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GUIDELINES

Peri-operative management of neuromuscular blockade

A guideline from the European Society of Anaesthesiology and Intensive Care

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Recent data indicated a high incidence of inappropriate management of neuromuscular block, with a high rate of residual paralysis and relaxant-associated postoperative complications. These data are alarming in that the available neuromuscular monitoring, as well as myorelaxants and their antagonists basically allow well tolerated management of neuromuscular blockade. In this first European Society of Anaesthesiology and Intensive Care (ESAIC) guideline on peri-operative management of neuromuscular block, we aim to present aggregated and evidence-based recommendations to assist clinicians provide best medical care and ensure patient safety. We identified three main clinical questions: Are myorelaxants necessary to facilitate tracheal intubation in adults? Does the intensity of neuromuscular blockade influence a patient's outcome in abdominal surgery? What are the strategies for the diagnosis and treatment of residual paralysis? On the basis of this, PICO (patient, intervention, comparator, outcome) questions were derived that guided a structured literature search. A stepwise approach was used to reduce the number of trials of the initial research ($n = 24\,000$) to the finally relevant clinical studies ($n = 88$). GRADE methodology (Grading of Recommendations, Assessment, Development and Evaluation) was used for formulating the recommendations based on the findings of the included studies in conjunction with their methodological quality. A two-step Delphi process was used to determine the agreement of the panel members with the recommendations: **R1** We recommend using a muscle relaxant to facilitate tracheal intubation (1A). **R2** We recommend the use of muscle relaxants to reduce pharyngeal and/or laryngeal injury following endotracheal intubation (1C). **R3** We recommend the use of a fast-acting muscle relaxant for rapid sequence induction intubation (RSII) such as succinylcholine 1 mg kg^{-1} or rocuronium 0.9 to 1.2 mg kg^{-1} (1B). **R4** We recommend deepening neuromuscular blockade if surgical conditions need to be improved (1B). **R5** There is insufficient evidence to recommend deep neuromuscular blockade in general to reduce postoperative pain or decrease the incidence of peri-operative complications. (2C). **R6** We recommend the use of ulnar nerve stimulation and quantitative neuromuscular monitoring at the adductor pollicis muscle to exclude residual paralysis (1B). **R7** We recommend using sugammadex to antagonise deep, moderate and shallow neuromuscular blockade induced by aminosteroidal agents (rocuronium, vecuronium) (1A). **R8** We recommend advanced spontaneous recovery (i.e. TOF ratio >0.2) before starting neostigmine-based reversal and to continue quantitative monitoring of neuromuscular blockade until a TOF ratio of more than 0.9 has been attained. (1C)

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Introduction

A recent survey addressed the practice of neuromuscular block management in Europe. In this survey, 17 150 patients were exposed to a neuromuscular blocking agent, but neuromuscular monitoring (NMM) was not used in more than 10 000 of them, timing of extubation was solely based on clinical criteria in around 12 000 patients, and over 8300 patients did not receive any reversal agent at the end of surgery. Finally, only 16.5% of patients (2839/17 150) exposed to a neuromuscular blocking agent were extubated with a documented train-of-four (TOF)-ratio at least 0.9.[1] Unsurprisingly, this very high incidence of inappropriate management of neuromuscular block increased the rate of residual paralysis and relaxant-associated postoperative pulmonary complications (POPCs).[1]

So far, the peri-operative management of neuromuscular blockade has not yet been addressed by a guideline from the European Society of Anaesthesiology and Intensive Care (ESAIC). Hence, in light of the above-mentioned distressing snapshot of the practice of neuromuscular blockade management across Europe and with the intention of improving patient safety, a task force was assigned by the ESAIC to critically appraise the current literature in the field and to provide a graded and evidence-based set of practice guidelines for the peri-operative management of neuromuscular blockade.

Materials and methods

The ESAIC appointed a task force to develop guidelines on the peri-operative management of neuromuscular blockade. Clinical queries were developed in the form of three Population/Intervention/Comparison/Outcome (PICO) groups and then further into eight elements for the search strategy. The initial list of PICOs was then revised and finally a consolidated set of PICOs was approved by the task force. PICOs generated were based on the research questions to be addressed in this article. The main clinical queries arising from the shortcomings in conjunction with the use of neuromuscular blocking agents and its monitoring and reversal that was explained in the Introduction were as follows:

(1) Is the use of myorelaxants necessary to facilitate tracheal intubation in adults?
(2) Does the intensity of neuromuscular blockade influence a patient's outcome in abdominal surgery (i.e. laparotomy or laparoscopy)?
(3) What are the strategies for the diagnosis and treatment of residual neuromuscular paralysis?

Criteria for considering studies for data analysis

Types of studies

Data analysis included all randomised, parallel and quasi-randomised studies (including crossover studies) and observational studies performed in adults that addressed any of the above queries. Previous meta-analyses and systematic reviews were considered when available and meeting the inclusion criteria. Data from quasi-randomised and observational and large retrospective studies were included to support the answer to the PICOs due to the small number of randomised controlled trials (RCTs) available. Narrative reviews, case series and case reports as well as published abstracts from conference proceedings and registered but not completed studies were excluded.

Types of participants

The qualitative and quantitative analysis of the literature was confined to adult patients undergoing surgery with general anaesthesia and tracheal intubation.

Type of interventions

We included the following interventions: neuromuscular blockade (type of neuromuscular blocking agent: suxamethonium, atracurium, cisatracurium, mivacurium, pancuronium, rapacuronium, vecuronium and rocuronium), quantitative NMM or acceleromyography or electromyography, sugammadex-based reversal.

Types of comparators

We included the following comparators: no or any different degree of neuromuscular blockade, no NMM or qualitative NMM [i.e. peripheral nerve stimulator (PNS)], neostigmine-based reversal.

Types of outcomes

Outcomes included assessment of intubation conditions, either by the criteria of Cormack and Lehane or those of the 'Good Clinical Research Practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents', sore throat, hoarseness, vocal cord injury, pharyngeal injury, dental injury, oesophageal intubation, inhalation lung disease, surgical field quality score, laparoscopic insufflation pressure, postoperative pain in the PACU, postoperative pain at 24 h postsurgery, intra-operative adverse events, postoperative complications within 30 days using the Clavien-Dindo classification, residual paralysis, TOF ratio less than 0.9, hypoxia, and POPC.

Search method for identification of studies

The literature search strategy was developed by the trial search and Cochrane information specialist Janne Vendt (Copenhagen University Hospital, Copenhagen, Denmark) in close collaboration with the author T.F-B. and the ESAIC group methodologist and Cochrane editor A.A. We searched for eligible studies in the following databases: Medline (Ovid SP, 1946 – search date), Embase (Ovid SP, 1974 – search date), Central (Cochrane Database of Systematic Reviews <https://www.cochranelibrary.com/>Issue 1 of 12 January 2021), Web of Science (1900

– search date), Biosis (1969 – search date). A combination of subject headings and free-text terms was used for the topic search. We added filters for study types inspired by NICE (i.e. National Institute for Health and Care Excellence), but adjusted for our use. (https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission#developing-search-strategies). An additional search for systematic reviews was run in Epistemonikos, and the bibliographic references and citations of included studies and systematic reviews were checked for other eligible studies. During the screening process, the search was limited to 1995 to 2021 and only references published in this period were screened. The task force members were also encouraged to add any missing articles of interest of which they were aware and to conduct additional searches themselves. The titles resulting from the searches were allocated to the three PICO groups and screened by respective task force members as follows: PICO 1: C-S.R, H.L., M.S., PICO 2: P.K., M.P., J.H., D.S., PICO 3: M.L., HDD.B., A-M.H, T.F-B.

The searches for the guideline were run on 1 February 2021 and updated on 31 December 2021.

Search results

Three of the authors first screened the titles and then relevant titles with abstracts in a two-stage procedure. In the first stage, a 'second opinion' was possible, later to be reviewed by T.F-B. The screening procedure was monitored by either A.A or P.K. The resulting potentially relevant articles were retrieved for full-text assessment and data extraction by the task force groups using Rayyan software (https://www.rayyan.ai).

During the initial research, 24 000 titles could be identified; after duplicate removal and limitation of the search period to 1996 to 2021, the remaining 13 115 titles were screened, resulting in 1988 abstracts. From these, 166 relevant abstracts were used to select a total of 88 appropriate titles for a detailed GRADE (Grading of Recommendations, Assessment, Development and Evaluation) analysis. Moreover, three systematic reviews and one meta-analysis were considered. For a more detailed description of the search strategy and PICO queries, the readers are referred to Appendix 1.

Data collection and analysis

Selection of studies

All articles meeting the inclusion criteria were included. At least two authors within each of the three PICO groups assessed the relevant full-text articles (PICO 1: H.L., C-S.R; PICO2: P.K., M.P., J.H., D.S.; PICO3: M.L., HDDB, T.F-B.). Disagreements were resolved by a third party (A.A, P.K., T.F-B.)

Data extraction and management

All authors extracted data in a similar manner in relation to study design, patient characteristics, intervention and outcome measures. The respective data were entered in a predesigned Excel sheet. Task force group authors reached consensus regarding extracted data through discussion.

Assessment of risk of bias in included studies

Review authors were supplied with literature for assessment of risk of bias by the ESAIC methodologist (A.A.), and then assessed the risk of bias of each of the studies selected for each PICO question. Risk of bias assessment was conducted in accordance with the Cochrane Handbook for Systematic Reviews and Interventions. The risk of bias was assessed for the following domains:

(1) Random sequence generation (selection bias);
(2) Allocation concealment (selection bias);
(3) Blinding of participants and personnel (performance bias);
(4) Blinding of outcome assessors (detection bias);
(5) Incomplete outcome data, intention-to-treat (attrition bias);
(6) Selective reporting.

Overall bias was defined by the assessor based on the assessment in the respective domains. Basically, trials were assessed as having a low risk of bias if all of the domains were considered adequate, as having a moderate risk of bias if one domain was considered inadequate, and as having a high risk of bias if more than one domain were considered inadequate or unclear. Disagreement regarding assessment of risk of bias was settled in discussion with the methodologist (A.A.).

Assessment of quality of the evidence

In accordance with the ESAIC policy, GRADE methodology was used for formulating the recommendations based on the findings of the included studies in conjunction with their methodological quality. The ESAIC guidelines committee selected the GRADE system for assessing levels of evidence and grading as this method has the merit of simplicity. Two levels also make the interpretation of the implications of strong and weak recommendations simpler for clinicians. The Taskforce members were asked to define relevant outcomes across all clusters and rank the relative importance of outcomes, following a process proposed by the GRADE group. After selecting the relevant articles for each cluster, one member per group was in charge for the final grading of the papers (C-S.R, P.K, T.F-B). Decisions to downgrade the level of evidence for a recommendation were based on the quality and type of the included literature, observed inconsistencies, indirectness or directness of the evidence, overall impression of the quality of the evidence and the presence of publication bias as indicated by GRADE. Decisions to upgrade the level of evidence for recommendations were based on study quality and magnitude of effect, dose-response gradient and

plausible residual confounding. The GRADE definitions are summarised in Table 1.

Development of recommendations

Each group developed recommendations relevant to their PICO and clinical questions. These were then discussed and re-discussed as required with the entire expert panel in light of the data synthesis, the risk of bias and the quality of the evidence.

A two-step Delphi process was used to produce expert recommendations and to discuss the methodological quality of the supporting literature when the quality of evidence was low or when rephrasing of recommendations was needed. Every single recommendation, suggestion or statement was subject to the voting and consensus process.

First round

At the first round, the statements of task force groups were discussed and refined at a hybrid meeting (face-to-face at EuroAnaesthesia 2022 in Milan and videoconferencing for task force members not present). A set of eight statements was identified for further development.

Second round

For the second and final round, a virtual meeting was used to ask the task force members to indicate approval or rejection of each of the eight statements, with the option for suggesting changes. An affirmative (positive) rating was adopted when the approval rate was 80%. Finally, all eight recommendations reached full agreement (10 supporting votes out of 10 participating members being eligible to vote).

In addition, recommendations for good practice (based on the experiences of the guideline task force and possibly incorporating the expertise of a wider reference group) were developed in addition to recommendations for the PICO questions based on the existent evidence. The guideline task force produced these clinical practice statements (CPS) on important topics rather than solely on evidence based recommendations when there was a lack of research evidence no predefined PICO and the conviction that the CPS added important opinions to the overall guideline topic.

The recommendations and CPS were merged into a shared document by one author (T.F-B.). The final version of the document was composed by the authors and subsequently reviewed and endorsed by all members of the expert panel.

Summary of recommendations (R)

R1: We recommend using a muscle relaxant to facilitate tracheal intubation (1A: high quality of evidence, strong recommendation).

R2: We recommend the use of muscle relaxants to reduce pharyngeal and/or laryngeal injury following endotracheal intubation (1C: low quality of evidence, strong recommendation).

R3: We recommend the use of a fast-acting muscle relaxant for RSII such as succinylcholine 1 mg kg^{-1} or rocuronium 0.9 to 1.2 mg kg^{-1} (1B: moderate quality of evidence, strong recommendation).

Table 1 GRADE definitions

Grade of recommendation	Clarity of risk/benefit	Quality of supporting evidence
1A: Strong recommendation, high-quality evidence	Benefits clearly outweigh risk and burdens, or *vice versa*.	Consistent evidence from well performed randomised, controlled trials or over-whelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
1B: Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risk and burdens, or *vice versa*.	Evidence from randomised, controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate
1C: Strong recommendation, low-quality evidence	Benefits appear to outweigh risk and burdens, or vice versa.	Evidence from observational studies, unsystematic clinical experience, or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain.
2A: Weak recommendation, high quality evidence	Benefits closely balanced with risks and burdens.	Consistent evidence from well performed randomised controlled trials or overwhelming evidence of some other form. Further research is unlikely to change our confidence in the estimate of benefit and risk.
2B: Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens, some uncertainly in the estimates of benefits, risks and burdens.	Evidence from randomised controlled trials with important limitations (inconsistent results, methodologic flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on our confidence in the estimate of benefit and risk and may change the estimate.
2C: Weak recommendation, low-quality evidence	Uncertainty in the estimates of benefits, risks and burdens benefits may be closely balanced with risks and burdens.	Evidence from observational studies, unsystematic clinical experience, or from randomised controlled trials with serious flaws. Any estimate of effect is uncertain.

R4: We recommend deepening neuromuscular blockade if surgical conditions need to be improved (1B: moderate quality evidence, strong recommendation).

R5: There is insufficient evidence to recommend deep neuromuscular blockade in general to reduce postoperative pain or decrease the incidence of peri-operative complications. (2C: low-quality evidence, weak recommendation)

R6: We recommend the use of ulnar nerve stimulation and quantitative NMM at the adductor pollicis muscle to exclude residual paralysis. (1B: moderate-quality evidence, strong recommendation)

R7: We recommend using sugammadex to antagonise deep, moderate and shallow neuromuscular blockade induced by aminosteroidal agents (rocuronium, vecuronium) (deep: posttetanic count >1 and TOF count 0, moderate: TOF-count 1 to 3, shallow: TOF-count 4 and TOF-ratio < 0.4) (1A: high-quality evidence, strong recommendation)

R8: We recommend advanced spontaneous recovery (i.e. TOF-ratio >0.2) before starting neostigmine-based reversal and to continue quantitative monitoring of neuromuscular blockade until a TOF-ratio of more than 0.9 has been attained. (1C: low-quality evidence, strong recommendation)

Summary of clinical practice statements

CPS1: Current evidence does not allow the recommendation of one reversal agent over another when reversing a TOF-ratio between 0.4 and 0.9. The choice between sugammadex and neostigmine must consider patient-related factors as well as availability.

CPS2: Recovery from succinylcholine-induced neuromuscular blockade should also be monitored quantitatively.

Is the use of muscle relaxants necessary to facilitate tracheal intubation?

(1) We recommend using a muscle relaxant to facilitate tracheal intubation (**1A**).
(2) We recommend the use of muscle relaxants to reduce pharyngeal and/or laryngeal injury following endotracheal intubation (**1C**).
(3) We recommend the use of a fast-acting muscle relaxant for RSII such as succinylcholine 1 mg kg^{-1} or rocuronium 0.9 to 1.2 mg kg^{-1} (**1B**).

Evidence summary and comment

In the assessment of the need for muscle relaxants for orotracheal intubation, 39 randomised clinical trials,[2–40] one cohort study,[41] two systematic reviews,[42,43] and one clinical guideline[44] were included. We considered studies that investigated succinylcholine, rocuronium, atracurium, cisatracurium, rapacuronium, mivacurium and vecuronium in the adult population. Whenever a study looked at different doses of neuromuscular blocking agents, the dose that doubled the ED_{95} (effective dose of muscle relaxant that induces a 95% blockade) was chosen. In studies characterising different protocols without muscle relaxant, only the one protocol leading to the best intubating conditions was considered. Thus, we obtained data from 1405 patients who received a muscle relaxant for endotracheal intubation and from 1364 patients who did not receive a muscle relaxant. Poor intubation conditions were observed in 370 patients without muscle relaxant and in 45 patients who received muscle relaxants (Table 2). These results correspond to poor intubation conditions in 27% in the group without muscle relaxants vs. 3% in the group wherein muscle relaxants were administered. From the data reported, the presence of poor intubation conditions resulted in an absolute risk reduction of 24% when using muscle relaxant drugs for intubation. These findings are further supported by Lundstrom *et al.*[41] identifying relaxant-free induction as an independent risk factor for difficult tracheal intubation.

Orotracheal intubation is not free of risks and discomfort for patients. Most commonly observed side effects are postextubation pain, hoarseness and transient voice changes, and vocal cord injury. Seven studies have described the occurrence of pharyngeal and/or laryngeal injury.[6,8,10,11,24,25,33] To address the occurrence of these injuries, we pooled the total number of intubated patients with the use of muscle relaxants and the total number of patients in whom the technique was carried out without the addition of muscle relaxants. From a total of 447 patients intubated with a relaxant-free induction regimen, 173 (38%) experienced pharyngeal or laryngeal injury. However, when neuromuscular relaxants were used on a total of 397 patients, only 109 (27%) experienced pharyngeal or laryngeal injury (Table 2). In light of these findings, the use of myorelaxants presents an absolute risk reduction of 11% in the occurrence of airway injury in patients during general anaesthesia. It has to be emphasised that pharyngeal or laryngeal injury may occur during extubation as well.[25] Thus, further reduction of their incidence could be obtained by avoidance of cuffing and bucking during extubation.

Patients may require a rapid sequence induction intubation (RSII) to protect against regurgitation of gastric content and pulmonary aspiration. Thus, to avoid mask ventilation, to improve intubation conditions and to reduce the risk of a difficult intubation in this situation, neuromuscular blocking agents given for a RSII should be rapid in onset. Traditionally, succinylcholine has been the most commonly used muscle relaxant for this purpose because of its fast onset and short duration; unfortunately, it can present serious side effects. Rocuronium has been suggested as an alternative to succinylcholine. According to a recent Cochrane Review, a regime with rocuronium at 0.6 to 0.7 mg kg^{-1} produces less frequent excellent

Table 2 Randomised controlled trials to facilitate tracheal intubation and reduce pharyngeal discomfort

						Main findings: Difficult intubation				Main findings: Upper airway discomfort			
						NMB Avoidance		NMB use		NMB Avoidance		NMB use	
Study	Dose finding design	Patients	ASA	Exclusions	NMB	Events	Total	Events	Total	Events	Total	Events	Total
Alexander, 1999[2]	yes	60/60	1 & 2	a	Sux	3	20	0	20	–	–	–	–
Barbosa, 2020[3]	–	34/34	1 & 2	a,b	Roc	29	34	0	34	–	–	–	–
Barclay, 1997[4]	yes	60/60	–	a,b	Roc	19	20	2	20	–	–	–	–
Beck, 1993[5]	–	64/64	1 & 2	–	Sux	1	31	0	33	–	–	–	–
Bouvet, 2008[6]	–	130/129	1 & 2	a	Cisatr	3	65	0	64	14	65	17	64
Collins, 2000[7]	–	48/48/48	1&2	a	Sux	6	48	0	48	–	–	–	–
Combs, 2007[8]	–	300/300	1 & 2	a,b	Roc	18	150	1	150	86	150	64	150
Dominici, 1990[9]	–	60	1,2,3	–	Sux	11	30	10	30	–	–	–	–
Gonzalez, 2010[10]	–	100/100	1 & 2	a	Roc	1	50	4	50	0	50	0	50
Gulhas, 2013[11]	–	80/80	1 & 2	–	Sux	0	40	5	40	4	40	2	40
Hanna, 2010[12]	–	50/47	1 & 2	a	Roc/Sux	3	23	2	24	–	–	–	–
Harsten, 1997[13]	–	80/79	1 & 2	–	Sux	6	39	0	40	–	–	–	–
Iamaroon, 2001[14]	–	120/120	1 & 2	a,b	Sux	4	60	0	60	–	–	–	–
Isesele, 2012[15]	–	96/88	1 & 2	a	Sux	18	44	0	44	–	–	–	–
Jiao, 2014[16]	–	55/55	1 & 2	b	Sux	13	28	1	27	–	–	–	
Kahwaji, 1997[17]	yes	181/176	1,2,3	a	Rapr	18	30	1	29	–	–	–	–
Kirkegaard–Nielsen, 1999[18]	yes	80/80	1 & 2	b	Roc	13	20	1	20	–	–	–	–
Kohli, 2008[19]	–	40/40	1&2	a,b	Sux	0	40	0	40	–	–	–	–
Kopman, 2001[20]	yes	100/100	1 & 2	b	Rapr	7	10	0	30	–	–	–	
Lieutaud, 2003[21]	yes	170/160	1 & 2	a	Atr	13	20	2	45	–	–	–	–
Lowry, 1999[22]	yes	140/140	1 & 2	a,b	Roc	19	20	2	20	–	–	–	–
McNeil, 2000[23]	yes	60/60	1 & 2	a,b	Sux	1	23	0	17	–	–	–	–
Mencke, 2014[24]	–	83/83	1,2,3	a,b	Roc	11	43	1	40	17	31	12	31
Mencke, 2003[25]	–	8073	1 & 2	a,b	Atr	12	36	2	37	18	36	6	37
Naguib, 2003[26]	yes	200/200	1	a	Sux	35	50	1	50	–	–	–	–
Naguib, 2006[27]	yes	180/180	1	a	Sux	21	30	0	30	–	–	–	–
Nimmo, 1995[28]	yes	60/60	1 & 2	–	Sux	9	20	0	20	–	–	–	–
Pang, 2014[29]	–	40/40	1 & 2	a,b	Cisatr	0	20	0	20	–	–	–	–
Pino, 1998[30]	yes	100/98	1 & 2	a,b	Miva/Roc	10	10	0	15	–	–	–	–
Rousseau, 1998[31]	–	152/152	1	a	Vec	4	75	2	77	–	–		–
Scheller, 1992[32]	yes	75/75	1	a	Sux	0	15	0	15	–	–	–	–
Schlaich, 2000[33]	–	120/120	1 & 2	a	Roc	12	30	0	30	–	–	–	–
Sivalingam 2001[34]	yes	100/100	1 & 2	a	Sux	2	25	1	25	34	75	8	25
Soltez, 2001[35]	–	30/30/30/30	1 & 2	a	Roc	24	30	0	30	–	–	–	–
Stevens, 1997[36]	yes	140/140	1 & 2	a	Sux	2	20	1	20	–	–	–	–
Striebel, A 1995[37]	yes	100/100	1 & 2	a	Vec/Sux	8	50	2	50	–	–	–	–
Wrong, 1996[38]	yes	120/120	1 & 2	a	Sux	0	30	0	30	–	–	–	–
Yazdi, 2016	–	66/66	1 & 2	a	Atr	14	35	4	31	–	–	–	–
Total[39]						370	1364	45	1405	173	447	109	397

a, exclusion of expected difficult intubation patients; b, exclusion of overweight patients; ASA, America Society Association Status; Atr, Atracurium; Cisatr, Cisatracurium; Miv, Mivacurium; NMB, neuromuscular blockade; Rapr, Rapacuronium; Roc, Rocuronium; Sux, succinycholine; Vec, Vecuronium. Risk of bias.

low | intermediate | high | no information.

intubation conditions for RSII than succinylcholine.[43] There were no statistical differences for either excellent or acceptable intubation conditions when the dose of rocuronium was increased at 0.9 to 1.0 or 1.2 mg kg^{-1}.[43] To overcome the longer muscular block duration of rocuronium compared with succinylcholine, an appropriate dose of sugammadex should be available in the operating room when using rocuronium for RSII.[40]

Does the intensity of neuromuscular blockade influence patient outcomes in abdominal surgery (i.e. laparotomy or laparoscopy)?

(1) We recommend deepening neuromuscular blockade if surgical conditions need to be improved (**1B**).

(2) There is insufficient evidence to recommend deep neuromuscular blockade in general to reduce postoperative pain or decrease the incidence of perioperative complications (**2C**).

Evidence summary and comment

In evaluating the need for muscle relaxants for optimal surgical conditions, 26 randomised clinical trials were included.[45–70] We considered studies that investigated deep (dNMB) vs. moderate (mNMB) or no neuromuscular block in the adult population. Across studies, dNMB was defined as a posttetanic count of 0 to 5 and mNMB as at least 1 response to TOF monitoring.

With very few exceptions,[56,63] the used surgical technique was a laparoscopic procedure; patients were managed with either volatile or total intravenous anaesthesia. Twenty-three studies compared dNMB with mNMB as the standard of care,[45–55,57–60,62–66,68,69] three studies used no neuromuscular block as control [56,61,67] and one study performed on-demand relaxation control.[70] In our analysis, 23 out of 26 studies were classified as having a low risk of bias. However, some shortcomings must be considered: even though the majority of included studies reported some benefit from dNMB for the surgical condition, patient comfort and/or patient safety, those results were from small studies (mostly ≤60 patients) and differences in the outcomes were marginal regarding clinical relevance. To conclude, we assess the quality of the evidence on this topic as moderate (Supplementary Table 1, http://links.lww.com/EJA/A781).

Overall, the studies included 1814 patients with 925 who were treated with dNMB during surgery and 889 patients who received mNMB or in three cases no relaxation. Surgical conditions and view of the surgical field were rated significantly better under dNMB in 17 studies.[46–48,53,55–61,63–66,69] However, the clinical benefits of this deep block concept still remain controversial. Surgical space conditions are not solely determined by the depth of neuromuscular block but also by nonrelaxation related factors such as depth or type of anaesthesia (volatile vs. intravenous). Moreover, patient-related factors such as abdominal wall constitution, adhesions, organ size, age or sex may also have an impact in this context. Finally, the requirements for neuromuscular block may not be constant during a procedure; at some stages, more relaxation might be needed than at others. Recently, it has been evaluated whether switching from moderate to deep neuromuscular block improves surgical conditions for laparoscopic surgery in the obese.[52] To better control nonrelaxation-related factors, each patient was taken as their own control and surgical conditions were evaluated twice within a few minutes at a predefined stage of the procedure (at the begin of the gastro-gastro-jejunal suture). In this setting, the surgical conditions during moderate neuromuscular blockade were already good to excellent in the 55 out of 85 patients. In addition, switching from moderate to deep block, here defined as a PTC (posttetanic count) 1 to 3, improved surgical conditions in 85% of patients whilst maintaining moderate neuromuscular block led to an improvement in only 12% of investigated patients.[52] These data are in favour of a personalised approach, that is rather than routinely applying a deep block, neuromuscular block should be deepened on demand if required to improve surgical conditions. A plausible mechanistic explanation that deeper neuromuscular block may enhance the surgical conditions or at least the view of the surgical field, for example open/laparoscopic abdominal or pelvic or retroperitoneal procedures should be present.

In only three of the 15 studies that measured postoperative pain did the authors report significant differences between the groups, with patients benefitting from dNMB.[49,55,62] Similarly, three out of 19 studies that looked for the occurrence of adverse events or complications in a broader sense reported overall fewer events in the dNMB group.[48,49,63] Unfortunately, some of these patients had no neuromuscular blockade or a spontaneous neuromuscular recovery was allowed rather than maintaining a moderate neuromuscular block. Thus, more well designed studies investigating whether a deep neuromuscular block is superior to moderate neuromuscular block vis-a-vis peri-operative patient outcome are needed.

What are the strategies for the diagnosis and treatment of residual neuromuscular paralysis?

(1) We recommend the use of ulnar nerve stimulation and quantitative NMM at the adductor pollicis muscle to exclude residual paralysis. (**1B**)
(2) We recommend using sugammadex to antagonise deep, moderate and shallow neuromuscular blockade induced by aminosteroidal agents (rocuronium, vecuronium) (deep: posttetanic count >1 and TOF count 0, moderate: TOF count 1 to 3, shallow: TOF count 4 and TOF ratio < 0.4). (**1A**)
(3) We recommend advanced spontaneous recovery (i.e. TOF-ratio >0.2) before starting neostigmine-based reversal and to continue quantitative monitoring of neuromuscular blockade until a TOF ratio of more than 0.9 has been attained. (**1C**)

Evidence summary and comment

In evaluating strategies for the diagnosis of residual paralysis, studies comparing quantitative NMM vs. qualitative NMM or clinical assessment were examined; a TOF ratio less than 0.9 was considered as residual paralysis. Overall, five RCTs and one retrospective observational study, including altogether 788 patients, were analysed.[71–76] Three hundred and thirty-four patients were monitored with quantitative NMM at the adductor pollicis and 19 patients (6%) had residual paralysis. The 454 remaining patients were either monitored with qualitative NMM at the adductor pollicis or with clinical judgement and 121 of them (27%) had residual paralysis: 29 out of 164 (18%) monitored with qualitative NMM and 92 out of 290 (32%) managed without NMM (Table 3). In addition, a meta-analysis, including 12 664 patients, was considered.[77] It revealed a pooled incidence of residual paralysis associated with the use of a quantitative NMM of 0.115 (95% CI: 0.057 to 0.188). This was significantly lower than with qualitative NMM (0.306, 95% CI: 0.09 to 0.411) or without NMM (0.331, 95% CI: 0.234 to 0.435); qualitative NMM was not significantly different from no NMM. Compared with continuous monitoring, the

Table 3 Residual paralysis: quantitative neuromuscular monitoring vs. qualitative neuromuscular monitoring or clinical signs

Ref.	Intervention	Study design	Primary outcome
Mortensen *et al.*[71]	quantitative NMM vs. clinical criteria	RCT	TOF ratio ≤ 0.7 1/10 vs. 11/17
Gatke *et al.*[72]	quantitative NMM vs. clinical criteria	RCT	TOF ratio ≤ 0.8 9/60 vs. 18/60
Murphy *et al.*[73]	quantitative vs. qualitative NMM	RCT	TOF ratio ≤ 0.9 4/89 vs. 15/90
Murphy *et al.*[74]	quantitative vs. qualitative NMM	RCT	TOF ratio ≤ 0.9 3/76 vs. 14/74
Wardhana *et al.*[75]	quantitative NMM vs. clinical criteria with neostigmine reversal	RCT	TOF ratio ≤ 0.9 1/36 vs. 6/36
Domenech *et al.*[76]	quantitative NMM vs. clinical criteria	Retrospective observational study	TOF ratio ≤ 0.9 1/63 vs. 57/177

Risk of bias.

low	intermediate	high	not applicable

isolated application of quantitative NMM at the end of surgery is less reliable to detect residual paralysis.[78] Hence, quantitative NMM should be performed continuously, starting before administration of the neuromuscular blocking agent and, depending of the respective device, calibration, determination of a reference value or identification of supramaximal stimulation may be required. A TOF ratio at least 0.9 is the minimum neuromuscular recovery required before extubation; however, when raw (uncalibrated and nonnormalised) AMG (acceleromyographic) TOF ratios are used, the threshold should be 1.0.[79]

The results emerge from small studies (mostly around 100 patients) and two of them considered a TOF ratio of 0.7 and 0.8 as the threshold to exclude residual paralysis.[71,72] Summarised, we assess the quality of the evidence on this topic as moderate. There is convincing evidence that quantitative NMM compared with qualitative NMM or clinical judgement reduces the risk of residual paralysis consistently and substantially.

To evaluate strategies for the treatment of residual paralysis, studies exploring neuromuscular recovery and POPCs after sugammadex-based and neostigmine-based reversal were examined; a TOF ratio less than 0.9 was considered as residual paralysis.

A Cochrane systematic review reported shorter times to a TOF ratio of at least 0.9 when the NMB in patients with moderate or deep neuromuscular block were antagonised with sugammadex compared with neostigmine (moderate: 2 vs. 12.9 min; deep: 2.9 vs. 48.8 min).[80] Four RCTs reported shorter times to a TOF ratio of 0.9 when shallow or minimal (TOF ratio 0.4 to 0.9) neuromuscular blocks were antagonised with sugammadex compared with neostigmine, and all sugammadex patients recovered to a TOF ratio of at least 0.9 within 5 min.[81–84] This threshold was not attained by all patients within 10, 15 or 30 min after neostigmine 40 to 50 $\mu g\,kg^{-1}$ given at a TOF ratio of 0.2 [79] and 0.1.[82] Given a TOF ratio of 0.5, all neostigmine patients recovered to a TOF ratio of at least 0.9 within 5 min.[84]

Nine RCTs and one retrospective observational study investigated the incidence of residual paralysis after sugammadex-based compared with neostigmine-based reversal (Table 4).[76,83,85–92] It was 2% (14/637 patients) with sugammadex 2 to 4 mg kg^{-1} and increased to 24% (141/584 patients) with neostigmine (30 to 50 $\mu g\,kg^{-1}$), corresponding to an absolute risk reduction of 22%. One prospective observational study and one RCT that investigated the incidence of POPCs after reversal with either neostigmine or sugammadex were considered.[89,92] The first study reported a significant reduction of POPC with sugammadex compared with neostigmine; the second RCT, although underpowered, could not confirm these findings. However, given the multifactorial causes of POPC, large observational studies may be more appropriate to answer this question.[93] A multicentre matched cohort analysis with 2 x 22 856 patients observed a lower incidence of pulmonary complications (3.5 vs. 4.8%), pneumonia (1.3 vs. 2.2%) and respiratory failure (0.8 vs. 1.7%) after sugammadex compared with neostigmine.[94] Similar results were reported in a cohort comprising 7316 patients, in whom the change from neostigmine, as a standard pharmacologic reversal agent, to sugammadex was associated with a reduction of POPC from 6.1 to 4.2%.[95]

There is convincing evidence that residual paralysis and POPC are more frequent after neostigmine-based reversal compared with sugammadex-based reversal, and the better is the neuromuscular recovery, the better is the pulmonary outcome.[96] However, the use of sugammadex is limited to vecuronium or rocuronium-induced neuromuscular blockade, a prerequisite that is not always fulfilled.[1] To increase the likelihood of effective reversal, the conditions that determined the action of neostigmine should be optimised. Ten minutes after 40 $\mu g\,kg^{-1}$ neostigmine was administered at the return of the fourth response of the TOF, 35% of patients still had a TOF ratio less than 0.9; this confirms that effective reversal is not guaranteed with a TOF count of 4 if the fourth response is still very weak.[97] Moreover, increasing the dose will not improve this result, as higher doses have not been reported as more effective. Reversal time and prereversal recovery are the only remaining variables to improve the action of neostigmine; the less the prereversal recovery, the more the time required to attain a TOF ratio of at least 0.9,[98–100] Table 5. Baurain *et al.*[98] observed the best recovery of the TOF ratio 15 min after

Table 4 Residual paralysis: neostigmine vs. sugammadex

Ref.	Intervention	Study design	TOF-ratio < 0.9
Blobner *et al.*[85]	Sugammadex 2.0 mg kg^{-1} ($n = 49$) vs. neostigmine 50 μg kg^{-1} and glycopyrrolate 10 μg kg^{-1} ($n = 49$)	Phase 3A, European, 13 centre, randomised, parallel-group, comparative, active-controlled, safety assessor-blinded trial	Neostigmine: 3/48 Sugammadex: 0/48
Brueckmann *et al.*[88]	sugammadex 2 or 4 mg kg^{-1} ($n = 76$) vs. neostigmine + glycopyrrolate ($n = 78$) (dosing per usual clinical practice; maximum dose 5 mg)	Randomised, controlled study	Neostigmine: 33/76 Sugammadex: 0/74
Khuenl-Brady *et al.*[86]	Sugammadex 2 mg kg^{-1} ($n = 51$) vs. neostigmine 50 μg kg^{-1} + glycopyrrolate 10 μg kg^{-1} ($n = 49$)	Multicentre, randomised, active control, safety assessor-blinded trial	Neostigmine: 8/45 Sugammadex: 0/48
Wu *et al.*[87]	Sugammadex 2 mg kg^{-1} (Chinese $n = 126$, white $n = 29$) vs. neostigmine 50 μg kg^{-1} and atropine 10 to 20 μg kg^{-1} (Chinese $n = 121$, white $n = 32$)	Randomised, parallel-group, multicentre, safety assessor-blinded study	Neostigmine: 0/141 Sugammadex: 0/148
Martinez-Ubierto *et al.*[89]	Sugammadex 2 to 4 mg kg^{-1} vs. Neostigmine 0.03 to 0.05 mg kg^{-1}	Prospective observational study	Neostigmine: 26/92 Sugammadex: 1/87
Nemes *et al.*[90]	Sugammadex 2.0 mg kg^{-1} ($n = 27$) vs. 0.05 mg kg^{-1} neostigmine + 0.015 mg kg^{-1} atropine ($n = 26$) vs. Placebo, 15 ml saline ($n = 22$)	Single-centre, partially randomised, placebo-controlled, double-blind, four-group parallel-arm study.	Neostigmine: 4/26 Sugammadex: 1/27
Aszatalos *et al.*[83]	Sugammadex 2 mg kg^{-1} ($n = 13$) vs. Sugammadex 1 mg kg^{-1} ($n = 13$) vs. Sugammadex 0.5 mg kg^{-1} ($n = 13$) vs. Neostigmine 0.05 mg kg^{-1} ($n = 13$) vs. Placebo ($n = 13$)	Single-centre, randomised, controlled, five parallel-arm superiority trial	Neostigmine: 3/13 Sugammadex: 0/13
Domenech[76]	Sugammadex 3.5 mg kg^{-1} vs. Neostigmine 0.03 mg kg^{-1}	Retrospective study, single-centre, tertiary hospital	Neostigmine: 2/14 Sugammadex: 3/61
Togioka *et al.*[92]	Sugammadex 2 mg kg^{-1} ($n = 98$) vs. Neostimgine 0.07 mg kg^{-1} + Glycopyrrolate ($n = 99$)	Open-label, assessor-blinded, randomised controlled parallel-group trial	Neostigmine: 46/93 Sugammadex: 9/94
Lee *et al.*[91]	Sugammadex 2 or 4 mg/kg ($n = 36$) vs. Neostigmine 0.02; 0.04 or 0.05 mg kg^{-1} + Glycopyrrolate ($n = 37$)	Prospective, randomised controlled study	Neostigmine: 16/36 Sugammadex: 0/37

Risk of bias.

low	intermediate	high	not applicable

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40 μg kg^{-1} neostigmine given at a prereversal twitch height of 25 to 50%. However, reversal times considerably longer than 30 min must be expected in some patients when neostigmine is given at lower degrees of spontaneous recovery. Thus, if reversal with neostigmine (40 μg kg^{-1}) is desired within 10 to 15 min of administration, we recommend advanced spontaneous recovery (i.e. TOF ratio >0.2) at the time of neostigmine administration. However, accepting a longer interval (i.e. 15 to 30 min) between administration of neostigmine and adequate neuromuscular recovery, neostigmine (40 μg kg^{-1}) can be given at the reappearance of TOF count of 4. In both scenarios, quantitative NMM should be continued until a TOF ratio more than 0.9 (TOF ratio 1.0 when using AMG monitoring) has been attained. Qualitative NMM with a PNS, however, may overestimate neostigmine-induced recovery, as fade following TOF-stimulation is no longer detectable for TOF-ratios more than 0.4.[81–83,97] For that reason, PNS are not suitable in this context.

Final remarks and discussion

We developed these first guidelines on the peri-operative management of neuromuscular blockade for the European Society of Anesthesiology and Intensive Care. The guidelines are intended to provide evidence-based recommendations to improve patient safety. To facilitate its implementation in current clinical practice, the guidance has been intentionally limited to three clinically relevant core issues: significance of neuromuscular blocking agents for tracheal intubation, contribution of neuromuscular blocking agents to improve surgical conditions and significance of NMM and pharmacological reversal to reduce residual paralysis and POPCs.

Table 5 Prereversal train-of-four and neostigmine-induced recovery

Prereversal revovery	Neostigmine dose	Neuromuscular outcome	Ref
TOF-ratio 0.6	30 μg kg^{-1}	TOF-ratio > 0.9 in all patients in < 10 min	99
TOF-ratio 0.5	34 μg kg^{-1}	TOF-ratio >0.9 in all patients in <5 min	84
TOF-ratio 0.4	30 μg kg^{-1}	TOF-ratio >0.9 in all patients in <10 min	99
TOF-ratio 0.2	10–70 μg kg^{-1}	Impossible to have a TOF-ratio >0.9 in all patients in <10 min, independent of neostigmine dose	81
TOF-count 4 and TOF-ratio 0.1	50 μg kg^{-1}	15 min after neostigmine still 25% of patients with TOF-ratio <0.9	82
TOF-count 4 and TOF-ratio 0.1	50 μg kg^{-1}	30 min after neostigmine 3/13 patients with TOF-ratio <0.9	83
TOF-count 4	40 μg kg^{-1}	10 min after neostigmine still 35% of patients with TOF-ratio <0.9	97
TOF-count 4	70 μg kg^{-1}	20 min after neostigmine still 25% of patients with TOF-ratio <0.9	100
TOF-count 4	70 μg kg^{-1}	10 min after neostigmine still 75% of patients with TOF-ratio <0.9	100

The main conclusion of the authors is that the decision making for any neuromuscular reversal strategy, that is neostigmine-based reversal, sugammadex-based reversal or spontaneous reversal, should be well founded on reliable quantitative NMM. The limitation of qualitative NMM with a PNS to detect a TOF ratio of at least 0.9 should be recognised. There is no way to confirm these levels of recovery by either tactile evaluation of TOF or DBS (double burst stimulation), as no fade can be detected when the TOF ratio exceeds 0.4 and 0.6, respectively.[101,102] Hence, detectable fade after TOF or DBS stimulation is a clear sign of inadequate neuromuscular recovery, but lack of fade does not exclude residual paralysis. Similarly, the use of 100-Hz, 5-s tetanus did not reliably exclude residual paralysis. It has a poor specificity, as about half of the patients without any degree of residual paralysis will exhibit manually detectable fade. In addition, one of four patients still had residual paralysis despite the absence of fade after a 100-Hz, 5-s stimulation.[78] However, quantitative NMM is not a magic bullet either, providing reliable results automatically. Most devices need calibration or a baseline value to be determined before relaxation otherwise their performance is significantly reduced.[78] It is not unusual in current clinical practice that quantitative NMM is applied only at the end of the surgical procedure, particularly if the same device is shared with several operating theatres. In this setting, however, even quantitative (uncalibrated, nonnormalised) NMM is insufficient to exclude residual paralysis reliably.[78] As a consequence, the availability of quantitative NMM in each single operating theatre is a prerequisite for its appropriate use.

Recently, Schaefer *et al.*[103] examined the association between succinylcholine and POPC; they observed that of 244 850 adult patients, 5.4% experienced POPC; the higher the dose of succinylcholine, the higher the risk of POPC.[103] This strongly implicates residual paralysis as an underlying mechanism. At first glance, this may be surprising, as generations of anaesthesiologists used succinylcholine for its unique properties of rapid onset and short duration. However, its pharmacodynamic profile is characterised by high inter-individual variability and data from the Danish Cholinesterase Research Unit identified a deficit in plasma butyrylcholinesterase activity as a major risk factor for unexpected residual paralysis, respiratory complications, and awareness during emergence after succinylcholine.[104,105] Moreover, lack of NMM increases the risk of these adverse events significantly.[106] Consequently, neuromuscular transmission should be monitored quantitatively regardless of type of neuromuscular-blocking drug is used, even if only succinylcholine has been administered.[107]

Our findings confirmed that residual paralysis is more common after neostigmine-based reversal than after sugammadex, as it occurred in 2% of patients after sugammadex but in 24% when neostigmine was used. This corresponds to an absolute risk reduction of 22% and a NNT (number needed to treat) of 4.5. In other words, a reversal strategy based on sugammadex instead of neostigmine may prevent residual paralysis in one out of four or five patients; however, this is not the sole benefit, as convincing evidence also suggests a significant reduction of the incidence of POPC. Concerning the risk associated with both reversal strategies, a recent Cochrane review reported a better safety profile for sugammadex (risk ratio, 0.6; 95% CI, 0.49 to 0.74; 28 studies, $n = 2298$) compared with neostigmine.[80] A few cases of anaphylaxis after sugammadex are reported. Recently, a retrospective multicentre observational study from Japan including 49 532 patients reported six cases of anaphylaxis attributable to sugammadex, whilst the 6th National Audit Project (NAP6) from the Royal College of Anaesthetists found a 10-fold lower incidence (one out of 64 121 patient).[108,109] It is certainly difficult to ascertain the true incidence of any rare adverse event; however, the risk of anaphylaxis alone should not be an over-riding factor in the choice of reversal agent.[110]

The implementation of these guidelines in current clinical practice is crucial to meaningfully improve patient care and outcomes. Hence, the task force proposes a bundle of measures to facilitate, accompany and monitor the implementation process. Amongst these, the following:

(1) Active knowledge sharing: in addition to display on the ESAIC website and publication in the *European Journal of Anaesthesiology*, the full text will be sent by ESAIC to National Anaesthesiology Societies to share the full text with their respective members.
(2) Implementation tools at departmental level, for example a checklist that facilitates tracking a 'before-and-after approach' to monitor guideline adoption.
(3) E-learning tools e.g. short videos, Q/A for specific details and decision algorithms for quantitative monitoring of residual paralysis and use of reversal agents (including timing and dosing)
(4) An internet-based reporting site intended to identify the main obstacles to implementation

Limitations and further research

(1) Paediatric patients may also be at risk of residual neuromuscular block, but the current guidelines do not address monitoring in this patient group. This, however, should be undertaken in a specific guideline.
(2) This guideline focuses on the peri-operative management of neuromuscular blockade; management and monitoring of neuromuscular block in ICU patients are not considered.
(3) This guideline did not examine monitoring sites other than the ulnar nerve/adductor pollicis muscle. Indeed, the nerve-muscle unit ulnar nerve/adductor pollicis muscle is most frequently used for NMM

because it is easily accessible intra-operatively and the risk of direct muscle stimulation can by minimised. However, monitoring strategies for clinical situations when the ulnar nerve/adductor pollicis is not accessible need to be validated.

(4) Studies how to manage emergency re-intubation soon after sugammadex reversal are missing.

(5) Additional studies to determine clinically relevant patient outcomes for TOF ratio cutoffs at least 0.9 and tools to assess stability and robustness of TOF ratios at least 0.9 are needed.

(6) Studies comparing sugammadex and neostigmine for reversal of minimal neuromuscular block, including appropriate dosing of sugammadex in this context, are needed.

(7) Further studies are needed to better understand clinical situations wherein a deep neuromuscular blockade may be beneficial.

In conclusion, there is convincing evidence that residual paralysis and relaxation-associated pulmonary complications are less common after sugammadex-based pharmacological reversal than after neostigmine. Moreover, reliable quantitative NMM is the principal prerequisite of any appropriate strategy for the peri-operative neuromuscular management, whether that is spontaneous recovery, sugammadex-based or neostigmine-based recovery.

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