

## Evidence for the need of a deep neuromuscular block during laparoscopic surgery?

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**Abstract** : Since sugammadex has been available, maintaining a continuous deep neuromuscular block (cDNMB) from tracheal intubation until closure of the fascia during laparoscopic surgery is no longer incompatible with a fast recovery. In this review, studies comparing cDNMB [0 train-of-four (TOF) counts, 1-2 post-tetanic counts] and continuous moderate neuromuscular block (cMNMB) (1-3 TOF counts) are analyzed. In 9 available studies for laparoscopy, the authors concluded that cDNMB provides superior surgical working conditions, with lower insufflation pressures, and, therefore, less pain. Regrettably for anesthesiologists, the main focus of those studies was the surgical working conditions (evaluated using a non-validated scale), with less emphasis on patient-related outcomes. Moreover, the control group often had very light block. Due to these problems, we suggest that there is not much evidence supporting the routine use of cDNMB at the moment. This does not mean that cDNMB could not have some advantages.

**Key words** : Deep neuromuscular block, neuromuscular blocking drugs, muscle relaxation, muscle relaxants, depth of neuromuscular block.

### INTRODUCTION

Neuromuscular blocking drugs (NMBD) were first clinically used in anesthesia in 1912. The routine use of NMBD was delayed until approximately 1942, when studies demonstrated that these drugs reduce the incidence of larynx trauma at intubation (1-4). In 1953, the use of acetylcholinesterase inhibitors was introduced to improve spontaneous ventilation at the end of surgery (5). However, this was not useful to antagonize a deep neuromuscular block (DNMB) (6). With neostigmine, indeed, there is rapid recovery only when 3 to 4 tactile train-of-four (TOF) counts are present (7). As a consequence, DNMB has been wisely avoided at the end of surgery for a long time (8, 9). In Belgium, sugammadex (Bridion®) became available in 2009 (10). This medication is a modified  $\gamma$ -cyclodextrin molecule that selectively encapsulates aminosteroidal NMBD such as rocuronium, vecuronium, and probably also

pancuronium (9-14). It reverses DNMB, depending on the dose, within 2 to 5 minutes, with high predictability, and without important side effects (6, 8-10, 12-15). This drug allows maintaining DNMB (cDNMB) until fascia closure, and having rapid reversal without any risks of residual paralysis (1, 15, 16).

Maintaining cDNMB until the end of surgery could have some advantages, because central muscles such as those constituting the diaphragm, the abdominal wall, the larynx, and the corrugator supercilii have a higher density of acetylcholine receptors than peripheral muscles such as the adductor pollicis and the orbicularis oculi. Therefore, central muscles are relatively resistant to NMBD, display a less intense peak effect, and recover faster from NMB. Consequently, these muscles may possibly be not relaxed adequately during surgery, when the adductor pollicis serves to monitor NMB depth. Obtaining a near complete block of these muscles would require using the post tetanic count (PTC) mode of monitoring, with less than 2 PTC responses at the adductor pollicis muscle (17-20). In this review, we were interested in addressing the question of the need for cDNMB during laparoscopic surgery.

### METHODS

Articles were searched in MEDLINE using the terms “deep neuromuscular block(ade)”. The articles were included or excluded by judgement on the title and relevance to this review. The reference lists of the relevant articles were studied for other usable articles. The last search was conducted on the 17<sup>th</sup> of March, 2017. This literature is hereby summarized, focusing on the comparison between

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cDNMB and continuous moderate neuromuscular block (cMNMB). This review was approved by the Supervisory Committee on Medical Ethics of the Catholic University of Leuven, Belgium.

## RESULTS

### *Definitions of NMB depth*

Definitions of NMB depth may vary, but, usually, 0 PTC response and 0 TOF response are considered intense block. DNMB is described as a 0 TOF with 1-2 PTC, and MNMB as a 1-3 TOF. A shallow block is considered to be present when there are 4 TOF responses. The extubation safety level is reached when the TOF ratio is higher than 0.9 (9, 10, 12, 14, 16, 21-27).

### *Advantages of cDNMB during laparoscopy*

Only 9 randomized clinical trials (RCT's) with a blind comparison between cDNMB and cMNMB during laparoscopy were found. In most of these studies, the cDNMB group received an intubation dose of rocuronium, followed by a continuous infusion, and the cMNMB group received one or more bolus doses. The details about each study can be found in the appendix. In two studies, a patient-related outcome was the primary endpoint. In the others, the subjective surgical conditions, rated using a non-validated scale (e.g. poor/acceptable/good/optimal) and the intra-abdominal pressure, were the primary outcome. Seven out of the 9 studies were at least partially supported by the manufacturer of sugammadex.

In the first study by Martini *et al.* (25), the main result was that the surgical conditions, rated on a 5 point scale, were significantly better in the cDNMB group ( $4.7 \pm 0.4$  as compared to  $4.0 \pm 0.4$ ). The difference of 0.7 points (18%) was considered important and clinically significant by surgeons. The scale used for the surgical evaluation was not validated, but it was tested during 5 surgical procedures that were not included in that study. The results of the secondary outcomes were that there was no difference in hemodynamic variables during surgery, time to TOF ratio  $> 0.9$ , and variables in the post-anesthesia care unit (PACU) (pain, sedation, and cardiorespiratory variables).

In another study, Dubois *et al.* (15) concluded that cDNMB significantly improved surgical conditions, and that unacceptable circumstances were completely eliminated. Surgical conditions

were always excellent when TOF count was 0, less optimal surgical conditions occurred only at TOF count  $> 0$ .

In the second study by Martini and Torensma *et al.* (28), cDNMB provided significantly better and more stable surgical conditions, as assessed by a 5 point scale ( $4.8 \pm 0.1$  for cDNMB, and  $4.2 \pm 0.1$  for cMNMB). There was significantly less pain immediately after surgery (Numerical Rating Scale scores (NRS) of cDNMB  $3.9 \pm 0.3$  for cDNMB and  $4.6 \pm 0.4$  for cMNMB), and less shoulder pain on the ward (NRS scores of  $1.3 \pm 0.2$  for cDNMB, and  $1.8 \pm 0.3$  for cMNMB). It is well known that referred shoulder pain is present when there remains a significant volume of gas around the diaphragm. In this study, concepts about the validation of the surgical rating scale were also mentioned (e.g. comparing the ratings of 3 different surgeons at different depths of NMB in 50 patients not included in the study).

Baete *et al.* (29) found no significant differences in surgical conditions, neither in the number of increases of intra-abdominal pressure (IAP) or in the duration of surgery. Respiratory failure causes 12% of mortality after their studied type of surgery, and the investigators measured the postoperative pulmonary function, which was substantially decreased to the same extent in both groups.

In the study by Staehr-Rye *et al.* (30), the goal was to use a low pressure pneumoperitoneum (LPP) of 8 mmHg. When the surgical conditions were inadequate, first, the intra-abdominal pressure (IAP) was raised to 12 mmHg, and, second, a bolus of  $0.6 \text{ mg Kg}^{-1}$  rocuronium was given in the MNMB group while a placebo bolus was given in the cDNMB group. Third, the surgeon undertook action according to usual clinical practice. The proportion of procedures with optimal surgical conditions during the entire procedure was only 28% in the cDNMB group, and 4% in the MNMB group. Sixty % of the procedures were completed at an IAP of 8 mmHg in the cDNMB group, and only 35% in the MNMB group. When the IAP was raised to 12 mmHg, NMB depth was at a PTC of 0-1 in 7 out of 8 patients in the cDNMB group, and the TOF count was  $\geq 2$  in 12 out of 13 patients in the MNMB group. There were no differences in the surgical conditions for the dissection of the gallbladder, or in post-operative pain intensity. The surgeons correctly identified the treatment group only in 42% of cases.

At the beginning of surgery in the Korean study by Koo *et al.* (16), a LPP (8 mmHg) was used. When the surgical conditions were inadequate,

the surgeon could increase the IAP to a Standard Pressure Pneumoperitoneum (SPP) of 12 mmHg. An increase in IAP was more frequent in the cMNMB group as compared to the cDNMB group (34.4% and 12.5%, respectively). The secondary outcome showed that, in the cDNMB group, the surgical conditions were significantly better, there was less intraoperative patient movement, the operating time was shorter, and there was less postoperative pain and shoulder pain after 24 hours.

The hypothesis of Madsen et al. (31) was that the most effective intervention to reduce the incidence of postoperative shoulder pain could be to lower IAP, and that cDNMB could compensate for the compromised surgical conditions associated with this lower pressure. They compared a LPP during a cDNMB with a SPP during a cMNMB. The incidence of pain, defined as a visual analogue scale (VAS) score of  $> 20/100$  during the first 14 postoperative days was significantly lower in the cDNMB group with LPP (28.6% versus 60%,  $p = 0.002$ ). There were no differences in the area under the curve of VAS scores for shoulder, abdominal, incisional and overall pain, oxycodone consumption, incidence of nausea and vomiting, time to recovery of activities of daily living, length of hospital stay, or duration of surgery. No rescue interventions for poor surgical view were necessary.

Rosenberg et al. (32) also compared a cDNMB with a cMNMB and a LPP with a SPP in a 2 x 2 design resulting in 4 groups. Their conclusion was that the cDNMB groups had significant better surgical conditions on a 10-point scale (cDNMB = 7.9 cMNMB = 6.8), and that the use of LPP did not result in improved VAS pain scores 24 hours postoperatively (LPP = 2.6 and SPP = 2.7). Although it was not the objective of the study, the authors also established that LPP with cDNMB could not replace a correct insufflation pressure of the SPP to provide adequate surgical conditions. The scores were still higher in the cMNMB-SPP group than in the cDNMB-LPP ( $9.03 \pm 1.56$  and  $6.77 \pm 3.52$ , respectively), no rescue interventions (i.e. increasing IAP or extra doses of rocuronium) were requested by the surgeons in the SPP group, while they asked it in 12 out of 60 patients in the LPP group. Finally, the surgical condition scores were comparable in the cDNMB-SPP and cMNMB-SPP groups ( $9.10 \pm 1.21$  and  $9.03 \pm 1.56$ , respectively).

In the Korean RCT by Kim et al. (33), the surgeons started with an IAP of 12 mmHg and titrated the IAP to the lowest value while preserving adequate surgical conditions. The cDNMB allowed using a lower IAP (cDNMB =  $9.3 \pm 1.3$  and cMNMB

=  $12.0 \pm 0.5$  mmHg), there was less postoperative pain, and a faster recovery of bowel function.

*Is it necessary to use cDNMB or could a shallower block suffice?*

Examples of successful laparoscopy without NMBD

Four studies (34-37) compared a NMB with no NMB, and 2 studies (38, 39) compared a cMNMB with only an intubation dose of NMBD followed by spontaneous recovery. The surgical conditions were adequate in all groups, except for one study (37) where 27% of patients without NMB had an inadequate pneumoperitoneum for trocar insertion. In one other study (39), a rescue dose of NMBD was needed in the group with only the intubation dose of NMBD. In that study, laparoscopic gastric banding was performed, and in the 5 other studies, laparoscopic pelvic surgery was carried out.

Advantages of low pressure pneumoperitoneum

Systematic reviews (40-42) comparing LPP and SPP show some evidence that LPP may reduce postoperative pain, but there is no evidence for other advantages such as hemodynamic stability.

Studies with objective measurements of abdominal space

The abdominal space was measured (volume or skin-sacral promontory distance) under DNMB and no NMB in four studies. One study (43) was performed in pigs, and there were no significant differences. Three human studies (27, 44, 45) found a significant difference in favor of DNMB, one of these (27) concluded that the skin-sacral promontory distance at 8 mmHg IAP with DNMB was comparable to the same distance at 12 mmHg without NMB.

One study (46) (comparing DNMB and MNMB) showed no significant improvements of these measurements under DNMB. In a second study (47), there were significant improvements in abdominal space, but the volumes under DNMB with LPP were smaller than under MNMB with SPP.

In 3 studies (44, 45, 47), there was much interpatient variability, the increase in volume/sacral-skin promontory distance with NMB was not recorded in all patients, or was small and of unknown clinical relevance.

## Issues with DNMB

### Postoperative residual block

In current practice, most anesthesiologists do not use quantitative neuromuscular monitoring, which is reflected in the high incidence (45%) of postoperative residual muscle relaxation (defined as a TOF ratio < 0.9) in the PACU (48-50). Even at levels of recovery as high as a TOF ratio of 0.7-0.8, residual paralysis may lead to complications (upper airway collapse, reduced protection against aspiration, patient anxiety, dyspnea, atelectasis, pneumonia) (48, 51-53). After using a continuous infusion of cisatracurium or rocuronium, which was discontinued at the beginning of surgical closure, and without antagonism, only 27% and 7%, respectively, had a TOF ratio  $\geq$  0.9 (54). It is mandatory to monitor muscle relaxation during cDNMB.

### Cost of sugammadex

To reverse DNMB, 4 mg kg<sup>-1</sup> of sugammadex is indicated, corresponding to 2 vials of 200 mg for a 75 Kg person. In Belgium, this costs €164 (55, 56). Such a direct cost must be balanced against significant delays in PACU discharge (9, 12). Pharmacoeconomic studies conclude that the routine use of sugammadex could be cost-effective, if the reduction in recovery time is associated with improvement of productivity (9).

### Potential for patient awareness

A study about the use of the bispectral index (BIS) in awake volunteers receiving NMBD concluded that the BIS algorithm requires both muscle and EEG activity to generate values indicating that the patient is awake. Total awareness is certainly possible at BIS values of 60-75 in a patient with a DNMB. So, BIS monitoring may be unreliable in patients receiving DNMB (57).

## DISCUSSION

In the above-mentioned 9 studies, extensive work was done to investigate cDNMB. In our opinion, these studies have some limitations. In most studies, the surgical conditions were the primary outcome. Only two RCT's used a patient-related primary outcome (post-operative pain and recovery of the bowel function). The main reason for this is that complications, such as accidental bowel or

vessel perforation, are rare during the investigated procedures. Consequently, an enormous sample size would be necessary to investigate the effect of DNMB on the incidence of such complications with sufficient power. Insofar as this is hardly achievable, the authors used the surgical conditions as a surrogate estimate of higher probability of complications (21, 22). The surgical conditions were assessed using a non-validated scale, except for 2 studies (25, 28). In 6 out of the 9 RCT's comparing cDNMB and cMNMB, surgery was performed by only 1 to 3 very experienced surgeons, to ascertain consistency in surgical technique and subjective ratings. In 7 out of 9 RCT's, the trials were financially supported by the manufacturer of sugammadex.

To our opinion, it is essential to compare cDNMB with a real cMNMB, if one wants to conclude that cDNMB is superior (29). The reason is that, when a study concludes that cDNMB is better than a shallow block, it is possible that cMNMB would also be adequate. Unfortunately, NMB depth was correctly assessed using TOF measurements in only one study (25). In 5 RCT's (16, 28, 29, 32, 33), cDNMB and cMNMB depths were probably correct for most patients, although measured numbers were not provided in the article. In the other 3 trials (15, 30, 31), the control group received an intubation dose only, which was followed by spontaneous recovery. This is clearly not a cMNMB. For example, in the study by Dubois *et al.* (15), extra doses of 5 mg rocuronium were given in the cDNMB group, when TOF count was > 2. Consequently, this group included patients with TOF counts of 1 and 2. A graph in the article shows that even TOF counts of 3 and 4 were measured in the cDNMB group. Hence, an unknown number of surgical field score observations were really made during MNMB in this group. In the group with the shallow block, the initial intubation bolus of rocuronium (0.45 mg Kg<sup>-1</sup>) was followed by spontaneous recovery. Normally, 25 minutes later, the TOF count would be 4, and, after 45 minutes, the twitch height is certainly 90% of control. When compared with the duration of surgery ( $74 \pm 23$  min), it becomes clear that, during half of the surgery length, there was no NMB at all in the group of the shallow block (9, 21, 23). Another example can be found in the study by Staehr-Rye *et al.*, where the control group received only an 0.3 mg Kg<sup>-1</sup> intubation dose of rocuronium, followed by spontaneous recovery. In this group, at 50% of surgery duration, 47% of patients had a TOF count of 4, and, at 75% of surgery duration, 89% had a TOF ratio > 0.4. Consequently, the exact comparison was between cDNMB and a very

shallow or minimal block during a considerable portion of the procedure (21, 23, 30, 58). When there are such big differences in NMB between the groups, it is likely that significant differences will be seen.

In an illustration of the article by Dubois et al., we see that, in the 14 patients with unacceptable surgical conditions, half of them had a TOF ratio > 0.4, and that the surgical conditions were unacceptable only when TOFc was  $\geq 3$  (9, 15, 21, 23). We learn from the study by Staehr-Rye et al. that cDNMB is not a “fit all”, given the low number of successes (28% optimal surgical conditions, 60% of surgery completed at LPP) (21, 23, 30, 58, 59). The study by Martini et al. is the only trial that compares real cDNMB and cMNMB with certainty. Unfortunately, the difference of 0.7 on a 5-point scale for the surgical condition score is very modest. Furthermore, the sample size was small in the first study (24 patients) (21, 22, 25).

Two reviews in favor of cDNMB (22, 59) state that a cDNMB improves surgical conditions and patient outcomes. Four reviews against cDNMB (9, 21, 23, 58) have been published. They mainly focus on the methodological limitations listed above, and conclude that there is not enough evidence to use cDNMB routinely. There is only one systematic review with meta-analysis (60). It concludes that cDNMB improves surgical conditions, with a mean difference of 0.65 on a 5-point scale. It facilitates the use of LPP, and reduces early post-operative pain scores by 0.52 VAS points.

The absence of studies of high quality does not directly imply that it is not needed to apply a cDNMB. cDNMB is a new technique, and the available studies are just starting to investigate it. The concept of a faster recovery of the central muscles (see introduction) is proven. Theoretically, cDNMB can be a solution for this. Indeed, surgeons mention that there are less movements of the diaphragm under cDNMB. It is the task of the anesthesiologist to facilitate surgery. There is certainly a need for well-designed studies comparing true cDNMB with true cMNMB, not only evaluating the surgical conditions with a standardized validated rating scale, but more importantly evaluating the patient-related outcomes. Possibly, cDNMB has advantages in only a subgroup of patients and procedures.

After discussing cDNMB, the focus could be on NMB in general, but it should not be forgotten that the surgical conditions are the end product of multiple factors (21, 23, 59). Rather than continuously maintaining NMB, it is very important to take immediate actions when the

surgeons mention that the surgical conditions are inadequate (21). Although it is true that NMBD are the most efficient way to allow muscles to stretch to their maximum length, other measures are also possible (15). Increasing the depth of anesthesia and administering opioids reduce the need for NMBD (10, 15, 21, 23, 25). Applying a light hyperventilation lowers the arterial CO<sub>2</sub> partial pressure, which reduces the respiratory drive and the movements of the diaphragm (21, 25, 58). Changes in body position and, as a last action, increasing the insufflation pressure can also improve the surgical conditions (15, 59).

## CONCLUSIONS

Most of the available studies compared cDNMB with a very shallow or minimal block for a considerable portion of the procedure length, the rating scales for the surgical conditions were not verified, and were surrogate parameters for the urge of complications. The differences in the results were often small and the sample size was sometimes too small. To date, there is not much evidence showing improvement in surgical outcome or reduction of complication rates. However, the absence of high quality studies about this subject does not mean that cDNMB may not have some advantages. There is certainly a need for more exploration to compare cDNMB and cMNMB with a need for a large sample size.

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## APPENDIX: TABLE WITH THE DETAILS OF THE STUDIES USED IN THIS REVIEW

P = patient outcomes

S = surgical conditions

The idea of making this table was inspired by the table in reference (59). All the references of this table can be found in the text where the studies are discussed. S = surgery; P = patient

Study	Surgical procedure	Treatment group	Control group	Results	Author's conclusions	Remarks by others
Martini CH, Boon M, Bevers RF, Arts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. <i>Br J Anaesth.</i> 2014 (25)	a) Elective laparoscopic prostatectomy or nephrectomy b) RCT with blinding c) 24 patients d) 1 very experienced surgeon 1. None 2 & 3. Propofol to target BIS 40-50, sufentanil	cDNMB: rocuronium: intubation dose 1 mg Kg <sup>-1</sup> , followed by infusion 0.6 mg Kg <sup>-1</sup> h <sup>-1</sup> Measured depth of NMB: TOFc: 0 PTC: 1.6 ± 1.5 Reversal by 4 mg Kg <sup>-1</sup> sugammadex	cMNMB: bolus 0.5 mg Kg <sup>-1</sup> atracurium, followed by infusion of 0.5 mg Kg <sup>-1</sup> h <sup>-1</sup> mivacurium Measured depth of NMB: TOFc: 2.2 ± 0.9 Reversal by 1-2 mg neostigmine + 0.5-1 mg atropine	-S: Improved surgical condition scores (on 5 points): 4.7 ± 0.4 ↔ 4.0 ± 0.4 (p < 0.001) -P: No benefits (no difference in hemodynamic parameters or pain) -Poor agreement about the surgical conditions between surgeons and anesthesiologists	Improved quality of surgical conditions.	-Only 1 experienced surgeon operated and assessed the rating scale. -This study is methodologically correct, but the difference in the scores is very modest and sample size is small. -p <sub>ET</sub> CO <sub>2</sub> was not well controlled (33-56 mmHg)
Dubois PE, Putz L, Jamart J, Marotta ML, Gourdin M, Donnez O. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: a randomized controlled trial. <i>Eur J Anaesthesiol.</i> 2014 (15)	a) Laparoscopic hysterectomy b) RCT with blinding c) 100 patients d) 1, 0.5 mg lorazepam 2. 0.15 µg Kg <sup>-1</sup> sufentanil, 0.5 mg Kg <sup>-1</sup> ketamine, 2-3 mg Kg <sup>-1</sup> propofol 3. 1 MAC desflurane	DNMB: rocuronium: intubation dose 0.6 mg Kg <sup>-1</sup> + extra doses of 5 mg when TOFc > 2 TOFc of 3-4 were observed Reversal by 2-4 mg Kg <sup>-1</sup> sugammadex	MNMB: rocuronium: intubation dose 0.45 mg Kg <sup>-1</sup> followed by spontaneous recovery Reversal by 0.05 mg Kg <sup>-1</sup> neostigmine + glycopyrrolate if TOF ratio < 0.9	-S: -Improved surgical condition scores (on 4 points): 1.3 ± 0.8 ↔ 1.1 ± 0.4 (p > 0.1) -Excellent surgical conditions: DNMB: 68% ↔ MNMB: 42%	DNMB significantly improved surgical field scores and made it possible to completely prevent unacceptable surgical conditions.	-TOFc: 1-2 ≠ DNMB -Mean operation time was 74 min → in the group of MNMB: for half of the surgery there was almost no block P Real comparison: DNMB (or moderate block for an unknown time) ↔ no block for probably half the duration of the surgery procedure
Torensma B, Martini CH, Boon M, Olofsen E, Veld B, Liem RS, et al. DNMB Improves Surgical Conditions during Bariatric Surgery and Reduces Postoperative Pain: A Randomized Double Blind Controlled Trial. <i>PLoS One.</i> 2016 (28)	a) Laparoscopic Roux-Y-gastric bypass b) RCT with blinding c) 100 patients 3 surgeons d) 1. not mentioned 2 & 3. propofol, remifentanyl titrated to BIS 40-60 (Ideal body weight was used.)	cDNMB: rocuronium intubation bolus of 30 mg, followed by extra doses of 10 mg titrated to PTC 2-3 Reversal by 4 mg Kg <sup>-1</sup> sugammadex Total dose of rocuronium used: median 70 mg, range 45-145 mg PTC measured: 3.6 ± 0.2	cMNMB: rocuronium intubation bolus of 30 mg, followed by extra doses of 10 mg titrated to TOFc 1-2 Reversal by 2 mg Kg <sup>-1</sup> sugammadex Total dose of rocuronium used: median 40 mg, range 30-130 mg TOFc measured: 1.9 ± 0.1	-S: Significant better and more stable surgical conditions rated on a 5-point scale (cDNMB: 4.8 ± 0.1 γ cMNMB: 4.2 ± 0.1, p < 0.001) -P: Significant improved NRS pain scores in PACU (cDNMB: 3.9 ± 0.3 ↔ cMNMB: 4.6 ± 0.4, p = 0.03) and reduced shoulder pain on the ward (cDNMB: 1.3 ± 0.2 ↔ cMNMB: 1.8 ± 0.3, p = 0.03).	cDNMB has advantages for the patient and for the surgeon: less postoperative pain and more stable and improved surgical conditions.	-The differences were statistically significant, but are they clinically relevant? -The achieved depth of NMB is only approximately according to the definitions.

Study	Surgical procedure a) Design b) Sample size c) Anesthesia 1. Premedication 2. Induction 3. Maintenance	Treatment group	Control group	Results	Author's conclusions	Remarks by others
Baete S, Vercruyse G, Vander Laenen M, De Vooght P, Van Melckebeek J, Dylst D, et al. The Effect of DNMB Versus MNMB on Surgical Conditions and Postoperative Respiratory Function in Bariatric Laparoscopic Surgery: A Randomized, Double Blind Clinical Trial. <i>Anesth Analg.</i> 2017 (29)	a) Bariatric laparoscopic surgery b) RCT with blinding c) 60 patients 1 surgeon d) 1. not mentioned 2 & 3. TIVA propofol TCI, remifentanyl 0.15-0.5 µg Kg <sup>-1</sup> min <sup>-1</sup>	cDNMB: rocuronium intubation bolus of 0.6 mg Kg <sup>-1</sup> + continuous infusion 0.6 mg Kg <sup>-1</sup> h <sup>-1</sup> titrated to PTC 1-2  Reversal by 4 mg Kg <sup>-1</sup> sugam-madex (Lean body mass was used)  Total dose of rocuronium used: 1.0 mg Kg <sup>-1</sup> ± 0.3	cMNMB: rocuronium intubation bolus of 0.6 mg Kg <sup>-1</sup> + extra doses of 10 mg titrated to TOFc 1-2  Reversal by 0.05 mg Kg <sup>-1</sup> neostig-mine + glycopyrrrolate  Total dose of rocuronium used: 0.7 mg Kg <sup>-1</sup> ± 0.2	-S: No significant differences in the surgical conditions rated on a 5-point scale (cDNMB: 4.2 ± 1.0 ↔ cMNMB: 3.9 ± 1.1, p = 0.16) -the number of increases of IAP > 13 mmHg (cDNMB: 0.2 ± 0.9 ↔ cMNMB: 0.3 ± 1.0, p = 0.69) -duration of surgery (cDNMB: 61.3 ± 15.1 ↔ cMNMB: 70.6 ± 20.8, p = 0.07) -P: Postoperative pulmonary function (peak expiratory flow, FEV <sub>1</sub> , FVC, need for respiratory support) was decreased substantially postoperatively in both groups, but there were no significant differences between cDNMB.	There was not enough evidence to demonstrate the superiority of the cDNMB.  No TOF measurements were given.	
Staeher-Rye AK, Rasmussen LS, Rosenber J, Juul P, Lindkaer AL, Riber C, et al. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade: a randomized clinical study. <i>Anesth Analg.</i> 2014 (30)	a) Elective laparoscopic cholecystectomy under LPP of 8 mmHg b) RCT with blinding c) 48 patients 2 experienced surgeons d) 1. none 2. 2 mg Kg <sup>-1</sup> propofol, 0.5 µg Kg <sup>-1</sup> min <sup>-1</sup> remifentanyl 3. TIVA: propofol, remifentanyl, adjusted under guidance of entropy and arterial blood pressure	cDNMB: rocuronium: intubation dose 0.3 mg Kg <sup>-1</sup> + 0.7 mg Kg <sup>-1</sup> bolus after 2 min + continuous infusion 3-4 mg Kg <sup>-1</sup> h <sup>-1</sup> started when PTC became > 0 and was titrated to PTC = 0-1  Median measured depth of NMB: 0-1 PTC during the whole surgery time  0-1 PTC were achieved during 91% of the procedure time  Reversal by 2-8 mg Kg <sup>-1</sup> sugam-madex if TOF ratio < 0.9	MNMB: intubation dose 0.3 mg Kg <sup>-1</sup> rocuronium followed by spontaneous recovery  Median measured depth of NMB (expressed as % height of first TOF twitch of control): -Incision: 0% (vs TOFc: 0) -50% duration surgery: 47% (vs TOFc: 4) -75% duration surgery: 89% (vs TOF ratio > 0.4) -End of surgery: 99%  TOFc ≥ 2 during 87% of procedure time  Reversal by 2-8 mg Kg <sup>-1</sup> sugam-madex if TOF ratio < 0.9	-P: No differences and cMNMB (post-operative pain, post-operative hospitalization time, time to normal activity, PONV) -S: -Proportion of procedures with optimal surgical space conditions during the entire procedure: DNMB: 28% ↔ MNMB: 4% -Proportion of procedures that could be completed under optimal conditions at 8 mmHg inflation: DNMB: 60% ↔ MNMB: 35% -Surgeons correctly identified 20 of 48 patients treatment group.	DNMB marginally improves surgical space conditions during LPP cholecystectomy but in half of the procedures intra-abdominal pressure had to be increased to secure acceptable surgical space conditions.  Even in the DNMB group, only in 60% of patients was the primary outcome reached ↔ DNMB is not a cure-all	

Study	Surgical procedure a) Design b) Sample size c) Anesthesia 1. Premedication 2. Induction 3. Maintenance	Treatment group	Control group	Results	Author's conclusions	Remarks by others
Koo BW, Oh AY, Seo KS, Han JW, Han HS, Yoon YS. Randomized Clinical Trial of Moderate Versus Deep Neuromuscular Block for Low-Pressure Pneumoperitoneum During Laparoscopic Cholecystectomy. World J Surg. 2016 (16)	a) Laparoscopic cholecystectomy under LPP of 8 mmHg b) RCT, blinding not fully described c) 64 patients d) 1. IV 0.02 mg Kg <sup>-1</sup> midazolam 2 & 3. TCI propofol & remifentanyl. BIS monitoring	cDNMB: intubation dose of 0.6 mg Kg <sup>-1</sup> rocuronium, bolus dose of 5-10 mg rocuronium was used to maintain DNMB Reversal by 4 mg Kg <sup>-1</sup> sugammadex	cMNMB: intubation dose of 0.6 mg Kg <sup>-1</sup> rocuronium, bolus dose of 5-10 mg rocuronium was used to maintain MNMB Reversal by 0.05 mg Kg <sup>-1</sup> neostigmine + 0.01 mg Kg <sup>-1</sup> glycopyrrolate	-P: -Pain and shoulder tip pain was significantly lower at 24 hours in cDNMB -No difference demonstrated in prevalence of dry mouth, nausea, vomiting -S: -Rate of increasing intra-abdominal pressure was significantly lower in the cDNMB group (12.5% ↔ 34.4%, p = 0.039) -Proportion of excellent or good surgical conditions: significantly higher in cDNMB (68.8% ↔ 34.4%, p = 0.006) -Operating time: significantly shorter in cDNMB -Intra operative movement was significantly lower in cDNMB (3.1% ↔ 21.9%, p = 0.023)	cDNMB was associated with a lower rate of conversion from LPP to SPP and better surgical conditions than cMNMB.	This was a real comparison of a cDNMB with cMNMB, but the blinding was not fully described
Madsen MV, Isre O, Staehle Rye AK, HH, Rosenberg J, Lund J, et al. Postoperative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low-pressure pneumoperitoneum: A randomized controlled trial. Eur J Anaesthesiol. 2016 (31)	a) Laparoscopic hysterectomy b) RCT, double blinded c) 99 patients -2 very experienced gynecologists d) 1. not mentioned 2. 2 mg Kg <sup>-1</sup> propofol, 0.5 µg Kg <sup>-1</sup> min remifentanyl 3. 3 mg Kg <sup>-1</sup> h <sup>-1</sup> propofol, remifentanyl 0.25-0.5 µg Kg <sup>-1</sup> min <sup>-1</sup>	DNMB (PTC = 0-1) + LPP (8 mmHg): -Intubation dose 0.3 mg Kg <sup>-1</sup> rocuronium just after intubation -Infusion of 0.3-0.4 mg Kg <sup>-1</sup> h <sup>-1</sup> rocuronium was started when PTC > 0 titration towards PTC = 0-1 Reversal by sugammadex	MNMB + SPP (12 mmHg): Intubation dose of 0.3 mg Kg <sup>-1</sup> rocuronium followed by spontaneous recovery	-P: -Significant reduction of proportion of shoulder pain (VAS > 20/100): 28.6% versus 60% -S: -No differences in: -Area under the curve VAS scores for shoulder, abdominal, incisional and overall pain during 4 and 14 postop days -Oxycodone consumption within 24 hours postop -Incidence of nausea and vomiting -Antiemetic consumption within 24 hours postop -Time to recovery of activities of daily living -Length of hospital stay -Duration of surgery	P: Shoulder pain was significantly reduced (28 ↔ 60%) A single intubation dose is not a MNMB, this intubation dose is also only half of the recommended dose → It is likely the authors were comparing DNMB with no block	

Study	Surgical procedure	Treatment group	Control group	Results	Author's conclusions	Remarks by others
Rosenberg J, Herring WI, Blohner M, Mulier JP, Rahe-Meyer N, Woo T, et al. DNMB Improves Laparoscopic Surgical Conditions: A RCT. Adv Ther. 2017(32)	a) Laparoscopic cholecystectomy b) RCT with blinding; 2 x 2 factorial design: cDNMB ↔ cMNMB and LPP ↔ SPP: patients were randomized to 1 of these 4 combinations c) 127 patients Probably 1 surgeon d) 1. not mentioned 2. 2.5 mg Kg <sup>-1</sup> propofol, 1 μg Kg <sup>-1</sup> remifentanyl 3. 6-12 mg Kg <sup>-1</sup> h <sup>-1</sup> propofol, 0.25 μg Kg <sup>-1</sup> min <sup>-1</sup> remifentanyl, titrated to BIS value of 40-50	cDNMB: intubation bolus 0.45 mg Kg <sup>-1</sup> rocuronium, followed by additional doses or continuous infusion titrated to a PTC of 1-2 (range PTC: 1-5)  In unacceptible surgical conditions: increasing IAP by 4 mmHg  Reversal by 4 mg Kg <sup>-1</sup> sugammadex  LPP: 8 mmHg IAP	cMNMB: intubation bolus 0.45 mg Kg <sup>-1</sup> rocuronium, followed by additional doses or continuous infusion titrated to a TOF ratio of 10% (range TOF <sub>c</sub> 2 to TOF ratio 20%)  In unacceptible surgical conditions: deepening the NMB to 1-2 PTC; increasing IAP by 4 mmHg  Reversal by 2 mg Kg <sup>-1</sup> sugammadex  SPP: 12 mmHg IAP	-S: -Significant better surgical conditions rated on an 11-point numerical scale in the cDNMB group and SPP (cDNMB: 7.9 ↔ cMNMB: 6.8, p = 0.026; SPP: 8.9 ↔ LPP: 5.9, p < 0.001) -Surgical condition scores in each group: -cMNMB+SPP: 9.03 ± 1.56 -cMNMB+LPP: 5.23 ± 3.94 -cDNMB+SPP: 9.10 ± 1.21 -cDNMB+LPP: 6.77 ± 3.52 -The surgeons asked for deepening of the NMB of raising the IAP in 7/30 patients in the cMNMB-LPP and in 5/30 patients in the cDNMB-LPP. In the SPP group, no rescue intervention was asked. -P: There were no significant differences in pain scores 24 hours postoperatively (LPP: 2.6 ↔ SPP: 2.7, p = 0.494; cMNMB: 2.5 ↔ cDNMB: 2.8, p = 0.148)	-The cDNMB provided better surgical conditions, but the results suggest a larger role of the IAP than the depth of NMB. The cDNMB + LPP does not replace the appropriate insufflation pressure of the cMNMB + SPP. -The (shoulder) pain scores were not improved by LPP.	-No TOF measurements are given in the article. -TOF <sub>c</sub> 3 - TOF ratio 20% is more shallow than a MNMB.
Kim MH, Lee KY, Min BS, Yoo YC. Maintaining Optimal Surgical Conditions with Low Insufflation Pressures is Possible with DNMB During Laparoscopic Colorectal Surgery: A Prospective, Randomized, Double-Blind, Parallel-Group Clinical Trial. Medicine (Baltimore). 2016 (33)	a) Laparoscopic colorectal surgery (low anterior resection, hemicolectomy), anterior resection, transverse colectomy) b) RCT with blinding The surgeon titrated the initial IAP of 12 mmHg to the lowest value possible with preserving the surgical conditions. c) 61 patients d) 1. 0.2 mg glycopyrrolate IV 2.1.5-2 mg Kg <sup>-1</sup> propofol, 1-2 mg Kg <sup>-1</sup> remifentanyl 3. 4-7V% desflurane, 0.05-0.2 μg Kg <sup>-1</sup> min <sup>-1</sup> remifentanyl	cDNMB: rocuronium 0.6 mg Kg <sup>-1</sup> intubation bolus, followed by continuous infusion titrated to a PTC of 1-2  Reversal by 4 mg Kg <sup>-1</sup> sugammadex	cMNMB: rocuronium 0.6 mg Kg <sup>-1</sup> intubation bolus, followed by continuous infusion titrated to a TOF <sub>c</sub> of 1-2  Reversal by 2 mg Kg <sup>-1</sup> sugammadex	-P: Advantages of the cDNMB: -It allowed a lower IAP (cDNMB: 9.3 ± 1.3 ↔ cMNMB: 12.0 ± 0.5 mmHg, p < 0.001) -Less postoperative shoulder tip pain (p = 0.026) and abdominal pain (p < 0.001) -Time to flatus (cDNMB: 40 ± 11.3 h ↔ cMNMB: 64 ± 31 h, p = 0.002) and sips of water time was shorter (cDNMB: 16 ± 5.4 h ↔ 19 ± 6 h, p = 0.005), but there were no differences in hospital stay duration. -S: -Surgical conditions rated on a 5 point scale were significantly superior in the cDNMB group (extremely poor/ poor / acceptable/ good/ optimal: cDNMB: 0/1/0/9/20 ↔ cMNMB: 0/0/7/22/22, p < 0.001)	cDNMB provided a lower IAP possible with preserved surgical conditions, less postoperative pain and a faster recovery of the bowel function. One should consider a cDNMB for patients undergoing laparoscopic surgery.	No TOF measurements are given.