Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study

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Summary

Background Results from retrospective studies suggest that use of neuromuscular blocking agents during general anaesthesia might be linked to postoperative pulmonary complications. We therefore aimed to assess whether the use of neuromuscular blocking agents is associated with postoperative pulmonary complications.

Methods We did a multicentre, prospective observational cohort study. Patients were recruited from 211 hospitals in 28 European countries. We included patients (aged ≥18 years) who received general anaesthesia for any in-hospital procedure except cardiac surgery. Patient characteristics, surgical and anaesthetic details, and chart review at discharge were prospectively collected over 2 weeks. Additionally, each patient underwent postoperative physical examination within 3 days of surgery to check for adverse pulmonary events. The study outcome was the incidence of postoperative pulmonary complications from the end of surgery up to postoperative day 28. Logistic regression analyses were adjusted for surgical factors and patients' preoperative physical status, providing adjusted odds ratios (OR_{adj}) and adjusted absolute risk reduction (ARR_{adj}). This study is registered with ClinicalTrials.gov, number NCT01865513.

Findings Between June 16, 2014, and April 29, 2015, data from 22 803 patients were collected. The use of neuromuscular blocking agents was associated with an increased incidence of postoperative pulmonary complications in patients who had undergone general anaesthesia (1658 [7·6%] of 21 694); OR_{adj} 1·86, 95% CI 1·53–2·26; ARR_{adj} –4·4%, 95% CI –5·5 to –3·2). Only 2·3% of high-risk surgical patients and those with adverse respiratory profiles were anaesthetised without neuromuscular blocking agents. The use of neuromuscular monitoring (OR_{adj} 1·31, 95% CI 1·15–1·49; ARR_{adj} –2·6%, 95% CI –3·9 to –1·4) and the administration of reversal agents (1·23, 1·07–1·41; –1·9%, –3·2 to –0·7) were not associated with a decreased risk of postoperative pulmonary complications. Neither the choice of sugammadex instead of neostigmine for reversal (OR_{adj} 1·03, 95% CI 0·85–1·25; ARR_{adj} –0·3%, 95% CI –2·4 to 1·5) nor extubation at a train-of-four ratio of 0·9 or more (1·03, 0·82–1·31; –0·4%, –3·5 to 2·2) was associated with better pulmonary outcomes.

Interpretation We showed that the use of neuromuscular blocking drugs in general anaesthesia is associated with an increased risk of postoperative pulmonary complications. Anaesthetists must balance the potential benefits of neuromuscular blockade against the increased risk of postoperative pulmonary complications.

Funding European Society of Anaesthesiology.

Introduction

An increasing proportion of the global population receives anaesthesia every year. Most anaesthetic procedures include intraoperative administration of neuromuscular blocking agents to produce muscle paralysis. Although this class of compounds improves surgical conditions[1] and reduces intraoperative adverse events,[2] there is a growing body of evidence that suggests the use of neuromuscular blocking agents could adversely affect respiratory outcomes.[3–5] Berg and colleagues[6] first suggested that incomplete recovery from muscle paralysis might have a causal link with postoperative pulmonary complications.

Therefore, measures have been proposed to avoid residual neuromuscular block postoperatively, including the use of neuromuscular monitoring,[7] administration of reversal agents to antagonise residual neuromuscular block (eg, neostigmine),[8] and even avoidance of neuromuscular blocking agents.[9] These measures alone or in combination[10] have been shown to reduce the incidence of residual neuromuscular block in the immediate postoperative period.[11,12] However, there is no evidence that any of these measures improves postoperative respiratory outcomes.[3,4]

We therefore aimed to assess the hypothesis that the use of neuromuscular blocking agents, neuromuscular monitoring, or reversal agents modifies the risk of postoperative pulmonary complications.[13] Because postoperative pulmonary complications are known to be affected by many surgical factors and the patient's preoperative condition,[14–16] we attempted to control for their confounding influence on postoperative pulmonary complications by including this information in our analyses.

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See Comment page 102

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Research in context

Evidence before this study

Postoperative pulmonary complications are a substantial risk of surgery and anaesthesia, which account for a considerable increase in morbidity and mortality in the perioperative period, and lead to prolonged hospital stays and increasing health-care costs. Large retrospective studies in the USA have found that neuromuscular blocking agents used during anaesthesia contribute to the risk of postoperative pulmonary complications. A known risk factor for postoperative pulmonary complications is residual neuromuscular block after the end of anaesthesia. Therefore, the use of neuromuscular monitoring and reversal agents are recommended to avoid residual neuromuscular block. We searched PubMed for the first time when designing the study in Sept 10, 2014, and the last time on Jan 23, 2018. We used search terms alone and in combination, such as "residual neuromuscular block", "muscle relaxants", "post-operative", "pulmonary complications", "critical respiratory events", "aspiration", "residual paralysis", "residual curarization", "sugammadex", "neostigmine", and "neuromuscular monitoring". We did not use any date or language restrictions, but we restricted the search to human studies. We also screened the webpages of the major anaesthesia societies to look for guidelines and searched the references of relevant review articles.

Added value of this study

POPULAR is the first multicentre cohort study to provide prospective data for postoperative pulmonary complications and the use and management of neuromuscular blocking agents in Europe. We included the known risk factors for postoperative pulmonary complications as confounding variables in the statistical model, and with the help of further sensitivity analyses POPULAR adds to the debate on the use and management of neuromuscular blocking agents. These findings show the increased risk of postoperative pulmonary complications from neuromuscular blocking agents, which especially affects patients who have no or only a few other risk factors for postoperative pulmonary complications; that neuromuscular monitoring and reversal agents do not reduce the risk of postoperative pulmonary complications; and that use of neuromuscular blocking agents has less effect on the risk of postoperative pulmonary complications than the type and duration of surgery, the patient's preoperative pulmonary function, or their American Society of Anesthesiology categorisation.

Implications of all the available evidence

The results from POPULAR added to the evidence from previous studies allowing us to recommend that patients with a low risk of postoperative pulmonary complications should be anaesthetised without the use of muscle paralysis whenever possible. Our findings regarding neuromuscular monitoring and reversal agents are intriguing because they contradict the expectation that their use can reduce the risk for postoperative pulmonary complications.

Methods

Study design and participants

We did a multicentre, prospective observational cohort study (POPULAR). Participants were recruited from 211 hospitals in 28 European countries. Participating hospitals chose a recruitment period of 14 consecutive days. Hospitals with more than 50 patients undergoing anaesthesia per week were allowed to reduce their sample size by a random selection process (appendix). Study centres needed approval from their local ethics committee or institutional review board to partake in the study. 123 of 211 centres were exempt from obtaining written informed consent based on the recommendation of the local ethics committee, and 88 centres had to obtain consent from every participating patient.

See Online for appendix

Patients (aged ≥18 years) receiving general anaesthesia for any in-hospital procedure except cardiac surgery were included. Primary exclusion criteria (ie, before recruitment) were surgery at a remote location (eg, outside of the operating theatre), scheduled hospital discharge within 12 h after surgery, preoperatively intubated trachea, preoperatively scheduled admission to an intensive care unit postoperatively, and surgery or anaesthesia (or both) within the last 7 days or scheduled within the next 7 days. Secondary exclusion criteria (ie, after recruitment and enrolment) were tracheal extubation more than 6 h after the end of surgery and unplanned hospital discharge within 12 h after surgery.

Procedures

When a neuromuscular blocking agent is used for tracheal intubation the dose is selected in terms of the effective dose that would be needed to produce 95% neuromuscular block for that drug (ED_{95}). It is usual to give two to three times this dose to ensure satisfactory intubating conditions in all patients. The depth of neuromuscular block required to provide these conditions can be assessed by neuromuscular monitoring. The train-of-four twitch response is commonly used, which involves applying four stimuli of 2 Hz each with a 10 s interval between trains to a peripheral nerve and recording the response in the innervated muscle. The recovery of these four twitches is used to assess the adequacy of recovery before tracheal extubation. The ratio of the fourth to the first twitch—ie, the train-of-four ratio—should be greater than 0·9 before tracheal extubation and wakening the patient from anaesthesia.[17] If the train-of-four ratio is only assessed by the clinician by feel or sight, this is referred to as qualitative monitoring. If a recording is made of the train-of-four ratio then it is known as quantitative monitoring.

For analyses of neuromuscular management, we defined seven key factors: use of neuromuscular blocking

agent, expected duration of neuromuscular blocking agents (the appendix provides details about the calculation of the dosing technique for neuromuscular blocking agents), use of neuromuscular monitoring, technique of neuromuscular monitoring (quantitative or qualitative), adherence to the recommended train-of-four ratio of 0·9 or more at extubation, use of any reversal agent, and type of reversal agent (neostigmine and sugammadex). Because these seven key factors do not apply to every patient, we constructed five subcohorts: patients receiving general anaesthesia, patients receiving neuromuscular blocking agents, patients with neuromuscular monitoring, patients with quantitative neuromuscular monitoring, and patients receiving a reversal agent.

Patient characteristics, medical history, surgical and anaesthetic details (including management of neuromuscular function), postoperative physical examination, and chart review at discharge were collected on paper-based case report forms (appendix). Anonymised data were entered into a secure online electronic data capture system (OpenClinica, version 3.1).

The study's national coordinators (one national coordinator per country) assisted local coordinators to ensure that the study was done according to the International Conference on Harmonisation Good Clinical Practice guidelines. Before the start of the study, all the national coordinators participated in two telephone conferences to clarify questions about data collection that had been raised by local study staff during review of the protocol. Throughout the study, the investigators received questions about the study from study staff by email or via a central study telephone and EK responded. The electronic case report forms only allowed data entry in given ranges. During three data cleaning rounds, we screened for incorrect data, outliers, or missing information and contacted the centres to correct invalid values.

Outcomes

The study outcome was the incidence of postoperative pulmonary complications from the end of surgery up to postoperative day 28. A postoperative pulmonary complication was assumed if at least one postoperative pulmonary event was observed on physical examination done during the anaesthetist's postoperative round or on review of the patient's chart after they had been discharged from hospital, according to the PERISCOPE study.[14,18]

Statistical analysis

Sample size was estimated using the rule of ten.[19]

$$\text{Sample size} = \frac{10 \times \text{number of factors and cofactors}}{\text{Incidence of postoperative pulmonary complications}}$$

We used data from previous studies to inform our sample size calculation. In PERISCOPE the incidence of postoperative pulmonary complications was 5%,[14,18] and McAlister and colleagues reported an incidence of 2·8%.[15] On the basis of a 2% incidence of pulmonary complications (equal to the lower limit of the 95% CI in the PERISCOPE study) and up to 43 factors, we estimated a sample size of 21000 patients would be necessary for the complete cohort in our study.

Continuous variables are shown as means and SD, and categorical variables as absolute numbers and percentages. Data were analysed with logistic regression, which provides confounder-adjusted estimates of odds ratios (OR_{adj}) and absolute risk reduction (ARR_{adj}) with their 95% CIs. Each key factor was included in the model irrespective of its significance. Cofactors were included if they affected the outcome variable univariately ($p<0·05$). Interaction terms between a key factor and the top six most influencing cofactors were included if they affected the outcome variable ($p<0·05$). If two factors were correlated ($r^2 \geq 0·5$), one of the factors was excluded on the basis of physiological considerations. Continuous factors were transformed into nominal variables because the assumption of linearity was not fulfilled in most of our factors. If available, we used published or commonly accepted categories (eg, body-mass index [BMI]). The key factor (ie, expected duration of neuromuscular blocking agents) and the cofactor (ie, expected duration of last neuromuscular blocking agent dose) were categorised using quintiles. To further reduce the number of parameters in the statistical models, we dichotomised all factors with more than two categories by χ^2 optimisation based on the outcome.

Because the missing information about postoperative pulmonary complications and the key factors was below 5%, the respective patients were excluded from the study analyses. Missing information about the cofactors is categorised as missing, and combined with another category using χ^2 optimisation.

Prespecified sensitivity analyses were also done. The time that passed before the diagnosis of a postoperative pulmonary complication was recorded and addressed using a Cox regression model. Results are presented as adjusted hazard ratios and illustrated by Kaplan-Meier curves. The propensity score was calculated for each key factor on the basis of all other factors to build ten deciles of patients with increasing propensity scores for the respective key factor. In each decile, the respective factors were tested against postoperative pulmonary complications. These results are gathered by random effects meta-analysis and presented as forest plots. In addition, a one-to-one matching ratio for the propensity score was used to build two identically sized groups.[20] The quality of this matching approach was characterised by the calliper, which is the maximum tolerated difference between the propensity score of matched pairs (nearest neighbours). Matching at a calliper of 0·001 results in a balanced covariate distribution—ie, no factor differs significantly in the resulting groups ($p>0·1$).

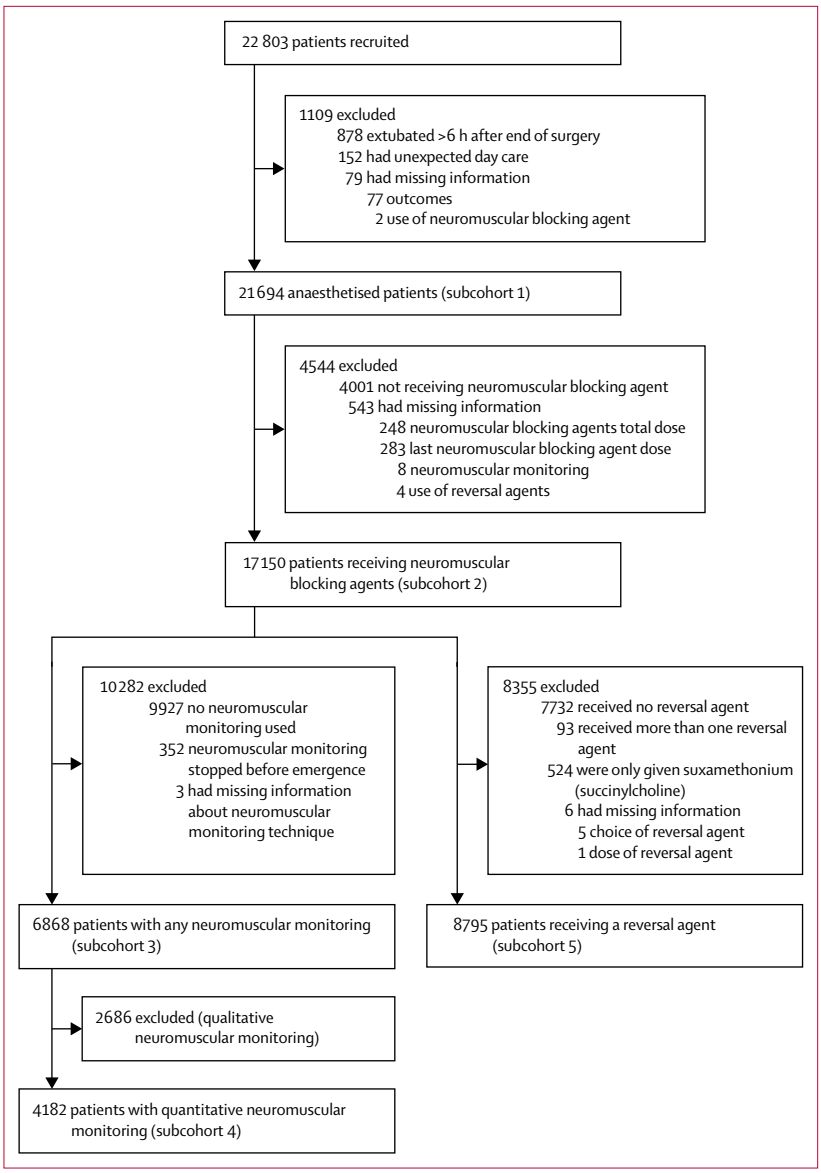

Figure 1: **Profile of study analysis**

Classification trees were done as a data mining tool to describe subsets of patients with a homogeneous pulmonary outcome. Starting with all patients in the respective subcohort, sets of patients were split into two subsets step-by-step. All cofactors could serve as the splitting variable. The optimal splitting variable was identified using the Gini impurity. Splitting is optimal if each of the resulting subset of patients is homogeneous for the incidence of postoperative pulmonary complications. To achieve meaningful subsets of patients, we terminated splitting at a maximum depth of five steps or earlier if splitting had resulted in a subset of less than 500 cases. In the resulting terminal subsets (terminal nodes), the effect of any available key factor on the incidence of postoperative pulmonary complication was univariately analysed. To address the relevant interactions within a subcohort, we combined the ORs of all terminal nodes by random effects meta-analysis.

We analysed all data with SPSS (version 23), which included an embedded R routine for propensity score testing.[20,21] This study is registered with ClinicalTrials.gov, number NCT01865513.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 16, 2014, and April 29, 2015, data from 22 803 patients were collected. Figure 1 shows reasons for exclusion from the study after recruitment and the five subcohorts. Table 1 presents frequency of outcomes and all the factors for the five subcohorts. A description of respiratory symptoms and the diagnosis of postoperative pulmonary complications is given in table 2.

The incidence of postoperative pulmonary complications in patients who had undergone general anaesthesia was 7·6% (1658 of 21 694; table 1), with an increased risk when neuromuscular blocking agents were used (table 3; ARR_{adj} –4·4%, 95% CI –5·5 to –3·2). Major risk factors for postoperative pulmonary complications were intrathoracic or open upper abdominal surgery (OR_{adj} 3·53, 95% CI 3·09 to 4·03), duration of surgery lasting more than 2 h (2·34, 2·09 to 2·63), preoperative peripheral blood oxygen saturation (SpO_2) of 94% or less (2·35, 2·05 to 2·70), emergency surgery (2·24, 1·96 to 2·56), American Society of Anesthesiology (ASA) categorisation of 3 or more (2·06, 1·81 to 2·35), and an age older than 60 years (1·69, 1·48 to 1·94; appendix). The increased risk of postoperative pulmonary complications with the use of neuromuscular blocking agents was confirmed by all sensitivity analyses, including propensity score methods (appendix). A single dose of any neuromuscular blocking agent for tracheal intubation (n=9043) was associated with an increased risk of postoperative pulmonary complications compared with no neuromuscular blocking agent (OR 1·53, 95% CI 1·20 to 1·90). No significant effect size modification was observed between the use of neuromuscular blocking agents and the six most common influencing cofactors (age, BMI, ASA classification, preoperative SpO_2, type of surgery, and duration of surgery (appendix).

Subgroups (deciles) with increased likelihood of receiving neuromuscular blocking agents based on the respective propensity score had an increased risk of postoperative pulmonary complications irrespective of the patients' treatment with neuromuscular blocking

	Anaesthetised patients (n=21 694)	Patients receiving NMBAs (n=17 150)	Patients with any NMM (n=6868)	Patients with quantitative NMM (n=4182)	Patients receiving a reversal agent (n=8795)
Outcomes*					
Any postoperative pulmonary complication	1658 (7·6%)	1441 (8·4%)	733 (10·7%)	441 (10·5%)	780 (8·9%)
Intermediate or severe postoperative pulmonary complication	1028 (4·7%)	884 (5·2%)	428 (6·2%)	245 (5·9%)	483 (5·5%)
Factors in neuromuscular management*					
NMBA used	17 693 (81·6%)	All	All	All	All
Any combination of NMBAs	NA	2070 (12·1%)	803 (11·7%)	422 (10·1%)	1290 (14·7%)
Expected duration of NMBA	NA	119 (79)	122 (77)	119 (79)	132 (74)
<68 min	NA	3448 (20·1%)	1335 (19·4%)	912 (21·8%)	997 (11·3%)
68 to <91 min	NA	3325 (19·4%)	1349 (19·6%)	849 (20·3%)	1516 (17·2%)
91 to <115 min	NA	3462 (20·2%)	1342 (19·5%)	768 (18·4%)	1904 (21·6%)
115 to <159 min	NA	3462 (20·2%)	1381 (20·1%)	804 (19·2%)	2197 (25·0%)
≥159 min	NA	3453 (20·1%)	1461 (21·3%)	849 (20·3%)	2181 (24·8%)
Expected duration of last NMBA dose	NA	59 (42)	55 (41)	55 (42)	55 (41)
No incremental NMBA	NA	8845 (51·6%)	3178 (46·3%)	2034 (48·6%)	3422 (38·9%)
<19 min	NA	2079 (12·1%)	1029 (15·0%)	647 (15·5%)	1443 (16·4%)
19 to <25 min	NA	2079 (12·1%)	900 (13·1%)	505 (12·1%)	1411 (16·0%)
25 to <39 min	NA	2101 (12·3%)	933 (13·6%)	537 (12·8%)	1358 (15·4%)
≥39 min	NA	2046 (11·9%)	828 (12·1%)	459 (11·0%)	1161 (13·2%)
NMM used	NA	7223 (42·1%)	All	All	4312 (49·0%)
Quantitative NMM during emergence	NA	NA	4182 (60·9%)	All	NA
Train-of-four ratio ≥0·90 at extubation	NA	NA	NA	2839 (67·9%)	NA
Reversal agent given	NA	8927 (52·1%)	4259 (62·0%)	2308 (55·2%)	All
Sugammadex but not neostigmine	NA	NA	NA	NA	1990 (22·6%)
Cofactors†					
Age (years)	56 (18)	55 (17)	56 (17)	56 (17)	55 (17)
≤40	4432 (20·4%)	3549 (20·7%)	1345 (19·6%)	790 (18·9%)	1789 (20·3%)
>40 to 60	7762 (35·8%)	6263 (36·5%)	2486 (36·2%)	1543 (36·9%)	3227 (36·7%)
>60 to 80	8050 (37·1%)	6349 (37·0%)	2607 (38·0%)	1613 (38·6%)	3272 (37·2%)
>80	1450 (6·7%)	989 (5·8%)	430 (6·3%)	236 (5·6%)	507 (5·8%)
Women	11 655 (53·7%)	9288 (54·2%)	3658 (53·3%)	2210 (52·8%)	4791 (54·5%)
Body-mass index (kg/m^2)	27·2 (6·1)	27·4 (6·2)	27·5 (6·6)	27·1 (6·4)	27·7 (6·6)
Underweight (≤17·5)	481 (2·2%)	375 (2·2%)	144 (2·1%)	88 (2·1%)	190 (2·2%)
Normal (17·5 to <25·0)	7973 (36·8%)	6320 (36·9%)	2523 (36·7%)	1612 (38·5%)	3121 (35·5%)
Overweight (25·0 to <30·0)	7556 (34·8%)	5979 (34·9%)	2380 (34·7%)	1498 (35·8%)	3037 (34·5%)
Obese (≥30·0)	5373 (24·8%)	4418 (25·8%)	1791 (26·1%)	975 (23·3%)	2415 (27·5%)
Missing	311 (1·4%)	58 (0·3%)	30 (0·4%)	9 (0·2%)	32 (0·4%)
ASA physical categorisation					
1	5050 (23·3%)	3855 (22·5%)	1578 (23·0%)	960 (23·0%)	1918 (21·8%)
2	10 893 (50·2%)	8701 (50·7%)	3531 (51·4%)	2192 (52·4%)	4601 (52·3%)
3	5297 (24·4%)	4251 (24·8%)	1655 (24·1%)	975 (23·3%)	2104 (23·9%)
4	425 (2·0%)	329 (1·9%)	99 (1·4%)	51 (1·2%)	164 (1·9%)
5	10 (<0·1%)	9 (0·1%)	3 (<0·1%)	3 (0·1%)	7 (0·1%)
History of heart failure (missing n=10)					
NYHA 0	19 147 (88·3%)	15 058 (87·8%)	6075 (88·5%)	3617 (86·5%)	7947 (90·4%)
NYHA 1	1174 (5·4%)	958 (5·6%)	374 (5·4%)	275 (6·6%)	416 (4·7%)
NYHA 2	962 (4·4%)	803 (4·7%)	290 (4·2%)	213 (5·1%)	311 (3·5%)
NYHA 3	368 (1·7%)	299 (1·7%)	117 (1·7%)	72 (1·7%)	107 (1·2%)
NYHA 4	33 (0·2%)	26 (0·2%)	9 (0·1%)	5 (0·1%)	12 (0·1%)
History of coronary artery disease (missing n=10)	2195 (10·1%)	1710 (10·0%)	644 (9·4%)	362 (8·7%)	764 (8·7%)

(Table 1 continues on next page)

	Anaesthetised patients (n=21 694)	Patients receiving NMBAs (n=17 150)	Patients with any NMM (n=6868)	Patients with quantitative NMM (n=4182)	Patients receiving a reversal agent (n=8795)
(Continued from previous page)					
History of neurological disease (missing n=4)	2595 (12·0%)	2056 (12·0%)	800 (11·6%)	487 (11·6%)	1068 (12·1%)
History of diabetes mellitus (missing n=5)	2595 (12·0%)	2056 (12·0%)	800 (11·6%)	487 (11·6%)	1068 (12·1%)
History of liver disease (missing n=6)	986 (4·5%)	844 (4·9%)	312 (4·5%)	192 (4·6%)	468 (5·3%)
Categorised creatinine clearance					
Creatinine not assessed	4016 (18·5%)	2815 (16·4%)	993 (14·5%)	613 (14·7%)	1168 (13·3%)
≥90 mL/min	10 024 (46·2%)	8333 (48·6%)	3325 (48·4%)	2022 (48·4%)	4488 (51·0%)
60 to <90 mL/min	4840 (22·3%)	3893 (22·7%)	1601 (23·3%)	971 (23·2%)	2041 (23·2%)
30 to <60 mL/min	2229 (10·3%)	1689 (9·8%)	729 (10·6%)	441 (10·5%)	900 (10·2%)
15 to <30 mL/min	307 (1·4%)	210 (1·2%)	106 (1·5%)	57 (1·4%)	106 (1·2%)
<15 mL/min	278 (1·3%)	210 (1·2%)	114 (1·7%)	78 (1·9%)	92 (1·0%)
History of COPD (missing n=5)	1429 (6·6%)	1165 (6·8%)	467 (6·8%)	263 (6·3%)	587 (6·7%)
History of asthma (missing n=4)	1497 (6·9%)	1136 (6·6%)	492 (7·2%)	239 (5·7%)	623 (7·1%)
History of sleep apnoea (missing n=5)	731 (3·4%)	610 (3·6%)	267 (3·9%)	159 (3·8%)	315 (3·6%)
Recent respiratory infection (missing n=10)	679 (3·1%)	581 (3·4%)	231 (3·4%)	148 (3·5%)	329 (3·7%)
Smoking (missing n=21)	3821 (17·6%)	3134 (18·3%)	1233 (18·0%)	748 (17·9%)	1621 (18·4%)
Preoperative SpO_2	97 (2)	97 (2)	97 (2)	97 (2)	97 (2)
≤94%	2213 (10·2%)	1779 (10·4%)	811 (11·8%)	555 (13·3%)	830 (9·4%)
≥95%	19 481 (89·8%)	15 371 (89·6%)	6057 (88·2%)	3627 (86·7%)	7965 (90·6%)
Emergency surgery (missing n=5)	3475 (16·0%)	2576 (15·0%)	1267 (18·4%)	618 (14·8%)	1475 (16·8%)
Surgical procedure					
Intrathoracic closed	330 (1·5%)	309 (1·8%)	131 (1·9%)	74 (1·8%)	179 (2·0%)
Intrathoracic open	463 (2·1%)	420 (2·4%)	108 (1·6%)	65 (1·6%)	170 (1·9%)
Upper abdominal open	1350 (6·2%)	1282 (7·5%)	545 (7·9%)	338 (8·1%)	818 (9·3%)
Upper abdominal closed	2109 (9·7%)	2024 (11·8%)	920 (13·4%)	563 (13·5%)	1380 (15·7%)
Lower abdominal closed	2392 (11·0%)	2085 (12·2%)	975 (14·2%)	540 (12·9%)	1276 (14·5%)
Lower abdominal open	2581 (11·9%)	2382 (13·9%)	1044 (15·2%)	597 (14·3%)	1465 (16·7%)
Head and neck	3717 (17·1%)	3272 (19·1%)	1124 (16·4%)	747 (17·9%)	1267 (14·4%)
Craniotomy	373 (1·7%)	330 (1·9%)	130 (1·9%)	113 (2·7%)	82 (0·9%)
Peripheral or other procedures	8379 (38·6%)	5046 (29·4%)	1891 (27·5%)	1145 (27·4%)	2158 (24·5%)
Duration of surgery	102 (79)	111 (81)	114 (81)	114 (81)	104 (77)
≤1 h	7771 (35·8%)	5253 (30·6%)	1961 (28·6%)	1188 (28·4%)	2929 (33·3%)
>1 to 2 h	7663 (35·3%)	6243 (36·4%)	2512 (36·6%)	1511 (36·1%)	3238 (36·8%)
>2 to 3 h	3404 (15·7%)	3060 (17·8%)	1286 (18·7%)	793 (19·0%)	1503 (17·1%)
>3 h	2856 (13·2%)	2594 (15·1%)	1109 (16·1%)	690 (16·5%)	1125 (12·8%)
Maintenance of anaesthesia (missing n=5)	3797 (17·5%)	2707 (15·8%)	1311 (19·1%)	960 (23·0%)	1048 (11·9%)
Endotracheal intubation (missing n=4)	17 582 (81·0%)	16 553 (96·5%)	6723 (97·9%)	4101 (98·1%)	8494 (96·6%)
Type of NMBA‡					
Suxamethonium (succinylcholine)	NA	524 (3·1%)	60 (0·9%)	38 (0·9%)	0
Mivacurium	NA	398 (2·3%)	120 (1·7%)	111 (2·7%)	27 (0·3%)
Atracurium	NA	3808 (22·2%)	1449 (21·1%)	493 (11·8%)	1981 (22·5%)
Vecuronium	NA	454 (2·6%)	153 (2·2%)	72 (1·7%)	356 (4·0%)
Rocuronium	NA	9890 (57·7%)	4382 (63·8%)	3121 (74·6%)	5734 (65·2%)
Cisatracurium	NA	1917 (11·2%)	654 (9·5%)	344 (8·2%)	586 (6·7%)
Pancuronium and pipecuronium	NA	159 (0·9%)	50 (0·7%)	3 (0·1%)	111 (1·3%)
Time from first NMBA to extubation	NA	153 (106)	158 (96)	160 (96)	140 (89)
≤1 h	NA	2083 (12·1%)	635 (9·2%)	356 (8·5%)	1207 (13·7%)
>1 to 2 h	NA	6220 (36·3%)	2334 (34·0%)	1376 (32·9%)	3420 (38·9%)
>2 to 4 h	NA	6328 (36·9%)	2811 (40·9%)	1757 (42·0%)	3170 (36·0%)
>4 h	NA	2519 (14·7%)	1088 (15·8%)	693 (16·6%)	998 (11·3%)

(Table 1 continues on next page)

	Anaesthetised patients (n=21 694)	Patients receiving NMBAs (n=17 150)	Patients with any NMM (n=6868)	Patients with quantitative NMM (n=4182)	Patients receiving a reversal agent (n=8795)
(Continued from previous page)					
Time from last NMBA injection to extubation	NA	104 (81)	100 (75)	104 (79)	77 (56)
No increment	NA	8845 (51·6%)	3178 (46·3%)	2034 (48·6%)	3422 (38·9%)
>60 min	NA	4490 (26·2%)	2046 (29·8%)	1247 (29·8%)	2365 (26·9%)
>30 to 60 min	NA	3059 (17·8%)	1364 (19·9%)	748 (17·9%)	2404 (27·3%)
>15 to 30 min	NA	663 (3·9%)	254 (3·7%)	135 (3·2%)	536 (6·1%)
≤15 min	NA	93 (0·5%)	26 (0·4%)	18 (0·4%)	68 (0·8%)
Extubation location (missing n=6)					
Operation room	NA	16 001 (93·3%)	6457 (94·0%)	3970 (94·9%)	8357 (95·0%)
Post-anaesthesia care unit or recovery room	NA	958 (5·6%)	358 (5·2%)	179 (4·3%)	409 (4·7%)
Intensive care unit	NA	385 (2·2%)	50 (0·7%)	32 (0·8%)	26 (0·3%)
Extubation criteria (missing n=13)					
Clinical criteria	NA	11 789 (68·7%)	1596 (23·2%)	481 (11·5%)	5690 (64·7%)
NMM	NA	273 (1·6%)	259 (3·8%)	170 (4·1%)	149 (1·7%)
Clinical criteria and NMM	NA	5075 (29·6%)	5011 (73·0%)	3530 (84·4%)	2949 (33·5%)
Geographical location					
Eastern Europe	4037 (18·6%)	3526 (20·6%)	578 (8·4%)	496 (11·9%)	2007 (22·8%)
Scandinavia	1442 (6·6%)	1070 (6·2%)	742 (10·8%)	732 (17·5%)	480 (5·5%)
UK and Ireland	6306 (29·1%)	4353 (25·4%)	1993 (29·0%)	221 (5·3%)	2869 (32·6%)
Mediterranean countries	5562 (25·6%)	4783 (27·9%)	1490 (21·7%)	1073 (25·7%)	2764 (31·4%)
Central Europe	4347 (20·0%)	3418 (19·9%)	2065 (30·1%)	1660 (39·7%)	675 (7·7%)
Recruitment rate (≥50%)	19 586 (90·3%)	15 475 (90·2%)	6001 (87·4%)	3492 (83·5%)	8192 (93·1%)
Recruitment during winter (November, 2014, to March, 2015)	18 093 (83·4%)	14 166 (82·6%)	5422 (78·9%)	3256 (77·9%)	7445 (84·7%)
Use of pulsoximetry for postoperative pulmonary complication screening	19 811 (91·3%)	15 600 (91·0%)	6471 (94·2%)	3912 (93·5%)	8223 (93·5%)
Anaesthesia cases per year					
≤5000	1404 (6·5%)	1062 (6·2%)	317 (4·6%)	167 (4·0%)	605 (6·9%)
>5000 to 10 000	5477 (25·2%)	4274 (24·9%)	1603 (23·3%)	968 (23·1%)	2416 (27·5%)
>10 000 to 20 000	8812 (40·6%)	6858 (40·0%)	2515 (36·6%)	1515 (36·2%)	3273 (37·2%)
>20 000	6001 (27·7%)	4956 (28·9%)	2433 (35·4%)	1532 (36·6%)	2501 (28·4%)

Data are n (%) or mean (SD). NMBA=neuromuscular blocking agent. NA=not applicable. NMM=neuromuscular monitoring. ASA=American Society of Anesthesiologists. NYHA=New York Heart Association. SpO_2=peripheral blood oxygen saturation. *Patients were excluded from the analyses if information on any outcome variable or any key factor was not available. †Missing information was imputed for multivariate testing. ‡In case of any combination, only the last given NMBA is provided.

Table 1: **Characteristics of patients in the five study subcohorts**

agents (figure 2). Only 2·3% of high-risk surgical patients and those with adverse respiratory profiles were anaesthetised without neuromuscular blocking agents. A classification tree analysis showed that almost all patients in subgroups known to be at high risk for postoperative pulmonary complications—such as patients with pre-existing disease or those undergoing high risk surgical procedures—had neuromuscular blocking agents during anaesthesia (appendix). Patients with or without neuromuscular blocking agents in the one-to-one ratio propensity score matching differed from all other anaesthetised patients with respect to the type of surgery (72·7% *vs* 38·6% for peripheral surgery), duration of surgery (51·4% *vs* 35·8% for durations ≤1 h), ASA classification (84·0% *vs* 73·5% for ASA ≤2), and preoperative oxygen saturation (94·6% *vs* 89·8% with SpO_2 ≥95%), and overall these patients had fewer comorbidities and were scheduled for minor invasive surgery as compared with other patients (table 4).

The incidence of postoperative pulmonary complications in patients receiving neuromuscular blocking agents (subcohort 2) was 8·4% (1441 of 17 150), and we further subdivided this cohort into quintiles of the expected duration of the muscle relaxant (ie, <68 min, 68 to <91 min, 91 to <115 min, 115 to <159 min, and ≥159 min). The incidence of postoperative pulmonary complications increased in the quintiles with a longer expected duration of neuromuscular blocking agents respectively (5·3%, 6·2%, 6·8%, 9·0%, and 14·6%). However, multivariate analysis did not confirm any association between expected duration of neuromuscular blocking agent and risk of postoperative pulmonary

	Clinical symptoms	Incidence
Respiratory failure		
Mild	PaO_2 <60 mm Hg, 8 kPa, or SpO_2 <90% in room air but responding to mask or nasal supplementary oxygen (excluding hypoventilation)	5·2%
Intermediate	PaO_2 <60 mm Hg, 8 kPa, or SpO_2 <90% and needing invasive or non-invasive mechanical ventilation (excluding hypoventilation)	0·7%
Severe	PaO_2-to-FiO_2 ratio <300 mm Hg or 40 kPa regardless of level of PEEP needing invasive mechanical ventilation (acute lung injury or acute respiratory distress syndrome)	0·3%
Suspected pulmonary infection	General signs of infection, at least one of the following criteria: patient receives antibiotics, core body temperature >38°C, leucocytosis >12 000 cells per µL; and signs of an infection of pulmonary origin, at least one of the following criteria: new or changed sputum, or new or changed lung opacity on chest x-ray when clinically indicated	2·5%
Suspected pulmonary infiltrates	Chest x-ray showing monolateral or bilateral opacities	2·0%
Atelectasis	Lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area and compensatory overinflation of the adjacent non-atelectatic lung	2·3%
Aspiration pneumonitis	Defined as respiratory failure after the inhalation of regurgitated gastric contents	0·2%
Bronchospasm	Defined as newly detected expiratory wheezing treated with bronchodilators	0·6%
Pulmonary oedema	Defined as diffuse alveolar interstitial infiltrates with dyspnoea and rales related to left ventricular failure, confirmed by one of the following: echocardiography, pulmonary catheter, or clinical improvement with specific treatment	0·6%
Primary outcomes	Postoperative pulmonary complications (at least one character)	8·1%
Secondary outcomes	Intermediate or severe postoperative pulmonary complications (at least one character except those that are mild)	5·1%
Day of postoperative pulmonary complications diagnosis	At postoperative physical examination on day 1,2, or 3*; via chart review†	5·9%; 6·2%

Relevant symptoms are the same as those used for the PERISCOPE study.[18] PaO_2=partial pressure of oxygen in arterial blood. SpO_2=peripheral blood oxygen saturation. FiO_2=fractional concentration of oxygen in inspired air. PEEP=positive end-expiratory pressure. *Because of earlier discharge on the first postoperative day, 238 patients missed the postoperative physical examination. †7327 patients were discharged immediately after their physical examination at the first postoperative day; accordingly, the chart review did not add any further information.

Table 2: **Definitions of postoperative pulmonary complications and their incidences observed in 22 165 patients**

	Postoperative pulmonary complications		OR_{adj} (95% CI)	p values
	Key factor does not apply	Key factor applies		
Use of any NMBA	131/4001 (3·3%)	1527/17 693 (8·6%)	1·86 (1·53–2·26)	<0·0001
High dose of NMBA*	936/13 697 (6·8%)	505/3453 (14·6%)	1·03 (0·88–1·20)	0·75
NMM used	676/9927 (6·8%)	765/7223 (10·6%)	1·31 (1·15–1·49)	<0·0001
Reversal agent given	645/8223 (7·8%)	796/8927 (8·9%)	1·23 (1·07–1·41)	0·0028
Quantitative (vs qualitative) NMM	292/2686 (10·9%)	441/4182 (10·5%)	1·07 (0·90–1·29)	0·44
Extubated at TOFR ≥0·9	157/1343 (11·7%)	284/2839 (10·0%)	1·03 (0·82–1·31)	0·78
Sugammadex (vs neostigmine)	567/6805 (8·3%)	213/1990 (10·7%)	1·03 (0·85–1·25)	0·74

Data are n/N (%), unless otherwise specified. OR_{adj}=adjusted odds ratio. NMBA=neuromuscular blocking agent. NMM=neuromuscular monitoring. TOFR=train-of-four ratio. *Defined as a dose of an expected duration of 159 min or more (5th quintile of dose).

Table 3: **Incidences and OR_{adj}s of postoperative pulmonary complications according to seven key factors in neuromuscular management**

complications (the <68 min quintile was the reference; OR_{adj} 0·97 [95% CI 0·77–1·24] for 68 to <91 min, 0·90 [0·71–1·15] for 91 to <115 min, 0·91 [0·71–1·17] for 115 to <159 min, and 0·91 [0·70–1·19] for ≥159 min; p_{trend}=0·9). Longer duration of anaesthesia—ie, the time between administration of the first neuromuscular blocking agent and extubation—was associated with an increased risk (≤1 h was the reference; OR_{adj} 1·27 [95% CI 0·95–1·70] for >1 to 2 h, 1·84 [1·35–2·51] for >2 to 4 h, and 3·22 [2·26–4·60] for >4 h; p_{trend}=0·0012). Other relevant risk factors are the same as those in subcohort 1: intrathoracic or open upper abdominal surgery, preoperative SpO_2 of 94% or less, emergency surgery, ASA categorisation of 3 or more, aged over 60 years, duration of surgery lasting 2 h or more (appendix). No effect for the expected duration of the neuromuscular blocking agents was observed, and this finding was confirmed by all sensitivity analyses (appendix).

Subgroups (deciles) with increased likelihood of receiving high doses of neuromuscular blocking agents (expected duration ≥159 min) based on the respective propensity score had a higher incidence of postoperative pulmonary complications irrespective of the actual dose given. The first decile with a high dose proportion of only 0·6% had an incidence of 4·0%, whereas the tenth decile with a high dose proportion of 77·7% had a 20·1% incidence of postoperative pulmonary complications. The use of neuromuscular monitoring was not associated with a decreased risk of postoperative pulmonary complications (table 3; ARR_{adj} –2·6%, 95% CI –3·9 to –1·4), which was confirmed by sensitivity analyses (appendix). The use of reversal agents was also not associated with a reduced risk of postoperative pulmonary complications (table 3; ARR_{adj} –1·9%, –3·2 to –0·7), as confirmed by all sensitivity analyses (appendix).

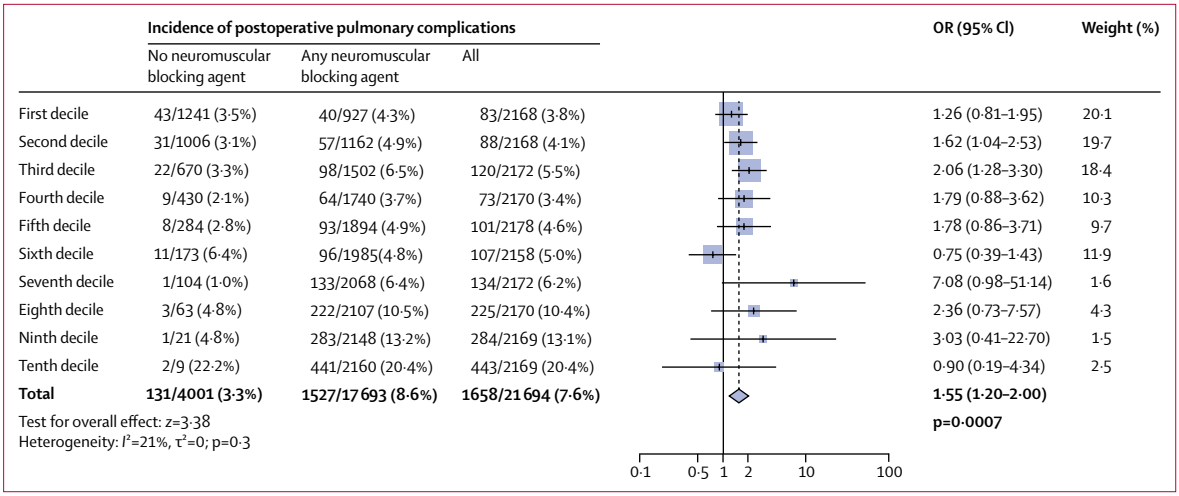

Figure 2: **Effects of neuromuscular blocking agents on postoperative pulmonary complications in ten equally sized subcohorts (deciles) of anaesthetised patients based on propensity scores**

Data are n/N (%), unless otherwise specified. The propensity score is calculated for use of neuromuscular blocking agents based on all other factors. The deciles are arranged along increasing propensity (likelihood) of using a neuromuscular blocking agent. In each decile, we did a univariate analysis of the effect of use of a neuromuscular blocking agent on postoperative pulmonary complication. Results are combined using random effect meta-analysis. In the first six deciles, where the mean likelihood of using a neuromuscular blocking agent is lower than in the second four deciles (70·8% *vs* 97·7%), the mean risk for developing a postoperative pulmonary complication is low (4·4%). These deciles (deciles 1–6) dominate the overall result with a combined weight of 90·1%. By contrast, in the other 40% of patients (deciles 7–10), the risk for developing a postoperative pulmonary complication is higher (12·5%). Importantly, no conclusion about the effect of neuromuscular blocking agents on postoperative pulmonary complications in deciles 7–10 can be drawn because they do not include sufficient patients who did not receive a neuromuscular blocking agent (197 [2·3%] of 8680). OR=odds ratio.

Neither the use of quantitative monitoring (table 3; ARR_{adj} –0·9%, 95% CI –3·1 to 1·3) nor extubation at a train-of-four ratio of 0·9 or more (–0·4%, –3·5 to 2·2) was associated with a reduced risk of postoperative pulmonary complications. Both results were confirmed by all sensitivity analyses (appendix). The use of sugammadex for reversal of neuromuscular blockade was not associated with a better pulmonary outcome than the use of neostigmine (table 3; ARR_{adj} –0·3%, 95% CI –2·4 to 1·5]), as confirmed by all sensitivity analyses (appendix).

Discussion

We report the results of a prospective European cohort study of 22 803 surgical inpatients who received general anaesthesia for non-cardiac surgery. The data show that using neuromuscular blocking agents during anaesthesia was associated with an increased risk of postoperative pulmonary complications irrespective of dose. We were unable to show that the use of neuromuscular monitoring and the administration of reversal agents was associated with a decreased risk of postoperative pulmonary complications. Therefore, the question is whether the evidence is sufficient to attribute the associations we observed to causation[22] and to take appropriate clinical action?

Strong effects are more likely to be causal than weak effects.[22] Therefore, we reported the effect sizes of all the tested factors (appendix). The adjusted effect size of using neuromuscular blocking agents is 1·86, which is weaker than the well recognised effects of the surgical procedure and the patient's preoperative condition on pulmonary outcome—which were also found in this study, especially

	NMBA not used (n=2275)	NMBA used (n=2275)	Subcohort 1 (n=21 694)
Age (years)			
≤40	521 (22·9%)	506 (22·2%)	4432 (20·4%)
>40 to 60	851 (37·4%)	832 (36·6%)	7762 (35·8%)
>60 to 80	787 (34·6%)	811 (35·6%)	8050 (37·1%)
>80	115 (5·1%)	127 (5·6%)	1450 (6·7%)
Sex			
Women	1024 (45·0%)	1016 (44·7%)	11 655 (53·7%)
Men	1251 (55·0%)	1259 (55·3%)	10 039 (46·3%)
Body-mass index 17·5–30·0 kg/m²	1738 (76·4%)	1705 (74·9%)	15 529 (71·6%)
ASA classification			
1	731 (32·1%)	695 (30·5%)	5050 (23·3%)
2	1190 (52·3%)	1207 (53·1%)	10 893 (50·2%)
3	336 (14·8%)	345 (15·2%)	5297 (24·4%)
4–5	19 (0·8%)	29 (1·3%)	435 (2·0%)
NYHA ≥2	51 (2·2%)	64 (2·8%)	1363 (6.3%)
Coronary artery	127 (5·6%)	146 (6·4%)	2195 (10·1%)
Neurological disease	164 (7·2%)	146 (6·4%)	2595 (12·0%)
Diabetes mellitus	162 (7·1%)	183 (8·0%)	2595 (12·0%)
Liver disease	35 (1·5%)	32 (1·4%)	986 (4·5%)
Creatinine clearance <90 mL/min	717 (31·5%)	720 (31·6%)	7654 (35·3%)
COPD	72 (3·2%)	71 (3·1%)	1429 (6·6%)
Asthma	105 (4·6%)	116 (5·1%)	1497 (6·9%)
Obstructive sleep apnoea syndrome	33 (1·5%)	42 (1·8%)	731 (3·4%)
Recent respiratory infection	31 (1·4%)	33 (1·5%)	679 (3·1%)
Smoker	305 (13·4%)	298 (13·1%)	3821 (17·6%)
Preoperative SpO_2 ≤94%	118 (5·2%)	128 (5·6%)	2213 (10·2%)

(Table 4 continues on next page)

	NMBA not used (n=2275)	NMBA used (n=2275)	Subcohort 1 (n=21 694)
(Continued from previous page)			
Surgical procedure			
Emergency surgery	305 (13·4%)	327 (14·4%)	3475 (16·0%)
Intrathoracic closed surgery	1 (<0·1%)	2 (0·1%)	330 (1·5%)
Intrathoracic open surgery	4 (0·2%)	6 (0·3%)	463 (2·1%)
Upper abdominal open surgery	22 (1·0%)	26 (1·1%)	1350 (6·2%)
Upper abdominal closed surgery	20 (0·9%)	18 (0·8%)	2109 (9·7%)
Lower abdominal closed surgery	167 (7·3%)	165 (7·3%)	2392 (11·0%)
Lower abdominal open surgery	94 (4·1%)	92 (4·0%)	2581 (11·9%)
Head and neck surgery	308 (13·5%)	282 (12·4%)	3717 (17·1%)
Craniotomy	18 (0·8%)	19 (0·8%)	373 (1·7%)
Peripheral surgery or other procedure	1641 (72·1%)	1665 (73·2%)	8379 (38·6%)
Duration of surgery			
≤1 h	1196 (52·6%)	1144 (50·3%)	7771 (35·8%)
>1 to 2 h	801 (35·2%)	859 (37·8%)	7663 (35·3%)
>2 to 3 h	191 (8·4%)	183 (8·0%)	3404 (15·7%)
>3 h	87 (3·8%)	91 (4·0%)	2856 (13·2%)
Hospital in eastern Europe	296 (13·0%)	310 (13·6%)	4037 (18·6%)
Recruitment rate (≥50%)	2092 (92·0%)	2100 (92·3%)	19 586 (90·3%)
Pulsoximetry for postoperative pulmonary complication screening	2141 (94·1%)	2140 (94·1%)	19 811 (91·3%)

Data are n (%). NMBA=neuromuscular blocking agents. ASA=American Society of Anesthesiology. NYHA=New York Heart Association. SpO_2=peripheral blood oxygen saturation.

Table 4: **Characteristics of patients who were anaesthetised with or without the use of NMBAs resulting from a propensity score matching (1:1) of subcohort 1 in comparison with the patients of subcohort 1 (anaesthetised patients)**

following intrathoracic and open upper abdominal surgery (OR_{adj} 3·53), long duration of surgery (2·34), preoperative SpO_2 of 94% or less (2·35), emergency surgery (2·24), and ASA categorisation of 3 or more (2·06). Importantly, although the model has to be adjusted for these cofactors, none of them modifies the effect of use of neuromuscular blocking agents because of insignificant interaction terms.

Sensitivity analyses suggest that the association we observed between the use of neuromuscular blocking agents and postoperative pulmonary complications can be attributed to patients who have a lower risk of worse pulmonary outcomes due to their pre-existing profile (eg, ASA categorisation) and the surgical procedure. This observation is consistent with previous studies,[3,4] which used propensity score-based one-to-one matching to build comparable groups. Using this technique in our cohort excludes almost all patients with a high probability of receiving neuromuscular blocking agents based on our set of cofactors. Importantly, about 40% of patients in deciles 7–10 received neuromuscular blocking agents on a regular basis (97·7%). In these subgroups, therefore, we cannot draw any conclusions about the effect of neuromuscular blocking agents on pulmonary outcomes. By contrast, pulmonary outcomes when surgery does not demand muscle paralysis—eg, in patients with ASA categorisation of 2 or less undergoing short peripheral surgery—might benefit from the avoidance of neuromuscular blocking drugs.

Dose-dependency of the association between neuromuscular blocking agents and postoperative complications would further strengthen the idea of causality. McLean and colleagues[23] found a weak increase in the risk of postoperative pulmonary complications with higher total doses of neuromuscular blocking agents (>5·15 ED_{95} *vs* <2·20 ED_{95}; OR 1·28, 95% CI 1·04–1·57). Using hospital readmission as the outcome variable, Thevathasan and colleagues[24] also showed an increased risk with higher doses of neuromuscular blocking agents. However, our study cannot confirm these findings. Because of the European-wide multicentre approach, patients were exposed to eight different neuromuscular blocking agents with varying durations. To address this heterogeneity, we had to define the dosing regimen as the expected duration of the total dose given. Nonetheless, we found that even a single dose of neuromuscular blocking agent for tracheal intubation had a similar effect size in increasing the risk for postoperative pulmonary complications, which does support the idea of dose-independency in postoperative complications.

Most importantly, POPULAR is the first prospective study to evaluate the effect of neuromuscular blocking agents on postoperative pulmonary complications in a European-wide, large-scale setting. Our results are consistent with analyses from US databases,[3,4] substantiating previous evidence that shows the disadvantage of using neuromuscular blocking agents during surgery in terms of patients' postoperative pulmonary outcomes. When considering the use of neuromuscular blocking agents, anaesthetists have to consider whether the potential benefits—eg, improvement of surgical conditions—justify the associated increased risk for postoperative pulmonary complications, especially in healthy patients undergoing relatively minor surgical procedures.

Because a substantial proportion of surgical procedures are done using muscle paralysis, measures taken to avoid residual paralysis should also reduce the risk for postoperative pulmonary complications. However, as with previous studies,[3] the results from POPULAR contradict the assumption that neuromuscular monitoring can decrease this risk. A false sense of security engendered by use of qualitative neuromuscular monitoring might explain the unfavourable outcomes, with anaesthetists being unable to identify residual neuromuscular blockade at a train-of-four ratio of 0·4 or more using the qualitative method.[12] The recommendation to extubate patients only on recovery of the train-of-four ratio to 0·9 or more measured by quantitative devices[25] raised expectations of improved pulmonary outcomes by reducing residual neuromuscular blockade, but in our study this approach was not associated with more favourable pulmonary outcomes either. There are two possible explanations for this finding. First, the cutoff for an acceptable train-of-four ratio of 0·9 or more (defined on the basis of research in healthy young conscious volunteers)[26] might not be

suitable for postoperative patients; and second, acceleromyography—which is now the most commonly used device to monitor neuromuscular function in Europe (87% of quantitative monitors in this study)—is known to overestimate neuromuscular recovery.[27] Both considerations suggest the need for further studies investigating recovery to a train-of-four ratio higher than 0·9.

Pharmacological reversal is thought to improve pulmonary outcomes by reducing the likelihood of residual neuromuscular block.[4,28] However, findings from POPULAR confirm previous studies[3,29] showing that administration of reversal agents is not associated with a decreased risk of postoperative pulmonary complications. Anaesthetists might underestimate the timing and the dose of neostigmine required to completely reverse neuromuscular blockade.[30] In Europe, the more effective and more rapidly acting reversal agent sugammadex is also available,[31,32] but sugammadex does not guarantee complete reversal if absence of residual block is not confirmed by quantitative neuromuscular monitoring,[33] and it can only be used to reverse aminosteroidal neuromuscular blocking agents. Data from POPULAR do not show any advantage of sugammadex over neostigmine with respect to pulmonary outcomes. Importantly, however, absence of proof that incidence of postoperative pulmonary complications is reduced by use of a reversal agent and neuromuscular monitoring does not necessarily mean that these measures are not able to reduce the incidence of postoperative residual neuromuscular blockade.

The POPULAR study has a number of limitations. It is important to acknowledge the potential effect of confounding factors—both those we were able to adjust for and those we could not account for. Sensitivity analyses showed that appropriate neuromuscular monitoring and reversal agents were more likely to be used in patients who had a higher postoperative pulmonary risk profile. Importantly, we did not collect data on the methods used for intraoperative ventilation. Reasons for this decision were that the use of neuromuscular blocking agents dictates that artificial ventilation must be used at least for the duration of the neuromuscular block, the height of end-expiratory pressure used during anaesthesia has not been proven to influence pulmonary outcomes,[34,35] and that protective ventilation (tidal volumes <8 mL/kg) is used as in all hospitals. Although we assume that the ventilation technique is addressed by the cofactor for the surgical procedure and the hospital-related cofactors, speculation might remain about its effect on postoperative pulmonary complications. Furthermore, because few patients (2·3%) were endotracheally intubated without neuromuscular blocking agents, resulting in a high correlation between endotracheal intubation and use of neuromuscular blocking agents (r=0·831), we removed endotracheal intubation as a cofactor from the analysis to avoid multicollinearity. If we assume that traumatic intubation due to omission of neuromuscular blocking agents led to vocal cord injury[36] followed by pulmonary complications in these patients, traumatic intubation cannot be the reason for the observed lower risk. On the contrary, it is quite consistent to consider that any endotracheal intubation—traumatic as well as non-traumatic—is an independent cofactor for postoperative pulmonary complications.

Because there was no obligation to use pulsoximetry during the post-anaesthesia ward round, mild hypoxaemia might have been detected less frequently in the hospitals that did not use pulsoximetry than in those that did.[37] However, we adjusted for this factor and the findings are robust if only intermediate or severe pulmonary complications are used as outcomes. Assessment for pulmonary complications including physical examination was done on postoperative day 1, 2, or 3, and patients who were not discharged after this visit were followed-up via chart review to register late-onset pulmonary complications, so pulmonary complications might not have been picked up in patients who were discharged early. Finally, the only outcome variable we used in POPULAR was pulmonary complications. Accordingly, a possible effect on other outcomes of the management of neuromuscular block cannot be ruled out. In particular, data from POPULAR do not account for the risks of poor surgical conditions or involuntary movements and hence iatrogenic injuries if no neuromuscular blocking agents have been given or low levels of neuromuscular block have been applied.

In conclusion, the POPULAR study showed that the use of neuromuscular blocking drugs is associated with an increased risk of postoperative pulmonary complications, and use of reversal agents or neuromuscular monitoring could not decrease this risk. Many patients undergoing minor surgical procedures might benefit from the use of supraglottical devices during anaesthesia and avoidance of neuromuscular blocking drugs. Future randomised clinical trials are necessary to investigate these findings.

Contributors

All authors contributed to the conception and design of the work. Data acquisition was done by EK. EK, KU, and MB had access to the raw data. Statistical analyses were done by KU and MB. All authors contributed to the interpretation of data. EK, JMH, and MB wrote the first draft of the manuscript. JMH and MB wrote the second and third drafts. All authors critically revised the manuscript and approved the submitted version. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

All authors report non-financial support from the European Society of Anaesthesiology during the conduct of the study. MB has received grants and personal fees from Merck Sharp & Dohme; personal fees from Grünenthal and GE Healthcare outside of the submitted work. LIE has received speaker's fee from Merck Sharp & Dohme outside of the submitted work. HL has received personal fees from Merck Sharp & Dohme outside of the submitted work. MH has received grants from Merck Sharp & Dohme, Eurocept BV Nigteveen, and CSL Behring outside of the submitted work. JMH has received personal fees from Merck Sharp & Dohme and GE Healthcare outside of the submitted work. CM reports personal fees from Merck Sharp & Dohme and GE Healthcare outside of the submitted work. MJF, KU, AH, and EK declare no other competing interests.

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References

1 Madsen MV, Staehr-Rye AK, Gatke MR, Claudius C. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: a systematic review. *Acta Anaesthesiol Scand* 2015; **59:** 1–16.

2 Blobner M, Frick CG, Stauble RB, et al. Neuromuscular blockade improves surgical conditions (NISCO). *Surg Endosc* 2015; **29:** 627–36.

3 Grosse-Sundrup M, Henneman JP, Sandberg WS, et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study. *BMJ* 2012; **345:** e6329.

4 Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. *Anesthesiology* 2016; **125:** 647–55.

5 Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS. Residual neuromuscular blockade and critical respiratory events in the postanesthesia care unit. *Anesth Analg* 2008; **107:** 130–37.

6 Berg H, Roed J, Viby-Mogensen J, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. *Acta Anaesthesiol Scand* 1997; **41:** 1095–103.

7 Ali HH, Utting JE, Gray TC. Quantitative assessment of residual antidepolarizing block. I. *Br J Anaesth* 1971; **43:** 473–77.

8 Mayrhofer O, Remes I, Schuster H. Antagonism of the long-acting depolarizing muscle relaxant imbretil. *Anaesthesist* 1955; **4:** 174–75.

9 Scheller MS, Zornow MH, Saidman LJ. Tracheal intubation without the use of muscle relaxants: a technique using propofol and varying doses of alfentanil. *Anesth Analg* 1992; **75:** 788–93.

10 Ripke F, Fink H, Blobner M. Concepts for the avoidance of residual neuromuscular blockades after the administration of nondepolarizing muscle relaxants. *Anasthesiol Intensivmed Notfallmed Schmerzther* 2014; **55:** 564–76.

11 Baillard C, Clec'h C, Catineau J, et al. Postoperative residual neuromuscular block: a survey of management. *Br J Anaesth* 2005; **95:** 622–26.

12 Murphy GS, Szokol JW, Marymont JH, et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. *Anesthesiology* 2008; **109:** 389–98.

13 Fagerlund MJ, Fink H, Baumuller E, et al. Postanaesthesia pulmonary complications after use of muscle relaxants in Europe: study protocol of the POPULAR study. *Eur J Anaesthesiol* 2016; **33:** 381–83.

14 Canet J, Sabate S, Mazo V, et al. Development and validation of a score to predict postoperative respiratory failure in a multicentre European cohort: a prospective, observational study. *Eur J Anaesthesiol* 2015; **32:** 458–70.

15 McAlister FA, Bertsch K, Man J, Bradley J, Jacka M. Incidence of and risk factors for pulmonary complications after nonthoracic surgery. *Am J Respir Crit Care Med* 2005; **171:** 514–17.

16 Smetana GW. Preoperative pulmonary evaluation. *N Engl J Med* 1999; **340:** 937–44.

17 Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology* 1997; **86:** 765–71.

18 Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 10; **113:** 1338–50.

19 Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol* 1996; **49:** 1373–79.

20 Bates D, Machler M, Bolker BM, Walker SC. Fitting linear mixed-effects models using lme4. *J Stat Softw* 2015; **67:** 1–48.

21 Thoemmes F, Liao W. An SPSS R menu for propensity score matching. 2012. https://sourceforge.net/projects/psmspss/files/ (accessed June 24, 2015).

22 Hill AB. The environment and disease: association or causation? *Proc R Soc Med* 1965; **58:** 295–300.

23 McLean DJ, Diaz-Gil D, Farhan HN, Ladha KS, Kurth T, Eikermann M. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. *Anesthesiology* 2015; **122:** 1201–13.

24 Thevathasan T, Shih S, Safavi K, et al. An association between intraoperative non-depolarising neuromuscular blocking agent dose and 30-day readmission following abdominal surgery. *Br J Anaesth* 2017; **119:** 595–605.

25 Murphy GS, Brull SJ. Residual neuromuscular block: lessons unlearned. Part I: definitions, incidence, and adverse physiologic effects of residual neuromuscular block. *Anesth Analg* 2010; **111:** 120–28.

26 Eriksson LI, Sundman E, Olsson R, et al. Functional assessment of the pharynx at rest and during swallowing in partially paralyzed humans: simultaneous videomanometry and mechanomyography of awake human volunteers. *Anesthesiology* 1997; **87:** 1035–43.

27 Capron F, Alla F, Hottier C, Meistelman C, Fuchs-Buder T. Can acceleromyography detect low levels of residual paralysis? A probability approach to detect a mechanomyographic train-of-four ratio of 0.9. *Anesthesiology* 2004; **100:** 1119–24.

28 Bronsert MR, Henderson WG, Monk TG, et al. Intermediate-acting nondepolarizing neuromuscular blocking agents and risk of postoperative 30-day morbidity and mortality, and long-term survival. *Anesth Analg* 2017; **124:** 1476–83.

29 Sasaki N, Meyer MJ, Malviya SA, et al. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. *Anesthesiology* 2014; **121:** 959–68.

30 Kirkegaard H, Heier T, Caldwell JE. Efficacy of tactile-guided reversal from cisatracurium-induced neuromuscular block. *Anesthesiology* 2002; **96:** 45–50.

31 Jones RK, Caldwell JE, Brull SJ, Soto RG. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology* 2008; **109:** 816–24.

32 Blobner M, Eriksson LI, Scholz J, Motsch J, Della Rocca G, Prins ME. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur J Anaesthesiol* 2010; **27:** 874–81.

33 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:** 345–51.

34 Serpa Neto A, Hemmes SN, Barbas CS, et al. Protective versus conventional ventilation for surgery: a systematic review and individual patient data meta-analysis. *Anesthesiology* 2015; **123:** 66–78.

35 Prove Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014; **384:** 495–503.

36 Mencke T, Echternach M, Kleinschmidt S, et al. Laryngeal morbidity and quality of tracheal intubation: a randomized controlled trial. *Anesthesiology* 2003; **98:** 1049–56.

37 Sun Z, Sessler DI, Dalton JE, et al. Postoperative hypoxemia is common and persistent: a prospective blinded observational study. *Anesth Analg* 2015; **121:** 709–15.