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# Clinical Impact of Deep Versus Moderate Neuromuscular Block for Bariatric Surgery: A Systematic Review and Meta-analysis

Lucas Ferreira Gomes Pereira[1], Regina El Dib[2, 3, 4], Carlos Darcy Alves Bersot[5, *], José Eduardo Guimarães Pereira[6, 7, 8]

[1]University Centre of Volta Redonda - UniFOA, Volta Redonda, Rio de Janeiro, Brazil

[2]Department of Community Health and Epidemiology, Dalhousie University, Halifax, Canada

[3]Department of Biosciences and Oral Diagnosis, Institute of Science and Technology, UNESP – São Paulo State University, São Paulo, São José dos Campos, Brazil

[4]McMaster Institute of Urology, McMaster University, Hamilton, Ontario, Canada

[5]Department of Anesthesiology, Lagoa Federal Hospital, Rio de Janeiro, Brazil

[6]Department of Anesthesiology, Botucatu Medical School, UNESP – São Paulo State University, São Paulo, Brazil

[7]Department of Anesthesiology, EsSEx, Army Central Hospital, Rio de Janeiro, RJ, Brazil

[8]Department of Anesthesiology, Barra Mansa Wholy House of Mercy Hospital, Barra Mansa, Rio de Janeiro, Brazil

## Email address

carlosbersot@gmail.com (C. D. A. Bersot)

[*]Corresponding author

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## Abstract

This systematic review and meta-analysis were designed to investigate the efficacy and safety of deep (DNMB) versus moderate (MNMB) neuromuscular block on the treatment of patients submitted to bariatric surgery. Randomized controlled trials (RCTs) were searched from inception to December 2017 in the following databases: PubMed, EMBASE, COCHRANE, Scopus, Web of Science and LILACS. Reviewers independently screened potentially eligible articles, extracted data from included studies and assessed their risk of bias. We used the GRADE approach to rate overall certainty of the evidence for each outcome. Two RCTs including 160 participants proved eligible, and their results yielded a statistically significant improvement on surgical field quality according to the Leiden-Surgical Rating Scale (L-SRS) with the use of DNMB compared to MNMB (MD 0.57, 95% CI 0.39 to 0.75; participants = 160; studies = 2; $I^2$ = 16%; $p < 0.00001$). Results from one RCT yielded a statistically significant reduction in pain scores at the post-anesthesia care unit (MD -0.50, 95% CI -0.71 to -0.29; participants = 100; studies = 1; $p < 0.00001$) and in referred shoulder pain at the surgical ward (MD -0.50, 95% CI -0.64 to -0.36; participants = 100; studies = 1; $p < 0.00001$) with the use of DNMB compared to MNMB. There was no increase in adverse outcomes detected. The quality of evidence was rated as very-low for both outcomes.

## Keywords

Anesthesia, Neuromuscular Blocking, Bariatric Surgery, Deep Neuromuscular Block, Moderate Neuromuscular Block

# 1. Introduction

Around 216,000 patients have been submitted to bariatric surgeries according to the American Society for Metabolic & Bariatric Surgery (ASMBS) [1] in USA. In Brazil a steady rise on the number of bariatric surgeries has taken place, from a total of 72,000 cases in 2012 rising to 100,500 cases in 2016, according to the Brazilian Society of Bariatric Surgery. [2]

Although laparoscopic surgery yields reduced intensity of postoperative pain and hospital length of stay [3], it is performed by producing pneumoperitoneum through insufflation of carbon dioxide ($CO_2$) into the peritoneal cavity, and that encompasses a rise in the intra-abdominal pressure (IAP).

Carbon dioxide absorption and elevated IAP during pneumoperitoneum (generally 1.6–2.1 kPa) [4] can cause specific pathophysiological effects, such as cardiovascular, pulmonary and splanchnic perfusion changes. [5] The diaphragm is shifted upwards, thereby decreasing pulmonary compliance and increasing peak airway pressures. [4] Mean systemic arterial pressure and systemic and pulmonary vascular resistances are increased and, at least during the early phase of pneumoperitoneum, the stroke volume and cardiac output are reduced. [4, 6]

In recent literature it has been suggested that deep neuromuscular block (NMB) improves surgical conditions during laparoscopy. Nevertheless, the evidence supporting this statement is limited. [7] Moreover, the occurrence of residual NMB could impair postoperative respiratory function.

Neuromuscular block depth monitoring is routinely used in video laparoscopic surgeries through acceleromyography, also known as train-of-four (TOF). Neuromuscular blockade is considered moderate when there are one to three responses to TOF, which means that 75-90% of the receptors are blocked. However, during deep neuromuscular block, there are no responses to TOF and two or fewer responses to the post-tetanic count (PTC). [8]

Several studies have been conducted in an effort to reduce $CO_2$ IAP and minimize adverse effects of pneumoperitoneum and have reported postoperative pain relief after low-pressure pneumoperitoneum. [9-11]

The outcome of this review might inform if DNMB is likely to result in a large public health benefit by reducing adverse outcomes in patients undergoing bariatric surgeries. We therefore conducted an updated systematic review of RCTs that assessed the impact of deep (DNMB) versus moderate (MNMB) neuromuscular block among patients submitted to bariatric surgeries.

# 2. Methods

The Cochrane Handbook for Intervention Reviews [12] guided our choice of methods. This systematic review of the literature on interventional studies was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement. [13] This review was registered at PROSPERO - *International Prospective Register of Systematic Reviews* (http://www.crd.york.ac.uk/prospero/index.asp), under the number CRD42018090614.

## 2.1. Eligibility Criteria

We considered all RCTs evaluating deep (DNMB) compared to moderate (MNMB) neuromuscular in adults (aged 18 years old and above) undergoing laparoscopic bariatric surgery, regardless of gender. We excluded participants who received neuraxial blockade and patients with prior cardiac chronic insufficiency, previous kidney dysfunction and previous restrictive or obstructive pulmonary disease.

Eligible studies reported one or more of the following: a) intra-abdominal pressure; b) cardiac depression measured by hemodynamic variables and/or by vasoactive drugs (e.g., noradrenaline) or inotropic (e.g., dopamine, adrenaline); c) renal insufficiency, measured by neutrophil gelatinase-associated lipocalin (NGAL), 'Risk, Injury, Failure, Loss, End-stage' kidney disease (RIFLE), creatinine, cystatin or other; d) length of stay in both hospital and intensive care unit and; e) adverse postoperative outcomes such as: mortality; re-operation; pneumonia; arrhythmia; nausea and vomiting measured by frequency and severity; pain measured by any validated tool such as the visual analogue scale (VAS).

## 2.2. Data Source and Searches

The search was performed in the following electronic databases: The Cochrane Central Register of Controlled Trials (CENTRAL, 2, 2017), PubMed (OvidSP, 1966 to 2017), EMBASE (Excerpta Medica database) (OvidSP, 1980 to 2017), LILACS (Literatura Latino-americana e do Caribe em Ciências da Saúde) (1982 to 2017). The databases were searched for available published and unpublished studies from inception up to 20th December 2017.

The search was conducted using multiple combinations of the following key words: "Neuromuscular Blockade" and "Laparoscopy" (Appendix Table 1). No restrictions were placed on language, year of publication or publication status. In addition, a manual search of the reference lists of potential primary studies was conducted, and several major anesthesiology journals (e.g., Anesthesia and Analgesia, Anesthesiology, European Journal of Anesthesiology) were hand-searched for additional eligible studies.

## 2.3. Selection of Studies

Using pre-standardized screening forms and protocols, two reviewers (LFGP, JEGP) independently screened all titles and abstracts identified by the literature search, obtained full-text articles of all potentially eligible studies, and evaluated these studies for eligibility. Reviewers resolved disagreement through discussion, with third party adjudication if necessary.

## 2.4. Data Extraction and Risk of Bias Assessment

Two reviewers (LFGP, JEGP) independently extracted the following data using a pre-standardized data extraction form:

characteristics of the study design; participants; interventions; outcome event rates and follow-up. Reviewers contacted authors of eligible studies whenever there were missing or incomplete data.

Reviewers independently assessed risk of bias by using the risk of bias approach for Cochrane reviews modified by Guyatt. [13-14] We used the following five separate criteria: adequacy of sequence generation, allocation sequence concealment, blinding (investigators, patients, data collectors, statisticians, outcome assessors), incomplete outcome data, selective outcome reporting. For incomplete outcome data, we considered loss to follow-up of 10% and a difference of 5% in missing data between intervention and control groups as low risk of bias.

### 2.5. Certainty of Evidence

The reviewers used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate certainty of evidence for each outcome as high, moderate, low, or very low. [13] Detailed GRADE guidance was used to assess overall risk of bias, [15] imprecision, [16] inconsistency, [17] indirectness [18] and publication bias [19] and results were summarized in an evidence profile.

### 2.6. Data Synthesis and Statistical Analysis

We calculated pooled risk ratios (RRs) for dichotomous outcomes and mean differences (MD) for continuous variables, with both the associated 95% confidence interval (CI) using random-effects models with the Mantel-Haenszel statistical method. We addressed variability in results across studies by using $I^2$ statistic and the P value obtained from the Cochrane chi square test. Our primary analyses were based on eligible patients who had reported outcomes for each study (complete case analysis).

We planned to perform separate analyses to assess publication bias through visual inspection of funnel plots for outcomes addressed in 10 or more studies. However, the information from the included studies was insufficient for performance of any of these analyses.

We used Review Manager (RevMan) (version 5.3; Nordic Cochrane Centre, Cochrane) for all analyses. [20]

## 3. Results

### 3.1. Search Results

We identified a total of 370 citations (Figure 1). After screening by title, and then by abstract, and excluding duplicates, we obtained full-text copies for 37 citations that were potentially eligible for inclusion in this review. Of those 35 did not fulfil our eligibility criteria and were excluded. We therefore included two studies [21-22] with a total of 169 participants in this review (Figure 1). No additional eligible studies were identified based on hand-searching of major anesthesia journals or manual review of reference lists of relevant primary studies and systematic reviews.

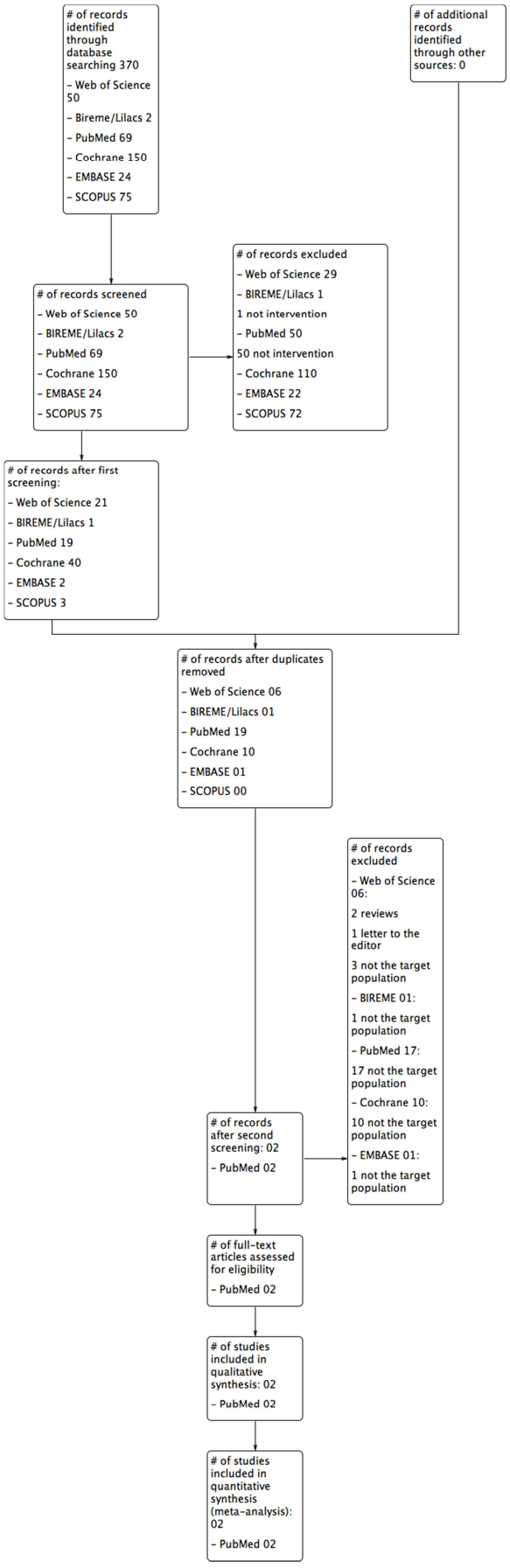


***Figure 1.*** *PRISMA flowchart.*

### 3.2. Characteristics of the Included Studies

Both of the two included studies were reported as RCTs. Both trials took place in Europe: One trial took place in Belgium; [21] One trial took place in the Netherlands. [22] (Table 1)

The studies included both male and female participants under 60 years of age. [21-22] The mean age of the participants in the DNMB group ranged from 41 years to 47.2 years, with an average mean age for the deep neuromuscular group of 45.03 years. The mean age of the participants in control group ranged from 42 years to 46.9 years, with an average mean age for the control group of 46.82 years (Table 1).

Both trials [21-22] included adult patients with ASA physical status ranging from 1 to 3. The studies excluded patients with neuromuscular disorders, allergy to muscle relaxants, family history of malignant hyperthermia and kidney insufficiency. One RCT did not report the follow-up time. [21] Torensma study reported a follow-up time of eight months [22] (Table 1).

***Table 1.*** *Study characteristics related to population and setting.*

| Author Year | Country | Number of randomized participants | Mean age per studied group | Male gender per group | Inclusion criteria | Exclusion criteria | Follow-up time (days) |
|---|---|---|---|---|---|---|---|
| Baete 2016 | Belgium | I: 30<br>C: 30 | I: 41<br>C: 42 | I: 8<br>C: 4 | - ASA 1-3;<br>- 18 years or older and younger than 66 years;<br>- BMI > 34 kg/m$^2$;<br>- Ability to give informed consent;<br>- Elective bariatric surgery. | - Known or suspected neuromuscular disorders impairing neuromuscular function;<br>- Allergies to muscle relaxants, anesthetics or narcotics;<br>- A (family) history of malignant hyperthermia;<br>- Women who are or may be pregnant or are currently breast feeding;<br>- Renal insufficiency, as defined by serum creatinine x 2 of normal, or urine output < 0.5 ml/kg/h for at least 6 h. When available, other indices will be considered such as glomerular filtration rate < 30 ml/h and proteinuria as well (a ratio of 30 mg albumin to 1 g of creatinine). | ? |
| Torensma 2016 | Netherlands | I: 56<br>C: 53 | I: 47,2<br>C: 46,9 | I: 11<br>C: 9 | - Obese or morbidly obese as defined by a BMI > 30 and >40 kg/m$^2$;<br>- ASA I, II or III;<br>- Able to give written informed consent. | - Neuromuscular disorders;<br>- Allergies to, or contraindication for muscle relaxants, neuromuscular reversing agents, anesthetics, narcotics;<br>- History of malignant hyperthermia;<br>- Pregnancy or lactation;<br>- Renal insufficiency defined as serum creatinine of 2× the upper normal limit, glomerular filtration rate <60 mL/min, urine output of <0.5 mL/kg/h for at least 6 h;<br>- Chronic obstructive pulmonary disease GOLD classification 2 or higher;<br>- Clinical, radiographic or laboratory findings suggesting upper or lower airway infection;<br>- Congestive heart failure;<br>- Pickwick syndrome;<br>- Psychiatric illness inhibiting cooperation with study protocol or possibly obscuring results. | 8 months |

Sample sizes ranged from 60 [21], to 109 [22] participants (Table 2). In both trials [21-22] the control group was maintained with moderate neuromuscular block (TOF 1-2) during the procedure (Table 2), and the intervention group with deep neuromuscular block (PTC < 4) (Table 2). In the two included studies [21-22], the intra-abdominal pressure was kept at 18 cm $H_2O$ (Table 2), and the anesthetic technique of choice was the total intravenous anesthesia using remifentanil and propofol. The average body mass index (BMI) was 42.06 for the DNMB group and 42.25 for the MNMB block group.

***Table 2.*** *Study characteristics related to intervention and control groups.*

| Author year | Number of randomized patients in intervention and control | Description of intervention | Total dose* | Description of control | Measured outcomes |
|---|---|---|---|---|---|
| Baete 2016 | I: 30<br>C: 30 | Sleeve surgery, TIVA, IAB pressure | Rocuronium I: 1MG/KG | Sleeve surgery, TIVA, IAP | I: Intrabdominal pressure = 18 (0.2 ± 0.9) cm $H_2O$; Discharged 24h after arrival on the ward; |

| Author year | Number of randomized patients in intervention and control | Description of intervention | Total dose* | Description of control | Measured outcomes |
|---|---|---|---|---|---|
| | | = 18cm $H_2O$, PTC 1-2<br>NMB reversal: Sugammadex 4mg/kg<br>Extubation at TOF >0.9 | C: 0.7MG KG | pressure = 18cm $H_2O$, TOF 1-2<br>NMB reversal: Neostigmine 50mcg/kg<br>Extubation at TOF >0.9 | SRS = 4.2 ± 1.0; Duration of the surgery: 61.3 ± 15.1 minutes PEF: 314 ± 109; FEV1: 2.4 ± 0.9; FVC: 3.0 ± 0.9; FEV1/FVC: 84 ± 8; 2 patients required postoperative noninvasive continuous positive airway pressure.<br>C: Intrabdominal pressure = 18 (0,3-1,0) cm $H_2O$; Discharged 24h after arrival on the ward; SRS = 3.9 ± 1.1; Duration of the surgery: 70.6 ± 20.8 minutes; PEF: 276 ± 81; FEV1: 2.2 ± 0.6; FVC: 2.7 ± 0.8; FEV1/FVC: 82 ± 9; 1 patient required postoperative noninvasive continuous positive airway pressure |
| Torensma 2016 | I: 56<br>C: 53 | RYGB surgery, TIVA, BIS (40-60), IAB pressure = 18 cm $H_2O$, PTC < 4<br>NMB reversal: Sugammadex 4mg/kg<br>TOF > 0.9 | Rocuronium<br>I: 1MG/KG<br>C: 0.6 MG/KG | Sleeve surgery, TIVA, BIS (40-60), IAP pressure = 18cm $H_2O$, TOF 1-2<br>NMB reversal: Sugammadex 2mg/kg<br>TOF > 0.9 | I: Intrabdominal pressure = 18 cm $H_2O$; Discharged 24h after arrival on the ward; L-SRS: 4,8 (4,7-4,9); Pain measured 3,9 (3,6-4,4); Nausea 54%;<br>C: Intrabdominal pressure = 18 cm $H_2O$; Discharged 24h after arrival on the ward; L-SRS: 4,2 (4,0-4,4) Pain measured 4,4 (4,2-4,9); Nausea 50%. |

## 3.3. Risk of Bias in Individual Studies

Allocation concealment was a major risk of bias limitation in both trials. [21-22] Blinding of participants and outcome assessors was judged to be at very low risk of bias in both trials [21-22] while blinding of personnel was considered of major risk in both trials [21-22] (Figure 2). Also, there is an additional risk of bias, since both studies received funding from Merck Sharp and Dohme (MSD), the company that exclusively markets Bridion® (Sugammadex), which is a necessary and indispensable drug if one considers to use deep neuromuscular block as an adjunct to the anesthetic technique.

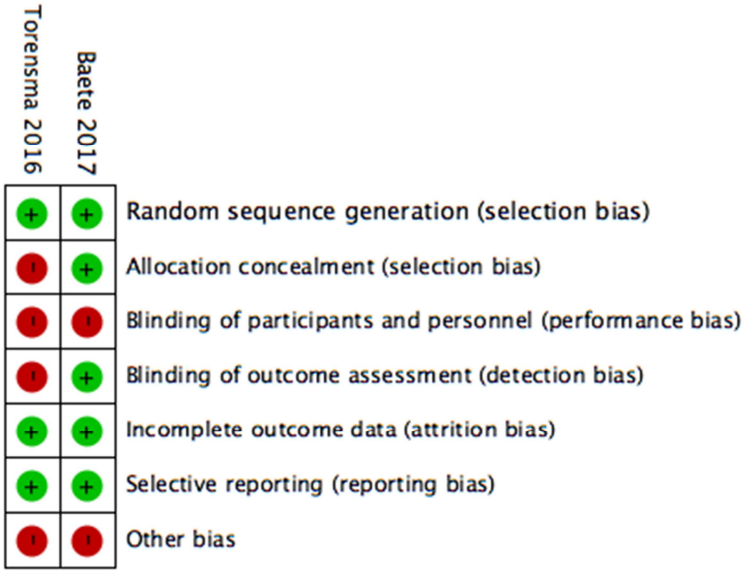


***Figure 2.*** *Risk of bias assessment.*

## 3.4. Effectiveness of Interventions

### 3.4.1. Statistically Significant Results

*i - Pain*

Results from one RCT [22] yielded a statistically significant reduction of pain scores at the post-anesthesia care unit with the use of DNMB compared to MNMB (MD -0.50, 95% CI -0.71 to -0.29; participants = 100; studies = 1; $I^2$ = not applicable; p < 0.00001) (Figure 3). The certainty of evidence was rated down to very low for this outcome because of serious risk of bias (allocation concealment [22]; blinding [22]), and serious limitations related to imprecision (Table 3).

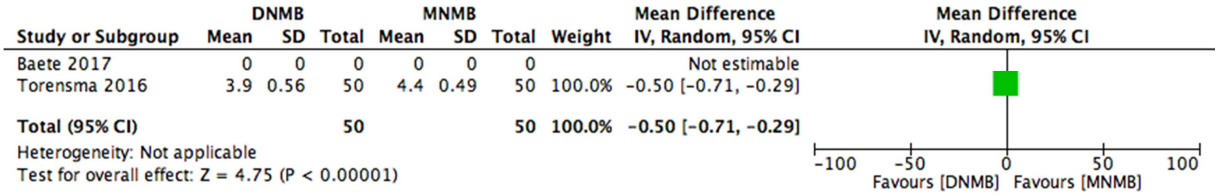


***Figure 3.*** *Meta-analysis on Post-anesthesia care unit pain.*

Results from one RCT [22] yielded a statistically significant reduction of referred shoulder pain score at the surgical ward with the use of DNMB compared to MNMB (MD -0.50, 95% CI -0.64 to -0.36; participants = 100; studies = 1; $I^2$ = not applicable; p < 0.00001) (Figure 4). The certainty of evidence was rated down to very low for this outcome due to serious risk of bias (allocation concealment [22]; blinding [22]) and serious limitations related to imprecision (Table 3).

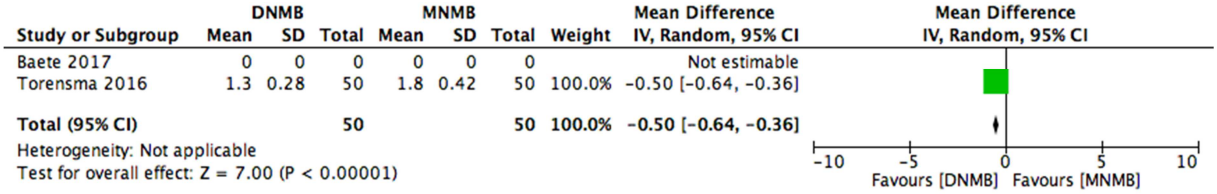


***Figure 4.*** *Meta-analysis on Referred shoulder pain.*

*ii - Surgical field quality*

Results from two RCTs [21-22], involving 160 patients, yielded a significant improvement with the use of DNMB compared to MNMB in surgical field quality, measured by the Leiden-Surgical Rating Scale (L-SRS) scale (MD 0.57, 95% CI 0.39 to 0.75; participants = 160; studies = 2; $I^2$ = 16%; p < 0.00001) (Figure 5). The certainty of evidence was rated down to very low for this outcome. We downgraded the certainty of evidence from high to very low because of serious risk of bias (allocation concealment [22]; blinding [21-22]), serious limitations related to inconsistency, and imprecision (Table 3).

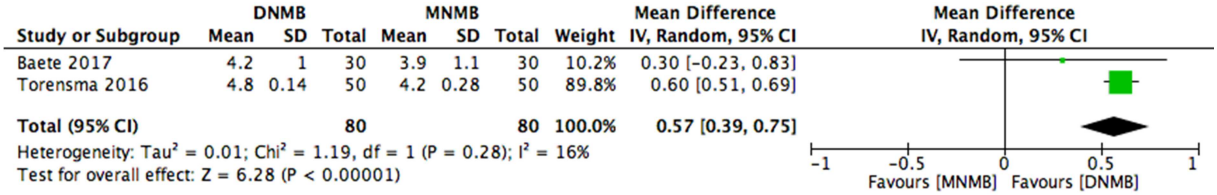


***Figure 5.*** *Meta-analysis on Surgical field quality.*

***Table 3.*** *GRADE evidence profile for clinical outcomes.*

| **Quality assessment** | | | | | |
|---|---|---|---|---|---|
| **Nº of participants (studies) Follow-up in months** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Publication bias** |
| Pain (VAS)<br>160 (2)<br>8 | Serious limitations[1] | No serious limitations | No serious limitations | Serious imprecision[2] | Undetected |
| Surgical field quality (L-SRS)<br>160 (2)<br>8 | Serious limitations[1] | No serious limitations | No serious limitations | Serious imprecision[2] | Undetected |

***Table 3.*** *Continued.*

| **Quality assessment** | **Summary of findings** | | | | | **Certainty in estimates** |
|---|---|---|---|---|---|---|
| | **Study event rates** | | **Average (CI 95%)** | **Anticipated absolute effects** | | |
| **Nº of participants (studies) Follow-up in months** | **Control** | **DNMB** | | **Control** | **DNMB** | |
| Pain (VAS)<br>160<br>(2)<br>8 | - | - | - | The mean pain score, considering DNMB was -0.50 | The mean continuous pain score in the intervention group was on average 0.50 lower (0.71 fewer to 0.29 lower) | VERY LOW |

| Quality assessment | Summary of findings | | | | | Certainty in estimates |
|---|---|---|---|---|---|---|
| | Study event rates | | Average (CI 95%) | Anticipated absolute effects | | |
| Nº of participants (studies) Follow-up in months | Control | DNMB | | Control | DNMB | |
| Surgical field quality (L-SRS) 160 (2) 8 | - | - | - | The mean surgical field score was 0.57 | The mean continuous surgical field score in the intervention group was on average 0.57 higher (0.39 higher to 0.75 higher) | ⊕OOO VERY LOW |

DNMB: deep neuromuscular block; VAS: visual analogue scale; L-SRS: Leiden-surgical rating scale.
[1]There was serious limitation related to risk of bias (allocation concealment [Torensma]; blinding [Baete, Torensma]; other bias [Baete, Torensma]).
[2]There was serious limitation related to imprecision.

### 3.4.2. Non-statistically Significant Results

*i - Remifentanil consumption*

There was no statistically significant difference between DNMB and MNMB [21-22] on remifentanil consumption (MD 0.01, 95% CI -0.01 to 0.04; participants = 160; studies = 2; $I^2$ = 0%; p = 0.36) (Figure 6).

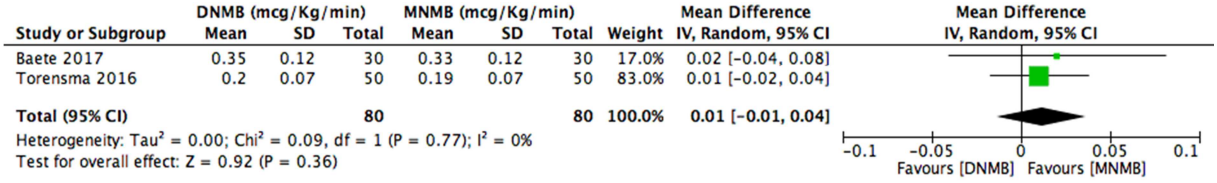


***Figure 6.*** *Meta-analysis on Remifentanil consumption.*

*ii - Propofol consumption*

There was no statistically significant difference between DNMB and MNMB [21-22] on propofol consumption (MD 1.35, 95% CI -0.01 to 2.71; participants = 160; studies = 2; $I^2$ = 17%; p = 0.05) (Figure 7).

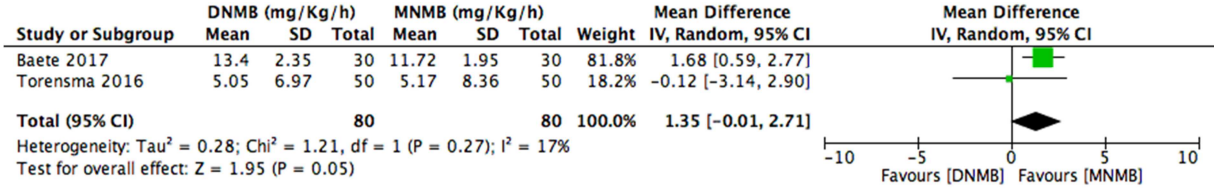


***Figure 7.*** *Meta-analysis on Propofol consumption.*

*iii - Surgical length of time*

There was no statistically significant difference between DNMB and MNMB [21-22] in surgical length of time (MD -4.03, 95% CI -15.08 to 7.01; participants = 160; studies = 2; $I^2$ = 59%; p = 0.47) (Figure 8).

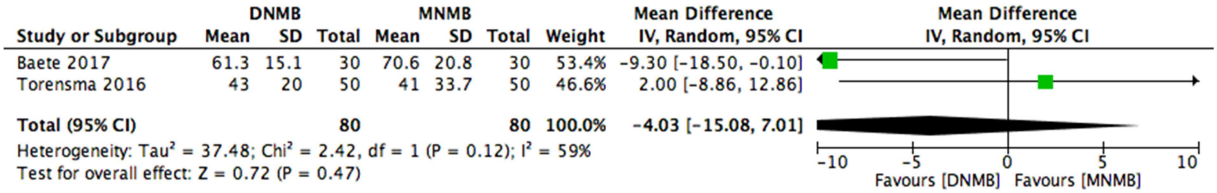


***Figure 8.*** *Meta-analysis on Surgical length of time.*

## 4. Discussion

### 4.1. Main Findings

To the best of our knowledge, this is the first systematic review to analyze the effectiveness and safety of deep neuromuscular block compared to moderate neuromuscular block focusing exclusively on laparoscopic bariatric surgery. The results yielded from this meta-analysis may shed some light on how DNMB may positively impact outcomes, especially postoperative pain and surgical field quality, which, in turn, may affect the overall stakeholder´s perception on the quality of the service provided.

Although there were statistically significant results on reduction of pain and improvement of surgical field quality, there were no improvements on surgery length, hospital

length of stay and anesthetic consumption by using the DNMB.

### 4.2. Strengths and Limitations

Our study has a number of strengths including the completion of a comprehensive literature search and we used a systematic approach to assess eligibility and risk of bias, with each step completed independently and in duplicate. This review is also strengthened using the GRADE approach to rate the certainty of evidence for each outcome.

In both studies [21-22], the anesthesia protocol was similar and consisted of total intravenous anesthesia with continuous infusion of propofol and remifentanil. Also, in both studies [21-22] rocuronium was the neuromuscular block of choice across both groups, and they adopted the same definition and criteria for evaluation and maintenance of moderate and deep neuromuscular blocks, which adds consistency to the analyses.

The primary limitation of our review is the high risk of bias across both included studies. [21-22] The main risk of bias included inadequate blinding of the anesthesiologists involved on patient care during surgery.

Another limitation of this review is the fact that given the limited number of included studies providing data for the meta-analysis, it reduced the precision of the estimates and precluded the assessment of publication bias.

It was also not possible to perform the analyses of difference in intra-abdominal pressure across groups because in both studies the intra-abdominal pressure was kept at 18 cm $H_2O$ across the entire intervention. Other limitation was that the grey literature evidence might have been missed.

### 4.3. Certainty of the Evidence

We selected RCTs for our review. The methodological certainty was difficult to assess as it was poorly reported in both included studies (three or more domains rated as unclear risk of bias).

Baete [21] did not inform the follow-up time, and Torensma [22] lost a total of nine patients for not collecting data, but without stating the reasons why data have not been collected on those patients.

The unavailability of data from several outcomes (cardiac depression; renal insufficiency; length of stay in both hospital and intensive care unit and; adverse postoperative outcomes such as: mortality; re-operation; pneumonia; arrhythmia) limited our capability of performing all pre-defined analyses. And trials involving DNMB versus MNMB were small regarding sample size. Thus the results must be interpreted with caution.

Methodological aspects of both studies had a high risk of introducing bias: inadequate blinding of personnel in both RCTs [21-22], and poor allocation concealment was a major risk of bias limitation in both trials [21-22]. There is also conflict of interest derived from the fact that both studies have been funded by MSD.

Our results indicate that deep neuromuscular block improves the quality of surgical field and reduces the pain scores at post-anesthesia care unit and referred shoulder pain scores at surgical ward when compared to moderate neuromuscular block. And that there are no differences in anesthetic consumption and surgical length of time with the use of deep neuromuscular block when compared to moderate neuromuscular block.

## 5. Conclusions

In conducting this review, we have attempted to answer the following clinical question: Is DNMB more effective and safer than MNMB for bariatric surgery patients? The results we obtained for this base question yield a very low-certainty evidence that deep neuromuscular block improves the quality of surgical field, reduces the pain scores at post-anesthesia care unit and referred shoulder pain scores at surgical ward. Another very low-certainty evidence indicates that there are no differences in anesthetic consumption and surgical length of time between deep and moderate neuromuscular block.

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## Conflict of Interest

The authors report no conflicts of interest. The funding agency played no role in the conduct of the research or preparation of the manuscript.

## Contributors

JEGP: conception, study design, data acquisition, and interpretation of data, analysis, drafting article, revision and final approval. LFGP: data acquisition, and interpretation of data, analysis, drafting article, revision and final approval. RED: interpretation of data, analysis, drafting article, revision and final approval. CDAB: interpretation of data, analysis, drafting article, revision and final approval.

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