammadex over neostigmine and the application of deep NMB during certain procedures. If and to what extend this improves outcomes is not yet fully determined. Good quality research in this scientific field is scarce, which leaves opportunities for the future.

Conclusions

From the data presented in this thesis, the following conclusions can be drawn:

1. Deep neuromuscular block results in superior surgical working conditions compared to a moderate neuromuscular block, during laparoscopic retroperitoneal surgery.

2. Superior surgical working conditions during laparoscopic retroperitoneal surgery are independent of arterial CO_2 levels during deep neuromuscular block.

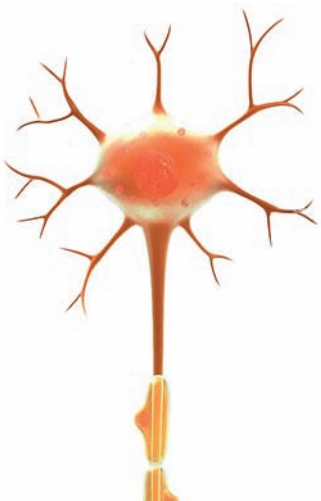
3. The application of deep NMB is safe and associated with less unplanned postoperative 30-day readmission rates when applied in laparoscopic urologic surgery.

4. Reversal of a moderate NMB with sugammadex results in less postoperative residual curarization and less postoperative hypoxemia compared to reversal with neostigmine, in a setting were intraoperative neuromuscular monitoring and postoperative supplemental oxygen are not allowed.

5. The Leiden - surgical rating scale is a high quality rating scale for assessment of surgical working conditions in laparoscopic surgery.

Hoofdstuk 9

Samenvatting en conclusies



De moderne toepassing van algehele anesthesie (narcose) bestaat uit een drietal pijlers: onderdrukking van het bewustzijn (hypnose), pijnstilling (analgesie) en spierverslapping (neuromusculaire relaxatie). Hypnose en analgesie worden beiden verkregen met sterke medicamenten die werken op het centrale zenuwstelsel. Neuromusculaire relaxatie wordt verkregen met medicamenten die de signaaloverdracht van zenuw naar spier blokkeren. De toepassing van spierverslapping tijdens algehele anesthesie kent vele voor- en nadelen. Een belangrijk voordeel is dat spierverslapping een bewegingsloze patiënt garandeert tijdens een chirurgische procedure. Zonder spierverslapping is dit laatste geen garantie.[1]

Het gebruik van spierverslappers kent echter ook belangrijke nadelen. Historisch gezien is het gebruik van spierverslapping tijdens algehele anesthesie een onafhankelijke risicofactor voor het optreden van ernstige complicaties of overlijden na een operatie.[2-4] Dit heeft te maken met het feit dat spierverslappers lang werkende middelen zijn, in tegenstelling tot de overige anesthetica, die vaak kort werkend zijn. Door deze tegenstelling in werkingsduur kan het voorkomen dat de spierverslappers in geringe mate nog werkzaam zijn, terwijl de anesthesie al beëindigd is. Dit heet restverslapping. Restverslapping is de oorzaak van ademhalingsproblemen op de verkoever en kan ernstige complicaties veroorzaken, zoals acute ademhalingsnood of longontsteking.[5] Ondanks het feit dat deze effecten bekend zijn, komt restverslapping in de praktijk toch nog vaak voor, met gerapporteerde incidenties van 20 tot 60% na algehele anesthesie.[6]

Er zijn verschillende methoden om restverslapping te voorkomen. Een belangrijke methode is het bepalen van de mate (diepte) van spierverslapping tijdens een ingreep. Hiertoe zijn diverse eenvoudige meetapparaten verkrijgbaar. Al deze apparaten werken ongeveer op dezelfde manier: een perifere zenuw (meestal de nervus ulnaris in de onderarm) wordt gestimuleerd door middel van een korte electrische stroom, waarna het effect van deze stimulatie wordt gemeten in een dichtbij zijnde spier (meestal de duim, musculus adductor pollicis). De mate van de opgewerkte spiercontractie is een afspiegeling van de mate van spierverslapping. De meest gebruikte meet methode in de praktijk is de *train-of-four* (TOF) methode. Tijdens een TOF meting worden er 4 korte stroompjes snel achter elkaar op de zenuw gegeven, welke in een normale situatie resulteert in 4 korte spiercontracties (twitches) van de duim. Naarmate de mate van spierverslapping toeneemt, zullen de spiercontracties in kracht en aantal afnemen, om uiteindelijk geheel te verdwijnen. De relatie van de vierde contractie ten opzichte van de eerste contractie kan ook uitgedrukt worden in een ratio, de *TOF ratio*. Er is sprake van restverslapping als de TOF ratio lager dan 0,9 is. Dat wil dus zeggen dat de contractie van de vierde twitch, gedeeld door de contractie van de eerste twitch lager is dan 0,9 of 90%. Vanaf een TOF ratio van 0,9 en hoger is het in het algemeen veilig om de anesthesie

te beëindigen en de beademingsbuis te verwijderen. We kunnen nu ook matige neuromusculaire blokkade definiëren, namelijk een TOF stimulatie met een reactie van 1 tot 3 spier contracties; en diepe neuromusculaire blokkade, namelijk een TOF met 0 spier contracties. Tijdens een diepe neuromusculaire blokkade kunnen er, door het toepassen van een langer durende stroom op de zenuw (een zgn. *tetanische* stimulus, 5 seconden 50 Hz.), toch nog spier contracties worden uitgelokt. Dit zijn post tetanische tellingen, in het Engels afgekort tot PTC (post-tetanic-count Diepe neuromusculaire blokkade in de onderzoeken gepresenteerd in dit proefschrift is gedefinieerd als een PTC van 1-2 twitches.

Naast het toepassen van neuromusculaire monitoring bestaat er nog een andere methode om restverslapping te voorkomen. Dit is het omkeren (*antagoneren*) van de spierverslapping aan het einde van een ingreep. Met antagoneren wordt getracht om de spierverslapping aan het einde van de ingreep versneld te doen uitwerken. Hiertoe bestaan twee methoden, die hierna kort besproken worden.

Neostigmine behoort tot de geneesmiddelengroep die de afbraak van acetylcholine verminderen (*acetylcholinesterase remmers*). Acetylcholine is het belangrijkste eiwit dat betrokken is bij de signaaloverdracht van zenuw naar spier. Door het remmen van de acetylcholine afbraak, neemt de beschikbaarheid hiervan toe. Toename van de hoeveelheid acetylcholine leidt tot een versterkte signaaloverdracht. Dit zorgt er voor dat het effect van spierverslappers (voor een deel) teniet wordt gedaan. Het gebruik van neostigmine kent echter ook nadelen. Ten eerste werkt het traag en is het resultaat van antagoneren vaak onvoldoende.[6] Bovendien heeft het bijwerkingen, waarvan de bekendste een vertraging van de hartslag is. Om dit tegen te gaan is het noodzakelijk dat atropine simultaan wordt toegediend.

Met de komst van sugammadex in het begin van deze eeuw is er echter een nieuwe manier van antagoneren beschikbaar gekomen. Sugammadex is een middel wat gebaseerd is op een een gemodificeerd zetmeel molecuul (gamma cyclodextrine). Sugammadex heeft de unieke eigenschap dat het selectief moleculen van spierverslappers kan inkapselen (encapsuleren).[7] Encapsuleren van deze moleculen, leidt tot een abrupte en voorspelbare beëindiging van spierverslapping. Bovendien zijn er nauwelijks bijwerkingen bij het gebruik van sugammadex.[8]

Sugammadex opent vele deuren die tot nu toe gesloten waren. Door de beschikbaarheid van sugammadex is het mogelijk geworden om tijdens operaties een hoge dosering spierverslapping te geven (diepe neuromusculaire blokkade), zonder dat dit leidt tot een langdurige hersteltijd of een verhoogd risico op restverslapping.[9] Diepe neuromusculaire blokkade leidt mogelijk tot gunstigere operatie condities voor de chirurg, doordat alle spieren in het operatie veld ontspannen zijn. Bovendien kan, door de

hoge effectiviteit van het sugammadex antagonisme, het optreden van restverslapping en ademhalingsproblemen op de verkoever mogelijk worden verminderd. Dit zijn de belangrijkste hypothesen die in dit proefschrift zijn onderzocht. In de hierna volgende paragrafen zullen de afzonderlijke hoofdstukken uit dit proefschrift worden besproken. Ter afsluiting zullen de belangrijkste conclusies uit het onderzoek gepresenteerd in dit proefschrift worden gepresenteerd.

SAMENVATTING

In *sectie 1* worden twee prospectief gerandomiseerde studies gepresenteerd die het effect van diepe neuromusculaire blokkade (NMB) op chirurgische werkomstandigheden tijdens laparoscopische urologische ingrepen beschrijven.

Hoofdstuk 2 presenteert de gegevens van een gerandomiseerde studie die het effect van matige NMB (train-of-four 1-3 contracties) *versus* diepe NMB (post tetanische tellingen 1-2 contracties) op chirurgische werkomstandigheden heeft geëvalueerd tijdens kijkoperaties van de prostaat of nier (laparoscopische retroperitoneale prostaat- en nier chirurgie). Specifiek deze ingrepen vinden plaats in een beperkte ruimte (het retroperitoneum) en de hypothese dat chirurgische werkomstandigheden tijdens deze procedures in het bijzonder grotendeels afhangen van de mate van spierverslapping, is getest. De belangrijkste einduitkomst was de kwaliteit van de chirurgische werkomstandigheden zoals deze tijdens de ingrepen werden beoordeeld door de uroloog. Hiertoe werd de vijf-punts Leiden - surgical rating scale ontwikkeld (L-SRS: 1. extreem slechte omstandigheden tot 5. optimale omstandigheden). De chirurgische werkomstandigheden werden elke 15 minuten beoordeeld door de uroloog. De belangrijkste bevinding van dit onderzoek waren dat een diep NMB resulteerde in een hogere L-SRS dan matige NMB (4,7 vs. 4,0, $p < 0.001$). Bovendien was slechts 1% van de L-SRS-scores 3 of lager in de diepe NMB groep tegen 18% in de gematigde NMB groep. Dit geeft aan dat diepe NMB superieure chirurgische werkomstandigheden bewerkstelligd. Bovendien voorkomt diepe NMB effectief het optreden van plotselinge verslechtering van het chirurgische werkveld door te verhinderen dat een patiënt onverwachts beweegt.

Hoewel diepe NMB de chirurgische werkomstandigheden verbeterde ten opzichte van matige NMB, varieerde de kwaliteit van de chirurgische werkomstandigheden aanzienlijk (bijvoorbeeld L-SRS scores <5 werden ook genoteerd tijdens diepe NMB). Dit zou te wijten kunnen zijn aan onwillekeurige bewegingen van het middenrif (diafragma) tijdens de ingreep. Deze bewegingen kunnen worden veroorzaakt door een verhoogd arterieel CO_2 niveau (hypercapnie) welke kan ontstaan doordat de buik tijdens een kijkoperatie wordt opgeblazen met CO_2. CO_2 is een krachtige ademhalingsstimulans

en kan aanleiding geven tot contracties van het diafragma. Deze contracties kunnen zelfs tijdens diepe NMB optreden doordat het diafragma relatief ongevoelig is voor spierverslappers. Het verlagen van arteriële CO_2 concentratie d.m.v. hyperventilatie zou zo bij kunnen dragen aan betere chirurgische werkomstandigheden tijdens diepe NMB. **Hoofdstuk 3** presenteert een onderzoek die het effect van het arteriële CO_2niveau op de chirurgische werkomstandigheden tijdens diepe NMB weergeeft. Wederom werd dit onderzoek gedaan tijdens laparoscopische retroperitoneale nier- en prostaat operaties. De patiënten voor dit onderzoek werden gerandomiseerd tussen een groep waarbij de arteriële CO_2 waarden op een laag niveau werd gehouden (hypocapnie, pCO_2 3,5 - 4,5 kPa) en een groep waarbij het CO_2 op een hoog niveau (hypercapnie, pCO_2 6,5 - 7,5 kPa) werd gehouden. De belangrijkste einduitkomst was opnieuw de kwaliteit van de chirurgische werkomstandigheden gemeten elke 15 minuten, met behulp van de L-SRS. Uit deze studie bleek dat er geen verschil was in de kwaliteit van de chirurgische werkomstandigheden tussen de twee groepen. Wederom waren 99% van de beoordelingen goed (L-SRS score 4) of uitstekend (L-SRS score 5), ongeacht de randomisatie. Deze studie bevestigt de resultaten van de vorige studie, namelijk dat diepe NMB over het algemeen goede chirurgische werkomstandigheden oplevert, maar verwierp de hypothese dat het arteriële CO_2 niveau hierop van extra van invloed is.

In *sectie 2* worden onderzoeken gepresenteerd die enkele belangrijke einduitkomsten na anesthesie beschrijven (postoperatieve outcome). Naar aanleiding van de eerder besproken studies, is het gebruik van diepe neuromusculaire relaxatie voor urologische ingrepen enkele jaren geleden standaard geworden in het LUMC. **Hoofdstuk 4** presenteert retrospectieve gegevens over het dagelijks gebruik van diepe neuromusculaire blokkade tijdens urologische procedures en vergelijkt deze met de gegevens van urologische ingrepen waarbij dit niet is gedaan. Elektronische data van patiënten die tussen januari 2014 en december 2016 algehele anesthesie ondergingen, werden onderzocht op toepassing van diepe NMB. Deze data werden vergeleken met data van procedures waarbij anesthesie werd gegeven met het gebruik van een matige NMB. De belangrijkste postoperatieve einduitkomst was het aantal ongeplande heropnames binnen 30 dagen na de operatie.

Data van 130 patiënten die algehele anesthesie techniek met diepe NMB hadden ontvangen werden gematched met data van 130 controle patiënten die matige NMB hadden gekregen. De patiënten die diepe NMB hadden ontvangen waren allemaal geantagoneerd met sugammadex in tegenstelling tot 20% van de patiënten die een matige NMB hadden gehad. Het aantal ongeplande heropnames was significant lager in de diepe NMB groep vergeleken met de matige NMB groep (3,8% vs. 12,7%; p= 0.03). De belangrijkste reden voor een ongeplande heropname was infectie in het geopereerde gebied (1 patiënt in de diepe NMB groep vs. 7 patiënten in de matige NMB groep). Bo-

vendien werden er bij de toepassing van diepe NMB geen onmiddellijke postoperatieve respiratoire complicaties gezien. Dit onderzoek laat zien dat het gebruik van diepe neuromusculaire blokkade tijdens laparoscopische urologische ingrepen geassocieerd is met een lagere kans op een ongeplande heropname. Toekomstige prospectieve studies zullen deze resultaten moeten bevestigen en moeten uitzoeken of de kosten van het sugammadex gebruik opweegt tegen de verminderde kosten van heropnames.

In **hoofdstuk 5** wordt het effect van antagoneren van matige neuromusculaire blokkade met sugammadex vergeleken met neostigmine. De belangrijkste einduitkomst van dit onderzoek was het optreden van restverslapping (gedefinieerd als een train-of-four ratio lager dan 0,9) en de laagst gemeten postoperatieve zuurstof saturatie. Hiertoe werden 100 patiënten gerandomiseerd voor het antagoneren van matige NMB met sugammadex 2 mg per kg of neostigmine 2,5 mg. Om de omstandigheden van de algemene dagelijkse praktijk na te bootsen, was neuromusculaire monitoring beschikbaar voor de onderzoekers, maar niet voor de verantwoordelijke anesthesioloog. De anesthesioloog besloot tot het beëindigen van de anesthesie en het verwijderen van de beademingsbuis (extubatie) op grond van klinische tekenen van voldoende spierkracht en herstel van het NMB. Op de verkoever was het gebruik van extra zuurstof niet toegestaan tenzij het zuurstof gehalte (saturatie) zakte onder 94%.

Patiënten die sugammadex hadden gekregen, hadden een gemiddelde TOF ratio van 0,99 bij extubatie, vergeleken met 0,74 bij patiënten die neostigmine hadden gekregen ($p<0.001$). Dit vertaalde zich naar een gemiddeld laagst gemeten zuurstof saturatie op de verkoever van respectievelijk 96,8% *versus* 93,3% ($p<0.001$). Na antagoneren met sugammadex had 90% van de patiënten een TOF ratio van > 0,9 bij extubatie *en* een zuurstofsaturatie> 94% op de verkoever, vergeleken met 16% van de met neostigmine geantagoneerde patiënten. Uit deze resultaten wordt geconcludeerd dat in een situatie waarin neuromusculaire monitoring en extra zuurstof niet wordt toegepast, het antagoneren van matige NMB met sugammadex vergeleken met neostigmine, leidt tot minder postoperatieve restverslapping (TOF ratio <0,9 na extubatie) en minder postoperatieve hypoxemie.

In sectie 3 wordt in **hoofdstuk 6** een systematische review van het gebruik van chirurgische beoordelingsschalen tijdens laparoscopische chirurgie gepresenteerd. Na een systematische zoekopdracht in Pubmed, Embase en Web of Science, werden 17 onderzoeken geïncludeerd. Een totaal van 10 unieke chirurgische beoordelingsschalen werden geïdentificeerd. Deze schalen werden beoordeeld op hun kwaliteit met behulp van een kwaliteitsscore. De gemiddelde kwaliteitsscore van de geïncludeerde beoordelingsschalen was laag en de meeste schalen waren niet gevalideerd. Bovendien verschilden de methoden van beoordeling en de rapportage van de resultaten aanzienlijk tussen de onderzoeken.

De enige volledig gevalideerde chirurgische beoordelingsschaal voor laparoscopische chirurgie was de Leiden - surgical rating scale. Een richtlijn voor de samenstelling en het gebruik van chirurgische beoordelingsschalen, evenals voor de methodologie van beoordelen en rapportage van resultaten voor toekomstig onderzoek werd voorgesteld.

Hoofdstuk 7 geeft een algemeen overzicht van de huidige stand van zake omtrent het gebruik van spierverslapping tijdens anesthesie. De literatuur is systematisch beoordeeld op de nieuwste gegevens betreffende het effect van sugammadex-antagonering en het gebruik van diepe neuromusculaire relaxatie tijdens chirurgie. Toenemend bewijs toont dat het antagoneren van spierverslapping met sugammadex kan leiden tot minder ademhalingsproblemen op de verkoever. Ook de toepassing van diepe neuromusculaire relaxatie tijdens bepaalde procedures brengt mogelijk voordelen met zich mee. Echter doordat er weinig kwalitatief goed onderzoek is gedaan, blijft de vraag hoe groot deze gunstige effecten zijn en voor welk type ingrepen en patiënten deze gelden. Toekomstig onderzoek zal hier uitsluitsel over moeten geven.

CONCLUSIES

Uit de gegevens van dit proefschrift worden de volgende conclusies getrokken:

1. Toepassing van diepe neuromusculaire blokkade tijdens laparoscopische retroperitoneale urologische ingrepen resulteert in superieure chirurgische werkomstandigheden in vergelijking met matige neuromusculaire blokkade.

2. De superieure chirurgische werkomstandigheden tijdens diepe neuromusculaire blokkade zijn onafhankelijk van het arteriële CO_2 gehalte.

3. De toepassing van diepe neuromusculaire blokkade is veilig en is geassocieerd met minder ongeplande heropnames binnen 30 dagen na laparoscopische urologische operaties.

4. Omkering van matige neuromusculaire blokkade met sugammadex ten opzichte van neostigmine resulteert in minder postoperatieve restverslapping en minder postoperatieve hypoxemie, in een situatie waarin neuromusculaire monitoring en postoperatieve extra zuurstof toediening niet is toegestaan.

5. De Leiden - surgical rating scale is een hoogwaardige en gevalideerde beoordelingsschaal voor het beoordelen van chirurgische werkomstandigheden tijdens laparoscopische chirurgie.

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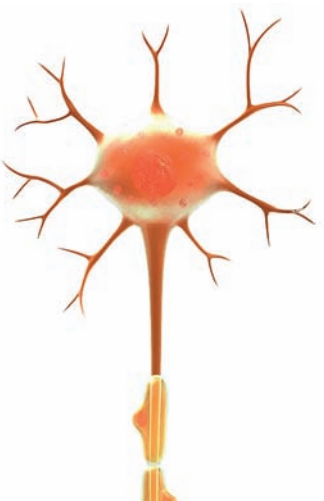
Addenda

Curriculum vitae

List of publications

Dankwoord



CURRICULUM VITAE

Martijn Boon was born on March 8th in 1985 in Bavel (Nieuw Ginneken), the Netherlands. He obtained his Atheneum degree at the Mencia de Mendoza Lyceum in Breda in 2003. In the same year, he was admitted at medical school of the Erasmus University of Rotterdam from which he graduated in 2010. During medical school, he took several extra rotations, including an internship of tropical medicine at the Macha Mission Hospital in Zambia. After medical school, he worked as a resident on surgery and intensive care departments at the IJsselland hospital in Capelle a/d IJssel and the Westeinde Hospital in The Hague respectively. In 2012 he was admitted at the Leiden University Medical Center for his anaesthesiology training, under supervision of Prof. dr. L.P.H.J. Aarts. At the same time, he started a PhD trajectory under supervision of Prof. dr. A. Dahan. During his anaesthesiology residency, he successfully combined the obligations for his anaesthesiology training as well as for his PhD trajectory. In his last year of residency, he specialised in cardio-thoracic anaesthesia. In 2018, he finished his anaesthesiology training and he is currently working as staff anaesthesiologist at the Leiden University Medical Center. In his current position, he remains involved with scientific research and he leads several ongoing projects. Martijn currently lives in Rotterdam, together with his wife Nienke and his daughter Juliette.

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1 Broens S, **Boon M**, Martini C, Niesters M, van Velzen M, Aarts L, Dahan A. Influence of reversal of a partial neuromuscular block on the carotid body response to hypoxia: an experimental randomized trial in healthy volunteers. *Submitted for publication*

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