Forty Years of Neuromuscular Monitoring and Postoperative Residual Curarization: a Meta-analysis and Evaluation of Confidence in Network Meta-Analysis.

Hugo Carvalho [1,§,*], Michael Verdonck [1,2,§], Wilfried Cools [3], Lieselot Geerts [4], Patrice Forget [5], Jan Poelaert [1]

[1] Department of Anaesthesia and Perioperative Medicine, Universitair Ziekenhuis Brussel, Belgium.

[2] Business Informatics Research Group, University of Ghent, Belgium.

[3] Interfaculty Center Data processing & Statistics, Vrije Universiteit Brussel, Belgium.

[4] Department of Anesthesiology, University of Ghent, Belgium.

[5] Department of Anaesthesia, NHS Grampian, Institute of Applied Health Sciences, Epidemiology group, School of Medicine, Medical Science and Nutrition, University of Aberdeen, United Kingdom.

Short running title: Neuromuscular Monitoring and PORC

* Corresponding author

carvalho.hn@gmail.com

Department of Anaesthesia and Perioperative Medicine, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.

§ Both authors equally contributed to the present work.

Abstract

Background: The reported incidence of Postoperative Residual Curarization (PORC) is still unacceptably high. Clinically counterintuitively, the capacity of intraoperative Neuromuscular Monitoring (NMM) to significantly reduce the incidence of PORC has yet to be established from pooled clinical studies. The present meta-analysis aimed to gather data from 1979 to 2019 to reanalyse this relationship.

Methods: English language, peer-reviewed and operation room adult anaesthesia setting articles published between 1979 and 2019 were searched for on PubMed, Cochrane Central Register of Controlled Trials, ISI-WoK and Scopus. The primary outcome was PORC incidence as defined by a at/post-extubation Train of Four ratio (TOFR) lower than 0.7, 0.9, or 1.0. Additional collected variables included the duration of action category of used NMBAs, sugammadex or neostigmine use and the technique of anaesthesia maintenance.

Results: Fifty-three studies (109 study arms, 12664 patients) were included. The pooled PORC incidence associated with the use of intermediate duration NMBAs and quantitative NMM was 0.115 (95%CI: 0.057 - 0.188). This was significantly lower than the PORC rate for both qualitative NMM (0.306; 95%CI: 0.09 - 0.411) and no NMM (0.331; 95%CI: 0.234 - 0.435). Anaesthesia type did not significantly affect PORC incidence. Sugammadex use was associated with lower PORC rates. The GRADE global level of evidence was very low and the refined assessment of the network meta-analysis by means of a CINeMA analysis raised concerns on within- and across-study bias.

Conclusions: Quantitative NMM significantly outperforms both subjective and no NMM monitoring in reducing PORC as defined by a TOFR < 0.9.

Keywords: meta-analysis; neuromuscular monitoring; neuromuscular block; postoperative residual curarization; train of four; train of four ratio;

Introduction

Neuromuscular Blocking Agents (NMBAs) are part of the daily anaesthetic practice world-wide.

In the United states alone, 51.4 million surgical procedures per annum are estimated to take place.[1] In Europe, estimations approximate 34.8 million procedures.[2] Combined worldwide estimates put forward a global volume of 234.4 million surgical procedures per year.[2] The proportion of these in which NMBAs are used is not accurately known and only speculated on.[1]

Despite international recognition of quantitative neuromuscular monitoring (NMM) as an absolute and core necessity in modern anaesthesia care, the incidence of Postoperative Residual Curarization (PORC) due to ineffective or absent NMM remains unacceptably high (up to 60%) – especially considering its preventable nature.[1,3]

The substandard NMM adoption is attributed to both logistical/material factors (limited availability, suboptimal practicality/ergonomics, time-pressure), as well as to operator-related phenomena (undereducation, overconfidence).[3,5–7]

Although clinical intuition and expert opinion put NMM forward as essential for PORC prevention, indexed literature reports heterogeneous findings and this subject has only been addressed once by means of a meta-analysis.[8] Pooling studies from 1979 to 2005, Naguib and co-workers have counter-intuitively failed to statistically demonstrate that intraoperative NMM leads to PORC prevention.[8,9]

The present meta-analysis aims to reanalyse evidence for the effect of different subtypes of intraoperative NMM on PORC. Building on the original meta-analysis, published data up to present has been pooled for re-analysis and complemented with a Confidence In Network Meta-analysis (CINeMA).[8]

Methods

Prior to commencement, the protocolized meta-analysis was registered on the PROSPERO Database (ID 137975, registration number CRD42020137975).

The literature search strategy involved the following databases: PubMed, Cochrane Central Register of Controlled Trials, ISI Web of Knowledge and Scopus. The keywords used were: Curarization, Post-operative, Neuromuscular blockers, Muscle relaxants, Residual block, Residual curarization. Inclusion criteria were: publication between January 2006 and May 2019; English language; peer-reviewed; human adult studies; operating room anaesthesia setting. Exclusion criteria were: abstracts; editorials; paediatric, cardiac surgery and neuromuscular disorder patients; duplicate populations.

The reported outcome was the incidence of PORC as defined by a at- or post-extubation Train of Four (TOF) ratio lower than 0.7, 0.9, or 1.0. The cut-off of 0.7 has been included for historical reasons. As reported by Naguib and colleagues, earlier studies used this value for PORC definition.[8] Conversely, more recent studies have reported on a threshold of 1.0.[10–14] Thus, this value was also included.

Data was screened by HC, MV and LG, with full text review of potential eligible studies. Disagreements were disputed recurring to a third co-author (WC, PF, JP). A standardised pre-piloted Excel form was used to extract data from the included studies. Extracted information included: study name, authorship and publication date; participant number subdivided per study arms; study setting; study population and recruitment dates; intervention (intraoperative NMM type, stimulating current in milliamperes) and control conditions; NMBA used and dose; NMBA duration category (short, intermediate, or long); type of anaesthesia (total intravenous anaesthesia - TIVA, volatile anaesthesia - VA - or combined); duration of anaesthesia; used of neostigmine or sugammadex; outcome (PORC defined by a TOF ratio <0.7/<0.9/<1.0) and timing of measurement; oxford quality scoring system and Cochrane Collaboration's risk of bias.[15] Short duration of action NMBAs included

the drug succinylcholine. Intermediate duration NMBAs included atracurium, cisatracurium, mivacurium, vecuronium and rocuronium. Long duration of action NMBAs included gallamine, pancuronium and d-tubocurarine. Missing data was requested from study authors by means of e-mail contact.

The level of certainty was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group guidance.[16,17]

To the constructed database involving articles from 2006 onwards, those of the meta-analysis of Naguib and colleagues (1979 - 2006) were added.[8] These were similarly re-analysed.

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram representing the data processing is presented in figure 1. The pooled studies and main collected variables are displayed on table 1.

Statistical Analysis

The primary analysis' goal was to examine whether PORC (defined by post-extubation TOF ratio values above the cut-off of either 0.7, 0.9 or 1.0) was more or less likely depending on the type of NMM used intraoperatively: no monitoring, qualitative monitoring (Peripheral Nerve Stimulation - PNS), or quantitative monitoring (TOF-ratio quantification). In as far as possible, the evaluation also accounted for the duration category of NMBAs used intraoperatively (short, intermediate or long duration of action), use of antagonizing drugs (sugammadex or neostigmine), type of anaesthesia maintenance technique (VA, TIVA or both) and year of publication. A three level mixed effect model was used to analyse one or more proportions per study obtained in different conditions.[18] The proportions in each of the relevant conditions were transformed in order to normalize them using the Freeman Tukey arcsine transformation which resulted in effect size estimates (proportion) and variance. Secondly, these transformed effect sizes were pooled using a linear mixed model conditional on these variances. The lowest of the three levels consists of the Freeman Tukey transformed proportions with appropriately transformed variances. A second level defines

the conditions under which these proportions were obtained, including information for example on the type of intraoperative NMM/NMBA. The third level is necessary to identify the study so that within study correlations between proportions can be incorporated. To accommodate the embedding of sometimes more than one proportion within a study, an extra level was used to incorporate within study correlations. Afterwards, the resulting estimates were back-transformed to the proportion scale.

The analysis was repeated twice, once for the proportions related to the TOF-ratio cut-off of 0.9 and once for the proportions related to the 0.7 cut-off. Pairwise contrasts were used to compare the 3 types of monitoring with Shaffer adjusted p-values. A forest plot was used to illustrate the back-transformed proportions for the various studies and their pooled proportions.

An intercorrelation analysis preceded the above-mentioned calculations in order to put forward a statistical model without confounding multicollinearity issues. In fact, due to high intercorrelation concerns between some of the collected variables, a model encompassing all relevant information could not be created. For this purpose, a model accounting for the monitoring type, NMBA duration category and type of anaesthesia maintenance (main model) was used as the central model to answer the main questions within the present meta-analysis. A secondary analysis addressed the effect of variables such as pharmacological antagonism in combination with monitoring type and anaesthesia maintenance but without NMBA duration category. Another secondary analysis addressed the trend over time with publication year in combination with NMM type only. No sensitivity analysis was planned.

Data was classified as missing only if not reported in the original article and eventual accompanying supplements, and only after attempts to contact the corresponding authors were unsuccessful. Further statistical processing was carried out by removing the missing data from the analysis for which missingness at random was assumed.

Selective outcome reporting and publication biases were assessed using an evaluation of the asymmetry in funnel plots according to Cochrane guidelines.[15,16]

The meta-analysis was performed with the R package metafor (R version 3.6.2, 12 December 2019; Metafor package 2.1-0).[19]

A Confidence In Network Meta-analysis (CINeMA) was used for purposes of confidence analysis in the Network meta-analysis (NMA).[17,20]

A 6-node treatment network was graphically summarized and used as base for the later bias relationship presentation within the network (supplementary material). The herein included elements were the duration category of the NMBA (short, intermediate, long) and NMM category (no, qualitative and quantitative). The included nodes and their relationships derive from their practical combination in the clinical setting. No alternative network geometries were explored.

The in the CINeMA analysis incorporated quality domains were: within-study bias; across-studies bias; indirectness; imprecision: heterogeneity; and incoherence. This analysis referred to the findings relating to the PORC TOF-ratio cut-off of 0.9. Data was listed in “arm per arm” fashion, with unreported data within a specific study leading to its exclusion from the global CINeMA analysis. Outcome was binarily analysed (presence vs absence of PORC) based on a Random Effects analysis model with Risk Ratio as the effect measure. The PRISMA extension statement for the NMA is provided as a supplementary file.

Results

The proportions obtained in 53 studies were pooled with a 3-level mixed model conditional on observed variances. Twenty-four of these studies refer to the time period between 1979 and 2006 and were upcycled and re-analysed from the original meta-analysis of Naguib and colleagues.[8] Further indexed database searches referring to the period from 2006 up to May 2019 ultimately yielded 29 additional studies. In total, 12664 patients were included in the analysis, distributed through a total of 109 study arms. There were no additional studies awaiting classification.

Short-acting NMBAs were used in only one of the studies and were thus excluded from the analysis.[21] Long-acting NMBAs were given to a total of 665 patients, having the remaining majority received intermediate-acting NMBAs (n = 11556). In one study with four intervention arms and a total of 255 patients, the duration category of the NMBA could not be identified.[22] Neostigmine was used in 6272 patients, and sugammadex on 663 patients. The remaining patients had either unreported antagonist use or an unclear reversal drug allocation that precluded an unbiased analysis. Only one study included the use of Pyridostigmine.[58]

A potent inhalational agent was used as the single anaesthesia maintenance technique in 4631 patients. TIVA was used in 1622 patients. Combined use of volatile anaesthesia and TIVA was used in 111 patients. The remaining cases had either unreported or unclear anaesthesia maintenance technique allocation.

In 4416 patients, no intraoperative neuromuscular monitoring was used. Qualitative monitoring was used on 1528 patients, and 6181 were monitored by means of a quantitative device.

The initial intercorrelation analysis showed that when only considering the monitoring type and NMBA duration category there was no multicollinearity impeding their combination into an additive model. The top-up with additional predictors (anaesthesia type and pharmacological antagonism) raised a clear multicollinearity issue, as the drug duration category was strongly correlated to pharmacological antagonism and publication year. Pharmacological antagonism was on itself strongly related to the publication year. Although publication year related in proximity to data collection year, this might not always be the case and heterogeneity exists for this purpose.

The relation of both the type of NMBA and of pharmacological antagonism with the publication year complicates drawing conclusions on whether changes in PORC proportions relate to changes in procedure or other changes over time. The correlation coefficients obtained when focusing solely on the intermediate duration NMBA, the most prevalent NMBA category, are as follows: NMM type vs publication year: - 0.005; NMM type vs Anaesthesia maintenance type: 0.047; NMM type vs antagonist use: 0.233; Anaesthesia maintenance type vs publication year: -0.293; antagonism use vs publication year: 0.287; anaesthesia maintenance type vs antagonist use: -0.287.

Not all combinations of intraoperative neuromuscular monitoring and neuromuscular blocking agent were frequent within the constructed data set. Additionally, as stated above, some studied variables were not reported in some of the included studies. At least marginally all three possible combinations of pharmacological antagonism (none, neostigmine, sugammadex) and all three types of anaesthesia maintenance options (potent inhalational agent, TIVA, or both) were observed at least 7 times.

Only the intermediate and long-duration NMBA category in combination with the different intraoperative neuromuscular monitoring modalities (none, qualitative or quantitative) were kept for further analysis.

Considering the above mentioned factors, the statistical analysis was subdivided into 3 different models:

1 - *Main model*: a model that included the variables NMM type, NMBA category and Anaesthesia maintenance type.

2 - *Antagonist model*: encompassed the NMM category, Anaesthesia maintenance type and Pharmacological Antagonism as variables.

3 - *Trend model*: a model combining the NMM type and publication year in order to make an evolution analysis of monitoring use.

The *main model* retained a total of 51 study arms, part of 39 studies. The *antagonist model, by excluding the NMBA duration category,* held 76 study arms for analysis. Finally, the *trend model* trimmed the observations down to 69.

In all statistical models, analysis of the primary outcome was subdivided according to the TOF-ratio cut-off used for its definition: 0.7, 0.9 and 1. It appeared that data on the PORC with 1.0 TOF-ratio cut-off was not often available, resulting in only 5 observed proportions. It was therefore excluded from the analysis. Data on PORC associated with the use of Pyridostigmine resulted in only 2 observed proportions and was similarly excluded from the analysis.

1 - Main model

1.1 - TOF-ratio cut-off 0.7

For the cut-off at 0.7, the analysis suggests that there is no sufficient evidence to conclude on any effect of the type of Anaesthesia maintenance to exist. Significant differences between monitoring methods could not be statistically objectivated, and 95% confidence intervals (95%CI) for the different NMM and NMBA combinations overlapped.

Both the test for residual heterogeneity ($QE(32df) = 378.47$, $p = 7.76\times10^{-54}$) and for moderators ($QM(6df) = 148.27$, $p = 1.9\times10^{-29}$) were strongly significant.

The variances at the study level and the within study level (different types of effect) are 0.0125 (27), 0.0217 (38) with the number of unique instances in between parentheses. The

corresponding forest plot includes the observed proportions and is available as supplementary material.

1.2 - TOF-ratio cut-off 0.9

The analysis suggests that quantitative monitoring results in lower PORC than both no (Coefficient of 0.208; 95%CI [0.048;0.368]; p = 0.005) and qualitative NMM (Coefficient of -0.269; 95%CI [-0.423;-0.114]; p < 0.001). No differences between the NMBA duration category were suggested (Coefficient of -0.340; 95%CI [-0.761;0.082]; p = 0.157). Qualitative NMM wasn't significantly different from no NMM (Coefficient of -0.061; 95%CI [-0.269;0.147]; p = 0.866). Similarly to the 0.7 cut-off, there is no suggestion the anaesthesia type influences cumulative PORC proportions.

The test for residual heterogeneity (QE(29df) = 803.20, p = 2.46×10^{-150}) and for moderators (QM(6df) = 139.49, p = 1.28×10^{-27}) were strongly significant. The variances at and within study level were, respectively, 0.0689 (30) and 0.0025 (35) with the number of unique instances in between parentheses.

The forest plot is presented as supplementary material. Due to the paucity of observations for the combinations of qualitative monitoring and both TIVA and the combination of TIVA and a potent inhalational agent, no back transformed pooled proportions could be computed.

Considering the absence of an effect of anaesthesia type, a model pooling the PORC rates independently of anaesthesia type was used in order to clearly summarize this meta-analysis findings (table 3). Within this model, quantitative monitoring resulted in lower PORC proportions than both none (Coefficient: 0.260; 95%CI [0.144;0.376]; p < 0.001) or qualitative intraoperative neuromuscular monitoring (Coefficient: 0.234; 95%CI [0.119;0.348]; p < 0.001). Qualitative monitoring didn't significantly differ from no monitoring (Coefficient of 0.026; 95%CI [-0.082;0.135]; p = 0.919). The strong significance of residual heterogeneity

(QE(45df) = 1178.63, p = 1.83×10^{-217}) and moderator tests (QM(4df) = 230.31, p = 1.13×10^{-48}) was maintained. A model-concordant forest plot is presented in figure 2.

2 - Antagonist model

2.1 - TOF-ratio cut-off 0.7

This sub-analysis suggests only a difference between quantitative and no NMM (Coefficient of 0.264; 95%CI [0.051;0.477]; p = 0.009). Neither pharmacological antagonism nor anaesthesia maintenance type seem to influence PORC. Residual heterogeneity testing (QE(32df) = 334.94, p = 3.56×10^{-52}) and moderator testing (QM(7df) = 147.30, p = 1.50×10^{-28}) showed strong significance. The variances at and within study level are 0.0073 (27) and 0.0298 (39), respectively, with the number of unique instances in between parentheses.

2.2 - TOF-ratio cut-off 0.9

Quantitative monitoring yielded lower PORC proportions than qualitative (Coefficient of -0.259; 95%CI [-0.413;-0.106]; p < 0.001) and no NMM (Coefficient of 0.214; 95%CI [0.055;0.372]; p = 0.004). Qualitative monitoring didn't differ significantly from no monitoring (Coefficient of -0.047; 95%CI [-0.253;0.159]; p = 0.932). Sugammadex was associated with lower PORC than Neostigmine (Coefficient of 0.196; 95%CI [0.060;0.332]; p = 0.002). The forest plot for the pooled PORC proportions is given as supplementary material.

Both the test for residual heterogeneity (QE(33df) = 678.84, p = 1.33×10^{-121}) and for moderators (QM(7df) = 145.49, p = 3.60×10^{-28}) are again strongly significant. The variances at the study level and the within study level (different types of effect) are 0.0714 (30) and 0.0023 (40), respectively, with the number of unique instances in between parentheses.

3 - Trend model

3.1 - TOF-ratio cut-off 0.7

The analysis suggests that there is only a difference between quantitative and no NMM (Coefficient of 0.221; 95%CI [0.012;0.430]; p = 0.035). There is a consistent reduction of PORC incidence with time, although with the variance coefficients' confidence intervals assuming both positive and negative values (Coefficient of -0.006; 95%CI [-0.014;0.003]; p = 0.295). The isolated proportions plot is available as supplementary material.

Both the test for residual heterogeneity (QE(42df) = 450.10, p = 9.17×10^{-70}) and for moderators (QM(4df) = 225.06, p = 1.53×10^{-47}) were strongly significant. The variances at and within study level are, respectively, 0.0075 (32) and 0.0273 (46), with the number of unique instances in between parentheses.

3.2 - TOF-ratio cut-off 0.9

The analysis confirms the earlier difference between quantitative and qualitative (Coefficient of -0.236; 95%CI [-0.343;-0.129]; p < 0.001), as well as of no NMM (Coefficient of 0.246; 95%CI [0.136;0.355]; p < 0.001), with the latter yielding higher PORC proportions. PORC significantly decreased over time (p = 0.001). Isolated plotting of proportions is represented in figure 3.

Again, residual heterogeneity (QE(48df) = 1649.48, p = 3.13×10^{-314}) and moderators (QM(4df) = 264.66, p=4.52×10^{-56}) tests were strongly significant. The variances at and within study level are, respectively, 0.0620 (41) and 0.0009 (52), with the number of unique instances in between parentheses.

Confidence In Network Meta-analysis (CINeMA)

A network plotting of bias relationship within the present meta-analysis was made selectively for the PORC TOF-ratio cut-off of 0.9 within the Main model. This selectivity pertained to the international recognition of this cut-off as the most clinically relevant for PORC definition[3]. The CINeMA analysis was based on a total of 82 study arms (17 excluded due to missing data). Risk of Bias and Indirectness were summarized as averages, risk ratio (RR) used as size of effect measure with a conservative cut-off of 0.1.

The network plot (supplementary material) illustrates the bias relationship for the different comparisons. The average risk of bias contribution per binary comparison is also available as supplementary material.

Direct evidence for the majority of the comparisons of interest was available, being absent for the comparisons of long duration NMBAs and quantitative NMM, as well as for short duration NMBAs and no/qualitative NMM. In fact, direct comparative evidence was present for the comparisons between Intermediate-duration NMBAs (A) and all the different monitoring modalities (D - No Monitoring; E - Qualitative monitoring; F- Quantitative monitoring).

There were moderate within-study bias concerns for the conclusions drawn for the abovementioned comparisons. All are suspect for across-study bias.

In terms of Indirectness rating, all of the abovementioned comparisons rated low on bias risk (illustrations available as supplementary material).

Imprecision analysis raised no concerns for the selected RR cut-off of 0.1, meaning there was agreement in relation to a clinically important effect. Quantitatively speaking, this is translated by the following estimates and ranges: Intermediate NMBA and No monitoring: RR 1 [0.941;1.062], I^2 = 0%, τ^2 = 0; Intermediate NMBA and Qualitative Monitoring: RR 1 [0.930;1.075], I^2 = 0%, τ^2 = 0; Intermediate NMBA and Quantitative Monitoring: RR 1 [0.927,1.079], I^2 = 0%, τ^2 = 0.

In terms of heterogeneity, no concerns were raised. The estimated value of between-study variance for the network meta-analysis was 0, with confidence and prediction intervals agreeing in relation to the clinically important effect. There were similarly no concerns raised

for incoherence within the network. A random-effects design-by-treatment interaction model for global testing yielded for this purpose a χ^2 statistic of 0 based on 2 degrees of freedom analysis ($p = 1$). The CINeMA summary of results is presented in table 2.

Publication bias was assessed by graphing residual values against the corresponding standard error in a funnel plot. The process was repeated for every statistical analysis model and for every analysed TOF-ratio cut-off. There was no serious indication of any systematic heterogeneity bias (figure 4). One study clearly shows a proportion that is different from what would be expected based on the available information in the model.[23]

The summary of findings for the clinically relevant TOF-Ratio cut-off of 0.9 is presented with Standard Cochrane format in table 3.[16] Bias grading has been specifically assessed by means of the CINeMA analysis as discussed above. Each individual studies' per domain GRADE Assessment for Risk of Bias is available for consultation as supplementary material.[15,16]

Discussion

In contrast with the work of Naguib and colleagues, the present meta-analysis suggests that intraoperative neuromuscular monitoring does significantly reduce PORC.[8] When considering a TOF-ratio cut-off of 0.7, no significant difference can be found between NMM subtypes, in spite of a tendency for objective monitoring to yield lower PORC proportions. Nonetheless, data analysis in the light of a more consensually accepted TOFR cut-off (0.9), reveals that objective monitoring significantly outperforms both subjective and absent monitoring.[1,3] The growing awareness for PORC and consistent reporting of high PORC rates with its associated negative clinical impact might partially explain this shift.[5,7,24–26] Publishing of consensus groups' updates on monitoring standards have also given this phenomenon a momentum.[3,25] This has additionally been paralleled with the marketing of new quantitative neuromuscular monitors and equivalent practical solutions.[27–29]

The observation in the original meta-analysis that long duration NMBAs are associated with a higher PORC incidence than its intermediate counterparts was not held statistically within the present study, although a same sided trend was present.[8] This must be interpreted in light of the relative absence of recent studies involving long-duration NMBAs. In fact, from the year 2006 onwards no additional articles involving long-acting NMBAs have been found.

The most recent of these dates back to 2000 and were already included in the original meta-analysis.[8,30] Considering that long-duration NMBAs are rarely used in modern western anaesthesia practice, this fact probably carries more historical than clinical relevance.

Concerning intermediate duration NMBAs (used on 91% of the pooled patient population), no subanalysis could be performed to study the effect of NMBA dosing on PORC. In fact, although the majority of studies did register cumulative administered doses, an anthropometric- and time-adjusted dose reporting (expressed as ED95 equivalent dose kg^{-1} h^{-1}) was scarce. This precluded what would be a representative analysis of the dosing effect.

The studies included in this meta-analysis are not fully homogeneous from a methodological point of view. In fact, the first heterogeneity aspect lies on the definition of the primary outcome itself. Although PORC is consistently defined throughout the included studies by means of a fixed TOF-ratio (0.7, 0.9 or 1.0), the time-point and method of measurement varied considerably. In fact, timing ranged from an immediate post-extubation moment [21,22,31–38], to measurement post-PACU arrival or at a fixed time-point.[10–14,39–53] Some studies didn't specify the measurement time point at the PACU at all.[54] Globally considered, 84 of the 109 included study arms (77%) reported PORC based on TOF-ratios measured at the PACU.[10–14,30,35,40–46,48–54,54–71]

Additional intra-study heterogeneity is introduced by the fact that measurements post PACU arrival were not consistently standardized. Moreover, there was no reporting on transport times between the operating room and the PACU, nor mentioning of a possible correction factor.

Monitoring techniques similarly presented inter-study heterogeneity. Although most study arms (88%) reported using either accelero- or kinemyographic techniques, electro- or mechanomyographic methods were used in smaller proportions (8 and 5 of the 109 study arms, respectively). It has been shown that accelero- and kinemyography can significantly diverge not only between themselves, but also from electromyography and mechanomyography.[72–78] It is similarly unclear if movement artifact prophylactic measures were adopted whenever accelero- or kinemyography was used, as well as if supra-maximal

current was used for electrical ulnar nerve stimulation. In fact, only 14 studies have explicitly protocolised usage of supra-maximal currents.[23,30–33,35,36,38,47–49,58,63,79] Moreover, the reliance of accelero- or kinemyographic techniques on movement for their measurements, associated with the fact that most of the PORC measurements took place on awake patients (thus possibly moving) and with the fact that these techniques have been used in the great majority of the included studies (35 out of 53, or 66%) to confirm the presence or absence of PORC, has to be seen as an important limitation on the global accuracy of the pooled primary outcome.

The presence of a strong relation between some of the collected variables impeded the construction of a larger PORC analysis model. Consequently, more restricted models were used to answer specific questions. Specifically, when considering the influence of the anaesthesia maintenance technique, the variable could be analysed in the light of the NMBA and type of monitoring use, but not co-corrected for pharmacological antagonism or publication year. The generalised absence of reporting on time- and anthropometric-corrected dosing of NMBAs further restricted a holistic analysis. In the light of these restrictions, although it is physiologically recognised that potent inhalational agents prolong neuromuscular block, their use does not seem to play a significant role according to our results.[80–83] The same conclusion applies to TIVA. These results align with those of Naguib and colleagues.[8]

Similarly to the anaesthesia maintenance technique, the effect of pharmacological antagonism is similarly based on more restricted statistical models. The analysis is further complicated by significant inter- and intra-study heterogeneity issues concerning the time of antagonist administration. For the cut-off of 0.9, the analysis suggests lower PORC incidences with sugammadex. Besides the pharmacological principles underlying its established efficacy and efficiency, the fact that sugammadex is less subject to the variable efficacy effects due heterogeneity in administration timing might explain the obtained results. Again, no accounting for dosing took place in significance testing for this purpose.

The pharmacological selectivity of sugammadex, the heterogeneity of the NMBAs used in the included studies, the non-holistic nature of the statistical models used, and the relative smaller number of patients receiving in sugammadex in comparison to neostigmine (663 vs. 6272, respectively) should be assumed as possible confounders when drawing conclusions related to sugammadex use. Notwithstanding the undisputable usefulness of a pharmacological milestone such as sugammadex, it is important to reiterate that although it reduces PORC, it does not eliminate it. Reported heuristics and overconfidence concerns with respect to NMM in general pre-emptively suggest a potential false sense of security that might be associated with sugammadex use.[5–7] As shown within the present analysis, sugammadex does not eliminate PORC and its use and monitoring should be guided by appropriate quantitative NMM. The use of infra-therapeutic dosing schemes ("vial-saving" dosing strategies) reinforces this need.[84,85]

The present analysis didn't control for variables that are similarly known to potentiate neuromuscular block (temperature, antibiotics, ionic imbalances, among others). Present inferences are thus dependent on active control of these factors within the included studies, which is sub-optimally reported.

When considering the yearly evolution of PORC, one observes a progressive reduction independent of the monitoring modality and cut-off. The differences are clearer when reporting on a TOF-ratio of 0.9. Curiously one observes a similar reduction of the PORC rates for the less accurate neuromuscular monitoring modalities (none or qualitative). Moreover, these are reduced through time to a proportionally greater extent than those with quantitative monitoring. In the light of the absence of flagrant publication bias signs, such positive evolution might translate the increased awareness and sensibilisation efforts within the anaesthesia community.[3,5–7,56] Unfortunately, a possible underlying effect of the almost effective extinction of long-duration NMBAs couldn't be analysed due to collinearity issues.

Within the year dependent PORC variation analysis one should acknowledge the potential intra-category bias due to the inherent limitations of each of the different quantitative monitoring modalities used for the quantification of PORC. In fact, the accurate but now

virtually extinct mechanomyography has been progressively replaced by kine- or acceleromyographic technologies. Within the included studies, its last reported use dates back to 2002.[36] The more practical and user-friendly nature of acceleromyography comes at a known practicality/accuracy trade-off due to its susceptibility to well described overestimation artefacts. These could potentially overestimate the reduction of PORC over time. [72–78]

The fact that acceleromyography has been used as the exclusive PORC quantification method on every study inluded after the year 2005 (cumulatively, 69,2% of the included studies) illustrates the potential magnitude of this effect.

Nonetheless, it should be emphasized that the clinical implications of the conclusions relating to qualitative monitoring are not invalidated by the possible aforementioned bias. In fact, despite increasing awareness and cumulative PORC incidence reduction over time even with qualitative methods, the fact that the latter failed to statistically differentiate itself from the absence of monitoring is not obviated. This conclusion bears particular relevance amid reports of a still high proportional use of qualitative NMM as well as tendencies of overconfidence and overestimation in terms of NMM management.[5–7]

The abovementioned acceleromyographic limitations have recently been resurfaced as grounds for the enforcement of more strict cut-offs for the definition of PORC. In fact, a post-hoc analysis of the POPULAR study has put forward a 7.8 percentual point adjusted risk reduction in post-operative pulmonary complications associated with the raising of the TOFR cut-off for extubation from 0.9 to 0.95.[21,86,87] This recognition of the importance of full neuromuscular recovery is similarly seen in publications using unity as the recovery cut-off.[11, 34] Due to the paucity of studies using these more restrictive TOFR values, a pooled analysis on the light of these raised cut-offs was not possible. Although a concordant widening of the difference gap between quantitative and qualitative/absent NMM modalities is intuitively expected when raising the TOFR, only the systematized anaesthetic community adoption of these cut-offs will allow of a later reiteration of their superiority.

Finally, the present analysis should be interpreted with the accompanying confidence analysis in the NMA. Although the CINeMA analysis didn't raise overwhelming concerns on the likelihood of this meta-analysis' conclusions to be modified by upcoming trials (geometric simplicity, stable heterogeneity, imprecision, indirectness and incoherence), significant within- and across-study bias concerns were found relating to the relationship between intermediate-duration NMBAs and all NMM modalities. The individual GRADE classification reflects similarly an overwhelming dominance of studies with a very low level of evidence. These are additional limiting issues that should be considered for the interpretation of the forwarded conclusions. Ideally, these should be addressed in the design of future studies.

Details of authors' contributions

All authors fulfilled the following participation criteria:

a) participation in design, execution, analysis and interpretation of the work

b) drafting or revising the manuscript critically for important intellectual content

c) giving final approval of the version to be published

d) taking accountability for all aspects of the work, including accuracy and validity of the contents, and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Declaration of Interests

The authors declare that they have no conflict of interest.

Funding

The present work has received support from the scientific fund Willy Gepts (Univeristair Ziekenhuis Brussel, Brussels, Belgium).

Appendices

None.

References

1. Brull SJ, Kopman AF. Current Status of Neuromuscular Reversal and Monitoring: Challenges and Opportunities. *Anesthesiology* 2017; 126:173–190.
2. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet Lond Engl* 2008*;* 372:139–144.
3. Naguib M, Brull SJ, Kopman AF, *et al.* Consensus Statement on Perioperative Use of Neuromuscular Monitoring. *Anesth Analg* 2008*;* 127:71–80.
4. Fleisher LA, Linde-Zwirble WT. Incidence, outcome, and attributable resource use associated with pulmonary and cardiac complications after major small and large bowel procedures. *Perioper Med Lond Engl* 2014*;* 7:3-7.
5. Harman A, Tung A, Fox C, Lien CA. Heuristics, Overconfidence, and Experience: Impact on Monitoring Depth of Neuromuscular Blockade. *Anesth Analg 2019;* 128:1057–1059.
6. Naguib M, Kopman AF, Lien CA, Hunter JM, Lopez A, Brull SJ. A survey of current management of neuromuscular block in the United States and Europe. *Anesth Analg* 2010*;* 111:110–119.

7. Naguib M, Brull SJ, Hunter JM, et al.Anesthesiologists' Overconfidence in Their Perceived Knowledge of Neuromuscular Monitoring and Its Relevance to All Aspects of Medical Practice: An International Survey. *AnesthAnalg 2019;* 128:1118–1126.
8. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth* 2007; 98:302–316.
9. Viby-Mogensen J, Claudius C, Eriksson LI. Neuromuscular monitoring and postoperative residual curarization. *Br J Anaesth* 2007; 99:297-299.
10. Murphy GS, Szokol JW, Avram MJ, et al. Residual Neuromuscular Block in the Elderly: Incidence and Clinical Implications. *Anesthesiology* 2015; 123:1322–1336.
11. Pietraszewski P, Gaszyński T. Residual neuromuscular block in elderly patients after surgical procedures under general anaesthesia with rocuronium. *Anaesthesiol Intensive Ther* 2013; 45:77–81.
12. Feltracco P, Tonetti T, Barbieri S, Frigo AC, Ori C. Cisatracurium- and rocuronium-associated residual neuromuscular dysfunction under intraoperative neuromuscular monitoring and postoperative neostigmine reversal: a single-blind randomized trial. *J Clin Anesth* 2016; 35:198–204.
13. Baykara N, HOŞTEN T, Özdamar D, Etiler N, Solak M, Toker K. High Incidence of Residual Curarization After Rocuronium Despite Administration of Neostigmine. *Turk Klin J Med Sci* 2010; 30:1325–1331.
14. Santos FNC, Braga AFA, Ribeiro CJBL, Braga FSDS, Carvalho VH, Junqueira FEF. Use of protocol and evaluation of postoperative residual curarization incidence in the absence of intraoperative acceleromyography - Randomized clinical trial. *Rev Bras Anestesiol* 2017; 67:592–599.
15. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343:d5928.
16. Schünemann H, Brożek J, Guyatt G, Oxman A. The GRADE handbook. Cochrane Collaboration, 2013.
17. Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality

of evidence from a network meta-analysis. *PloS One* 2014*; 9:*e99682.

18. Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J. Meta-analysis of multiple outcomes: a multilevel approach. *Behav Res Methods* 2015; 47:1274–1294.
19. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; 36 :1–48.
20. CINeMA: Confidence in Network Meta-Analysis [Software]. Institute of Social and Preventive Medicine, University of Bern, 2017. Available from cinema.ispm.unibe.ch (last accessed 19 December 2019).
21. Kirmeier E, Eriksson LI, Lewald H, et al*.* Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Respir Med* 2019; 7:129–140.
22. Saager L, Maiese EM, Bash LD, et al. Incidence, risk factors, and consequences of residual neuromuscular block in the United States: The prospective, observational, multicenter RECITE-US study. *J Clin Anesth* 2019; 55:33–41.
23. Kopman AF, Kopman DJ, Ng J, Zank LM. Antagonism of profound cisatracurium and rocuronium block: the role of objective assessment of neuromuscular function. *J Clin Anesth* 2005*;* 17:30–35.
24. Grabitz SD, Rajaratnam N, Chhagani K, et al. The Effects of Postoperative Residual Neuromuscular Blockade on Hospital Costs and Intensive Care Unit Admission: A Population-Based Cohort Study. *Anesth Analg* 2019; 128:1129–1136.
25. Naguib M, Kopman AF. Neuromuscular Monitoring: Keep It Simple! *Anesth Analg* 2019; 128:1063–1064.
26. Biro P, Paul G, Dahan A, Brull SJ. Proposal for a Revised Classification of the Depth of Neuromuscular Block and Suggestions for Further Development in Neuromuscular Monitoring. *Anesth Analg* 2019; 128:1361–1363.
27. Iwasaki H, Nemes R, Brull SJ, Renew JR. Quantitative Neuromuscular Monitoring: Current Devices, New Technological Advances, and Use in Clinical Practice. *Curr*

Anesthesiol 2018; 8:134–144.

28. Murphy GS. Neuromuscular Monitoring in the Perioperative Period. *Anesth Analg* 2018; *126(2):464-468.*
29. Carvalho H, Verdonck M, Berghmans J, Poelaert J. Development and validation of an android-based application for anaesthesia neuromuscular monitoring. *J Clin Monit Comput* 2019; 33:863–870.
30. Bissinger U, Schimek F, Lenz G. Postoperative residual paralysis and respiratory status: a comparative study of pancuronium and vecuronium. *Physiol Res* 2000; 49:455–462.
31. Rahe-Meyer N, Berger C, Wittmann M, et al. Recovery from prolonged deep rocuronium-induced neuromuscular blockade: A randomized comparison of sugammadex reversal with spontaneous recovery. *Anaesthesist* 2015; 64:506–512.
32. Thilen SR, Ng IC, Cain KC, Treggiari MM, Bhananker SM. Management of rocuronium neuromuscular block using a protocol for qualitative monitoring and reversal with neostigmine. *Br J Anaesth* 2018; 121:367–377.
33. Maybauer DM, Geldner G, Blobner M, *et al.* Incidence and duration of residual paralysis at the end of surgery after multiple administrations of cisatracurium and rocuronium. *Anaesthesia* 2007; 62:12–17.
34. Kotake Y, Ochiai R, Suzuki T, et al. Reversal with sugammadex in the absence of monitoring did not preclude residual neuromuscular block. *Anesth Analg* 2013; 117:345–351.
35. Murphy GS, Szokol JW, Marymont JH, Franklin M, Avram MJ, Vender JS. Residual paralysis at the time of tracheal extubation. *Anesth Analg* 2005; 100:1840–1845.
36. Gätke MR, Viby-Mogensen J, Rosenstock C, Jensen FS, Skovgaard LT. Postoperative muscle paralysis after rocuronium: less residual block when acceleromyography is used. *Acta Anaesthesiol Scand* 2002; 46:207–213.
37. Fruergaard K, Viby-Mogensen J, Berg H, el-Mahdy AM. Tactile evaluation of the response to double burst stimulation decreases, but does not eliminate, the problem of postoperative residual paralysis. *Acta Anaesthesiol Scand* 1998. 42:1168–1174.

38. Mortensen CR, Berg H, el-Mahdy A, Viby-Mogensen J. Perioperative monitoring of neuromuscular transmission using acceleromyography prevents residual neuromuscular block following pancuronium. *Acta Anaesthesiol Scand* 1995; 39:797–801.
39. Kumar GV, Nair AP, Murthy HS, Jalaja KR, Ramachandra K, Parameshwara G. Residual neuromuscular blockade affects postoperative pulmonary function. *Anesthesiology* 2012; 117:1234–1244.
40. González-Cárdenas VH, Salazar-Ramírez KJ, Coral-Sánchez GT. Postoperative residual paralysis in patients aged over 65 years old at the Post-Anaesthesia Care Unit. *Rev Colomb Anestesiol* 2016; 44:209–215.
41. Wardhana A, Kurniawaty J, Uyun Y. Optimised reversal without train-of-four monitoring versus reversal using quantitative train-of-four monitoring: An equivalence study. *Indian J Anaesth* 2019; 63:361–367.
42. Omar AM. Effect of systemic lidocaine infusion on train-of-four ratios during recovery from general anaesthesia. *Egypt J Anaesth* 2012; 28:281–286.
43. El-Tahan MR, Regal M. Target-Controlled Infusion of Remifentanil Without Muscle Relaxants Allows Acceptable Surgical Conditions During Thoracotomy Performed Under Sevoflurane Anaesthesia. *J Cardiothorac Vasc Anesth* 2015; 29:1557–1566.
44. Murphy GS, Szokol JW, Avram MJ, et al. Neostigmine Administration after Spontaneous Recovery to a Train-of-Four Ratio of 0.9 to 1.0: A Randomized Controlled Trial of the Effect on Neuromuscular and Clinical Recovery. *Anesthesiology* 2018; 128:27–37.
45. Errando CL, Mazzinari G, Díaz-Cambronero O, Garutti I; Grupo español de estudio del bloqueo neuromuscular. Residual neuromuscular blockade in the postanaesthesia care unit: observational cross-sectional study of a multicenter cohort. *Minerva Anestesiol* 2016; 82:1267–1277.
46. Khan S, Divatia JV, Sareen R. Comparison of residual neuromuscular blockade between two intermediate acting nondepolarizing neuromuscular blocking agents-rocuronium and vecuronium. *Indian J Anaesth* 2006; 50:115–17.
47. Kaan N, Kocaturk O, Kurt I, Cicek H. The incidence of residual neuromuscular blockade

associated with single dose of intermediate-acting neuromuscular blocking drugs. *Middle East J Anaesthesiol* 2012; 21:535–541.

48. Kocaturk O, Kaan N, Kayacan N, Ertugrul F. The incidence of postoperative residual curarization following the use of intermediate-acting muscle relaxants and related factors. *Middle East J Anaesthesiol* 2014; 22:583–590.
49. Yazar E, Yılmaz C, Bilgin H, et al. A Comparision of the Effect of Sugammadex on the Recovery Period and Postoperative Residual Block in Young Elderly and Middle-Aged Elderly Patients. *Balk Med J* 2016; 33:181–187.
50. Thilen SR, Hansen BE, Ramaiah R, Kent CD, Treggiari MM, Bhananker SM. Intraoperative neuromuscular monitoring site and residual paralysis. *Anesthesiology* 2012; 117:964–972.
51. Brueckmann B, Sasaki N, Grobara P, et al. Effects of sugammadex on incidence of postoperative residual neuromuscular blockade: a randomized, controlled study. *Br J Anaesth* 2015; 115:743–751.
52. Murphy GS, Szokol JW, Marymont JH, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanaesthesia care unit. *Anesthesiology* 2008; 109:389–398.
53. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanaesthesia care unit. *Anesth Analg* 2008; 107:130–137.
54. Koo CH1, Chung SH, Kim BG, et al. Comparison between the effects of deep and moderate neuromuscular blockade during transurethral resection of bladder tumor on endoscopic surgical condition and recovery profile: a prospective, randomized, and controlled trial. *World J Urol* 2019; 37:359–365.
55. Murphy GS, Szokol JW, Avram MJ, et al. Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. *Anesthesiology* 2011; 115:946–954.
56. Baillard C, Clec'h C, Catineau J, et al. Postoperative residual neuromuscular block: a

survey of management. *Br J Anaesth* 2005*;* 95:622–626.

57. Debaene B, Plaud B, Dilly MP, Donati F. Residual paralysis in the PACU after a single intubating dose of nondepolarizing muscle relaxant with an intermediate duration of action. *Anesthesiology* 2003; 98:1042–1048.
58. Kim KS, Lew SH, Cho HY, Cheong MA. Residual paralysis induced by either vecuronium or rocuronium after reversal with pyridostigmine. *Anesth Analg* 2002; 95:1656–1660.
59. Hayes AH, Mirakhur RK, Breslin DS, Reid JE, McCourt KC. Postoperative residual block after intermediate-acting neuromuscular blocking drugs. *Anaesthesia* 2001; 56:312–318.
60. Baillard C, Gehan G, Reboul-Marty J, Larmignat P, Samama CM, Cupa M. Residual curarization in the recovery room after vecuronium. *Br J Anaesth* 2000; 84:394–395.
61. Kopman AF, Ng J, Zank LM, Neuman GG, Yee PS.. Residual postoperative paralysis. Pancuronium versus mivacurium, does it matter? *Anesthesiology* 1996; 85:1253–1259.
62. Fawcett WJ, Dash A, Francis GA, Liban JB, Cashman JN. Recovery from neuromuscular blockade: residual curarisation following atracurium or vecuronium by bolus dosing or infusions. *Acta Anaesthesiol Scand* 1995; 39:288–293.
63. Shorten GD., Merk H, Sieber T. Perioperative train-of-four monitoring and residual curarization. *Can J Anaesth* 1995; 42:711–715.
64. Ueda N, Muteki T, Tsuda H, Inoue S, Nishina H. Is the diagnosis of significant residual neuromuscular blockade improved by using double-burst nerve stimulation? *Eur J Anaesthesiol* 1991; 8:213–218.
65. Brull SJ, Ehrenwerth J, Connelly NR, Silverman DG. Assessment of residual curarization using low-current stimulation. *Can J Anaesth* 1991; 38:164–168.
66. Pedersen T, Viby-Mogensen J, Bang U, Olsen NV, Jensen E, Engboek J. Does perioperative tactile evaluation of the train-of-four response influence the frequency of postoperative residual neuromuscular blockade? *Anesthesiology* 1990; 73:835–839.
67. Howardy-Hansen P, Rasmussen JA, Jensen BN. Residual curarization in the recovery room: atracurium versus gallamine. *Acta Anaesthesiol Scand* 1989; 33:167–169.

68. Andersen BN, Madsen JV, Schurizek BA, Juhl B. Residual curarisation: a comparative study of atracurium and pancuronium. *Acta Anaesthesiol Scand* 1988; 32:79–81.
69. Beemer GH, Rozental P. Postoperative neuromuscular function. *Anaesth Intensive Care* 1986; 14:41–45.
70. Lennmarken C, Löfström JB. Partial curarization in the postoperative period. *Acta Anaesthesiol Scand* 1984; 28:260–262.
71. Viby-Mogensen J, Jørgensen BC,Ording H. Residual curarization in the recovery room. *Anesthesiology* 1979; 50:539–541.
72. Kopman AF, Chin W, Cyriac J. Acceleromyography vs. electromyography: an ipsilateral comparison of the indirectly evoked neuromuscular response to train-of-four stimulation. *Acta Anaesthesiol Scand* 2005; 49:316–322.
73. Claudius C, Viby-Mogensen J. Acceleromyography for Use in Scientific and Clinical Practice: A Systematic Review of the Evidence. *Anesthesiol J Am Soc Anesthesiol* 2008; 108:1117–1140.
74. Liang SS, Stewart PA, Phillips S. An Ipsilateral Comparison of Acceleromyography and Electromyography During Recovery from Nondepolarizing Neuromuscular Block Under General Anaesthesia in Humans. *Anesth Analg* 2013; 117:373-9.
75. Murphy GS, Szokol JW, Avram MJ, et al. Comparison of the TOFscan and the TOF-Watch SX during Recovery of Neuromuscular Function. *Anesthesiol J Am Soc Anesthesiol* 2018; 129:880–888.
76. Trager G, Michaud G, Deschamps S, Hemmerling TM. Comparison of phonomyography, kinemyography and mechanomyography for neuromuscular monitoring. *Can. J. Anesth* 2006; 53:130-5.
77. Salminen J, van Gils M, Paloheimo M, Yli-Hankala A. Comparison of train-of-four ratios measured with Datex-Ohmeda's M-NMT MechanoSensor™ and M-NMT ElectroSensor™. *J Clin Monit Comput* 2016; 30:295–300.
78. Stewart PA, Freelander N, Liang S, Heller G, Phillips S. Comparison of Electromyography and Kinemyography during Recovery from Non-Depolarising

Neuromuscular Blockade. *Anaesth Intensive Care* 2014; 42:378–384.

79. Cammu G, de Baerdemaeker L, den Blauwen N, de Mey JC, Struys M, Mortier E. Postoperative residual curarization with cisatracurium and rocuronium infusions. *Eur J Anaesthesiol 2002;* 19:129–134.
80. Rupp SM, Miller RD, Gencarelli PJ. Vecuronium-induced neuromuscular blockade during enflurane, isoflurane, and halothane anaesthesia in humans. *Anesthesiology* 1984*;* 60:102–105.
81. Eriksson LI. The Effects of Residual Neuromuscular Blockade and Volatile Anesthetics on the Control of Ventilation. *Anesth Analg* 1999*;* 89:243-251.
82. Sekimoto K, Nishikawa K, Ishizeki J, Kubo K, Saito S, Goto F*.* The Effects of Volatile Anesthetics on Intraoperative Monitoring of Myogenic Motor-Evoked Potentials to Transcranial Electrical Stimulation and on Partial Neuromuscular Blockade During Propofol/Fentanyl/Nitrous Oxide Anaesthesia in Humans. *J Neurosurg Anesthesiol* 2006*;* 18:106-11.
83. Paul M, Fokt RM, Kindler CH, Dipp NC, Yost CS. Characterization of the Interactions Between Volatile Anesthetics and Neuromuscular Blockers at the Muscle Nicotinic Acetylcholine Receptor. *Anesth Analg* 2002*;* 95:362-367.
84. Kaufhol N, Schaller SJ, Stäuble CG, Baumüller E, Ulm K, Blobner M, Fink H. Sugammadex and neostigmine dose-finding study for reversal of residual neuromuscular block at a train-of-four ratio of 0.2 (SUNDRO20). *Br J Anaesth* 2016; 116(2):233-240.
85. Schaller SJ, Fink H, Ulm K, Blobner M. Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. *Anesthesiology* 2010; 113(5):1054-1060.
86. Blobner M, Hunter JM, Meistelman C, Hoeft A, Hollmann MW, Kirmeier E, Lewald H, Ulm K. "Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. *Br J Anaesth* 2020; 124.1:63-72.

87. Fuchs-Buder T, Brull SJ. Is less really more? A critical appraisal of a POPULAR study reanalysis. *Br J Anaesth* 2020; 124.1:12-14.
88. Kopman AF, Zank LM, Ng J., Neuman GG. Antagonism of cisatracurium and rocuronium block at a tactile train-of-four count of 2: should quantitative assessment of neuromuscular function be mandatory? *Anesth Analg* 2004; 98:102–106.
89. Carron M, Baratto F, Zarantonello F, Ori C. Sugammadex for reversal of neuromuscular blockade: a retrospective analysis of clinical outcomes and cost-effectiveness in a single center. *Clin Outcomes Res* 2016*;* 8:43–52.

Tables

Year	Author	Primary Outcome	n	NMB Duration Category	Type of Anaesthesia Maintenance	Intraop NMM	NMB Antagonism	PORC (TOF<0.7) (n)	PORC (TOF<0.9) (n)	PORC (TOF<1.0) (n)	PORC determination time-point	NMM Method for PORC definition
1979	Viby-Mogensen [71]	PORC	72	Long	NR	None	Neostigmine (67)	30	52	NR	At PACU arrival	Mechanomyography
1984	Lennmarken [70]	PORC	48	Long	VA	None	Neostigmine	12	NR	NR	At the PACU (time-point not specified)	Mechanomyography
1986	Beemer [69]	PORC	100	Long	VA	None	Neostigmine	21	40	NR	At PACU arrival	Not mentioned.
1988	Andersen [68]	PORC	30	Intermediate	VA	None	Neostigmine	0	NR	NR	After PACU arrival (time-point not specified)	Mechanomyography
			30	Long	VA	None	Neostigmine	6	NR	NR		

1989	Howardy-Hansen [67]	PORC	9	Intermediate	VA	NR	Neostigmine	0	NR	NR	At PACU arrival	Mechanomyography
			10	Long	VA	NR	Neostigmine	5	NR	NR		
1990	Pedersen [66]	PORC	20	Long	VA	Qualitative	Neostigmine	12	NR	NR	At PACU arrival	Mechanomyography
			20	Long	VA	None	Neostigmine	12	NR	NR		
			20	Intermediate	VA	Qualitative	Neostigmine	8	NR	NR		
			20	Intermediate	VA	None	Neostigmine	3	NR	NR		
1991	Brull [65]	PORC	29	Long	VA	Qualitative	Neostigmine	13	NR	NR	Within 15 minutes of PACU arrival	Unclear
			25	Intermediate	VA	Qualitative	Neostigmine	2	NR	NR		

1991	Ueda [64]	PORC	30	Long	NR	None	Neostigmine	25	28	NR	At PACU arrival	Mechanomyography
			60	Long	NR	Qualitative	Neostigmine	19	53	NR		
1995	Shorten [63]	PORC	20	Long	VA	Qualitative	Neostigmine	3	NR	NR	At the PACU (20 minutes after Neostigmine administration)	Electromyography
			19	Long	VA	None	Neostigmine	9	NR	NR		
1995	Fawcett [62]	PORC	88	Intermediate	NR	Qualitative	Neostigmine	14	74	NR	At PACU arrival	Electromyography
			62	Intermediate	NR	None	Neostigmine	10	52	NR		
1995	Mortensen [38]	PORC	21	Long	VA (5), Both (16)	None	Neostigmine	11	17	NR	Immediately after extubation	Acceleromyography
			19	Long	VA (3), Both	Quantitative	Neostigmine	1	10	NR		

					(16)							
1996	Kopman [61]	PORC	56	Long	VA (29), TIVA (27)	Qualitative	Neostigmine	2	36	NR	Intra-operatively (5 and 10 minutes post-reversal) and PACU (if TOF ratio post reversal <0.9)	Mechanomyography
1998	Fruergaard [37]	PORC	30	Long	NR	None	Neostigmine	17	25	NR	Immediately after extubation	Mechanomyography
			29	Long	NR	Qualitative	Neostigmine	7	20	NR		
2000	Bissinger [30]	PORC Hypoxia Hypercarbia	49	Long	VA (30), TIVA (19)	None	Neostigmine	10	NR	NR	After PACU arrival (at least more than 10 minutes after arrival)	Acceleromyography
			27	Intermediate	VA (18), TIVA (9)	None	Neostigmine	2	NR	NR		

2000	Baillard [60]	PORC	568	Intermediate	TIVA	None (557) Qualitative (11)	Neostigmine (1)	239	NR	NR	At PACU arrival	Acceleromyography
2001	Hayes [59]	PORC	19	Intermediate	NR	Qualitative	Neostigmine	NR	13	NR	At PACU Arrival	Acceleromyography
			18	Intermediate	NR	Qualitative	Neostigmine	NR	6	NR		
			24	Intermediate	NR	Qualitative	Neostigmine	NR	8	NR		
			31	Intermediate	NR	None	Neostigmine	NR	19	NR		
			32	Intermediate	NR	None	Neostigmine	NR	20	NR		
			24	Intermediate	NR	None	Neostigmine	NR	11	NR		

2002	Kim [58]	PORC	364	Intermediate	VA	None	Pyridostigmine	90	NR	NR	At PACU Arrival	Acceleromyography
			238	Intermediate	VA	None	Pyridostigmine	35	NR	NR		
2002	Gatke [36]	PORC	60	Intermediate	TIVA	Quantitative	Neostigmine	1	9	NR	At extubation	Mechanomyography
			60	Intermediate	TIVA	None	Neostigmine	6	18	NR		
2002	Cammu [79]	PORC	15	Intermediate	TIVA	Quantitative	Neostigmine (11)	0	0	NR	At extubation	Electromyography
			15	Intermediate	TIVA	Quantitative	Neostigmine (14)	1	1	NR		
2003	Debaene [57]	PORC	79	Intermediate	VA	None	None	13	33	NR	At PACU arrival	Acceleromyography
			47	Intermediate	VA	None	None	8	22	NR		

			400	Intermediate	VA	None	None	64	180	NR		
2004	Kopman [88]	PORC	30	Intermediate	VA	Qualitative	Neostigmine	0	2	NR	5, 10 and 15 minutes after Neostigmine reversal	Electromyography
			30	Intermediate	VA	Qualitative	Neostigmine	0	5	NR		
2005	Murphy [35]	PORC	120	Intermediate	VA	Qualitative	Neostigmine	9	38	NR	At extubation and PACU	Acceleromyography
2005	Baillard [56]	PORC	218	Intermediate	NR	Quantitative (131)	Neostigmine (92)	NR	8	NR	At PACU arrival	Acceleromyography
2005	Kopman [23]	PORC	20	Intermediate	VA	Quantitative	Neostigmine	8	19	NR	5, 10, 15 and 20 minutes after Neostigmine reversal	Acceleromyography
			20	Intermediate	VA	Quantitative	Neostigmine	9	19	NR		

2006	Khan [46]	PORC	49	Intermediate	NR	None	Neostigmine	17	NR	NR	At PACU arrival	Acceleromyography
			58	Intermediate	NR	None	Neostigmine	10	NR	NR		
2007	Maybauer [33]	PORC	142	Intermediate	TIVA	Quantitative	None	NR	62	NR	At extubation	Acceleromyography
			175	Intermediate	TIVA	Quantitative	None	NR	99	NR		
2008	Murphy [53]	PORC and Respiratory Events	42	Intermediate	VA	Qualitative	Neostigmine	31	7	NR	15 minutes after PACU admission	Acceleromyography
			42	Intermediate	VA	Qualitative	Neostigmine	0	4	NR		
2008	Murphy [52]	PORC	89	Intermediate	VA	Quantitative	Neostigmine	0	4	NR	At PACU arrival	Acceleromyography
			90	Intermediate	VA	Qualitative	Neostigmine	12	15	NR		

2010	Baykara [13]	PORC	130	Intermediate	TIVA	None	Neostigmine	12	39	67	At PACU arrival	Acceleromyography
2011	Murphy [55]	PORC	76	Intermediate	VA	Quantitative	Neostigmine	3	11	NR	At PACU arrival	Acceleromyography
			74	Intermediate	VA	Qualitative	Neostigmine	14	37	NR		
2012	Thilen [50]	PORC	99	Intermediate	VA	Qualitative	Neostigmine	NR	51	NR	Within 5 minutes of arrival at the PACU	Acceleromyography
			51	Intermediate	VA	Qualitative	Neostigmine	NR	11	NR		
2012	Kaan [47]	PORC	28	Intermediate	VA	None	Neostigmine	NR	3	NR	At PACU arrival	Acceleromyography
			29	Intermediate	VA	None	Neostigmine	NR	5	NR		
			27	Intermediate	VA	None	Neostigmine	NR	3	NR		

2012	Kumar [39]	PFT, PORC	50	Intermediate	VA	None	Neostigmine	NR	23	NR	At PACU arrival	Acceleromyography
			50	Intermediate	VA	None	Neostigmine	NR	33	NR		
			50	Intermediate	VA	None	Neostigmine	NR	30	NR		
2012	Omar [42]	PORC	23	Intermediate	VA	Quantitative	Neostigmine	3	8	NR	At PACU arrival.	Acceleromyography
			23	Intermediate	VA	Quantitative	Neostigmine	0	2	NR		
2013	Kotake [34]	PORC	23	Intermediate	VA (17) TIVA (6)	None	None	NR	3	16	After tracheal extubation	Acceleromyography
			109	Intermediate	VA (73) TIVA (36)	None	Neostigmine	NR	26	73		

			117	Intermediate	VA (80) TIVA (37)	None	Sugammadex	NR	5	54		
2013	Pietraszewski [11]	PORC	184	Intermediate	VA	None	None	49	51	12	Within 10 minutes of arrival at the PACU	Acceleromyography
			231	Intermediate	VA	None	None	46	132	53		
2014	Kocaturk [48]	PORC	51	Intermediate	VA	None	Neostigmine	NR	4	NR	At PACU arrival	Acceleromyography
			94	Intermediate	VA	None	Neostigmine	NR	13	NR		
			63	Intermediate	VA	None	Neostigmine	NR	5	NR		
2015	Brueckmann [51]	PORC	64	Intermediate	NR	Quantitative	Sugammadex	NR	0	NR	At PACU arrival	Acceleromyography
			10	Intermediate	NR	None	Sugammadex	NR	0	NR		

2015	Murphy [10]	PORC	150	Intermediate	VA	Qualitative	Neostigmine	9	45	NR	At PACU arrival	Acceleromyography
			149	Intermediate	VA	Qualitative	Neostigmine	25	86	NR		
2015	El-Tahan [43]	PORC	33	Intermediate	VA	Quantitative	Neostigmine	0	2	NR	15 minutes after PACU arrival	Kinemyography
2015	Rahe-Meyer [31]	PORC	69	Intermediate	VA (21) TIVA (47)	Quantitative	Sugammadex	NR	0	NR	At tracheal extubation	Acceleromyography
			67	Intermediate	VA (16) TIVA (53)	Quantitative	None	NR	0	NR		
2016	Yazar [49]	PORC	60	Intermediate	VA	Quantitative	Sugammadex	NR	1	NR	5 minutes after PACU arrival	Acceleromyography

2016	Errando [45]	PORC	285	Intermediate	NR	NR	NR	NR	58	NR	At PACU arrival	Acceleromyography
			433	Intermediate	NR	None	NR	NR	132	NR		
2016	Carron [89]	Neuromuscular monitoring cost analysis, PORC	128	Intermediate	VA (102) TIVA (26)	Quantitative	Sugammadex	0	0	NR	At tracheal extubation	Not reported.
			128	Intermediate	VA (96) TIVA (32)	Quantitative	Neostigmine	16	41	NR		
			96	Intermediate	VA (71) TIVA (25)	Quantitative	Neostigmine, Sugammadex	61	27	NR		
			96	Intermediate	VA (76) TIVA (20)	Quantitative	Neostigmine	9	14	NR		

2016	Feltracco [12]		60	Intermediate	TIVA	Quantitative	Neostigmine	0	2	0	At the PACU (15 minutes post-extubation)	Acceleromyography
			60	Intermediate	TIVA	Quantitative	Neostigmine	0	4	0		
2016	G-Cardenas [40]	PORC	228	Intermediate	NR	Quantitative	Neostigmine (17) Sugammadex (15)	NR	21	NR	At PACU arrival	Acceleromyography
2017	Santos [14]	PORC	62	Intermediate	VA	None	Neostigmine	NR	NR	28	At PACU arrival	Acceleromyography
			60	Intermediate	VA	None	Neostigmine	NR	NR	15		
2018	Murphy [44]	PORC	47	Intermediate	VA	Quantitative	Neostigmine	NR	0	NR	15 minutes after PACU arrival	Acceleromyography
			43	Intermediate	VA	Quantitative	None	NR	0	NR		
2018	Thilen [32]	PORC	41	Intermediate	VA	Qualitative	Neostigmine	1	22	NR	At tracheal	Acceleromyography

			38	Intermediate	VA	Qualitative	Neostigmine	12	14	NR	extubation	
2018	Kirmeier [21]	Pulmonary complications after NMBAs	4182	Short, Intermediate, Long	NR	Quantitative	Neostigmine (1874)	NR	1343	NR	At extubation	At extubation
2019	Koo [54]	Endoscopic surgical conditions (PORC, secondary endpoint)	53	Intermediate	VA	Quantitative	Sugammadex	NR	0	NR	At the PACU (no time-point specification)	Acceleromyography
			51	Intermediate	VA	Quantitative	Sugammadex	NR	0	NR		
2019	Saager [22]	PORC	171	NR	NR	Qualitative	Neostigmine	NR	112	NR	At tracheal extubation	Acceleromyography
			2	NR	NR	Qualitative	None	NR	1	NR		
			81	NR	NR	None	Neostigmine	NR	51	NR		

			1	NR	NR	None	None	NR	0	NR		
2019	Wardhana [41]	PORC	36	Intermediate	VA	None	Neostigmine	NR	6	NR	At PACU arrival	Acceleromyography
			36	Intermediate	VA	Quantitative	Neostigmine	NR	1	NR		

Table 1 - Summary of studies included in the meta-analysis.

VA - Volatile Anaesthesia; TIVA - Total Intravenous Anaesthesia; NR - Not reported; PACU – Post Anesthesia Care Unit; PORC – Post Operative Residual Curarization; PFT – Pulmonary function tests; NMM – Neuromuscular Monitoring

PORC determination time-point: point in time at which the TOF ratio was measured and used to define the presence or absence of PORC according to the selected TOFR cut-off.

Comparison	**Study arms (n)**	**Within-study bias**	**Across-studies bias**	**Indirectness**	**Imprecision**	**Heterogeneity**	**Incoherence**
Intermediate NMBA and No Monitoring	26	Some Concerns	Suspected	No concerns	No concerns	No concerns	No concerns

Intermediate NMBA and Qualitative Monitoring	17	Some Concerns	Suspected	No concerns	No concerns	No concerns	No concerns
Intermediate NMBA and Quantitative Monitoring	29	Some Concerns	Suspected	No concerns	No concerns	No concerns	No concerns

Table 2 - CINeMA Analysis - Summary; NMBA - neuromuscular blocking agent

Quantitative vs. Quantitative vs. No NMM									
Patients: Adults patients. Setting: Elective surgical procedures under general anaesthesia in operation room setting requiring administration of intermediate duration NMBAs. Intervention: Quantitative or Qualitative Neuromuscular Monitoring Comparison: No Neuromuscular Monitoring									
Outcome	**Absolute Risk (95% CI)**			**Relative Risk**			**Number Studies**		
	Quantitative NMM	**Qualitative NMM**	**No NMM**	**Quantitative vs No NMM**	**Qualitative vs No NMM**	**Quantitative vs Qualitative NMM**	**Quantitative NMM**	**Qualitative NMM**	**No NMM**
PORC (TOF-R <0.9)	0.119 (0.061; 0.191)	0.311 (0.216; 0.415)	0.338 (0.243; 0.440)	0.352	0.920	0.383	18	11	20

Table 3 - Summary of Findings for intermediate NMBAs and PORC defined by a TOF-ratio <0.9.

PORC - Postoperative residual curarization; TOF-R - Train of Four Ratio; NMM - Neuromuscular monitoring.

Legends to figures

Figure 1. - Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

Figure 2. - Main Model with subtracted anaesthesia type, Cut-off 0.9 - Forest plot - Pooled postoperative residual curarization PORC proportions.

Study arm label structure (left): Author, publication year, NMM subtype, NMBA duration category. Individual and pooled PORC rates and respective 95% Confidence Intervals presented on the right hand side of the plot.

NMM - Neuromuscular monitoring subtype; none - no NMM; pns - qualitative NMM; tft - Quantitative monitoring; imed=intermediate - intermediate duration NMBAs; long - Long duration NMBAs.

For intermediate duration NMBAs, the use of quantitative neuromuscular monitoring is associated with lower PORC rates when compared to both no monitoring and qualitative monitoring, as exemplified by the absence of overlap of the respective confidence intervals.

Figure 3. - Trend Model, Cut-off 0.9 - Isolated proportion plotting - Publication year vs Neuromuscular monitoring type (monitor).

There is a global reduction in the incidence of PORC with time, independently of the subtype of Neuromuscular monitoring. Although the chronological decrease is most evident when no monitoring is used, the PORC are consistently higher when compared to quantitative monitoring.

Figure 4. – Funnel plotting per statistical model and TOF-ratio cut-off. x axis: residual value, y axis: standard error; A - Main Model with subtracted anesthesia type, Cut-off 0.9; B– Antagonist Model, Cut-off 0.7; C - Antagonist Model, Cut-off 0.9; D - Main Model, Cut-off 0.7; E - Main Model, Cut-off 0.9; F - Trend Model, Cut-off 0.7; G - Trend Model, Cut-off 0.9.

There is no serious indication of any systematic heterogeneity bias. For the antagonist model with a cut-off of 0.7, one study clearly shows a proportion that is different from what would be expected based on the available information in the model.[23]