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Review Article

Deep neuromuscular blockade in gynecological laparoscopic surgery: a review

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Summary

Minimally invasive surgery has achieved remarkable progress during the last three decades in the field of operative gynecology. The intrinsic advantages of laparoscopy i.e. shorter operative time, less abdominal trauma, faster recovery and shorter hospitalization, combined with new advances in instrumentation, energy sources, and operative techniques, contributed to this shift towards laparoscopy for the operative management of a variety of gynecological conditions. One of the most important prerequisites for an effective and complications-free laparoscopic operation is the need to constantly maintain a good operative field. Concomitant advances in the area of anesthesia, like the use of objective neuromuscular monitoring and the introduction of new reversal agents have allowed clinicians to apply deep neuromuscular blockade (NMB) during laparoscopic operations with markedly reduced postoperative residual curarization. This evolution appears to contribute significantly to the establishment of a good operative field, especially during advanced and lengthy laparoscopic procedures, maintaining optimal conditions even when low-pressure laparoscopy (eight mmHg) is performed. The aim of this review is to present the principles of deep NMB and examine the possible benefits of its use during laparoscopy.

Key words: Laparoscopy; Deep neuromuscular blockade; Gynaecology; Neuromuscular monitoring; Operating field improvement.

Introduction

Over the last three decades, laparoscopy has been gradually expanding its use in gynecological surgery and constitutes today a valid alternative to laparotomy. Improvements in laparoscopic instrumentation, energy sources, and techniques have enabled surgeons to increasingly utilize this modality in a large number of gynecological procedures [1, 2]. Apart from traditional indications of laparoscopy, such as infertility surgery and operative management of benign uterine and ovarian pathology, gynecological oncology and urogynecology are the two major domains in which laparoscopy has recently acquired an extended therapeutic role [3].

Well recognized advantages of laparoscopy include: reduced intraoperative blood loss, lower transfusion rates, less postoperative pain and need for analgesia, faster recovery, shorter hospitalization times, and better cosmetic results [4]. The increased and systematic practice of laparoscopy was followed worldwide by intensive training of the performing surgeons, a fact that has contributed to the reduction of complication rates and has turned laparoscopy into a safe and very effective operative tool. However several factors such as patient characteristics, the technique used for establishing intra-abdominal access, the quality of instrumentation, the type of energy used for hemostasis, and intraoperative ergonomics, may influence the surgical outcome, the complication rates, and the laparoconversion rates. One of the most important prerequisites for an effective laparoscopic operation is the need to constantly maintain a good operative field throughout the procedure [5, 6].

Anesthesia with its different aspects plays an important role, affecting the outcome of any type of procedure. Laparoscopy with its inherent characteristics of a limited operative field and a constant need for precise manipulations is strongly dependent on anesthesia for a favorable peri- and postoperative result. Neuromuscular blockade (NMB) and the degree of its depth largely determine surgical conditions in laparoscopic and open surgery. Few studies have investigated the effects of NMB on surgical conditions during abdominal surgery, mainly in radical prostatectomy and upper abdominal procedures, with the majority of them concluding that deep NMB optimizes surgical conditions. Other studies were conducted to assess the impact of NMB on the laparoscopic operative field.

The purpose of this review is to provide an overview of the principles of deep NMB regarding muscle relaxants, neuromuscular monitoring, complications, reversal agents, and their effects during gynecologic endoscopic surgery.

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Neuromuscular blocking agents

Neuromuscular blocking agents were first introduced in clinical anesthesia in 1912, but it was not until 1942 that their routine use was described as part of the concept of balanced anesthesia [7]. Muscle relaxants can be categorized as depolarizing or non-depolarizing.

The main depolarizing agent is succinylcholine, a short acting agent, with less than a minute interval to maximal blockade, and short duration of action. These characteristics make this drug ideal for rapid sequence intubation (RSI) in case of emergency, and it is the most widely utilized paralytic for that reason. However, succinylcholine has a number of side effects, and as a consequence, its use is contraindicated in certain circumstances, and it should be avoided in clinical conditions where its depolarizing effect can cause a substantial increase in extracellular potassium: sustained muscle weakness, prolonged immobility, massive trauma with significant muscle injury, severe abdominal infections, concomitant acidosis, and severe hypovolemia [8]. Furthermore, it is a potential trigger of malignant hyperthermia among susceptible patients [9].

Non-depolarizing agents act as competitive antagonists of nicotinic receptors, blocking the action of acetylcholine. Aminosteroids with pancuronium, vecuronium, and rocuronium is the one group and benzylisoquinoliniums with cisatracurium, atracurium, mivacurium, and doxacurium constitute the other one. Duration of action can further divide these drugs into long-acting (pancuronium) and intermediate ones (rocuronium, cisatracurium, vecuronium) [10]. Major indications of NMB are tracheal intubation and surgery [11]. Although non-depolarizing blockers have few side effects during anesthesia, residual NMB, beyond the end of the procedure in the post-anesthesia care unit, is a common problem with an incidence varying from 2% to 64% in different studies [12].

Neuromuscular monitoring

Different degrees of NMB can be measured by using objective or subjective neuromuscular transmission (NMT) monitoring. Stimulation of a peripheral motor nerve with electric impulse results in a muscular response with 'all or nothing' principles. The final response of the muscle and the achievement of its maximal contraction depend on the stimulating intensity. Therefore, providing an electric stimulus, 15-20% above the one that implies maximal muscular force (supramaximal stimulus), ensures that we will have the desired result, regardless of variability factors [13].

Technical issues of neuromuscular monitoring

Proper placing of electrodes and cleansing of the skin before their application is of primary importance. Temperature is also a very important factor that can influence not only the pharmacodynamics properties of NMB but may also affect the response to nerve stimulation [14].

Location of neuromuscular monitoring is another critical issue. Some prerequisites entail: firstly, easy access of the site, secondly, avoidance of direct muscle stimulation, and finally a nerve-muscle unit appropriate for quantitative monitoring. The commonly used combination is the ulnar nerve-adductor pollicis muscle unit. Undesirable patient movements may have an effect on the measurement result and for that reason fixation of the patients' arm, as well as the ipsilateral four fingers, is a common practice to overcome possible artifacts. Facial nerve and a number of muscles such as orbicularis occuli, corrugator supercilii, masseter, and myohyoid have been used for monitoring NMB. However adductor pollicis is always the best option with a view to achieve excellent intubating conditions [15]. It is of great significance, although it must be remembered that different muscle groups have different sensitivities to NMB, and monitoring of one unit can only provide limited information about other muscle groups [16].

Nerve stimulation patterns

There are a few stimulation patterns with a clinical use: single twitch, train-of-four (TOF), tetanic stimulation, post-tetanic count (PTC), and double–burst stimulation (DBS). These patterns have a variable ability in monitoring different degrees of NMB and the onset of block or recovery. Nerve stimulators use a monophasic impulse with a rectangular waveform and most often a duration of 0.2 ms. A brief review of these patterns and its characteristics is shown in Table 1.

The degree of NMB is defined by the responses through quantitative neuromuscular monitoring. Therefore the different levels of NMB are: intense NMB: no response on TOF and PTC; deep NMB: PTC of 1 and on, up to the reappearance of TOF count 1, but without including this; moderate NMB: TOF 1-4; recovery in progress: throughout the detection of four responses of TOF and calculation of TOF ratio up to 0.90; safe extubation: TOF ratio of 0.90 [22].

Quantitative neuromuscular monitoring

A number of different methods of quantitative monitoring are used today in daily clinical practice. Regardless of the equipment utilized, the goal is to provide an accurate and numerical displayed measurement of the applied stimulation pattern (TOF, PTC). Mechanomyography (MMG), electromyography (EMG), and acceleromyography (AMG) are the most widely used methods for clinical and research purposes, followed by kinemyography (KMG) and phonomyography (PMG) [23].

Mechanomyography is the gold standard for quantification of NMB measures isometric contraction of the peripheral muscle after its nerve stimulation. A preload is necessary for signal stabilization and the results are precise

Table 1. — *Nerve stimulation patterns.*

	Consistence	Clinical significance	Disadvantages
Single twitch	Supramaximal stimulus to the nerve with a frequency of 0.1 to 1 Hz	Important for neuromuscular research	Limited value in clinical setting
Train-of-four (TOF)	Four supramaximal stimuli every 0.5 seconds are delivered and the muscle response is recorded TOF count: number of induced muscular responses TOF ratio: ratio of the amplitude of the fourth response (T4) divided by the first (T1)	TOF ratio is a useful indicator of the recovery from neuromuscular blockade and is of great significance concerning the conditions appropriate for safe extubation and possibility of residual curarisation.	Tactile estimation accuracy is increased only when TOF ratio is < 0.3 [17].
Tetanic stimulation	Stimulation pattern with o frequency of 50-200 Hz applied for 5 seconds.	It can be used in recovery from NMB when a fade can be observed in cases of residual curarisation.	Limited value in detecting residual curarisation with low sensitivity and specificity (70% and 50%). It is also very painful [20].
Post-tetanic count (PTC)	A 50 Hz supramaximal tetanic stimulus applied for five seconds followed by a one Hz supramaximal single twitch three seconds later.	Indicator of deep neuromuscular blockade	Useless for moderate blockade.
Double-burst stimulation (DBS)	Two short lasting 40 msec 50 Hz tetanic stimuli or bursts separated by a 750-ms interval.	Better indicator for small degrees of residual paralysis than TOF. DBS allows detect fade at a TOF ratio 0.6-0.7 whereas threshold for detecting fade with TOF is 0.4 [19, 20, 21].	

and reproducible. This method tends to be abandoned due to time-consuming, cumbersome, and difficult set up of the equipment.

Electromyography measures the electrical activity of the stimulated muscle [24]. The basic principle of this method is that the force of contraction depends on the compound muscle action potential. This method has been used, not only on the grounds that it is the main site, but also applies on other sites such as the diaphragm and the laryngeal muscles. EMG has a less cumbersome although expensive equipment and the results can be adversely affected by factors such as hand temperature, inappropriate electrode positions or use of diathermy [25].

Acceleromyography since its first appearance in clinical practice in 1988, has been the most widely used method due to the convenient and relatively inexpensive equipment. The method is based on Newton's second law (force=mass×acceleration). A piezoelectric wafer is used for measuring the acceleration. It is usually fixed to the thumb and any movement generates an electrical signal that is monitored. This method can be influenced by artifacts and incidental movements caused by surgeons during the operation. It is therefore very important to place the hand in such a way that will avoid disturbances without this preventing us from being able to move freely [26].

Kinemyography has a limited use in research and consists of two electrodes usually placed along the ulnar nerve, and a piezoelectric polymer sensor between the thumb and index finger. The degree of the movement of the thumb and subsequently of the sensor produces electric signals proportional to the force of contraction [27].

Phonomyography (PMG) is based on recording the low frequency sounds evoked by muscle contraction with special designed microphones. There are a few clinical trials about this method.

Neuromuscular monitoring refers to a term that includes the entire sequence from nerve stimulation (applied with the nerve stimulator) to the quantitative measurement of the muscle response. The provoked stimulation can have the form of different stimulation patterns (TOF, PTC) and the muscle response can be recorded thanks to different monitoring methods (AMG, MMG, EMG, KMG, and PMG).

A severe complication of deep NMB: postoperative residual curarization (PORC)

Basic principles

Residual NMB is defined as the presence of signs and symptoms of muscle weakness in the postoperative period after the intraoperative administration of a non-depolarizing blocking agent which is a common problem in post-anesthesia care units [28]. This specific drawback is the major inhibiting factor in the maintenance of DNMB during the complete duration of the surgical procedure. PORC can also be defined by means of train-of-four ratio. Studies mainly by the inventors of TOF ratio have proposed a value of 0.7 as the threshold of safe extubation [29]. However more recent data suggest that TOF ratio of 0.9 is indispensable.

Incidence of PORC

The incidence of PORC in the post-anesthesia care unit is between 2% and 64% in different studies. This extended variability can be explained by substantial differences in methodology among the studies. Discrepancies at the TOF ratio threshold of PORC, the duration of action of blocking agents, the use of neuromuscular monitoring, and use of reversal agents contributed to variable outcome concerning residual blocking. More specific if TOF ratio of < 0.7 was used to define PORC, the incidence was lower (6–40%) than < 0.8 (52%) and < 0.9 (29–85%) [28, 30]. Use of long acting NMBAs results in a higher incidence of PORC (36–8%) [31]. The value of intraoperative neuromuscular monitoring in reducing PORC is a matter of debate. In a recent meta-analysis from Naguib *et al.*, the authors were unable to demonstrate that the use of monitoring reduced the incidence of residual paralysis. However, in this study qualitative and quantitative neuromuscular monitoring was used and many of the studies reviewed were poorly designed to detect any advantages conferred by monitoring [32].

Methods for detection of residual paralysis

Clinical tests and qualitative and quantitative assessment of neuromuscular blockade are the methods used so far for the detection of possible residual paralysis. Each method has advantages and limitations.

Clinical tests: Clinical tests can only be used in conscious and cooperative patients. Head lift, leg lift, sustained hand grip, tongue depressor test, and the inability to smile, swallow or speak are some of the tests utilized and they are unable to reliably predict the occurrence of PORC [33].

Qualitative or subjective tests consist of visual or tactile evaluation of the response to peripheral nerve stimulation which is one of the most widely used methods for neuromuscular monitoring. These tests appreciate subjectively the muscular response fading after stimulation with the patterns already described (TOF and DBS). Fade detection is difficult as TOF ratio is increased. Therefore the majority of anesthetists are unable to detect fade when TOF ratio exceeds 0.4 [18, 19]. If DBS is used, this ability can be accurate at values of TOF ratio 0.6–0.7 [21].

Quantitative or objective monitoring is the best method to measure accurately TOF ratio > 0.4 that is difficult to estimate with qualitative tests. The equipment of objective monitoring has already been described above (AMG, MMG, EMG, KMG, and PMG). Although there is good evidence that the monitoring with AMG improved detection of PORC, the majority of clinicians do not use neuromuscular monitoring in daily practice [34]. In UK only 10% of anesthetists routinely use neuromuscular monitoring and > 60% never utilize it, while in Germany 18% of anaesthesia departments only use monitoring [35, 36]. An interesting Danish study with questionnaires in 251 anaesthetists (physicians and nurses) revealed that 27% incorrectly believed that it is always possible to exclude PORC with clinical tests, 91% underestimated the incidence of PORC, and only 45% knew that TOF ratio must exceed 0.9 to exclude residual curarization. Therefore, the authors concluded that this not evidence-based clinical practice is a consequence of lack of knowledge and not of limited resources [37].

Adverse effects of PORC

It is well established that residual muscle weakness may potentially impair recovery after the operation and provoke unwanted postoperative complications. Therefore, respiratory impairment, abnormal swallowing, upper airway collapse, and general weakness are some of the results of PORC. Other drugs used for anesthesia such as opioids, volatile agents, benzodiazepines, and induction drugs can potentially contribute to a certain degree in the above events.

At a TOF ratio < 0.8 there is impairment of pharyngeal coordination, reduced force of constrictor muscles, and delayed initiation of the swallowing reflex, while at < 0.9, reduction in upper esophageal sphincter tone is observed, increasing in this manner the risk of aspiration [38]. Hypoxic ventilator response reduced at a TOF ratio of 0.7, recovers only when TOF ratio is restored at > 0.9. Impairment of carotid body chemoreceptor function by NMB agents seem to be the reason for this [39]. Finally, symptoms of muscle weakness such as diplopia, visual disturbances, difficulty in speaking and drinking, severe facial weakness, and generalized weakness are some effects of PORC when TOF ratio is 0.7 [40].

Large database studies have demonstrated an association between residual curarization and increased anesthetic-related morbidity and mortality. Clinical studies on surgical candidates have demonstrated increased risk of postoperative pulmonary complications, postoperative hypoxemia, and higher risk of critical respiratory events in post-anesthesia care unit (PACU) and delays in discharge from PACU when TOF ratio is < 0.9 [30, 41].

NMB and laparoscopy

The basis of laparoscopic surgery, so far, is the creation of sustained pneumopritoneum using CO2 in the majority of cases, in order to obtain optimal operating space and conditions. Despite the fact that increased intra-abdominal pressures are frequently desirable by the surgeon to maintain a good operative field, they contribute to a series of adverse physiologic alterations that have to be taken into account. Hemodynamic, respiratory, ventilator effects (diaphragmatic compression of the lungs and alterations in renal physiology and perfusion), and finally direct effects on perfusion of abdominal organs provoked by the iatrogenic compartment syndrome are some of the consequences of pneumoperitoneum [42]. More specifically, cardiac output is decreased, arterial pressure is increased, and both systemic and pulmonary vascular resistances are elevated. Heart rate remains unchanged or slightly increased. The decrease in cardiac output is proportional to the increase in abdominal pressure resulting in approximately 10−30% reduction during peritoneal insufflation. Normal intraoperative values of venous oxygen saturation (SvO2) and lactate concentrations suggest that changes in cardiac output occurring during pneumoperitoneum are well tolerated by healthy adults. The mechanism of the decrease in cardiac output is multifactorial. Increased intra-abdominal pressure results in caval compression, pooling of blood in the legs, and an increase in venous resistance. The resulting decline in venous return can be measured as a reduction in left ventricular end-diastolic volume. However cardiac filling pressure rises during peritoneal insufflation and this paradox can be explained by the increase in intrathoracic pressure associated with pneumoperitoneum. Intermittent sequential pneumatic compression device and compression stockings prevent the blood pooling and partially compensate this mechanism.

Moreover most studies describe an increase in systemic vascular resistance during the existence of the pneumoperitoneum. This increase in afterload is mostly mediated by mechanical and neurohumoral factors and is not a reflex sympathetic response to the decreased cardiac output. Catecholamines, renin-angiotensin, and especially vasopressin are all released during the presence of the pneumoperitoneum and may contribute to the afterload increase. Mechanical stimulation of peritoneal receptors also results in systemic vascular resistance and arterial pressure increase through vasopressin release. Finally, the effect of CO2 pneumoperitoneum on renal function has also been investigated. Urine output, renal plasma flow, and glomerular filtration rate decrease to less than 50% of baseline values during laparoscopic cholecystectomy and are significantly lower than those during open cholecystectomy. These alterations are significantly restored after deflation [43].

Insufflation pressure is desirable when between eight and 15 mmHg. Numerous factors can also affect intra-abdominal pressure; insufflator settings chosen, steepness of Trendelenburg position, patient's BMI, and finally level of neuromuscular blockade. Except for BMI that is unchangeable, alterations in patient's position and insufflating pressure may have adverse effects on surgical field and physiology. Therefore, NMB is a factor we can manage during the operation to manipulate intra-abdominal pressure.

The impact of deep NMB on reducing inflating pressure has been studied in a few studies in gynecological endoscopy and in laparoscopic cholecystectomy. A pilot study from Lindekaer *et al.* attempted to assess the surgical space in two different inflating pressures (8 and 12 mm Hg) when using deep NMB or no NMB in hysterectomies and myomectomies. Using a laparoscopic grasper, they measured the distance between the sacral promontory and the skin and concluded that the operating space of deep NMB and eight mm Hg pressure was comparable with no NMB and 12 mm Hg [44]. In a similar randomized blinded study form Madsen *et al.*, deep NMB increased the above distance by 0.33 cm in the 12-mm Hg intra-peritoneal pressure group, and by 0.30 cm in the eight-mm Hg pressure group, compared with the respective no-NMB groups, patients undergoing gynecological laparoscopic operations. However the authors questioned the clinical significance of this enlargement of the surgical space [45]. These studies compared deep NMB to no-NMB and not to moderate blockade that is the usual practice in gynecologic laparoscopy. It would be interesting to assess possible superiority of deep NMB comparing to moderate NMB. A study on this direction was designed from Staehr-Rye *et al.* comparing surgical space conditions using deep or moderate muscle relaxation during low pressure (eight mmHg) laparoscopic cholecystectomy. The proportion of optimal surgical conditions was marginally greater in the group of deep NMB compared with moderate blockade (28−4%). However only 60% of operations on eight-mmHg and deep NMB were completed in that pressure while the other 40% had to continue on higher pressure to optimize operating conditions [46].

Beyond surgical conditions optimization, the effects of intra-peritoneal pressure on the peritoneal environment is another important issue. Postoperative adhesion formation and peritoneal dissemination of malignant cells are major clinical problems to date for laparoscopy. Animal studies have suggested that a high intra-peritoneal pressure (IPP) may adversely affect the peritoneal environment, resulting in higher rates of tissue hypoxia and peritoneal dissemination [47]. Furthermore low IPP (eight mmHg) may be better to standard IPP concerning its effects on the fibrinoytic system. Finally there is higher expression of hyaluronic acid genes at eight mmHg compared with 12 mmHg. Considering the biological importance of hyaluronic acid in peritoneal physiology as a protective barrier around mesothelial cells and its potential role in preventing postoperative adhesions, a low IPP of eight mmHg might be better than 12 mmHg for minimizing the adverse impact on the surgical peritoneal environment [48].

IPP alterations may have an impact also on postoperative shoulder pain after laparoscopic surgery. Therefore, Topcu *et al.* assessed the intensity of postoperative pain after gynecologic laparoscopy in different IPPs of eight, 12, and 15 mmHg, and concluded that pain is reduced by low insufflation pressure (eight mmHg) compared with standard and high (12 or 15 mmHg) pressures [49]. More data on this important issue originate from studies on laparoscopic cholecystectomy. In a recent meta-analysis by Hua *et al.*, with a total of 1,263 patients, the authors concluded that low-pressure pneumoperitoneum is feasible and safe and results in reduced postoperative pain and near-equal operative times compared with standard-pressure pneumoperitoneum [50]. Furthermore, in a Cochrane Database Review, a peritoneal pressure below 12 mmHg was associated with significantly less post-operative pain intensity [51]. These data point towards a trend to lower working IPPs when performing laparoscopic procedures, and deep NMB could contribute to this purpose.

Deep NMB may also have an impact on operating conditions in general, affecting the visual field during gynecologic laparoscopic surgery. Only a few studies investigate the effect of NMB on surgical condition improvement and most of them compare NMB and no blockade without considering specifically deep NMB. Only two studies, one in gynecologic laparoscopy and one in laparoscopic prostatectomy and nephrectomy, attempted to compare moderate and deep NMB regarding optimal surgical conditions. In a well designed study by Dubois *et al.*, 102 women who underwent laparoscopic hysterectomy were divided in two groups: one with moderate and one with deep NMB, and the quality of the surgical field was assessed with a four-degree visual analogue scale. The authors concluded that deep NMB significantly improved surgical field scores and prevented unacceptable surgical conditions [52]. Despite some methodological issues concerning the definition of deep NMB, the results have demonstrated the value of deep blockade in optimizing surgical conditions during laparoscopy. In another study from Martini *et al.*, 24 patients undergoing elective laparoscopy for prostatectomy or nephrectomy were divided in two groups: one with moderate and one with deep NMB and the quality of the visual field was assessed with a five-point VAS. The result was a significant improvement of surgical conditions at the group of deep NMB (4.7/5 *vs.* 4/5) [53].

In an early study from Bertrand *et al.*, the quality of NMB was assessed from the operating surgeon and anesthetist as excellent, sufficient or light on different doses of vecuronium [54]. In this study, no NMB monitoring was utilized and the level of NMB was subjectively measured and indirectly connected with the quality of the surgical conditions. They found that increased doses of vecuronium may result in improved operative conditions and reduced insufflating pressures. In another study, Williams *et al.* compared the effect of NMB on surgical conditions during day-case gynecologic laparoscopies. The results showed that the group of NMB had significantly more cases with adequate pneumoperitoneum for trocar insertion than the group with no NMB. However, in view of the surgical field quality, with the use of a four-grade analog scale, there was no difference between the two groups [55]. On the other hand, deep NMB may improve visibility and reduce involuntary movements during laparoscopic cholecystectomy compared with no NMB [56].

Other studies in gynecologic laparoscopy have shown no benefit of NMB concerning operating conditions without examining though deep levels of NMB. Therefore Chen *et al*. found no difference in surgical conditions comparing the use of NMB and no NMB at all in patients undergoing short laparoscopic operations with a ProSeal laryngeal mask airway. This study had some drawbacks as there is no description of the assessment tool that the surgeons used for surgical condition evaluation, the kind of gynecological operations performed, and also no neuromuscular monitoring was used [57]. Two other studies from Swann *et al.* and Chassard *et al.* also found no difference in operating conditions when NMB and no NMB was compared in gynecologic laparoscopic surgery [58, 59].

NMB reversal

NMB reversal agents are used in daily practice to reduce the incidence of residual NMB and for quick recovery of neuromuscular function postoperatively. Nevertheless, not all of the clinicians routinely reverse NMB at the end of an anesthetic because most of them have the erroneous perception that spontaneous recovery occurs by the end of surgery when no NMB agent has been administered within the previous one to four hours [36].

So far anesthesiologists have had two options except not using NMB at all in order to eliminate residual curarization. They could wait for spontaneous reversal via metabolism and diffusion of blocking agents from the neuromuscular junction or use an acetylcholinesterase inhibitor, such as neostigmine to antagonize the residual effect of neuromuscular blocker (NB). Both of these practices however have shortcomings. When considering waiting, anesthetists were facing the problem of inter-individual differences in the speed that NBs were metabolized and the time to patient recovery could not be determined [28]. Neostigmine on the other hand has major limitations concerning the side effects, its inability to reverse deep blockade, and the relatively slow reversal [60].

A new option in anesthesia clinical practice and specifically on NMB reversal has been introduced recently with sugammadex. This agent can antagonize rapidly any degree of NMB from rocuronium and vecuronium with minor side effects. Therefore the ability of maintaining deep NMB during laparoscopic surgery is a reality.

Neostigmine reversal

Neostigmine is a cholinesterase inhibitor that works indirectly by increasing the acetylcholine concentration in the neuromuscular junction, a more effective competitive antagonism with the blocking agent and therefore a faster recovery of the neuromuscular function. The efficacy of anticholinesterase agents is well established in reducing postoperative curarization. Neostigmine however, has several drawbacks that clinicians are obligated to know. Due to their inherent characteristics and mode of action cholinesterase inhibitors act also in the parasympathetic system stimulating the muscarinic receptors resulting in numerous side effects such as arrhythmias and prolonged QT interval (mainly bradycardia), increased secretions, hypotension, and bronchoconstriction [61]. For this reason, neostigmine is concomitantly co-administered with a muscarinic antagonist (atropine or edrophonium) to overcome its side effects. These drugs have their own side effects such as tachycardia, urinary retention, dry mouth, and blurred vision. This combination of neostigmine and atropine is contraindicated in cases of chronic obstructive pulmonary disease, cardiac failure, arrhythmias, glaucoma, and prostatic hypertrophy [62].

Another issue with neostigmine use is its relative slow onset of action and the ceiling effect that it exhibits when increasing the dose to overcome NMB. Therefore above the dose of 70 μg/kg there is no additional effect and further recovery is a result of spontaneous clearance [63]. The degree of acetylcholine increase at neuromuscular junction is limited and when cholinesterase is inhibited maximally, no further increase in Acetylcholine is possible. Consequently neostigmine cannot be used for reversal of deep neuromuscular blockade; at a PTC 1 to 2, the mean time between neostigmine administration and recovery to a TOF ratio of 0.9 was 50.4 minutes [64].

Neostigmine can be used only when neuromuscular function has already recovered to a certain degree. Experts recommend that anesthesiologists should wait at least for the reappearance of the third twitch of TOF response for administering neostigmine in order to achieve maximal efficacy and safety [65]. Anesthetists should also be aware that neostigmine induces itself neuromuscular weakness when administered at higher doses, or after spontaneous recovery from non-depolarizing block [66].

Reversal with sugammadex

Sugammadex is a new drug introduced in the daily clinical practice a few years ago and contributes to the beginning of a new era concerning NMB reversal, the efficacy of maintaining deep NMB during certain operations, and prevention of residual paralysis.

This agent is a modified γ-cyclodextrin specifically designed to encapsulate the NB rocuronium and chemically similar NBs such as vecuronium. The binding affinity of vecuronium is 2.5 times lower compared with that of rocuronium. It binds 1:1 the molecules of rocuronium. When it is intravenously injected, it immediately captures the free intravascular molecules of rocuronium decreasing this way very rapidly the concentration of the blocking agent. This way, the rocuronium, on one hand is rapidly diffused away from the neuromuscular junction, and on the other hand the increase in its total plasma concentration (bound and free) leads to rapid its' filtration by the glomerulus and elimination from the kidney [67]. The usual dose required for reversal is four mg/kg for deep NMB and two mg/kg for moderate block. Doses from 0.5–96 mg/kg have been tested and did not show any adverse effects in adults [68].

The major advantage of sugammadex over neostigmine reversal is the achievement of faster recovery after NMB. Blobner *et al.* compared the mean time needed for reaching TOF ratio 0.9 after re-appearance of second twitch of TOF following neostigmine and sugammadex administration [69]. The geometric mean time to recovery was 18.6 minutes for neostigmine and 1.5 minutes for sugammadex. Finally, sugammadex administered at re-appearance of second twitch of TOF was significantly faster in reversing rocuronium-induced blockade than neostigmine was in reversing cisatracurium-induced block (geometric mean 1.9 min *vs.* nine minutes) [70]. What makes the difference though is the ability of sugammadex to reverse rapidly and reliably intense NMB from rocuronium and vecuronium. Geldner *et al.* found that sugammadex causes a 3.4 times faster recovery on deep block than moderate blockade [71]. In another study by Jones *et al.*, neostigmine or sugammadex where administered at PTC 1-2, and the reversal time (TOF ratio 0.9) from the deep blockade was 2.9 minutes for sugammadex and 50.4 minutes for neostigmine [64]. Other studies also agree with these results and confirm the effectiveness of sugammadex on reversing any degree of NMB [72].

Sugammadex is an agent with only a few undesirable effects related to the rapid reversal of NMB combined with a patient already awake, mostly cough, suckling of the endotracheal tube and movements, plus possible allergic reactions [73]. Impaired renal function and bleeding disorders are contraindications for using this agent. Although administration of sugammadex is associated with a dose-related prolongation of APTT and PT (29% and 19%, respectively) occurring within 30 minutes post-dose, Raft *et al.* though did not find any significant clinical differences between sugammadex and control groups in 142 patients undergoing major abdominal surgery for cancer, concerning hemorrhagic complications [74].

The major concern so far regarding the use of sugammadex is its relative high cost compared to other reversal agents. It is supposed to be one of the most expensive drugs in anesthesia (100 USD) and this price is considered by some experts as prohibitive to use it in daily clinical practice when neostigmine only costs four USD [75]. Most reviews agree that although sugammadex could be in certain circumstances a cost-effective option compared with neostigmine because it has the potential to improve the recovery times, however this alone does not ensure scheduling extra operations within a normal workday, a fact that could counterbalance the expense. In order to overcome the cost of sugammadex, other factors such as OR organization, staff productivity, and flexibility in the operating area are necessary for a faster patient turnover [76]. Raft *et al.* apposing their one-year experience in routine sugammadex use calculated that the increase of Euro 8.22/case was minimal compared to the time gained and the increased number of operated cases [77]. Finally Schaller *et al.* proposed the use of lower doses of the drug in order to lower the cost, but this management could reduce its efficacy and predictability on reversal, and increase the recovery time, eliminating tin this way major advantage of rapid recovery [78].

Conclusions

Laparoscopy has made great progress during the last years concerning most gynecological domains. Therefore from the small, simple, and relatively short operations of diagnostic laparoscopy or tube ligation, we are now moving to more time consuming, demanding, challenging, and tiresome operations such as lymphadenectomy, radical hysterectomy, and nine- to ten-cm myomectomy. In order to perform with safety this type of laparoscopic surgery, there is a requirement for the best possible quality of surgical field.

Surgery and anesthesiology always had a close relationship and this occasion should not be an exception. Maintaining deep NMB throughout the laparoscopic operation, could contribute in achieving a sustainable optimal operative field. Lately, the introduction of a new reversal agent sugammadex has revolutionized the way anesthesiologists think about drug reversal and has permitted the application of deep NMB without waiting for a long time for the patient to recover, or facing the risk of postoperative residual curarization. Moreover, despite the shortcoming of costs, with proper management and coordination of resources in the operating theater, a collateral benefit may occur from shorter recovery times, i.e. scheduling of extra operations during each workday.

The proper use though of NMB agents and reversal drugs demands the establishment of quantitative monitoring, a practice that is not yet widespread among the majority of clinicians. Additionally, better designed studies are required to assess feasibility of performing safe low-pressure gynecological laparoscopy with deep NMB, and its possible superiority over higher-pressure laparoscopy with moderate blockade which is the current standard of care.

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