Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: a systematic review and meta-analysis

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Abstract

Neuromuscular block (NMB) is frequently used in abdominal surgery to improve surgical conditions by relaxation of the abdominal wall and prevention of sudden muscle contractions. The evidence supporting routine use of deep NMB is still under debate. We aimed to provide evidence for the superiority of routine use of deep NMB during laparoscopic surgery. We performed a systematic review and meta-analysis of studies comparing the influence of deep vs moderate NMB during laparoscopic procedures on surgical space conditions and clinical outcomes. Trials were identified from Medline, Embase, and Central databases from inception to December 2016. We included randomized trials, crossover studies, and cohort studies. Our search yielded 12 studies on the effect of deep NMB on the surgical space conditions. Deep NMB during laparoscopic surgeries improves the surgical space conditions when compared with moderate NMB, with a mean difference of 0.65 (95% confidence interval (CI): 0.47–0.83) on a scale of 1–5, and it facilitates the use of low-pressure pneumoperitoneum. Furthermore, deep NMB reduces postoperative pain scores in the postanaesthesia care unit, with a mean difference of $0.52$ (95% CI: $0.71$ to $0.32$). Deep NMB improves surgical space conditions during laparoscopic surgery and reduces postoperative pain scores in the postanaesthesia care unit. Whether this leads to fewer intraoperative complications, an improved quality of recovery, or both after laparoscopic surgery should be pursued in future studies. The review methodology was specified in advance and registered at Prospero on July 27, 2016, registration number CRD42016042144.

Key words: laparoscopy; neuromuscular blockade; pneumoperitoneum, artificial

In the last decades, the number of laparoscopic surgeries has increased tremendously. When compared with open surgery, laparoscopic procedures provide less postoperative pain, shorter duration of hospital admission, and improved patient satisfaction.1 However, the elevated intra-abdominal pressure (IAP) during pneumoperitoneum created during laparoscopic procedures can affect several homeostatic systems, causing alterations in cardiovascular, pulmonary, and renal physiology. It is also speculated that the pneumoperitoneum is an important factor in the cause of postoperative shoulder pain.2
Lowering the IAP might decrease postoperative pain and the risk of laparoscopy-related complications. However, low-pressure pneumoperitoneum impairs the quality of the surgical field, which can increase the risk of intraoperative complications or conversion to open surgery.

The quality of the working space is determined by non-modifiable factors (i.e. patients’ obesity, previous pregnancies, or previous abdominal surgery) and by modifiable factors, such as anaesthesia-related factors, IAP, and body position. Several trials have been performed showing that deep neuromuscular block (NMB) improves surgical conditions in different types of laparoscopic procedures. The depth of NMB is assessed mostly by acceleromyography, also known as train-of-four (TOF) monitoring. During the use of non-depolarizing neuromuscular blocking agents, such as rocuronium, a TOF of 4 means there are four twitches after stimulation, meaning 0–75% of the acetylcholine receptors at the neuromuscular junction receptors are blocked and there is no or shallow NMB. In moderate NMB, there are one to three responses to TOF, meaning that 75–90% of the receptors are blocked. During deep NMB, there are no responses to TOF and two or fewer responses to post-tetanic count (PTC).

A major advantage of NMB is the improvement of intubation conditions for the anaesthetist. Nevertheless, NMB (and especially deep NMB) can lead to postoperative residual curarization, which exposes the patient to additional risks of a delayed recovery of respiratory function, including aspiration. Since the discovery of sugammadex, it is possible to antagonize a deep NMB, which minimizes the risk of occurrence of adverse events of residual NMB. Nowadays, NMB is frequently used in abdominal surgery to improve surgical conditions, by relaxation of the abdominal wall and prevention of sudden muscle contractions. However, the routine use of deep NMB is still under debate. Last year, Madsen and colleagues and Kopman and Naguib wrote, respectively, a ‘pro-’ and ‘con-’ position paper concerning the available evidence supporting (or not) the clinical practice of deep NMB during laparoscopic procedures. Madsen and colleagues stated that there are a few low-risk-of-bias studies to indicate that the use of deep NMB improves surgical conditions and patient outcomes, such as postoperative pain. In contrast, Kopman and Naguib concluded that there is not enough good evidence available to justify the routine use of deep NMB in laparoscopic procedures. They stated that evidence for the superiority of deep NMB vs moderate block is non-existent.

We performed the first systematic review including a meta-analysis to obtain data regarding the influence of moderate and deep NMB during laparoscopic surgeries on surgical space conditions and clinical outcomes.

Methods

This review was performed in accordance with the PRISMA guidelines; see Supplementary material supplement 1 (S1). The review methodology was specified in advance and registered at Prospero on July 27, 2016, registration number CRD42016042144, provided as Supplementary material supplement 2 (S2).

Amendments to the review protocol

In order to optimize the meta-analysis of the surgical space conditions, we converted the scales to 1–5 instead of 0–100. Furthermore, we specified the item ‘other risks of bias’ of the Cochrane risk-of-bias tool. We took into account whether studies reported on calibration of the TOF watch, defined deep NMB as PTC ≤ 2, and if they mentioned use of rocuronium as an escape in the moderate NMB group in the event of insufficient surgical field. To invest the robustness of our findings on postoperative pain, we added a sensitivity analysis to evaluate the influence of different levels of IAP.

Literature search strategy

We conducted a systematic, computerized search on PubMed, EMBASE, and Cochrane library. We used the search components ‘laparoscopic surgery’ and ‘deep neuromuscular blockade’. The search strategy is provided as Supplementary material supplement 3 (S3). We also conducted a search on ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) on December 1, 2016 (see Supplementary material S3). Search results from each database were combined, with removal of duplicates. In addition, we checked the reference lists of all included studies and relevant reviews identified by our search for additional eligible references. No language or publication date restrictions were applied. The search was performed on August 3, 2016 and updated on December 1, 2016. The search update yielded one additional included reference.

Study selection

Two authors (M.H.B., E.V.v.H.) independently screened the studies for eligibility based on title and abstract. In a second phase, the same authors performed a full-text assessment for final inclusion. Studies were included if they met all of the following criteria: (i) the study was an original full paper that presented unique data; (ii) the study was performed in human adults; (iii) the study compared deep or intense NMB with no, shallow, or moderate NMB; (iv) the study was performed in patients undergoing a laparoscopic (intra-abdominal) procedure; and (v) the study reported on the outcome measure surgical space conditions.

Type of outcome measures

The primary outcome measure was the quality of the surgical space conditions. Studies measuring the distance between the skin and sacral promontory were included in the systematic review but not in the meta-analysis. Secondary outcome measures were postoperative pain, conversion to higher pneumoperitoneum pressure or open surgery, duration of surgery, intraoperative complications, and length of hospital stay.

Study characteristics and data extraction

The following characteristics were extracted: author, journal and year of publication, sex, age, weight, BMI, and ASA class, body positioning during surgery, type of procedure, type of NMB, level of NMB in experimental and control groups, scale used to score the surgical space conditions, pain scores, conversion rates, complications, and timing of scoring the outcome measurements. Two review authors (M.H.B., E.V.v.H.) extracted the data independently; discrepancies were identified and resolved through discussion. Data were extracted if the mean, SD, and number of patients (n) were reported, or could be calculated, for the experimental and control groups. If the SD, the range, or the 95% confidence interval (CI) was reported, it was converted to SD for meta-analysis. In the event of incomplete data, we contacted authors via e-mail with a request for additional data.
Study quality and risk-of-bias assessment

Quality assessment of the included studies was performed using the Cochrane Collaboration’s tool for assessing risk of bias by two authors independently (M.H.B., E.V.v.H.). Disagreements between the authors concerning the risk of bias in particular studies were resolved by discussion. In addition to the risk-of-bias assessment, we also assessed reporting of a power calculation ahead of starting the study.

Data synthesis and meta-analysis

Data were analysed using Review Manager (RevMan Version 5.3; the Nordic Cochrane Centre, Copenhagen: the Cochrane Collaboration, 2014). Meta-analysis was performed only if sufficient data were available from at least three studies. We computed the raw difference in means (MD; experimental group mean minus control group mean) for all studies. The surgical space conditions were converted to a scale from one (extremely poor conditions) to five (optimal conditions). The duration of surgery was measured in minutes. Postoperative pain was reported as an 11-point numerical rating scale. Data were pooled using a random-effects model in all analyses to account for anticipated heterogeneity. We reported the effect estimates as MD with the corresponding 95% CIs. Heterogeneity was analysed and reported as the I²-test. We aimed to assess publication bias by examining funnel plot asymmetry if the analysis contained at least 10 comparisons.

Subgroup and sensitivity analyses

We predefined and performed subgroup analyses, if the necessary data were available, to explore possible causes for heterogeneity and to assess which variables influence the effect of NMB on surgical space conditions. The subgroup variables were as follows: IAP (standard or low), type of surgery, and BMI.

We performed sensitivity analyses to investigate the robustness of our findings. We tested the effect of different levels of NMB and IAP. Additionally, we checked whether our results changed after excluding the non-randomized trials from the meta-analysis.

Results

Study selection and characteristics

The electronic search strategy retrieved 315 records in total, 210 of which were unique. We excluded 195 records during the screening phase. Fifteen papers were retrieved for full-text assessment. Three studies were excluded in the eligibility phase because they did not report on relevant outcome measures. The 12 remaining studies fulfilled the inclusion criteria. The study selection process is depicted in a flow chart (see Fig. 1). The characteristics of the included studies are summarized in Table 1.

All records were published in English. The most commonly performed procedures were laparoscopic cholecystectomies (36%) or laparoscopic hysterectomies (36%); other procedures included laparoscopic prostatectomies (18%), colorectal surgeries, nephrectomies, Roux-en-Y gastric bypasses, or gynaecological laparoscopies other than hysterectomy. The applied level of pneumoperitoneum differed between 1.1 kPa (8 mm Hg) and 2.0 kPa (15 mm Hg). The patients’ BMI was, in the majority of the studies (67%), between 18 and 31 kg m⁻². The remaining four studies also included obese patients with a BMI >31 kg m⁻². All studies used rocuronium to create a (deep) NMB. The intubation dose differed between 0 and 1 mg kg⁻¹. In eight studies (67%), deep NMB was compared with moderate NMB, in one study deep NMB was compared with shallow NMB, and in three studies (25%) patients without NMB were used as the control group. The studies were not completely consistent in their definition of deep NMB; however, the majority (nine studies) kept to a maximal PTC of 2. The other three studies specified deep NMB as PTC 2–3, PTC <5 or PTC 1, TOF 1. Nine of the 12 studies reported on the surgical space conditions, our primary outcome measure. For two of these studies, we could not extract all necessary data to include them in the meta-analysis.

Applied surgical condition scales were 1–4 (44%), 1–5 (44%) and 0–100 (12%). We included the overall conditions at the end of the procedure in the meta-analysis. Two studies evaluated the quality of the surgical field only by measuring the distance from the sacral promontory to the skin. These studies could not be included in the meta-analysis. Other reported outcome measures were postoperative pain (67%), duration of surgery (75%), conversion rate (50%), complications (83%), and length of hospital stay (17%).

Study quality and risk of bias

Nine of the 12 studies included in this systematic review reported a power calculation. The results of the quality assessment of the 12 included studies are presented in Fig. 2 (averaged per item). The quality assessment per individual study is provided as Supplementary material supplement 4 (S4). Ten (83%) out of 12 studies were randomized. Allocation concealment was unclear in 42% of all studies. Blinding of participants and personnel and blinding of outcome assessment were reported in 84% of the studies. None of the studies was guilty of selective outcome reporting or attrition bias. Two studies had unclear other risks of bias, attributable to no mentioning of calibration. Three studies had high other risks of bias, because of an inadequate deep NMB. Last but not least, there was a high risk of conflict of interest (75% of the studies), because many authors of the included studies received honoraria or funding from companies promoting deep NMB (and its reversal by sugammadex).

Meta-analysis of the surgical space conditions

Seven studies could be pooled in the meta-analysis of the surgical space conditions. Overall, the surgical space conditions improved with deep NMB by a MD of 0.65 (95% CI: 0.47–0.83) on a scale of 1–5 (see Fig. 3). Between-study heterogeneity was 46%. As a result of the small number of studies included in the meta-analysis, data were insufficient to perform subgroup analyses.

Meta-analysis of duration of surgery

Eight studies were included in the meta-analysis of the duration of surgery. Overall, there was no significant difference in the duration of surgery between groups with deep NMB and groups with moderate NMB [MD −1.47 (95% CI: −4.00 to 1.05) min; see Fig. 4]. Only the study of Koo and colleagues reported a significantly shorter operation time in the deep NMB group. Between-study heterogeneity was 0%.

Meta-analysis of postoperative pain in the postanaesthesia care unit

Five studies could be pooled in the meta-analysis of postoperative pain in the postanaesthesia care unit (PACU) during the first
hour after surgery. Overall, there was a significant reduction of early postoperative pain in the group with deep NMB (MD −0.52 [95% CI: −0.71 to −0.32] on an 11-point scale; see Fig. 5). Between-study heterogeneity was 0%. We were not able to perform meta-analyses of postoperative pain after 24 h, because fewer studies reported on this outcome.

Descriptive summary of other secondary outcome measures

Distance from sacral promontory to skin

The studies of Barrio and colleagues,4 Lindekaer and colleagues,18 and Madsen and colleagues,19 quantified the surgical space conditions by measuring the distance from the sacral promontory to the skin. All three studies concluded that deep NMB increased the promontory-to-skin distance in a significant manner; 0.48, 1.57, and 0.33 cm, respectively, at an insufflation pressure of 1.6 kPa (12 mm Hg).

Postoperative pain after 24 h

Six studies reported on postoperative pain after 24 h or later. Two studies15 2 showed a significant reduction of pain scores on the first postoperative day, both for overall pain and for shoulder tip pain. Torensma and colleagues15 found a significant reduction of shoulder tip pain, but showed no proof of reduction of abdominal pain 24 h after surgery. Madsen and colleagues2 reported an absolute risk reduction of shoulder pain during the 14 days after surgery, but did not find a significant

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315 records identified through database searching:
- MEDLINE: 50
- EMBASE: 73
- Cochrane Central Register of Controlled Trials: 33
- ClinicalTrials.gov: 127
- WHO ICTRP: 32

No additional records identified through other sources

210 records after duplicates removed

195 records excluded after screening titles and abstracts:
- Review: 8
- Abstract without original data: 19
- Case report: 6
- Letter/comment: 9
- Study protocol: 5
- Study in children: 1
- No deep vs moderate NMB: 19
- Ongoing relevant trials without data: 22
- Completed relevant trials without data: 11
- Irrelevant registered trials: 95

210 records screened

3 articles excluded: No relevant outcome data: 3

15 full-text articles assessed for eligibility

10 studies included in quantitative synthesis (meta-analysis)

12 studies included in qualitative synthesis

Fig 1 PRISMA flow diagram of study selection process.
difference between abdominal pain scores. The studies of Staehr-Rye and colleagues\(^6\) and Blobner and colleagues\(^16\) found no difference at all in postoperative pain between the two groups.

**Pressure level of pneumoperitoneum**

The studies of Blobner and colleagues\(^16\), Dubois and colleagues\(^14\), Martini and colleagues\(^20\), and Torensma and colleagues\(^15\) used a stable standard pressure level of pneumoperitoneum in both groups. The papers of Barrio and colleagues\(^4\), Lindekaer and colleagues\(^18\), and Madsen and colleagues\(^19\) compared a pneumoperitoneum pressure of 1.1 kPa (8 mm Hg) and 1.6 kPa (12 mm Hg) in both groups. They concluded that deep NMB increased the intra-abdominal space at both pressure levels. The other study of Madsen and colleagues\(^2\) compared deep NMB combined with low-pressure pneumoperitoneum (1.1 kPa) and moderate NMB combined with standard-pressure pneumoperitoneum (1.6 kPa). Low-pressure pneumoperitoneum facilitated by deep NMB reduced postoperative shoulder pain, without prolongation of operating time or influencing completion of the operation. Koo and colleagues\(^5\), Staehr-Rye and colleagues\(^6\), and Yoo and colleagues\(^17\) started in both groups at a pneumoperitoneum pressure of 1.1 kPa and increased the pressure in the event of inadequate surgical conditions. All three studies showed that deep NMB reduced the rate of conversion to standard-pressure pneumoperitoneum. Finally, Kim and colleagues\(^1\) titrated the lowest IAP allowing acceptable surgical conditions in both groups. The titrated average IAP was significantly lower in the deep NMB group.

**Complications**

Kim and colleagues\(^1\) reported five patients in the deep NMB group and three patients in the moderate NMB group who dropped out after randomization because of conversion to open colorectal resection or concurrent operations. None of the other included studies reported instances of conversion. Serious

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### Table 1: Primary study characteristics

<table>
<thead>
<tr>
<th>Article code [no.]</th>
<th>Laparoscopic procedure</th>
<th>NMB level experimental group</th>
<th>NMB level control group</th>
<th>Number of patients</th>
<th>Surgical rating scale</th>
<th>Other outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barrio 2016(^4)</td>
<td>Chol/Gyn</td>
<td>Deep</td>
<td>Mod</td>
<td>41</td>
<td>NA</td>
<td>IAP, comp</td>
</tr>
<tr>
<td>Blobner 2015(^16)</td>
<td>Chol</td>
<td>Deep</td>
<td>No NMB</td>
<td>50</td>
<td>0-100%</td>
<td>Dur, pain, comp</td>
</tr>
<tr>
<td>Dubois 2014(^14)</td>
<td>Hyst</td>
<td>Deep</td>
<td>Shallow</td>
<td>100</td>
<td>1-4</td>
<td>Dur,</td>
</tr>
<tr>
<td>Kim 2016(^1)</td>
<td>Colorectal</td>
<td>Deep</td>
<td>Mod</td>
<td>61</td>
<td>1-5</td>
<td>Dur, pain, LOS, IAP, comp</td>
</tr>
<tr>
<td>Koo 2016(^5)</td>
<td>Chol</td>
<td>Deep</td>
<td>Mod</td>
<td>64</td>
<td>1-4</td>
<td>Dur, pain, IAP, comp</td>
</tr>
<tr>
<td>Lindekaer 2013(^18)</td>
<td>Hyst</td>
<td>Deep</td>
<td>No NMB</td>
<td>15</td>
<td>NA</td>
<td>IAP, comp</td>
</tr>
<tr>
<td>Madsen 2015(^19)</td>
<td>Gyn</td>
<td>Deep</td>
<td>No NMB</td>
<td>14</td>
<td>1-4</td>
<td>IAP, comp</td>
</tr>
<tr>
<td>Madsen 2016(^2)</td>
<td>Hyst</td>
<td>Deep</td>
<td>Mod</td>
<td>99</td>
<td>NA</td>
<td>Dur, pain, LOS, IAP, comp</td>
</tr>
<tr>
<td>Martini 2014(^20)</td>
<td>Prost/Nephr</td>
<td>Deep</td>
<td>Mod</td>
<td>24</td>
<td>1-5</td>
<td>Dur, pain, comp</td>
</tr>
<tr>
<td>Staehr-Rye 2014(^6)</td>
<td>Chol</td>
<td>Deep</td>
<td>Mod</td>
<td>48</td>
<td>1-4</td>
<td>Dur, pain, IAP, comp</td>
</tr>
<tr>
<td>Torensma 2016(^15)</td>
<td>RYGB</td>
<td>Deep</td>
<td>Mod</td>
<td>100</td>
<td>1-5</td>
<td>Dur, pain</td>
</tr>
<tr>
<td>Yoo 2015(^17)</td>
<td>Prost</td>
<td>Deep</td>
<td>Mod</td>
<td>66</td>
<td>1-5</td>
<td>Dur, pain, IAP, comp</td>
</tr>
</tbody>
</table>

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### Fig 2: Assessment of risk of bias

[Diagram showing the assessment of risk of bias]
### Surgical space conditions

**Fig 3** Surgical space conditions are improved by the use of deep neuromuscular block (NMB). Forest plot of studies comparing surgical space conditions during laparoscopic procedures with deep NMB vs moderate, shallow, or no NMB. The effect size is calculated as the mean difference in surgical rating score (range 1–5) and corresponding 95% confidence intervals (95% CI).

### Duration of surgery

**Fig 4** The duration of surgery is not significantly decreased by the use of deep NMB. Forest plot of studies comparing the duration of surgery during laparoscopic procedures with deep vs moderate or no NMB. The effect size is calculated as the mean difference in duration of surgery in minutes and corresponding 95% confidence intervals (95% CI).

### Postoperative pain

**Fig 5** Postoperative pain in the postanaesthesia care unit is reduced by the use of deep neuromuscular block (NMB). Forest plot of studies comparing postoperative pain 1 h after laparoscopic procedures with deep NMB vs moderate NMB. The effect size is calculated as the mean difference in NRS (range 0–10) and corresponding 95% confidence intervals (95% CI).

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#### Table 1: Surgical space conditions

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dubois 2014</td>
<td>4.58</td>
<td>0.67</td>
<td>30</td>
<td>3.79</td>
<td>0.67</td>
<td>31</td>
<td>12.5%</td>
<td>0.80 [0.40, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Koo 2016</td>
<td>4.6</td>
<td>0.67</td>
<td>30</td>
<td>3.84</td>
<td>0.52</td>
<td>31</td>
<td>16.9%</td>
<td>0.76 [0.46, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Madsen 2015</td>
<td>4.13</td>
<td>1.13</td>
<td>32</td>
<td>3.16</td>
<td>1.02</td>
<td>32</td>
<td>8.6%</td>
<td>0.97 [0.44, 1.50]</td>
<td></td>
</tr>
<tr>
<td>Martini 2013</td>
<td>5.0</td>
<td>0.00001</td>
<td>7</td>
<td>4.29</td>
<td>0.49</td>
<td>7</td>
<td>14.0%</td>
<td>0.71 [0.35, 1.07]</td>
<td></td>
</tr>
<tr>
<td>Staehr-Rye 2014</td>
<td>4.7</td>
<td>0.4</td>
<td>12</td>
<td>4.0</td>
<td>0.4</td>
<td>12</td>
<td>16.0%</td>
<td>0.70 [0.38, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Torensma 2016</td>
<td>4.8</td>
<td>0.36</td>
<td>50</td>
<td>4.2</td>
<td>0.76</td>
<td>50</td>
<td>20.9%</td>
<td>0.60 [0.37, 0.83]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 206

**Heterogeneity:** $\tau^2=0.03; \text{Chi}^2=11.19, \text{df}=6 (~P=0.08); I^2=46%$

**Test for overall effect:** $Z=7.04 (P<0.00001)$

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#### Table 2: Duration of surgery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
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<tr>
<td>Blobner 2015</td>
<td>10.2</td>
<td>25</td>
<td>25</td>
<td>13.8</td>
<td>15</td>
<td>15</td>
<td>9.8%</td>
<td>0.00 [-8.95, 8.95]</td>
<td></td>
</tr>
<tr>
<td>Koo 2016</td>
<td>197.2</td>
<td>59</td>
<td>30</td>
<td>213.6</td>
<td>77.4</td>
<td>31</td>
<td>0.2%</td>
<td>-16.40 [-90.87, 18.07]</td>
<td></td>
</tr>
<tr>
<td>Madsen 2015</td>
<td>39.3</td>
<td>9</td>
<td>32</td>
<td>46.8</td>
<td>15.7</td>
<td>32</td>
<td>16.2%</td>
<td>-7.50 [-13.77, -1.23]</td>
<td></td>
</tr>
<tr>
<td>Martini 2013</td>
<td>65</td>
<td>46.5</td>
<td>49</td>
<td>70</td>
<td>26.5</td>
<td>50</td>
<td>2.8%</td>
<td>-5.00 [-19.95, 9.95]</td>
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<tr>
<td>Staehr-Rye 2014</td>
<td>144</td>
<td>35</td>
<td>12</td>
<td>141</td>
<td>50</td>
<td>12</td>
<td>0.5%</td>
<td>3.00 [-31.53, 37.53]</td>
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</tr>
<tr>
<td>Torensma 2016</td>
<td>43</td>
<td>13.5</td>
<td>50</td>
<td>41</td>
<td>22.75</td>
<td>50</td>
<td>11.8%</td>
<td>2.00 [-5.33, 9.33]</td>
<td></td>
</tr>
<tr>
<td>Yoo 2015</td>
<td>111</td>
<td>21</td>
<td>34</td>
<td>115</td>
<td>32</td>
<td>32</td>
<td>3.7%</td>
<td>-4.00 [-17.14, 9.14]</td>
<td></td>
</tr>
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</table>

**Total (95% CI):** 257

**Heterogeneity:** $\tau^2=0.04; \text{Chi}^2=11.19, \text{df}=7 (P=0.08); I^2=46%$

**Test for overall effect:** $Z=1.15 (P=0.25)$

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#### Table 3: Postoperative pain

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean difference IV, random, 95% CI</th>
<th>Mean difference IV, random, 95% CI</th>
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<tr>
<td>Kim 2016</td>
<td>2.3</td>
<td>0.6</td>
<td>30</td>
<td>2.9</td>
<td>0.3</td>
<td>31</td>
<td>66.2%</td>
<td>-0.60 [-0.84, -0.36]</td>
<td></td>
</tr>
<tr>
<td>Koo 2016</td>
<td>6.1</td>
<td>1.5</td>
<td>32</td>
<td>6.175</td>
<td>32</td>
<td>32</td>
<td>5.9%</td>
<td>0.00 [-0.80, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Martini 2013</td>
<td>2.1</td>
<td>2.2</td>
<td>12</td>
<td>2.6</td>
<td>1.6</td>
<td>12</td>
<td>1.6%</td>
<td>-0.50 [-2.04, -1.04]</td>
<td></td>
</tr>
<tr>
<td>Torensma 2016</td>
<td>3.9</td>
<td>1.44</td>
<td>50</td>
<td>4.4</td>
<td>1.86</td>
<td>50</td>
<td>13.5%</td>
<td>-0.50 [-1.03, 0.03]</td>
<td></td>
</tr>
<tr>
<td>Yoo 2015</td>
<td>2.62</td>
<td>0.7</td>
<td>34</td>
<td>2.97</td>
<td>1.42</td>
<td>32</td>
<td>12.7%</td>
<td>-0.35 [-0.90, 0.20]</td>
<td></td>
</tr>
</tbody>
</table>

**Total (95% CI):** 158

**Heterogeneity:** $\tau^2=0.00; \text{Chi}^2=2.44, \text{df}=4 (P=0.66); I^2=0%$

**Test for overall effect:** $Z=2.15 (P=0.00001)$
adverse events were reported by Blobner and colleagues and Staehr Rye and colleagues. In the study of Blobner and colleagues, one patient of the no NMB group had an acute bleed during surgery. The study of Staehr-Rye and colleagues reported two patients with prolonged hospitalization because of postoperative observation and two patients who were re-admitted to the hospital because of pain. Moreover, there were no studies that described deep NMB-related complications, such as allergic reactions, cardiovascular reactions, or residual NMB.

Length of hospital stay
Length of hospital stay was reported in two studies, which showed no significant difference between the patients who received deep or moderate NMB.

Publication bias
The analyses of the surgical conditions data contained too few studies to assess funnel plot asymmetry reliably.

Sensitivity analysis
The study of Dubois and colleagues and the study of Madsen and colleagues compared deep NMB with shallow and no NMB, respectively. Therefore, these studies differ from studies using moderate NMB as the control group and could exaggerate the mean effect of deep NMB. Removing these studies from the meta-analysis did not significantly alter the results of the meta-analysis; see Supplemental material supplement S5. The studies of Dubois and colleagues and Torensma and colleagues defined deep NMB as PTC 2–3 and PTC 1, TOF 1, respectively, instead of PTC <2. Removing these studies from the meta-analysis did not significantly alter the results (data not shown).

The study by Lindekaer and colleagues was the only non-randomized study and therefore at high risk of bias. However, this study was not included in the meta-analysis, because it did not report on surgical rating scales.

We performed an additional analysis to compare the outcome of postoperative pain between studies with equal levels of IAP and studies with different levels of IAP in combination with deep or moderate NMB. Both analyses showed a comparable reduction of pain scores, respectively MD = −0.50 (−1.00 to 0.00) and MD = −0.48 (−0.76 to −0.21); see Supplementary material supplements 6 and 7 (S6 and S7).

Discussion
Our results show that the use of deep NMB during laparoscopic surgery improves the surgical space conditions when compared with moderate NMB, with a mean difference of 0.65 (95% CI: 0.47–0.83). Use of deep NMB did not influence the duration of surgery. Moreover, our data indicate that deep NMB facilitates the use of low-pressure pneumoperitoneum, while increasing the intra-abdominal space. During deep NMB, there were fewer conversions to higher pressure pneumoperitoneum, and a lower pressure pneumoperitoneum could be achieved with acceptable surgical space conditions. Furthermore, no complications related to the use of deep NMB were reported. Regarding the postoperative outcomes, the meta-analysis of postoperative pain in the PACU shows a reduction of early postoperative pain in the group with deep NMB, and possibly, it reduces postoperative pain after 24 h. There was no proof of shortening the length of hospital stay.

Important strengths of this study are related to its design as a systematic review including a meta-analysis with a review protocol published beforehand. Furthermore, it adds the first evidence concerning the improved surgical conditions and reduced postoperative pain scores after laparoscopic surgery with deep NMB.

A limitation of the present study is the heterogeneity between studies comparing different types of laparoscopic surgery with different postoperative pain management protocols. For example, Kim and colleagues and Torensma and colleagues used patient-controlled analgesia, whereas Koo and colleagues used on demand fentanyl i.v., resulting in higher pain scores in the PACU. Another explanation for the heterogeneity between studies might be related to differences in the control treatment. Some studies used no or shallow NMB as a control treatment, whereas others used moderate NMB. This might have influenced the outcome of the meta-analysis. However, the more recent studies maintained a TOF count of 1–2 in the moderate NMB group and found comparable significant superior effects of deep NMB on the surgical space conditions, when compared with moderate NMB. Furthermore, these findings are supported by the sensitivity analysis, which did not alter the conclusions. Another limitation of the present study is the high risk of conflict of interests, revealed by the risk-of-bias analysis (73% of the studies), because some of the authors received grants or funding from Merck Sharp & Dohme Corp. (MSD), including some authors of the present review. However, they all state that the opinions expressed in the papers are those of the authors and do not necessarily represent those of MSD. Although the impact of this potential source of bias remains uncertain, it is important to note that the risk of bias with regard to blinding of personnel and outcome assessors was low.

The included studies reported different scales to quantify the surgical space conditions. Most of them used Likert scales ranging from one (poor conditions) to four (optimal conditions) or from one (extremely poor conditions) to five (optimal conditions), or in an inverted manner. All reported scales were converted to the Leiden Surgical Rating Scale (L-SRS), as reported by Martini and colleagues, of which some initial proof of validity is given in the study by Torensma and colleagues. The L-SRS is a Likert scale ranging from one (extremely poor conditions) to five (optimal conditions). Scores of other scales were inverted if necessary. Studies using a four-point scale in all instances differentiated between optimal/excellent, good, acceptable, and poor conditions. We converted this to five for optimal/excellent conditions, to four for good conditions, three for acceptable conditions, and two for poor conditions. As (extremely) poor conditions almost never occurred, it is unlikely that conversion of the four-point scale influenced the result of our meta-analysis. The study by Torensma and colleagues used 0.5 as the smallest clinical relevant difference on the L-SRS. Meta-analysis of the surgical space conditions revealed a mean difference of 0.65, which in our view can be considered as a clinically relevant improvement of the surgical space conditions, as a result of deep NMB. In theory, improved surgical conditions could lead to a reduction in intraoperative complications during laparoscopy (i.e. bleeding and organ injury). Unfortunately, this outcome measure was poorly reported and therefore this important issue could not be addressed in the meta-analysis.

The study of Staehr-Rye and colleagues was the only study included in the meta-analysis without a significant effect of deep NMB on the surgical space conditions. This study is the reason for the relatively high heterogeneity. The I² in Fig. 3 changes from 46 to 0% when removing the study of Staehr-Rye.
and colleagues\textsuperscript{5} from the meta-analysis. A possible explanation could be that only the studies by Kim and colleagues,\textsuperscript{1} Koo and colleagues,\textsuperscript{3} and Staehr-Rye and colleagues\textsuperscript{4} used low-pressure pneumoperitoneum. Kim and colleagues\textsuperscript{1} decreased the IAP from standard pressure (1.6 kPa) without compromising the surgical conditions. Koo and colleagues\textsuperscript{3} and Staehr-Rye and colleagues\textsuperscript{4} titrated the IAP from a low to higher pressure (1.1 kPa) if surgical conditions were inadequate. In the study by Staehr-Rye and colleagues,\textsuperscript{4} the surgery was completed at 1.1 kPa in only 35% of the patients in the moderate NMB group, vs 60% in the deep NMB group. This explains why Staehr-Rye and colleagues\textsuperscript{4} did not observe a difference in surgical conditions between moderate and deep NMB.

The results of this systematic review show that deep NMB facilitates the use of low intraperitoneal pressure. Several studies have been performed regarding the advantages of the use low-pressure pneumoperitoneum. A recent systematic review of studies comparing low vs standard-pressure pneumoperitoneum\textsuperscript{21} reveals lower postoperative pain scores after laparoscopy performed with low-pressure pneumoperitoneum. However, another recent systematic review\textsuperscript{22} comparing low vs standard intraperitoneal pressure during laparoscopy found that the use of a lower pressure was associated with a deterioration of the surgical space conditions. At least in theory, this disadvantage can be resolved by the use of deep NMB. This is supported by the study of van Wijk and colleagues,\textsuperscript{23} who found that, when combined with deep NMB, an almost 25% lower IAP (1.0 kPa) still provided adequate surgical conditions.

The meta-analysis of postoperative pain in the PACU showed a significant reduction of pain in the group with deep NMB. However, in three studies the deep level of NMB was accompanied by a lower pressure pneumoperitoneum when compared with the moderate NMB group. Therefore, it is difficult to distinguish whether the reduction of pain scores could be attributed to the effect of the deep NMB or the lower pressure pneumoperitoneum. Nevertheless, separate analyses of the studies with equal IAP\textsuperscript{15 20} and the studies with different pressure levels\textsuperscript{1 5 17} both showed a comparable significant reduction in pain scores in the deep NMB group (see Supplementary material supplements 6 and 7 (S6 and S7)). The numerical rating scale to assess postoperative pain is a valid, reliable, and appropriate tool for use in clinical practice.\textsuperscript{23} However, owing to the subjective nature of pain, it remains difficult to determine clinically important treatment effects. The studies of Farrar and colleagues\textsuperscript{18} and Salaffi and colleagues\textsuperscript{23} point out that the highest degree of improvement in patients’ global impression of change was associated with a mean reduction of two points. Nonetheless, Salaffi and colleagues\textsuperscript{23} emphasized that clinically significant changes in pain are not uniform along the entire numerical rating scale. The minimal clinically important difference might be higher in patients with higher pain scores, when compared with patients with lower levels of pain. Nevertheless, a reduction of 0.5 in postoperative pain scores in general might not be considered as clinically relevant. A potential mechanism through which a deep NBM reduces postoperative pain scores could be its effect on the tension of the abdominal wall musculature. Relaxation of the abdominal wall possibly decreases pain related to stretch of the abdominal wall, exerted by the IAP during laparoscopic procedures.

In conclusion, this study provides evidence that deep NMB, when compared with moderate NMB, improves the surgical space conditions during laparoscopic surgery and facilitates the use of low-pressure pneumoperitoneum. Furthermore, deep NMB reduces the postoperative pain scores in the PACU. Whether this leads to fewer intraoperative complications, an improved quality of recovery, or both after laparoscopic surgery should be pursued in future studies.

Authors’ contributions

Conception and design of this review: M.H.B., M.C.W.
Database searches: M.H.B.
Study assessment for inclusion in the review: M.H.B., E.V.v.H.
Data extraction: M.H.B., E.V.v.H.
Risk-of-bias assessment: M.H.B., E.V.v.H.
Data analysis: M.H.B., M.C.W.
Wrote the first draft of the manuscript: M.H.B., M.C.W.
Critical revision of the manuscript: E.V.v.H., A.E.B., A.D., G.J.S., C.J.v.L., M.C.W.
All authors read and approved the final manuscript.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Declaration of interests

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