Does deep neuromuscular blockade during laparoscopy procedures change patient, surgical, and healthcare resource outcomes? A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background

Deep neuromuscular blockade may facilitate the use of reduced insufflation pressure without compromising the surgical field of vision. The current evidence, which suggests improved surgical conditions compared with other levels of block during laparoscopic surgery, features significant heterogeneity. We examined surgical patient- and healthcare resource use-related outcomes of deep neuromuscular blockade compared with moderate neuromuscular blockade in adults undergoing laparoscopic surgery.

Methods

We conducted a systematic literature review according to the quality standards recommended by the Cochrane Handbook for Systematic Reviews. Randomized controlled trials comparing outcomes of deep neuromuscular blockade and moderate neuromuscular blockade among adults undergoing laparoscopic surgeries were included. A random-effects model was used to conduct pair-wise meta-analyses.

Results

The systematic literature review included 15 studies—only 13 were analyzable in the meta-analysis and none were judged to be at high risk of bias. Compared with moderate neuromuscular blockade, deep neuromuscular blockade was associated with improved surgical field of vision and higher vision quality scores. Also, deep neuromuscular blockade was associated with a reduction in the post-operative pain scores in the post-anesthesia care
unit compared with moderate neuromuscular blockade, and there was no need for an increase in intra-abdominal pressure during the surgical procedures. There were minor savings on resource utilization, but no differences were seen in recovery in the post-anesthesia care unit or overall length of hospital stay with deep neuromuscular blockade.

**Conclusions**

Deep neuromuscular blockade may aid the patient and physician surgical experience by improving certain patient outcomes, such as post-operative pain and improved surgical ratings, compared with moderate neuromuscular blockade. Heterogeneity in the pooled estimates suggests the need for better designed randomized controlled trials.

**Introduction**

Deep neuromuscular block (dNMB) may facilitate the use of reduced insufflation pressure without compromising the surgical field of vision.[1, 2] However, its usage is limited due to a lack of predictable and rapid recovery with conventional neuromuscular block (NMB) antagonists (neostigmine) or spontaneous recovery. With the availability of selective relaxant binding agents—such as sugammadex for rocuronium/vecuronium bromide-induced NMB, which is uniquely indicated for the reversal of dNMB—rapid recovery can be achieved.

Bruintjes et al. and Park et al. reported surgical conditions and post-operative conditions related to the use of dNMB in laparoscopic procedures through a systematic review and meta-analysis of randomized controlled trials (RCTs) published up to December 2016 and October 2017, respectively. In both studies, dNMB showed improved surgical conditions when compared with other levels of block during laparoscopic surgery. However, pooled estimates had significant heterogeneity, suggesting the need for further studies accounting for these variations.[3, 4] Neither study included all peri-operative outcomes, such as need to change intra-abdominal pressure (IAP) during surgery, healthcare resource use-related outcomes, or patient-reported outcomes.[3, 4].

A systematic literature review (SLR) and meta-analyses were conducted to assess surgical patient- and healthcare resource use-related outcomes of dNMB compared with moderate neuromuscular blockade (mNMB) in adults undergoing laparoscopic surgery.

**Methods**

The SLR was conducted in accordance with the quality standards recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and the Cochrane Handbook for Systematic Reviews.

**Criteria for inclusion in systematic review**

We planned to include RCTs comparing outcomes of dNMB (defined as a train-of-four [TOF] count of zero or a post-tetanic count [PTC] count of 1–2) and mNMB (defined as a TOF count of 1–4) among adults undergoing laparoscopic surgeries. We excluded trials that reported a comparison of dNMB with no NMB, or shallow/restricted/standard NMB, and observational studies. We intended to capture all outcomes pertaining to surgical outcomes, post-operative patient-reported outcomes, and healthcare resource utilization. Outcomes relating to the quality of surgical field (#1) and the need to increase IAP levels (#2) were
included to indicate any impact on the surgical procedure itself. The impact on the patient was assessed using measures of post-operative pain in the post-anesthesia care unit (PACU) (#3) and at 24 hours after surgery (#4), as measured by pain scores using an 11-point Likert scale (0 = no pain, 10 = worst possible pain); post-operative nausea/vomiting (#5) was also included. Duration of surgery (minutes; #6), length of hospital stay (days; #7), and length of recovery room stay (in minutes; #8) were included to consider the impact on healthcare resource utilization.

**Database search**

The following electronic databases were searched (from inception to September 14, 2018) for publications relating to laparoscopic abdominal surgery in adults: Embase; MEDLINE, and MEDLINE In-Process via PubMed; Cochrane Library; the Cochrane Central Register of Controlled Trials; and the Database of Abstracts of Reviews of Effects. The searches were limited to publications in English, studies in humans, RCTs, and SLRs of RCTs only. No geographical restrictions were applied.

The search was conducted using the following keywords: “surgery,” “surgical operation,” “surgical procedure,” “laparoscopy,” “minimally invasive surgery,” “endoscopy,” “neuromuscular blocking agent,” “neuromuscular blocking,” “pneumoperitoneum,” “insufflation,” and “intra-abdominal pressure.” See S1 Table for full details of the search strings used.

A grey literature search was conducted for key conference proceedings from 2017 and 2018 (specifically, the American Society of Anesthesiologists, the European Society of Anesthesiology, and the International Anesthesia Research Society) and registries of ongoing clinical trials (clinicaltrials.gov; World Health Organization). The bibliographies of SLRs identified by the searches (published since 2016) were hand-searched for potentially relevant publications.

**Study selection**

Two independent researchers screened publication abstracts against the study inclusion criteria described above; for publications that passed this first screening stage, publications were reviewed in full text. Any disagreements between the researchers were resolved by a third, senior investigator.

**Data extraction and risk-of-bias assessment**

Data were extracted by one reviewer and validated by an independent reviewer in a standardized template developed a priori. The specific data elements extracted included study design, population baseline characteristics, interventions/comparators, and outcomes (including timing and definitions used). A quality assessment of the included studies was undertaken using the Cochrane Risk of Bias tool for RCTs,[5] with each included study with sufficient information (full publication) graded as being at low, moderate, or high risk of bias.

**Statistical analysis**

Pair-wise meta-analyses based on a random-effects (RE) model were used to calculate pooled estimates and 95% confidence intervals (CI) for the relationships between levels of NMB and the outcomes of interest. For dichotomous variables, the effect size was expressed as a pooled odds ratio (pOR); for continuous variables, the effect size was expressed as a pooled mean difference (pMD) across studies if all studies used the same scale, or a pooled standardized mean difference (pSMD) if the scales used were different. A significance level of $p = 0.05$ was used for all variables. In each analysis, the heterogeneity of the estimates between studies was
examined by computing $I^2$ statistics, estimating between study variance ($\tau^2$) using restricted maximal likelihood (REML) methodology, and computing the p-value in the Cochrane's Q test of homogeneity. The robustness of the study was explored using sensitivity analyses that included meta-analyses performed by a fixed-effects (FE) model and by serial single trial exclusions of studies causing heterogeneity. All analyses were performed using the “meta” package in R (version 3.5.1).

**Results**

Of the 6,982 records identified (including records from grey literature), 15 fulfilled the study-selection criteria (Fig 1).

Table 1 describes the RCTs included in the SLR. Most were carried out in Asia (n = 6) or Europe (n = 7). The number of patients enrolled in each study ranged from 20 to 127. Table 2 describes the baseline characteristics of the study population in each RCT. The mean age across studies ranged from 41 to 63.9 years, and all trials enrolled patients with an American Society of Anesthesiologists (ASA) status ranging from I–III. Three studies enrolled patients with a high body mass index ($\geq 40$ kg/m$^2$). Baseline characteristics were balanced between the intervention and comparator groups across all studies.

Although 15 studies met the inclusion criteria, only 13 were included in the meta-analysis, as two (Matsuzaki 2018[6], Schmartz 2016[7]) did not report any analyzable outcomes.

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*Fig 1. PRISMA diagram: Surgical, patient and HCRU outcomes from RCTs. Abbreviations: DARE: Database of Abstracts of Reviews of Effects; HCRU: healthcare resource utilization; IAP: intra-abdominal pressure; MA: meta-analyses; NMB: neuromuscular block; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: randomized controlled trial; SLR: systematic literature review.*

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Risk of bias assessment

Quality assessment via the Cochrane Risk of Bias tool was possible for the 10 studies for which full-text publications were available—of these, none were deemed to have a high risk of bias (Fig 2; 60% low risk [n = 6], 40% moderate risk [n = 4]). There was insufficient information available for the remaining five studies, since these were published as conference abstracts only.

Surgical outcomes

Quality of surgical field. Five studies reported the quality of surgical field and were included in a meta-analysis (a total of six comparisons, as one study (Zino 2017[8]) reported results separately for two IAP populations). There was high heterogeneity across the studies ($I^2 = 77\%$; $p<0.01$). The outcome was measured subjectively using a 4-point rating scale (1 = excellent; 4 = poor; Hojo 2017[9]) or 5-point Leiden rating scale (1 = extremely poor; 5 = optimal; Baete 2017[10], Martini 2014[11], Torensma 2016[12], Zino 2017[8]). For a continuous outcome, if different studies used measurement scales in opposite directions, means in all

### Table 1. Characteristics of included studies.

| Study ID          | Blinding Personnel | Laparoscopic Surgical Procedure | dNMB   | mNMB   | Country                        | N Randomized | N Completed |
|-------------------|---------------------|---------------------------------|--------|--------|--------------------------------|--------------|-------------|
| Torensma, 2016    | A+S + N             | Bariatric surgery               | PTC 2–3| TOF 1–2| Netherlands                    | 109          | 100         |
| Zino, 2017        | A                   | Bariatric surgery               | PTC 0–1| TOF 1–2| US                             | 107          | 107         |
| Barrio, 2017      | S                   | Cholecystectomy                 | PTC <5 | TOF 1–3| Spain                          | 90           | 90          |
| Hojo, 2017        | A                   | Cholecystectomy                 | PTC 1–2| TOF 1–2| Japan                          | 60           | 60          |
| Koo, 2016         | A+P+S               | Cholecystectomy                 | PTC 1–2| TOF 1–2| Republic of Korea              | 70           | 70          |
| Rosenberg, 2017   | A+P+S               | Cholecystectomy                 | PTC 1–2| TOF 1–2| Austria, Finland, Germany, Italy, the UK | 127          | 117         |
| Kim, 2016         | A+P+S               | Colorectal resection            | PTC 1–2| TOF 1–2| Republic of Korea              | 72           | 72          |
| Koo, 2018         | A+S                 | Colorectal surgery              | PTC 1–2| TOF 1–2| Republic of Korea              | 70           | 64          |
| Higaki, 2018      | A                   | Gastrectomy                     | PTC 1–2| TOF 1–2| Japan                          | 36           | 33          |
| Baete, 2017       | P + S               | Gastric bypass                  | PTC 1–2| TOF 1–2| Belgium                        | 60           | 60          |
| Schmartz, 2016    | S                   | Gastric bypass                  | PTC 1–5| TOF 1–4| France                         | 69           | 69          |
| Madsen, 2016      | P+S+N+A             | Hysterectomy                     | PTC 1–2| TOF 1–2| Denmark                        | 110          | 99          |
| Martini, 2014     | S+P+A               | Prostatectomy                    | PTC 1–2| TOF 1–2| Netherlands                    | 24           | 24          |
| Matsuaki, 2018    | -                   | Robotic prostatectomy            | PTC 0–2| TOF 1–3| —                               | 20           | 20          |
| Yoo, 2015         | P+A+S               | Robotic prostatectomy            | PTC 1–2| TOF 1–2| Republic of Korea              | 67           | 66          |

Abbreviations: dNMB: deep neuromuscular blockade; mNMB: moderate neuromuscular blockade; A: Assessors of Outcomes; N: Nurse; P: Patient; S: Surgeon; PTC: post-tetanic count; TOF: train-of-four; UK: United Kingdom; US: United States.

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treatment arms were expressed in the same direction before conducting meta-analyses (standard deviation [SD] does not require changing sign). For instance, if a study measured pain using a 0–4 scale, where a higher score means worse pain, and most other studies reported pain using scales where a higher score means less pain, then the mean in that study was calculated as 4 (maximum possible score) minus the observed mean in the study. If different studies used a different range of scales to measure the same outcome, the standardized mean difference (SMD) was calculated in all studies and meta-analyzed.

Table 2. Baseline characteristics of study population in the included studies.

| Study ID    | NMB Level | N at Baseline | Mean Age (SD) [years] | Male (%) | Mean BMI (SD) [kg/m²] | ASA Physical Status Classification (%) |
|-------------|-----------|---------------|----------------------|----------|-----------------------|----------------------------------------|
| Baete, 2017 | dNMB      | 30            | 41 (13)              | 27       | 40.0 (3.0)            | ASA I–III                              |
|             | mNMB      | 30            | 42 (11)              | 13       | 41.0 (7.0)            | ASA I–III                              |
| Barrio, 2017| dNMB      | 30            | 51.13 (10.13)        | 33.3     | 25.6 (3.3)            | I: 33.3; II: 66.7                       |
|             | mNMB      | 30            | 51.43 (10.28)        | 36.7     | 26.5 (3.0)            | I: 30; II: 70                          |
| Kim, 2016   | dNMB      | 30            | 57.1 (7.7)           | 60       | 23.0 (1.2)            | I: 63.4; II: 33.3; III: 3.3             |
|             | mNMB      | 31            | 56.8 (9.6)           | 58.1     | 24.2 (1.3)            | I: 51.6; II: 45.2; III: 3.2             |
| Koo, 2016   | dNMB      | 32            | 48.5 (28–67)         | 40.6     | 23.7 (2.4)            | I: 72; II: 28                          |
|             | mNMB      | 32            | 45.1 (27–68)         | 59.4     | 24.1 (3.4)            | I: 75; II: 25                          |
| Koo, 2018   | dNMB      | 32            | 60.0 (12.0)          | 62.5     | 24.0 (3.0)            | I: 56; II: 44                          |
|             | mNMB      | 32            | 58.0 (12.0)          | 59       | 24.0 (4.0)            | I: 50; II: 50                          |
| Higaki, 2018| dNMB      | 16            | -                    | -        | -                     | -                                      |
|             | mNMB      | 17            | -                    | -        | -                     | -                                      |
| Hojo, 2017  | dNMB      | -             | -                    | -        | -                     | -                                      |
|             | mNMB      | -             | -                    | -        | -                     | -                                      |
| Madsen, 2016| dNMB     | 55            | 47.0 (5.0)           | 0        | 23.1 (3.0)            | I: 94.5; II: 5.5                       |
|             | mNMB      | 55            | 48.0 (5.0)           | 0        | 24.2 (3.1)            | I: 89.1; II: 10.9                      |
| Martini, 2014| dNMB     | 12            | 59 (28–74)           | 83.3     | 25.8 (3.2)            | ASA II–III                            |
|             | mNMB      | 12            | 60 (24–70)           | 83.3     | 25.9 (3.9)            | ASA II–III                            |
| Matsuzaki, 2018| dNMB    | 5             | -                    | 100      | -                     | ASA II–III                            |
|             | mNMB      | 5             | -                    | 100      | -                     | ASA II–III                            |
|             | mNMB§     | 5             | -                    | 100      | -                     | ASA II–III                            |
| Rosenberg, 2017 | dNMB | 36§           | 46.1 (17.7)          | 58.3     | 25.9 (2.9)            | I: 41.7; II: 36.1; III: 5.6            |
|             | mNMB      | 30            | 39.1 (13.6)          | 63.3     | 27.5 (4.0)            | I: 53.3; II: 43.3; III: 3.3            |
|             | mNMB§     | 31§           | 43.5 (15.6)          | 58.1     | 27.1 (3.7)            | I: 54.8; II: 32.3; III: 9.7            |
|             | mNMB      | 30            | 46.7 (13.8)          | 70       | 28.7 (2.7)            | I: 56.7; II: 36.7; III: 6.7            |
| Schmartz, 2016 | dNMB    | 36            | -                    | -        | -                     | -                                      |
|             | mNMB      | 33            | -                    | -        | -                     | -                                      |
| Torensma, 2016| dNMB    | 50            | 46.9 (10.6)          | 18       | 43.0 (4.5)            | I: 0; II: 92; III: 8                   |
|             | mNMB      | 50            | 47.2 (11.1)          | 22       | 43.3 (5.1)            | I: 0; II: 84; III: 16                  |
| Yoo, 2015   | dNMB      | 32            | 63.9 (6.1)           | 100      | 24.4 (2.5)            | I: 25; II: 75                         |
|             | mNMB      | 34            | 61.5 (5.4)           | 100      | 23.6 (2.0)            | I: 38.2; II: 61.8                     |
| Zino, 2017  | dNMB      | 27            | -                    | -        | 47.4 (6.6)            | -                                      |
|             | mNMB      | 27            | -                    | -        | 47.1 (6.3)            | -                                      |

§ study arm had peripheral nerve blockade
£ study arm with low intra-abdominal pressure.

Abbreviations: ASA: American Society of Anesthesiology Physical Status Classification; BMI: body-mass index; dNMB: deep neuromuscular blockade; mNMB: moderate neuromuscular blockade; NMB = neuromuscular block; SD: standard deviation.
RE analyses showed that, compared with mNMB, dNMB was associated with a marginally statistically significant 0.5-point improvement in surgical field rating score: pSMD = 0.51 (95% CI: 0.05, 0.98; Fig 3).

**Need to increase IAP level.** Four studies reported on the need to increase IAP during surgical procedures and were included in this meta-analysis (Koo 2016[13], Yoo 2015[14], Koo 2018[15], Zino 2017[8]). RE analyses showed that the odds of this outcome were significantly reduced by 62% with dNMB compared with mNMB: pOR 0.38 (95% CI 0.20, 0.72; Fig 3). There was no heterogeneity across the studies (I² = 0%; p = 0.44).

**Patient outcomes**

**Post-operative pain in the PACU.** Five studies (Kim 2016[16], Koo 2016[13], Martini 2014[11], Yoo 2015[14], Torensma 2016[12]) reported on patient outcomes and were included in this meta-analysis. RE analyses showed that, compared with mNMB, dNMB reduced post-operative pain in the PACU by a modest 0.5-point improvement in pain scores: pSMD: –0.51 (95% CI: –0.70; –0.31; Fig 3). This reduction was observed as directionally consistent across different laparoscopic surgeries in subgroup RE analyses: colectomy (two studies) pSMD (95% CI): –0.34 (–1.01; 0.33); bariatric surgery (one study): pSMD (95% CI): –0.50 (–1.03; 0.03); and prostatectomy (two studies): pSMD (95% CI): –0.37 (–0.88; 0.15). There was no heterogeneity across the studies (I² = 0%; p = 0.50). In addition, when one study that reported only median data (Koo 2016[13]) was removed from the analysis, the resulting RE analysis was highly consistent with the main analysis: RE pSMD (95% CI): –0.55 (–0.75; –0.35).

**Post-operative pain at 24 hours.** Three studies reported on post-operative pain at 24 hours and were included in this meta-analysis (Kim 2016[16], Koo 2016[13], Rosenberg 2017[17]). RE analyses suggested there was no statistically significant difference between dNMB and mNMB for post-operative pain at 24 hours and also varied by surgical procedure (lower pain scores for colorectal surgery; higher pain scores for cholecystectomy). Given there was high heterogeneity between trials, the results could not be interpreted with any degree of certainty (I² = 95%; p<0.01; Fig 3).
Post-operative nausea/vomiting. Four studies reported on post-operative nausea/vomiting and were included in this meta-analysis (Kim 2016[16], Koo 2016[13], Torensma 2016[12], Yoo 2015[14]). RE analyses showed no conclusive difference between dNMB and mNMB with regards to this outcome (pOR [95% CI]: 0.62 [0.27, 1.43]; Fig 3). There was little heterogeneity across the studies ($I^2 = 23$%; $p = 0.27$).

Healthcare resource utilization

Duration of surgery. Nine studies reported on duration of surgery and were included in this meta-analysis (Baete 2017[10], Torensma 2016[12], Barrio 2017[18], Kim 2016[16], Koo 2016[13], Koo 2018[15], Madsen 2016[19], Martini 2014[11], Yoo 2015[14]). RE analyses showed that, compared with mNMB, dNMB was associated with a modest (but statistically significant without heterogeneity, $I^2 = 0$; $p = 0.56$) reduction in this outcome (pSMD [95% CI]: $-3.62$ minutes [$-6.87$; $-0.37$]; Fig 3).

Length of hospital stay. Three studies (Kim 2016[16], Koo 2018[15], Madsen 2016[19]) reported on the length of hospital stay and were included in this meta-analysis. RE analyses
showed no conclusive difference between dNMB and mNMB for this outcome (pSMD [95% CI]: 0.68 days [–1.95, 0.59]; Fig 3). Heterogeneity was high between trials ($I^2 = 70%$; $p = 0.04$).

**Length of recovery room stay.** Three studies (Kim 2016[16], Martini 2014[11], Yoo 2015 [14]) reported on the length of recovery room stay and were included in this meta-analysis. RE analyses showed no conclusive difference between dNMB and mNMB on the time spent in the PACU (pSMD [95% CI]: –4.36 minutes [–10.83, 2.11]; Fig 3). There was no heterogeneity across the studies ($I^2 = 0%$; $p = 0.49$).

**Discussion**

Our study compared patient, surgical, and healthcare resource outcomes between dNMB and mNMB in adults undergoing laparoscopic surgery, with an aim to address key questions regarding the relative merits of the two approaches in this clinical setting. Findings suggest that compared with mNMB, dNMB was associated with improved surgical field of vision and higher vision quality scores; it should be noted there was considerable heterogeneity between studies for this outcome. In addition, dNMB was associated with a reduction in the post-operative pain scores in the PACU compared with mNMB (without any significant heterogeneity), as well as with greater consistency in maintaining the desired level of IAP without a need for an increase during the surgical procedures. With respect to resource utilization, we noted minor savings in surgical operation time (reduction of <5 minutes), but no differences in terms of recovery in the PACU or overall length of hospital stay with dNMB.

Our findings are broadly consistent with prior systematic reviews. Bruintjes et al. reported similar outcomes in favor of dNMB versus mNMB for improvements in surgical field of vision, reduced need to increase IAP during surgery, and improvements in post-operative pain in the PACU.[3] However, our study adds evidence with five other studies (Higaki 2018[20], Hojo 2017[9], Matsuzaki 2018[6], Schmartz 2016[7], Zino 2017[8]) beyond those included in the Bruintjes et al. analysis,[3] as well as robust methods with stricter criteria for consistently defining dNMB and mNMB.

Park et al. reported similar outcomes in favor of dNMB versus mNMB in terms of surgical field conditions and duration of surgery, while also observing—consistent with our analysis—no difference in terms of post-operative nausea and vomiting.[4] However, as well as including the five additional studies mentioned above, our analysis provided more comprehensive coverage of key outcomes, including reduced need to increase IAP levels during surgeries with dNMB. This is a more challenging endpoint to assess (due to the subjective nature of the rating scale)—in our study, it was associated with less heterogeneity across trials than vision-quality outcomes, thereby increasing confidence in the finding. This result may encourage future trials to capture this as a study endpoint.

A recently published RCT comparing dNMB and mNMB for patients undergoing gastric bypass surgery concluded that dNMB improves surgical conditions.[21] Due to the timing of the SLR and publication of this RCT, it was not included, though findings of our SLR are in line with its conclusion.

Thus, while evidence strongly suggests that dNMB improves surgical rating in certain procedures, less is known on the consequences of dNMB on patients’ outcome. The depth of NMB may affect patient outcome by two distinct mechanisms: improving surgical stillness and surgical conditions.

Sutton contractions or impaired visibility has been shown in a randomized trial in patients undergoing laparoscopic cholecystectomy (2 x 25 patients) with no NMB or dNMB.[22] The investigators assessed several sudden diaphragmatic or abdominal muscle contractions and
instances with inadequate visibility at intrabdominal pressure at 15 mmHg. The total number of patients having these adverse events were 12/25 in the no NMB group; in one of them, a perforation of the liver capsule with the trocar following sudden diaphragmatic movements, leading to important bleeding, occurred. In the dNMB group, adverse events were observed in 1/25 (p<0.001). Another randomized trial in patients undergoing laparoscopic hysterectomy (2 x 55 patients randomized to mNMB versus dNMB) found that 12/55 patients in the mNMB group experienced contractions in the diaphragm or abdominal muscles compared with 0/55 in the dNMB group (p<0.001[23]). The diaphragm is known to be significantly more resistant to non-depolarizing neuromuscular blocking agents than peripheral muscles, such as the adductor pollicis muscle typically used for intraoperative neuromuscular monitoring.[24]

Deeper levels of NMB corresponding to a PTC 1–3 have shown to paralyze reliably the diaphragm and thus prevents sudden diaphragmatic or abdominal muscle movements.[25]

Of interest in this context, in a retrospective study, Boon et al. reported a significant reduction in unplanned 30-day readmission rates in retroperitoneal laparoscopic surgery in patients with an anesthesia protocol including high-dose rocuronium, and thus dNMB, compared with low-dose rocuronium. Better surgical conditions are supposed to explain these findings.[26]

Similarly, Fuchs-Buder et al. recently demonstrated that switching from moderate to deep block improves surgical conditions, and poor surgical conditions were associated with a higher incidence of postoperative surgical complications.[21] Thus, increasing evidence suggests that dNMB not only improves surgical conditions, but better surgical conditions may lead to a better surgical outcomes.

The lack of association observed between the PACU stay and level of NMB block deserves further discussion. According to the findings from a Cochrane systematic review of RCTs, and consistent with the indicated use of reversal agents, sugammadex 4 mg/kg reversed dNMB (PTC 1–5) 45.78 minutes faster than neostigmine 0.07 mg/kg.[27] In the absence of sugammadex, which is uniquely indicated to reverse dNMB with its direct encapsulating mechanism of action, maintenance of dNMB through the end of surgery[28] would require prolonged intubation and mechanical ventilation (before reversal with neostigmine may be possible), which could lead to prolonged recovery room stay.

Before administration, because of their indirect mechanism of action, using cholinesterase inhibitors (e.g., neostigmine) to antagonize non-depolarizing NMB requires some degree of spontaneous recovery.[29, 30] While cholinesterase inhibitors decrease the enzymatic metabolism of acetylcholine and lead to an increase in acetylcholine—which competes with the non-depolarizing NMBA for the postsynaptic n-acetylcholine receptor, indirectly diminishing the effect the NMBA and facilitating neuromuscular recovery[29]—neostigmine-based reversal is limited to moderate and shallow NMB and doesn’t antagonize dNMB.[30, 31]

Similarly, five studies reporting the length of recovery room stay or length of hospital stays as outcomes utilized sugammadex as the reversal agent in the dNMB arms,[11, 14–16, 19] while two reported using neostigmine to reverse mNMB.[11, 15] Because sugammadex offers a rapid and predictable NMB recovery, even in deep block, it is possible that its impact on early NMB recovery resulted in observations in PACU length of stay that were not significantly different between dNMB and mNMB. Similarly, it is possible that if dNMB was maintained through the end of surgery and without the use of sugammadex, prolonged length of stay may be more common.

These analyses were robust in their use of consistent and rigorous definitions for dNMB and mNMB (including the exclusion of trials that used no NMB as the control arm) and the use of standardized scales for surgical ratings and SMD.

Our study is not without limitations. As with other SLRs, we noted the high degree of heterogeneity across trials for some outcomes (including quality of surgical vision and pain at 24
hours) and the limited number of studies available for some endpoints of interest. Therefore, findings should be interpreted in the context of these limitations. Due to the limited number of studies, we were not able to conduct all planned subgroup or sensitivity analyses. A majority of trials were industry sponsored. Also, our searches were limited to identify studies published in English only; however, we would have captured some studies in other languages that have English versions.

Conclusion

Findings suggest that the use of dNMB may improve the patient and physician surgical experience by improving certain patient outcomes, such as post-operative pain and improved surgical ratings, compared with mNMB. However, to avoid post-operative residual paralysis and assure appropriate functioning of the upper airway once the patient is extubated (at recovery of the TOF ratio to >0.9, or even to unity) assessing neuromuscular recovery with acceleromyography is mandatory.[32–34]

Heterogeneity in the pooled estimates suggests the need for future, well-designed RCTs and standard definition of terms and rating scales to improve the precision of these findings and provide reliable data that can be used to inform clinical practice.

Supporting information

S1 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Table. Search strategies.
(DOCX)

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