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Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents (Review)

Lundstrøm LH, Duez CHV, Nørskov AK, Rosenstock CV, Thomsen JL, Møller AM, Strande S, Wetterslev J

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[Intervention Review]

Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

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ABSTRACT

Background

Tracheal intubation during induction of general anaesthesia is a vital procedure performed to secure a patient's airway. Several studies have identified difficult tracheal intubation (DTI) or failed tracheal intubation as one of the major contributors to anaesthesia-related mortality and morbidity. Use of neuromuscular blocking agents (NMBA) to facilitate tracheal intubation is a widely accepted practice. However, because of adverse effects, NMBA may be undesirable. Cohort studies have indicated that avoiding NMBA is an independent risk factor for difficult and failed tracheal intubation. However, no systematic review of randomized trials has evaluated conditions for tracheal intubation, possible adverse effects, and postoperative discomfort.

Objectives

To evaluate the effects of avoiding neuromuscular blocking agents (NMBA) versus using NMBA on difficult tracheal intubation (DTI) for adults and adolescents allocated to tracheal intubation with direct laryngoscopy. To look at various outcomes, conduct subgroup and sensitivity analyses, examine the role of bias, and apply trial sequential analysis (TSA) to examine the level of available evidence for this intervention.

Search methods

We searched CENTRAL, MEDLINE, Embase, BIOSIS, International Web of Science, LILACS, advanced Google, CINAHL, and the following trial registries: Current Controlled Trials; ClinicalTrials.gov; and www.centerwatch.com, up to January 2017. We checked the reference lists of included trials and reviews to look for unidentified trials.

Selection criteria

We included randomized controlled trials (RCTs) that compared the effects of avoiding versus using NMBA in participants 14 years of age or older.

Data collection and analysis

Two review authors extracted data independently. We conducted random-effects and fixed-effect meta-analyses and calculated risk ratios (RRs) and their 95% confidence intervals (CIs). We used published data and data obtained by contacting trial authors. To minimize the risk of systematic error, we assessed the risk of bias of included trials. To reduce the risk of random errors caused by sparse data and repetitive updating of cumulative meta-analyses, we applied TSA.

Main results

We identified 34 RCTs with 3565 participants that met our inclusion criteria. All trials reported on conditions for tracheal intubation; seven trials with 846 participants described 'events of upper airway discomfort or injury', and 13 trials with 1308 participants reported on direct laryngoscopy. All trials used a parallel design. We identified 18 dose-finding studies that included more interventions or control groups or both. All trials except three included only American Society of Anesthesiologists (ASA) class I and II participants, 25 trials excluded participants with anticipated DTI, and obesity or overweight was an excluding factor in 13 studies. Eighteen trials used suxamethonium, and 18 trials used non-depolarizing NMBA.

Trials with an overall low risk of bias reported significantly increased risk of DTI with no use of NMBA (random-effects model) (RR 13.27, 95% CI 8.19 to 21.49; P < 0.00001; 508 participants; four trials; number needed to treat for an additional harmful outcome (NNTH) = 1.9, I^2 = 0%, D^2 = 0%, GRADE = moderate). The TSA-adjusted CI for the RR was 1.85 to 95.04. Inclusion of all trials resulted in confirmation of results and of significantly increased risk of DTI when an NMBA was avoided (random-effects model) (RR 5.00, 95% CI 3.49 to 7.15; P < 0.00001; 3565 participants; 34 trials; NNTH = 6.3, I^2 = 70%, D^2 = 82%, GRADE = low). Again the cumulative z-curve crossed the TSA monitoring boundary, demonstrating harmful effects of avoiding NMBA on the proportion of DTI with minimal risk of random error. We categorized only one trial reporting on upper airway discomfort or injury as having overall low risk of bias. Inclusion of all trials revealed significant risk of upper airway discomfort or injury when an NMBA was avoided (random-effects model) (RR 1.37, 95% CI 1.09 to 1.74; P = 0.008; 846 participants; seven trials; NNTH = 9.1, I^2 = 13%, GRADE = moderate). The TSA-adjusted CI for the RR was 1.00 to 1.85. None of these trials reported mortality. In terms of our secondary outcome 'difficult laryngoscopy', we categorized only one trial as having overall low risk of bias. All trials avoiding NMBA were significantly associated with difficult laryngoscopy (random-effects model) (RR 2.54, 95% CI 1.53 to 4.21; P = 0.0003; 1308 participants; 13 trials; NNTH = 25.6, I^2 = 0%, D^2= 0%, GRADE = low); however, TSA showed that only 6% of the information size required to detect or reject a 20% relative risk reduction (RRR) was accrued, and the trial sequential monitoring boundary was not crossed.

Authors' conclusions

This review supports that use of an NMBA may create the best conditions for tracheal intubation and may reduce the risk of upper airway discomfort or injury following tracheal intubation. Study results were characterized by indirectness, heterogeneity, and high or uncertain risk of bias concerning our primary outcome describing difficult tracheal intubation. Therefore, we categorized the GRADE classification of quality of evidence as moderate to low. In light of defined outcomes of individual included trials, our primary outcomes may not reflect a situation that many clinicians consider to be an actual difficult tracheal intubation by which the patient's life or health may be threatened.

PLAIN LANGUAGE SUMMARY

The effect of avoiding neuromuscular blocking agents on conditions for placing a tube in the windpipe of patients undergoing general anaesthesia

Background

General anaesthesia abolishes spontaneous respiration. Use of general anaesthesia is frequently unavoidable during surgical procedures. The ability to maintain breathing by placing a tube in the windpipe of patients undergoing general anaesthesia is therefore crucial. A neuromuscular blocking agent (NMBA) is used for relaxation of muscles of the throat and is traditionally used to ease correct placement of the tube. However, use of an NMBA may cause unwanted side effects. On the other hand, large observational studies have indicated that avoiding NMBA may cause difficulties when the tube is placed during anaesthesia.

Objective

In the present systematic review, we assessed the effect of avoiding NMBA instead of using NMBA on difficulties associated with placing a tube in the windpipe of patients undergoing general anaesthesia. Further, we evaluated the consequences of using or avoiding NMBA on events of pain or injury in the upper part of the throat following placement of a tube in the windpipe.

Study characteristics

We identified 34 randomized controlled trials that met our inclusion criteria. These trials included 3565 patients who were undergoing various surgical procedures in hospital departments. Most trials were conducted in high-income countries, and most patients were undergoing elective surgery. Trials included patients of both sexes; most were healthy and non-obese, and staff members did not expect difficulty when placing the tube in the windpipe.

Key results

This review supports that use of NMBA may ensure the best conditions for placing a tube in the windpipe during general anaesthesia. When an NMBA is avoided, risk for pain or injury in the throat is increased following placement of a tube in the windpipe.

Quality of the evidence

Conditions for which a tube is placed in the windpipe are defined in individual trials and may not reflect a situation that many clinicians would consider to be clinically serious. Regarding events of injury and sore throat, only sparse data are available from trials with low risk of bias, although among all included trials, avoiding NMBA increased the risk of pain or injury. We therefore consider our overall findings to reflect evidence of moderate quality.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Avoidance vs use of neuromuscular blocking agent for improving conditions during tracheal intubation in adults and adolescents

Patient or population: improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents
Setting: people undergoing various surgical procedures in hospital departments. Most trials were conducted in high-income countries, and most participants were undergoing elective surgery. Participants of both genders were included; most were ASA class I or II, were non-obese, and had no expected airway management difficulties
Intervention: avoidance of NMBA
Comparison: use of NMBA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI) of avoidance vs use of NMBA	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Risk with use of NMBA	Corresponding risk Risk with avoidance of NMBA				
Primary outcomes						
Difficult tracheal intubation: low risk of bias trials	Study population		RR 13.27 (8.19 to 21.49)	508 (4 studies)	⊕⊕⊕◯ Moderate[a]	TSA shows that the required information size of 8195 for a 20% RRR has not been achieved, but the trial sequential monitoring boundary has been crossed and the TSA-adjusted CI for the RR is 1.85 to 95.04
	47 per 1000	620 per 1000 (383 to 1000)				
Difficult tracheal intubation: all trials	Study population		RR 5.00 (3.49 to 7.15)	3565 (34 studies)	⊕⊕◯◯ Low[b]	TSA shows that the required information size of 44,661 for a 20% RRR has not been achieved, but the trial sequential monitoring boundary has been crossed

						and the TSA-adjusted CI for the RR is 1.20 to 20.77
	81 per 1000	406 per 1000 (284 to 597)				
One or more events of upper airway discomfort or injury: low risk of bias trials	Study population		RR 2.74 (1.21 to 6.21)	73 (1 study)	See comments	Because only 1 low risk of bias trial was identified, no quality of evidence assessment was performed
	162 per 1000	444 per 1000 (196 to 1000)				
One or more events of upper airway discomfort or injury: all trials	Study population		RR 1.37 (1.09 to 1.74)	846 (7 studies)	⊕⊕⊕◯ Moderate[c]	TSA shows that the required information size of 1981 for a 20% RRR has not been achieved, but the trial sequential monitoring boundary has been crossed and the TSA-adjusted CI for the RR is 1.00 to 1.86
	273 per 1000	374 per 1000 (298 to 475)				
Mortality	Not estimated	Not estimated	Not estimated	0 (34 studies)	Not estimated	
Secondary outcomes						
Difficult laryngoscopy: low risk of bias trials	Study population		RR 4.00 (0.47 to 34.20)	78 (1 study)	See comments	Because only 1 low risk of bias trial was identified, no quality of evidence assessment was performed
	26 per 1000	103 per 1000 (12 to 877)				
Difficult laryngoscopy: all trials	Study population		RR 2.54 (1.53 to 4.21)	1308 (13 studies)	⊕⊕◯◯ Low[d]	TSA shows that the required information size of 22,911 for a 20% RRR was not

				achieved, and in no trials were sequential monitoring boundaries crossed. The TSA-adjusted CI for the RR is 0.27 to 21.75
	33 per 1000	85 per 1000 (51 to 141)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI)

CI = confidence interval; RR = risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to the estimate of effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Downgraded one level because of indirectness
[b] Downgraded two levels because of indirectness, heterogeneity, and high or uncertain risk of bias
[c] Downgraded one level because of high or uncertain risk of bias
[d] Downgraded two levels because of imprecision and high or uncertain risk of bias

BACKGROUND

Patients undergoing general anaesthesia lose consciousness and the ability to control breathing and protect their airway. Tracheal intubation is considered a vital procedure that secures the airway and provides the possibility of continued oxygenation. Several studies have identified difficult or failed tracheal intubation as one of the major reasons for anaesthesia-related mortality and morbidity. Types of morbidity range from sore throat, hoarseness, vocal cord lesion, pharyngeal oedema, and pharyngeal necrosis (Domino 1999), to more severe damage such as rupture or perforation of the pharynx and the oesophagus, aspiration pneumonia, and brain and heart injuries caused by anoxia (Rosenstock 2001). These severe complications may even be fatal (Cooper 2008; Hove 2007; Peterson 2005; Rosenstock 2001). Several studies have focused on one or more patient-related risk factors associated with difficult intubation (Adnet 1997; el-Ganzouri 1996; L'Hermite 2009; Lundstrom 2009a; Shiga 2005). Successful tracheal intubation is determined by the anaesthetist's technical and non-technical skills, as well as by available facilities and the local environment (Rosenstock 2004; Rosenstock 2006).

Use of neuromuscular blocking agents (NMBA) to facilitate tracheal intubation is a widely accepted procedure. Owing to adverse effects, the use of NMBA may be undesirable. Cohort studies (Baillard 2005; Lundstrom 2009a; Lundstrom 2009b; Lundstrom 2009c) have demonstrated that avoidance of neuromuscular blocking drugs may be an independent risk factor for difficult and failed tracheal intubation. Randomized trials have evaluated the conditions for tracheal intubation, possible side effects, and postoperative discomfort by comparing different regimens of anaesthesia induction and avoidance versus use of NMBA (Alcock 1993; Alexander 1999; Bouvet 2008; Combes 2007; Harsten 1997; Lieutaud 2003; McNeil 2000; Mencke 2003; Naguib 2006; Scheller 1992; Stevens 1997).

Description of the condition

A successful tracheal intubation is considered to provide a safe airway. The tube is placed directly and is cuffed within the patient's trachea, thereby ensuring a direct connection to the lower airway. The risk of aspiration of gastric contents into the lungs may be reduced by an appropriately placed tracheal tube. Difficulties with tracheal intubation by direct laryngoscopy can cause serious soft tissue damage (Domino 1999) and are the principal causes of hypoxaemic anaesthetic death and brain damage (Henderson 2004). A review identified difficult airway management, including difficult or failed tracheal intubation, as the main cause of death and severe morbidity related to anaesthesia (Braz 2009). The literature presents various definitions of difficult tracheal intubation (DTI). Performance and graduation of tracheal intubation are described by various parameters such as the number of attempts made for intubation; the span of time needed for intubation; the experience and number of anaesthetists performing the intubation; the type and number of alternative techniques used other than direct laryngoscopy; the lifting force required during the laryngoscopy; whether laryngeal pressure was needed and information on vocal cord mobility (Adnet 1997; ASA guideline 1993; Lundstrom 2009a; Viby-Mogensen 1996).

Difficult laryngoscopy, which is often used as a surrogate outcome measure for a DTI, is traditionally defined by the (modified) Cormack and Lehane classification (Cormack 1984; Yentis 1998) (Appendix 1).

Description of the intervention

Induction of general anaesthesia can include or exclude the use of a neuromuscular blocking agent. A combination of adjuvant drugs such as hypnotics, opioids, and occasionally local anaesthetic agents is traditionally used for the induction.

The NMBA used for induction may be a depolarizing or a non-depolarizing drug. Hypnotics may include propofol, thiopental, or etomidate, and opioids may consist of fentanyl, alfentanil, or remifentanil. A local anaesthetic such as lidocaine (Tanaka 2015) may be used intravenously or topically to facilitate tracheal intubation (Woods 2005). After induction has been completed, the patient will undergo tracheal intubation or attempted tracheal intubation with a standard direct laryngoscope.

How the intervention might work

Neuromuscular blocking agents obstruct the nerve impulse at the neuromuscular junction propagated by acetylcholine, causing paralysis of the skeletal muscles. Direct laryngoscopy normally stimulates the oropharynx and activates oropharyngeal reflexes. Use of an NMBA inhibits muscular contractions and improves the conditions for tracheal intubation (Bowman 2006). Both depolarizing and non-depolarizing NMBA may produce side effects, such as anaphylaxis, cardiovascular effects related to histamine release or direct vagolytic or sympathomimetic properties, bronchospasm, and prolonged paralysis. Depolarizing NMBA may specifically cause muscle pain, increased serum potassium, malignant hyperthermia, and increased intraocular pressure (Appiah-Ankam 2004).

Why it is important to do this review

Difficult airway management, including a difficult or failed tracheal intubation, remains a major cause of death and severe morbidity related to anaesthesia (Braz 2009). The risk of DTI may be reduced by the choice of an induction strategy including, or avoiding, NMBA for facilitating tracheal intubation by direct laryn-

goscopy. Use of NMBA may be associated with serious adverse events.

OBJECTIVES

To evaluate the effects of avoiding neuromuscular blocking agents (NMBA) versus using NMBA on difficult tracheal intubation (DTI) for adults and adolescents allocated to tracheal intubation with direct laryngoscopy. To look at various outcomes, conduct subgroup and sensitivity analyses, examine the role of bias, and apply trial sequential analysis (TSA) (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008) to examine the level of available evidence for this intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs).
We included unpublished trials only if trial data and methodological descriptions were provided in written form or through direct contact with study authors.
We excluded trials using quasi-randomization as well as observational studies.

Types of participants

We included participants 14 years of age or older who underwent (attempt of) tracheal intubation by direct laryngoscopy regardless of acute or elective surgical status or investigational procedures.

Types of interventions

Avoidance of neuromuscular blocking agents (= intervention) versus use of neuromuscular blocking agents (= control) to facilitate tracheal intubation. We defined use of NMBA as the control intervention, as it is considered usual standard for airway management, and we defined avoidance of NMBA as the experimental intervention.

Types of outcome measures

Primary outcomes

1. Difficult tracheal intubation: As no international consensus has been reached on defining an intubation score, we accepted the definitions of DTI presented in the individual articles. If study authors defined a difficult laryngoscopy by the Cormack and Lehane score (Cormack 1984) or by the modified Cormack and Lehane score (Yentis 1998) as a difficult intubation, we included and reported the Cormack and Lehane score as the outcome measure. Difficult laryngoscopy is a surrogate outcome for a DTI. Therefore, if a trial reported both an intubation score and the Cormack and Lehane score based on the same population in the same assessment, we extracted only the intubation score for outcome assessment
2. Overall mortality: We used maximal follow-up data from each trial
3. One or more events of upper airway discomfort or injury (e.g. sore throat, hoarseness, vocal cord lesion, minor pharyngeal injury)

Secondary outcomes

1. One or more major serious events: pulmonary aspiration, brain and heart injuries (e.g. caused by anoxia, hypotension, bradycardia or tachycardia during tracheal intubation)
2. Difficult laryngoscopy**,** as defined by the Cormack and Lehane score (Cormack 1984) or the modified Cormack and Lehane score (Yentis 1998)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 1) (the Cochrane Library); MEDLINE (Ovid) (1950 to January 2017); Embase (Ovid) (1980 to January 2017); BIOSIS (Ovid) (1993 to January 2017); International Web of Science (1964 to January 2017); Latin American Caribbean Health Sciences Literature (LILACS) via BIREME (1982 to January 2017); the Chinese Biomedical Literature Database; advanced Google; and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO host (1980 to January 2017).
We utilized a systematic and sensitive search strategy to identify relevant RCTs with no language or date restrictions. We conducted the search within six months of the date the draft review was emailed to the editorial office. For specific information regarding our search strategies, please see the Appendices (Appendix 2, CENTRAL; Appendix 3, MEDLINE; Appendix 4, Embase; Appendix 5, BIOSIS; Appendix 6, CINAHL; Appendix 7, LILACS).

Searching other resources

We searched for ongoing clinical trials and unpublished studies on the following Internet sites (11 January 2017).
1. Current Controlled Trials.

2. ClinicalTrials.gov.
3. www.centerwatch.com.

We handsearched the reference lists of reviews, randomized and non-randomized studies, and editorials for additional studies.

Data collection and analysis

Selection of studies

In the process of selecting trials for inclusion in the review, two review authors (LHL and AN or CD) independently screened titles and abstracts to identify eligible trials and remove obviously irrelevant reports. After retrieving the full texts of potentially eligible reports, the review authors (LHL and one of the following: AN, CD, CVR, JT) examined the full-text reports. We contacted the main authors of studies and experts in this field and asked about missed, unreported, and ongoing trials. Finally, two review authors (LHL and one of the following: AN, CD, CVR, JT) decided which trials would be included and proceeded to data collection. We resolved disagreements by discussion, and a third review author (JW) resolved residual disagreements.

Data extraction and management

LHL and AN, CD, CVR, or JT independently extracted and collected data on a standardized paper form (Appendix 8). We were not blinded to study author, institution, or source of trial publication. We resolved disagreements by discussion, and a third review author (JW) resolved residual disagreements. If necessary, we approached all corresponding authors of included trials for additional information on the review's outcome measures and risk of bias components. For more information, please see the section titled Contributions of authors.

Investigators in some trials randomized participants to multiple intervention and control groups or both (more than two groups, as in dose-finding studies). We combined all relevant experimental intervention groups into a single intervention group and combined all relevant control intervention groups into a single control group (Higgins 2011).

Assessment of risk of bias in included studies

We evaluated the validity and design characteristics of each trial. To draw conclusions about the overall risk of bias for an outcome, we found it necessary to evaluate trials for major sources of bias, also defined as domains (random sequential generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other bias). Assessment of overall risk of bias involved consideration of the relative importance of the different domains (Higgins 2011).

Even the most realistic assessment of the validity of a trial may involve subjectivity because it was impossible to know the extent of bias (or even the true risk of bias) of a given trial. Some domains affected risk of bias across trial outcomes (e.g. sequential generation, allocation sequential concealment), and others, such as blinding and incomplete outcome data, may have had different risks of bias for different outcomes within a trial. Thus, risk of bias was not the same for all outcomes in a trial. We performed separate sensitivity analyses for patient-reported outcomes (subjective outcomes; e.g. upper airway discomfort) and for mortality (Higgins 2011).

We defined trials as having low risk of bias only if they adequately fulfilled the criteria listed in the *Cochrane Handbook for Systematic Reviews of Interventions*, and we performed summary assessments of risk of bias for each important outcome (across domains) within and across studies. We applied a 'risk of bias graph' and a 'risk of bias summary figure' (Higgins 2011).

We presented results for all outcomes including adverse events in a 'Summary of findings' table (Higgins 2011).

As no sufficiently well-designed formal statistical method is available to combine the results of trials with high and low risk of bias, Cochrane review authors usually incorporate risk of bias assessments by comparing meta-analyses of trials with low risk and high or uncertain risk of bias (Higgins 2011). We used the risk of bias table described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 8.5) (Higgins 2011) as a tool for assessing risk of bias in included studies. We assessed risk of bias for different domains as described below.

Random sequence generation

Low risk of bias: The method used generates random sequences (e.g. random number generation, toss of coin).

Unclear: No information on random sequence generation is available.

High risk of bias: Alternate medical record numbers or other non-random sequence generation was used.

Allocation concealment

Low risk of bias: Allocation method prevents investigators or participants from knowing the next allocation (e.g. central allocation; sealed opaque envelopes; serially numbered, sequentially numbered but otherwise identical vehicles, including their contents; other descriptions of convincing concealment of allocation).

Unclear: No information on allocation method is available, or the description provided did not allow a clear distinction.

High risk of bias: Allocation method allowed investigators or participants to know the next allocation (e.g. alternate medical record numbers; reference to case record numbers or date of birth; open allocation sequence, unsealed envelopes).

Blinding

Low risk of bias: We considered blinding as adequate if participants and personnel were kept unaware of intervention allocations after

participants were enrolled into the study, and if the method of blinding involved placebo.
Unclear: Blinding was not described.
High risk of bias: Study was not double-blinded; was categorized as an open-label study; or was conducted without use of placebo.

Incomplete outcome data

Low risk of bias: Numbers and reasons for dropouts and withdrawals in the intervention groups were described, or it was specified that no dropouts or withdrawals occurred.
Unclear: The report gave the impression that no dropouts or withdrawals had occurred, but this was not specifically stated.
High risk of bias: Numbers and reasons for dropouts and withdrawals were not described.

Selective reporting

Low risk of bias: Report includes predefined or clinically relevant and reasonably expected outcomes.
Unclear: Study did not report or did not report fully all predefined or clinically relevant and reasonably expected outcomes, or it is unclear whether data on these outcomes were recorded.
High risk of bias: Report did not include one or more clinically relevant and reasonably expected outcomes; data on these outcomes were likely to have been recorded.

Baseline imbalance

Low risk of bias: We noted no baseline imbalance in important characteristics.
Unclear: Baseline characteristics were not reported.
High risk of bias: Baseline imbalance was due to chance or to imbalanced exclusion after randomization.

Measures of treatment effect

Most often, a dichotomous outcome measure is used to assess whether an intubation is difficult or not. We reported all dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI). For mortality, which we expected to be a rare outcome, we calculated the Peto odds ratio.

Unit of analysis issues

We planned to include studies with a non-standard design, such as cluster-randomized trials and studies with more than two intervention groups. We considered 'cross-over trials', 'repeated observations on participants', and 'multiple treatment attempts' as unlikely designs for evaluating the current intervention. We included all studies with a non-standard design and analysed them as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We contacted all first authors and contact persons of trials with missing data to retrieve relevant data. We performed a modified intention-to-treat (ITT) analysis while including, if possible, all randomized participants who underwent tracheal intubation or did not withdraw their consent before surgery.
ITT analysis is recommended to minimize bias in design, follow-up, and analysis of the efficacy of RCTs. It yields a pragmatic estimate of the benefit of a change in treatment policy rather than of potential benefit for patients who received treatment exactly as planned (Hollis 1999). Full application of ITT is possible only when complete outcome data are available for all randomized participants. Although about half of all published reports of RCTs state that ITT was used, handling of deviations from randomized allocation varies widely, and many trials have missing data for the primary outcome variable; methods used to deal with this are generally inadequate, potentially leading to bias (Hollis 1999).
Performing an ITT analysis in a systematic review is not straightforward in practice, in that review authors must decide how to handle missing outcome data from contributing trials (Gamble 2005). No consensus exists about how missing data should be handled in ITT analyses, and different approaches may be appropriate in different situations (Higgins 2011; Hollis 1999).
In the case of missing data, we used a 'complete-case analysis' for our primary outcomes, which simply excluded all participants for whom outcome data were missing from the analysis. Additionally, we performed sensitivity analyses covering best- and worst-case scenarios (with 'best' and 'worst' defined with respect to effect on the chosen outcome with use of NMBA).

Assessment of heterogeneity

We quantified the degree of heterogeneity observed in the results using diversity (D^2) (Wetterslev 2009) and inconsistency factor (I^2) statistics, which we interpreted as the proportion of total variation observed between trials that was attributable to differences between trials rather than to sampling error (chance) (Higgins 2002). A finding of $P \leq 0.10$ indicated significant heterogeneity, and the I^2 statistic has suggested thresholds for low (25% to 49%), moderate (50% to 74%), and high (≥ 75%) heterogeneity (Higgins 2003). If $I^2 = 0\%$, we reported only results from the fixed-effect model. In the case of $I^2 > 0\%$, we reported results from both random-effects and fixed-effect models. However, we believe that use of a fixed-effect model provided little value in cases of substantial heterogeneity, which we suspected would be the case in this review owing to inclusion of various patient types, adjuvant medicines, and outcome reporting. So we emphasized results from the random-effects model unless a few trials dominated the meta-analysis (e.g. > 50% of the accumulated fixed weight percentage). In cases of $I^2 > 0\%$ (for mortality and difficult intubation outcomes), we explored possible causes of heterogeneity by performing meta-regression analyses and relevant subgroup and sensitivity

analyses. We aimed to meta-analyse trial results only in cases of low to moderate clinical heterogeneity.

Assessment of reporting biases

Publication bias occurs when publication of research results depends on their nature and direction (Dickersin 1990). We examined this by creating funnel plots to detect publication bias or a difference between small and large studies ('small study effects') expressed by asymmetry (Egger 1997). In cases of asymmetry, we applied the Arcsine-Thompsen test, as proposed by Rücker (Rücker 2008). We defined funding bias as bias in the design, outcome, and reporting of industry-sponsored research to show that a drug has a favourable outcome (Bekelman 2003). Relationships between industry, scientific investigators, and academic institutions are widespread and often result in conflicts of interest (Bekelman 2003). We conducted a sensitivity analysis to examine the role of funding bias.

Data synthesis

We used Review Manager Software (RevMan 5.3). We calculated the RR with 95% CIs for dichotomous variables (binary outcomes) as well as the risk difference (Keus 2009), but if results were similar, we reported only the RR. We used D^2 (Wetterslev 2009) and the I^2 statistic (Higgins 2002) to describe heterogeneity among included trials. We planned to explore causes of substantial heterogeneity by performing meta-regression using Comprehensive Meta-Analysis (CMA), version one, and Stata, version nine. We used the Chi ^{2} test to provide an indication of heterogeneity between studies, with $P \leq 0.10$ considered significant.

Adverse effects may be rare but serious and hence important (Sutton 2002) when meta-analysis is applied in combining results from several trials with binary outcomes (i.e. event or no event). Most meta-analytical software packages do not include options for analyses that include trials with 'zero event' in both arms (intervention vs control) for calculating RR. Exempting these trials from calculation of RR and CI may lead to overestimation of a treatment effect, as the control event proportion may be overestimated. Thus we performed a sensitivity analysis by applying empirical continuity corrections to our zero event trials, as proposed by Sweeting et al (Keus 2009; Sweeting 2004), and by applying imaginary small numbers in both arms.

Meta-analyses may result in type I errors due to systematic errors (bias) or may produce random errors due to repeated significance testing when meta-analyses are updated with new trials (Brok 2008; Brok 2009; Thorlund 2009; Wetterslev 2008; Wetterslev 2009). Bias from trials with high risk of bias, outcome reporting bias, publication bias, early stopping for benefit, and small trial bias may result in spurious P values.

In a single trial, interim analysis increases the risk of type I errors. To avoid type I errors, we applied group sequential monitoring boundaries (Lan 1983) to decide whether a trial could be terminated early because of a sufficiently small P value, that is, when the cumulative z-curve crosses the monitoring boundary. Sequential monitoring boundaries can be applied to meta-analyses; these are called trial sequential monitoring boundaries. In trial sequential analysis (TSA), the addition of each trial to a cumulative meta-analysis is regarded as an interim meta-analysis and helps to show whether additional trials are needed (Wetterslev 2008). So far, several meta-analyses and reviews have been published, and these have included increasing trial results as new trials have been published (Al-Niaimi 2009; Chura 2007; Qadan 2009). Therefore, it seems appropriate to adjust new meta-analyses for multiple testing on accumulating data to control the overall type 1 error risk in cumulative meta-analysis (Pogue 1997; Pogue 1998; Thorlund 2009; Wetterslev 2008).

The idea in TSA is that if the cumulative z-curve crosses a boundary, a sufficient level of evidence is reached and no further trials may be needed. However, evidence is insufficient to permit a conclusion if the z-curve does not cross a boundary or does not surpass the required information size. To construct trial sequential monitoring boundaries (TSMB), the required information size is needed and will be calculated as the least number of participants needed to conduct a well-powered single trial (Brok 2008; Pogue 1998; Wetterslev 2008). We adjusted the required information size for heterogeneity by applying a D^2 adjustment factor (Wetterslev 2009). We will apply TSA because it prevents an increase in the risk of type I error (< 5%) caused by potential multiple updating and testing on accumulating data whenever new trial results are included in a cumulative meta-analysis (Pogue 1997; Pogue 1998) and provides important information needed to estimate the level of evidence for the experimental intervention (Pogue 1997; Pogue 1998; Thorlund 2009). Additionally, TSA provides important information regarding the need for additional trials and required information size (Wetterslev 2008; Wetterslev 2009). We applied TSMB according to an information size suggested by trials with low risk of bias (Wetterslev 2008; Wetterslev 2009), an *a priori* 20% relative risk reduction (RRR) of difficult or failed intubation, and an intervention effect suggested by the 95% confidence limit closest to 1 in the traditional random-effects meta-analysis. As mortality seems low or even absent in the trials conducted so far, and hence the ability to detect small intervention effects is low, we also planned to perform a TSA with an information size estimated on the basis of an a priori 50% RRR of mortality (Wetterslev 2008; Wetterslev 2009).

Subgroup analysis and investigation of heterogeneity

We performed the following subgroup analyses of our primary outcomes.

1. Avoidance of NMBA versus use of NMBA (comparisons of subgroups of depolarizing vs non-depolarizing NMBA).
2. Avoidance of NMBA versus use of NMBA in combination with or without remifentanil or alfentanil.

3. Avoidance of NMBA versus use of NMBA in combination with or without local anaesthetic drug.

4. Avoidance of NMBA versus use of NMBA (comparisons of subgroups of trials using anticipation of a difficult airway as an inclusion criterion vs those not using anticipation of a difficult airway as an inclusion criterion).

When analyses of various subgroups with a binary outcome were significant, we performed a test of interaction (Altman 2003). We considered $P < 0.05$ to be indicative of significant interaction between the effect of no use of NMBA on DTI and the subgroup category (Higgins 2011; Chapters 9.6.1 and 9.7).

We planned to explore causes of moderate to high heterogeneity using meta-regression including the covariates listed below. We ranked these covariates according to their importance and included them in the meta-regression according to the number of relevant trials included in this review.

1. Mean age of trial population at baseline.
2. Fraction of gender of trial population at baseline.
3. Fraction of a Mallampati score grade I to IV.
4. Thyromental distance (dichotomous or continuous measurement).
5. Mouth opening or interincisor gap (dichotomous or continuous measurement).
6. Neck extension (dichotomous or continuous measurement).
7. Mandible subluxation (dichotomous or continuous measurement).
8. Mean body mass index (BMI) of trial population at baseline.
9. Time from induction to start of intubation (seconds).

Sensitivity analysis

We performed a sensitivity analysis to evaluate the impact of trials with high or uncertain risk of bias versus trials with low risk of bias.

'Summary of findings' tables

We used the principles of the GRADE system (Guyatt 2013; Guyatt 2011) to assess the quality of the body of evidence associated with specific outcomes.

1. DTI.
2. All-cause mortality (maximal follow-up data from each trial).
3. One or more events of upper airway discomfort or injury (e.g. sore throat, hoarseness, vocal cord lesion, minor pharyngeal injury).
4. One or more major serious events (defined by pulmonary aspiration, brain and heart injuries (caused by e.g. anoxia, hypotension, bradycardia, or tachycardia during tracheal intubation)).
5. Difficult laryngoscopy, defined by the Cormack and Lehane score (Cormack 1984) or the modified Cormack Lehane score (Yentis 1998).

The GRADE approach appraises the quality of a body of evidence according to the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Quality considers:

1. within-study risk of bias (methodological quality);
2. directness of the evidence;
3. heterogeneity of the data;
4. precision of effect estimates; and
5. risk of publication bias.

RESULTS

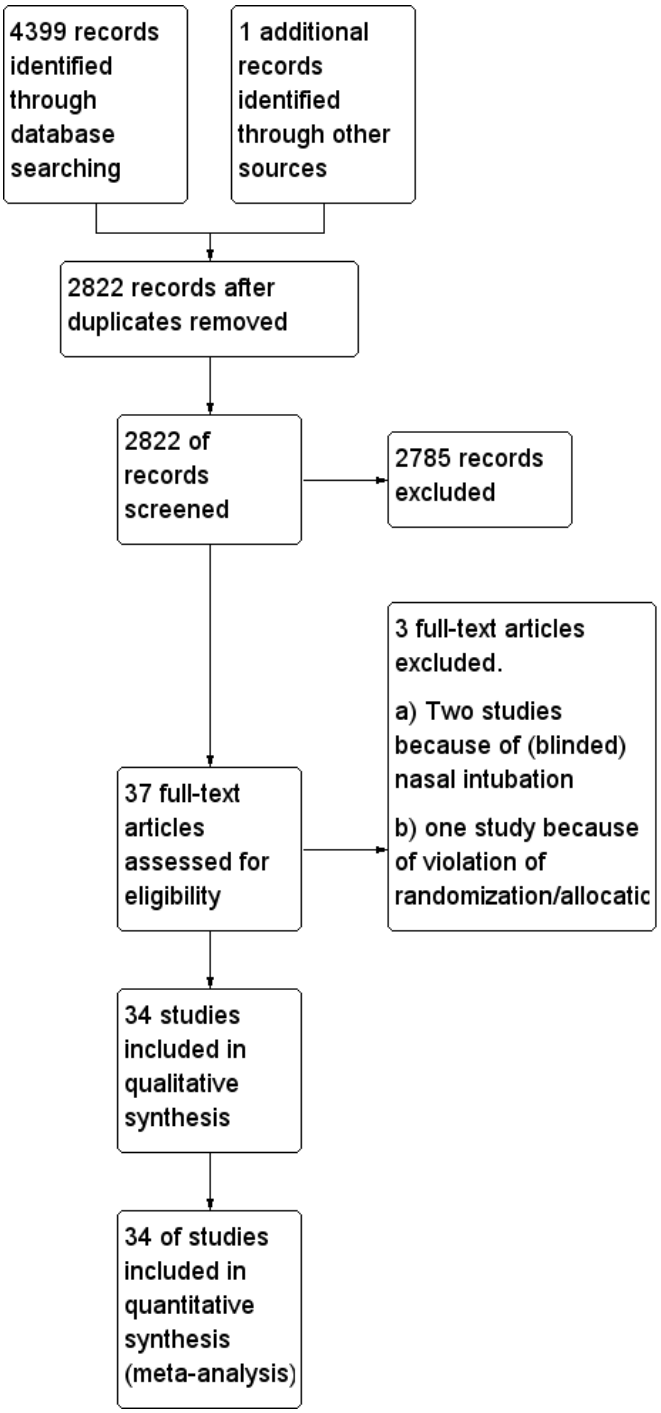
Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We identified 4400 references through electronic and manual searches (Figure 1). We updated the search on 11 January 2017. After excluding duplicate reports, we screened the abstracts of 2822 references. We obtained 37 publications for full-text review. Thirty-four publications were RCTs and met our inclusion criteria for the comparison of avoiding NMBA or using NMBA to facilitate tracheal intubation.

Figure 1. Study flow diagram.



Included studies

Most of the trials identified for this comparison were published in English. Two trials were published in French (Dominici 1990; Rousseau 1995), one in German (Striebel 1995), and one in Spanish (González Obregón 2010). Included trials enrolled 3565 participants, 1507 of whom were randomized to no use of NMBA, and 2058 to use of NMBA. Table 1 shows characteristics of the 34 included trials, and Table 2 shows characteristics of the interventions. The number of randomized participants included in individual trials ranged from 40 to 300.

Trial design

All 34 studies were RCTs using parallel design. Eighteen dose-finding studies comprised more intervention or control groups, or both (Alexander 1999; Barclay 1997; Kahwaji 1997; Kirkegaard-Nielsen 1999; Kopman 2001; Lieutaud 2003; Lowry 1999; McNeil 2000; Naguib 2003; Naguib 2006; Nimmo 1995; Pino 1998; Scheller 1992; Schlaich 2000; Sivalingam 2001; Stevens 1997; Striebel 1995; Wong 1996) A total of 16 trials included one intervention group and one control group (Beck 1993; Bouvet 2008; Combes 2007; Dominici 1990; González Obregón 2010; Gulhas 2013; Hanna 2010; Harsten 1997; Iamaroon 2001; Isesele 2012; Jiao 2014; Mencke 2003; Mencke 2014; Pang 2014; Rousseau 1995; Yazdi 2016).

Trial participants

All included trials except one (Barclay 1997) enrolled only American Society of Anesthesiologists (ASA) class I and III participants. A total of 25 trials (Alexander 1999; Barclay 1997; Bouvet 2008; Combes 2007; González Obregón 2010; Hanna 2010; Iamaroon 2001; Isesele 2012; Kahwaji 1997; Lieutaud 2003; Lowry 1999; McNeil 2000; Mencke 2003; Mencke 2014; Naguib 2003; Naguib 2006; Pang 2014; Pino 1998; Rousseau 1995; Scheller 1992; Schlaich 2000; Sivalingam 2001; Stevens 1997; Wong 1996; Yazdi 2016) excluded participants with anticipated DTI, and 13 trials excluded obese participants and overweight participants (Barclay 1997; Combes 2007; Iamaroon 2001; Jiao 2014; Kirkegaard-Nielsen 1999; Kopman 2001; Lowry 1999; McNeil 2000; Mencke 2003; Mencke 2014; Pang 2014; Pino 1998; Stevens 1997). Definitions of 'obese' and 'overweight' varied among trials. We accepted the definitions presented by study authors in the individual articles.

Characteristics of interventions

Investigators in 18 trials used suxamethonium as the depolarization NMBA (Alexander 1999; Beck 1993; Dominici 1990; Gulhas 2013; Hanna 2010; Harsten 1997; Iamaroon 2001; Isesele 2012; Jiao 2014; McNeil 2000; Naguib 2003; Naguib 2006; Nimmo 1995; Scheller 1992; Sivalingam 2001; Stevens 1997; Striebel 1995; Wong 1996), and researchers in 18 trials used one or more non-depolarizing NMBA (Barclay 1997; Bouvet 2008; Combes 2007; González Obregón 2010; Hanna 2010; Kahwaji 1997; Kirkegaard-Nielsen 1999; Kopman 2001; Lieutaud 2003; Lowry 1999; Mencke 2003; Mencke 2014; Pang 2014; Pino 1998; Rousseau 1995; Schlaich 2000; Striebel 1995; Yazdi 2016). Thus, two trials (Hanna 2010; Striebel 1995) combined depolarizing and non-depolarizing NMBA as the intervention. Among trials using one or more non-depolarizing NMBA, 10 applied rocuronium (Barclay 1997; Combes 2007; González Obregón 2010; Hanna 2010; Kirkegaard-Nielsen 1999; Kopman 2001; Lowry 1999; Mencke 2014; Pino 1998; Schlaich 2000). Three trials applied atracurium (Lieutaud 2003; Mencke 2003; Yazdi 2016), two trials vecuronium (Rousseau 1995; Striebel 1995), and two trials rapacuronium (Kahwaji 1997; Kopman 2001). Single trials applied both cisatracurium (Bouvet 2008) and mivacurium (Pino 1998), respectively.

Characteristics of outcome measures

In 16 trials, investigators described intubation conditions by the original (Alexander 1999; Bouvet 2008; Combes 2007; Hanna 2010; Jiao 2014; Kirkegaard-Nielsen 1999; Kopman 2001; Lowry 1999; Mencke 2003; Naguib 2003; Naguib 2006 Schlaich 2000) or a modified (Barclay 1997; Harsten 1997; Kahwaji 1997; Mencke 2014) version of "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996). Thirteen trials reported laryngoscopy conditions defined by the criteria described by Cormack and Lehane (Cormack 1984) (Beck 1993; Bouvet 2008; Combes 2007; Dominici 1990; González Obregón 2010; Harsten 1997; McNeil 2000; Mencke 2003; Mencke 2014; Pang 2014; Scheller 1992; Stevens 1997; Striebel 1995). Seven studies reported events of upper airway discomfort or injury (Bouvet 2008; Combes 2007; González Obregón 2010; Gulhas 2013; Mencke 2003; Mencke 2014; Sivalingam 2001).

Excluded studies

We excluded three trials. One study intubated an unspecified number of participants blind nasal (Alcock 1993), and another (Ide 2015) intubated participants nasally using a Magill forceps. One trial terminated inclusion of participants exclusively in the intervention group because of unacceptable intubation conditions. Thus, this trial violated randomization and blinding as planned (Baumgarten 1988) (see Characteristics of excluded studies for more information).

Studies awaiting classification

No studies are awaiting classification.

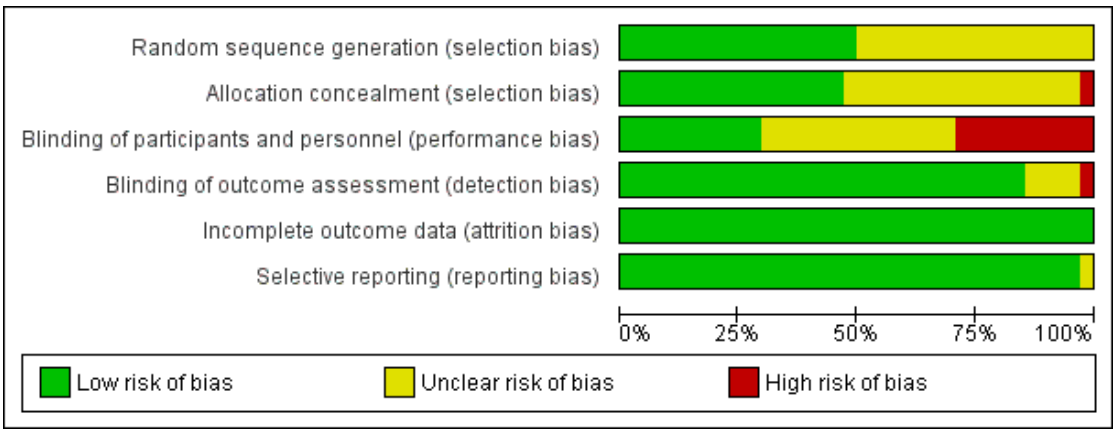
Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

We performed the 'Risk of bias' assessment of included trials using previously described criteria. For details of judgements made for individual trials, please see Risk of bias in included studies (Figure 2). When we could not judge a 'Risk of bias' domain as having low risk, we asked study authors for additional information.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



We judged four trials as having low risk of bias in all domains (Jiao 2014; Mencke 2003; Naguib 2003; Naguib 2006), and 13 trials as having high risk of bias in at least one bias domain. We divided trials into trials with overall low risk of bias and those with high or uncertain risk of bias according to assessment of sequence generation, concealment of allocation, blinding of outcome assessment, and blinding of participants and personnel according to the *Cochrane Handbook for Systematic Reviews of Interventions* 'Risk of bias' tool. When we judged all domains as adequately assessed, we considered the trial as having an overall low risk of bias.

Random sequence generation

Seventeen trials adequately described generation of the allocation sequence (Alexander 1999; Bouvet 2008; Dominici 1990; González Obregón 2010; Gulhas 2013; Harsten 1997; Jiao 2014; Kopman 2001; Lieutaud 2003; Lowry 1999; Mencke 2003; Mencke 2014; Naguib 2003; Naguib 2006; Pang 2014; Pino 1998; Rousseau 1995). The remaining trials were described as randomized, but investigators did not adequately describe the method used for sequence generation.

Allocation

Sixteen trials adequately described the method used to conceal allocation (Bouvet 2008; Combes 2007; González Obregón 2010; Hanna 2010; Harsten 1997; Isesele 2012; Jiao 2014; Kirkegaard-Nielsen 1999; Lieutaud 2003; McNeil 2000; Mencke 2003; Mencke 2014; Naguib 2003; Naguib 2006; Sivalingam 2001; Stevens 1997). We categorized one trial as having high risk of bias (Kopman 2001) and judged the method used for allocation concealment as unclear for the remaining 16 trials.

Blinding

Ten trials adequately described the method used to blind participants and personnel responsible for treatment (Combes 2007; Gulhas 2013; Jiao 2014; Mencke 2003; Naguib 2003; Naguib 2006; Nimmo 1995; Stevens 1997; Striebel 1995; Wong 1996). We categorized ten trials as having high risk of bias (Bouvet 2008; González Obregón 2010; Harsten 1997; Kopman 2001; Lieutaud 2003; Lowry 1999; McNeil 2000; Mencke 2014; Rousseau 1995; Scheller 1992) and judged the method used to blind participants and personnel responsible for the treatment as unclear for the remaining trials.

All except five trials adequately described the method used to blind the person performing airway management and outcome assessment. We judged four trials as having unclear risk of bias (Isesele 2012; Nimmo 1995; Rousseau 1995; Yazdi 2016) and one trial as having high risk of bias (Scheller 1992).

Incomplete outcome data

All trials adequately addressed incomplete data. Most trials provided complete outcome data for all randomized participants. However, six trials (Bouvet 2008; Combes 2007; Hanna 2010; Isesele 2012; Kahwaji 1997; Pino 1998) excluded a few participants from the ITT because "patients were lost to follow-up", or because investigators encountered missing data or equipment failure or various clinical reasons for exclusion. In six trials (Harsten 1997; Jiao 2014; Mencke 2003; Mencke 2014; Nimmo 1995; Sivalingam 2001), study authors excluded a few participants from ITT if tracheal intubation failed. We have provided further details in the Characteristics of included studies table.

Selective reporting

All trials adequately addressed selective reporting bias, except one trial for which we judged risk as unclear (Nimmo 1995).

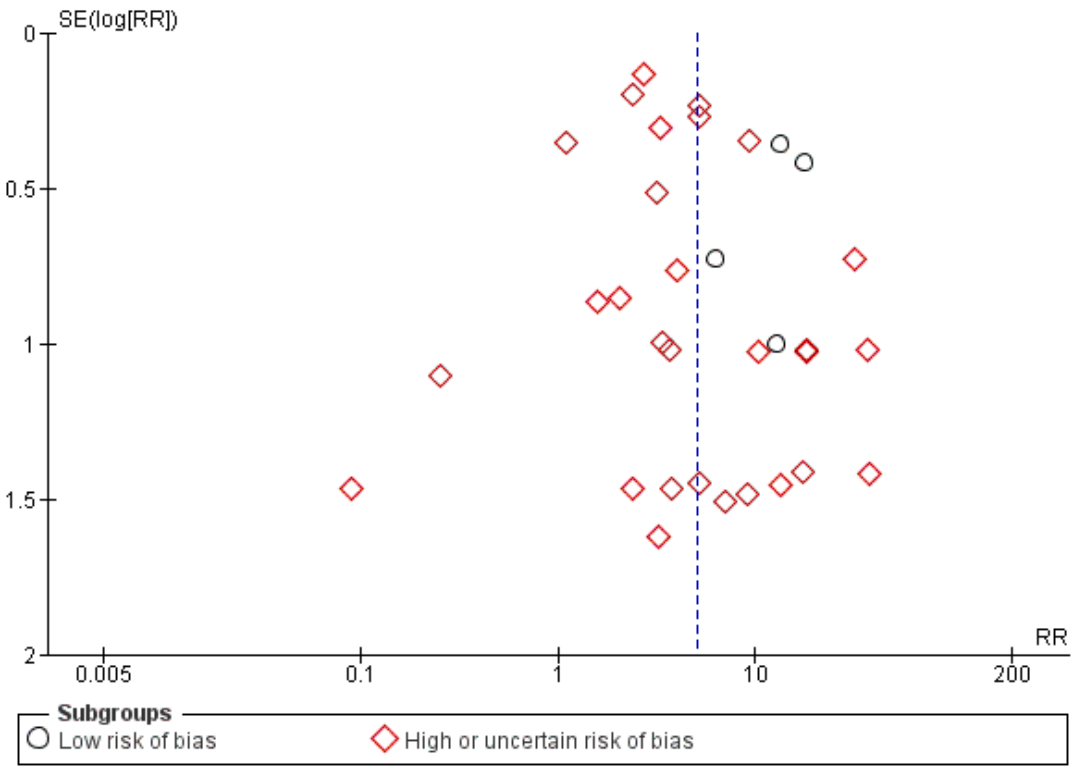
Other potential sources of bias

We did not assess other potential sources of bias.

Assessment of reporting bias

The funnel plots that we have provided for our primary outcomes did not express asymmetry and thereby did not indicate publication bias (Figure 3).

Figure 3. Funnel plot of comparison: 1 Avoidance vs use of NMBA, outcome: 1.1 Difficult tracheal intubation: low risk of bias vs high or uncertain risk of bias.



Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings table: primary and secondary outcomes

See our main results on all investigated outcomes in the 'Summary of findings' table (Summary of findings for the main comparison), which presents assessment of the quality of the evidence, including imprecision, according to the GRADE approach (Guyatt 2013; Guyatt 2011).

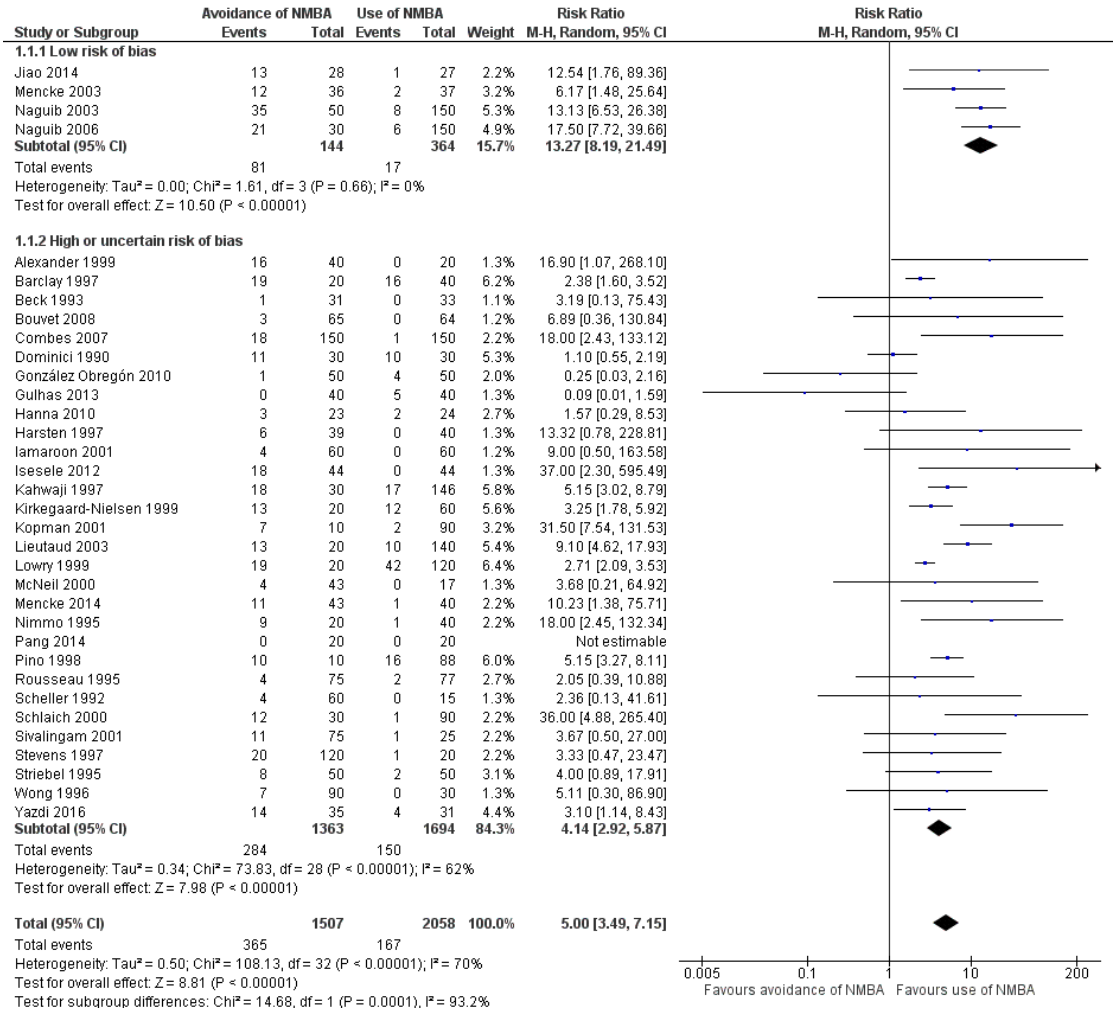
Primary outcome: difficult tracheal intubation

Difficult tracheal intubation in trials with low risk of bias (Analysis 1.1)

We categorized four trials (Jiao 2014; Mencke 2003; Naguib 2003; Naguib 2006) with 508 participants as trials with low risk of bias. Among 144 participants undergoing tracheal intubation without the use of NMBA, investigators intubated a crude proportion of 56.3% (n = 81; 95% CI 49.3% to 64.4%) with difficulties. The median prevalence of a DTI in the individual studies was 58.2% (range 33% to 70%). Of 364 participants intubated with the use of NMBA, the proportion of DTI was 4.7% (n = 17; 95% CI 2.8% to 6.8%). The median prevalence of a DTI among individual studies was 4.7% (range 3.7% to 5.4%). In a random-effects model, risk of DTI was increased with no use of NMBA (RR 13.27, 95% CI 8.19 to 21.49; P < 0.00001; number needed to treat for an additional harmful outcome (NNTH) = 1.9, I^2 = 0%, D^2 = 0%), likewise in a fixed-effect model (RR 12.50, 95% CI 7.62 to 20.52; P < 0.00001). Comparisons of subgroups in trials with low risk of bias and trials with high or uncertain risk of bias revealed significant subgroup differences (P = 0.0002). Among trials of high or uncertain risk, avoidance of NMBA was associated with DTI in a random-effects model (RR 4.23, 95% CI 2.93 to 6.09; P < 0.00001; NNTH = 8.7, I^2 = 64%). We performed TSA of non-NMBA versus NMBA using a D^2-adjusted required information size of 8195 participants to detect or reject a 20% relative risk increase with power of 80%, a control event proportion of 8%, and an overall type 1 error of 5%. The cumulative z-curve crossed the TSMB for harm, and the TSA-adjusted CI for the

RR was 1.85 to 95.04. These findings provide firm evidence of the smallest possible harmful effect on the proportion of DTI in the traditional meta-analysis of avoiding NMBA compared with using NMBA, even when the significance level was adjusted for repetitive testing and sparse data in a cumulative meta-analysis. We downgraded the quality of the evidence (GRADE) one level to moderate because of indirectness (Analysis 1.1; Figure 4).

Figure 4.



Difficult tracheal intubation in all trials (Analysis 1.1)

A total of 34 trials with 3565 participants provided data on DTI. Among 1507 participants undergoing tracheal intubation without the use of NMBA, a crude proportion of 24.2% (n = 365; 95% CI 22.4% to 26.4%) were intubated with difficulties. The median prevalence of a DTI among individual studies was 29.5%

(interquartile range 7.0% to 60.0%). Of 2058 participants intubated with the use of NMBA, the crude proportion of DTI was 8.1% (n = 167; 95% CI 7.1% to 9.3%). The median prevalence of a DTI among individual studies was 3.9% (interquartile range 0.0% to 8.3%). In a random-effects model, avoidance of NMBA significantly increased the risk of a DTI with direct laryngoscopy (RR 5.00, 95% CI 3.49 to 7.15; P < 0.00001; NNTH = 6.3, I^2 = 70%, D^2 = 82%). In a fixed-effect model, RR was 4.79 (95% CI 4.04 to 5.69; P < 0.0001). Our TSA of all included trials did not contradict our findings in trials with low risk of bias. Again, the cumulative z-curve crossed the TSMB for harm, and the TSA-adjusted CI for the RR was 1.20 to 20.77. These findings provide evidence of the smallest possible harmful effect on the proportion of DTI in the traditional meta-analysis of avoiding NMBA compared with using NMBA, even when the significance level was adjusted for repetitive testing and sparse data in a cumulative meta-analysis. We downgraded the quality of the evidence (GRADE) two levels to low because of indirectness, heterogeneity, and high or uncertain risk of bias (Analysis 1.1; Figure 4).

Subgroup analyses of difficult tracheal intubation

Depolarizing versus non-depolarizing NMBA (Analysis 1.2)

In the subgroup of trials that used depolarizing NMBA, risk of DTI was increased with no use of NMBA (RR 5.79, 95% CI 2.64 to 12.72; P < 0.0001; NNTH = 5.6, I^2 = 69%). Likewise, in the subgroup using non-depolarizing NMBA, DTI was associated with no use of NMBA (RR 4.72, 95% CI 3.17 to 7.02; P < 0.0001; NNTH = 5.8, I^2 = 74%). Results show no significant subgroup differences (P = 0.65) (Analysis 1.2).

Remifentanil versus other opioids (Analysis 1.3)

Investigators in 11 trials (Alexander 1999; Bouvet 2008; González Obregón 2010; Gulhas 2013; Hanna 2010; Jiao 2014; McNeil 2000; Mencke 2014; Pang 2014; Schlaich 2000; Yazdi 2016) used remifentanil as an opioid. However, researchers in four studies (Alexander 1999; Hanna 2010; McNeil 2000; Yazdi 2016) used remifentanil only in the intervention groups and used no opioids in the control group. One (Alexander 1999) of the three trials used remifentanil and alfentanil as opioids in two different intervention groups. Another three trials (González Obregón 2010; Gulhas 2013; Jiao 2014) used an amount of remifentanil in the intervention group that exceeded the amount used in the control group. Among trials using equal amounts of remifentanil in intervention and control groups (Bouvet 2008; Mencke 2014; Pang 2014; Schlaich 2000), results showed significantly increased risk of DTI when NMBA was avoided for tracheal intubation (RR 15.86, 95% CI 4.43 to 56.71; P < 0.0001; NNTH = 6.4, I^2 = 0%). In trials in which opioids other than remifentanil were used, avoiding NMBA was significantly associated with DTI (RR 5.20, 95% CI 3.53 to 7.64; P < 0.0001; NNTH = 6.5, I^2 = 74%). Results showed no significant subgroup differences (P = 0.10). One trial provided no opioids (Isesele 2012) (Analysis 1.3).

Alfentanil versus other opioids (Analysis 1.4)

Thirteen trials (Alexander 1999; Barclay 1997; Beck 1993; Combes 2007; Dominici 1990; Harsten 1997; Kopman 2001; Nimmo 1995; Rousseau 1995; Scheller 1992; Sivalingam 2001; Stevens 1997; Wong 1996) used alfentanil as the opioid. Five trials (Alexander 1999; Beck 1993; Scheller 1992; Stevens 1997; Wong 1996) used alfentanil only in the intervention group and used no opioids in the control group. One of the five trials used remifentanil and alfentanil as opioids in two different intervention groups (Alexander 1999). In two trials, the amount of alfentanil used in the intervention group exceeded the amount used in the control group (Combes 2007; Sivalingam 2001). The six trials with equal amounts of alfentanil in the intervention and control groups reported significantly increased risk of DTI when NMBA was avoided for tracheal intubation (RR 4.46, 95% CI 1.66 to 11.98; P = 0.0002; I^2 = 79%, NNTH = 5.2) (Barclay 1997; Dominici 1990; Harsten 1997; Kopman 2001; Nimmo 1995; Rousseau 1995). In trials using opioids other than alfentanil, risk of DTI was increased when NMBA was avoided (RR 5.10, 95% CI 3.34 to 7.79; P < 0.0001; I^2 = 72%, NNTH = 4.8). Results showed no significant subgroup differences (P = 0.81). One trial provided no opioids (Isesele 2012) (Analysis 1.4).

Local anaesthetic versus no use of local anaesthetic (Analysis 1.5)

Eight trials used a local anaesthetic. However, three trials (Isesele 2012; Rousseau 1995; Stevens 1997) used a local anaesthetic only in the intervention group - not in the control group. Thus, we included five trials (Barclay 1997; Dominici 1990; Hanna 2010; Pang 2014; Striebel 1995) that used local anaesthesia for intubation in both control and intervention groups. In comparisons of trials using local anaesthesia versus trials not using local anaesthesia, risk of DTI was increased with no use of NMBA. With use of local anaesthesia, the RR was 1.90 (95% CI 1.14 to 3.18; P = 0.01; NNTH = 9.4, I^2 = 35%), and with no use of local anaesthesia, the RR was 6.26 (95% CI 4.15 to 9.44; P < 0.0001; NNTH = 5.7, I^2 = 69%), respectively. Results showed significant subgroup differences (P < 0.0001) (Analysis 1.5).

Exclusion of patients with expected DTI versus no exclusion of patients with expected DTI (Analysis 1.6)

In the subgroup in which patients with expected DTI were excluded from the individual trials, risk of DTI was significantly increased when NMBA was avoided (RR 5.32, 95% CI 3.54 to 8.00; P < 0.00001; NNTH = 6.3, I^2 = 72%). In the subgroup in which patients with expected DTI were not excluded, risk of DTI was

significantly increased when NMBA was avoided (RR 4.40, 95% CI 1.71 to 11.29; P = 0.0002; NNTH = 5.7, I^2 = 74%). Results showed no significant subgroup differences (P = 0.72) (Analysis 1.6).

Explorative assessments of difficult tracheal intubation

A best-case scenario (Analysis 1.7)

A total of 18 trials were dose-finding studies that included more intervention or control groups, or both (Alexander 1999; Barclay 1997; Kahwaji 1997; Kirkegaard-Nielsen 1999; Kopman 2001; Lieutaud 2003; Lowry 1999; McNeil 2000; Naguib 2003; Naguib 2006; Nimmo 1995; Pino 1998; Scheller 1992; Schlaich 2000; Sivalingam 2001; Stevens 1997; Striebel 1995; Wong 1996). In attempting to estimate a sufficient level of intervention or adjuvant drugs, or both, these trials may have included intervention or control groups, or both, in which participants were suboptimally anaesthetized. Therefore, we performed a supplementary sensitivity analysis of a best-case scenario. Here, dose-finding studies were represented only by control and intervention groups with the lowest prevalence of difficult intubation. Among 1180 participants undergoing tracheal intubation without the use of NMBA, a crude proportion of 25.0% (n = 295; 95% CI 22.9% to 27.5%) were intubated with difficulties. Among 1230 participants intubated with the use of NMBA, the crude proportion of DTI was 3.4% (n = 42; 95% CI 2.5% to 4.4%). Avoidance of NMBA significantly increased the risk of DTI with direct laryngoscopy (RR 5.99, 95% CI 3.46 to 10.38; P < 0.0001; NNTH = 4.4, I^2 = 57%) (Analysis 1.7).

Excluding dose-finding studies (Analysis 1.8)

In our attempt to exclude comparisons of suboptimal anaesthetic dosing regimens, we performed a sensitivity analysis that excluded all dose-finding trials. Thus we included 16 trials that had one intervention group and one control group (Beck 1993; Bouvet 2008; Combes 2007; Dominici 1990; González Obregón 2010; Gulhas 2013; Hanna 2010; Harsten 1997; Iamaroon 2001; Isesele 2012; Jiao 2014; Mencke 2003; Mencke 2014; Pang 2014; Rousseau 1995; Yazdi 2016). Among 769 participants undergoing tracheal intubation without the use of NMBA, a crude proportion of 15.5% (n = 119; 95% CI 13.3% to 18.0%) were intubated with difficulties. Among 767 participants intubated with the use of NMBA, the crude proportion of DTI was 4.2% (n = 32; 95% CI 3.0% to 5.6%). Avoidance of NMBA significantly increased the risk of DTI (RR 3.40, 95% CI 1.63 to 7.10; P = 0.001; NNTH = 8.8, I^2 = 59%).

We wanted to explore possible causes of heterogeneity by performing meta-regression analyses. However, owing to a low degree of heterogeneity in trials with low risk of bias in terms of DTI, we did not perform these assessments. Regarding our other secondary outcome, we categorized only one trial describing upper airway discomfort and/or injury as having low risk of bias. Among all trials describing upper airway discomfort or injury, or both, we found no heterogeneity; thus we performed no meta-regression analysis (Analysis 1.8).

Funding from pharmaceutical industry (Analysis 1.9)

We identified 10 trials that reported funding from the pharmaceutical industry (Barclay 1997; Hanna 2010; Harsten 1997; Iamaroon 2001; Kahwaji 1997; Kopman 2001; Lowry 1999; Pino 1998; Scheller 1992; Wong 1996). In attempting to identify any potential bias caused by industrial funding, we performed a sensitivity analysis to compare trials receiving industrial funding versus the remaining trials. We included all trials receiving industrial funding, thus we did not distinguish between the types of funding that studies had received. Among the 10 trials that reported receipt of industrial funding, results showed a significant association between avoidance of NMBA and DTI (RR 4.10, 95% CI 2.67 to 6.31; P = 0.003; I^2 = 64%). In the remaining trials, which reported no industrial funding, results showed a significant association between avoidance of NMBA and DTI (RR 5.33, 95% CI 3.16 to 8.98; P < 0.00001; I^2 = 68%). Findings showed no significant subgroup differences (P = 0.45) (Analysis 1.9).

Primary outcome: overall mortality

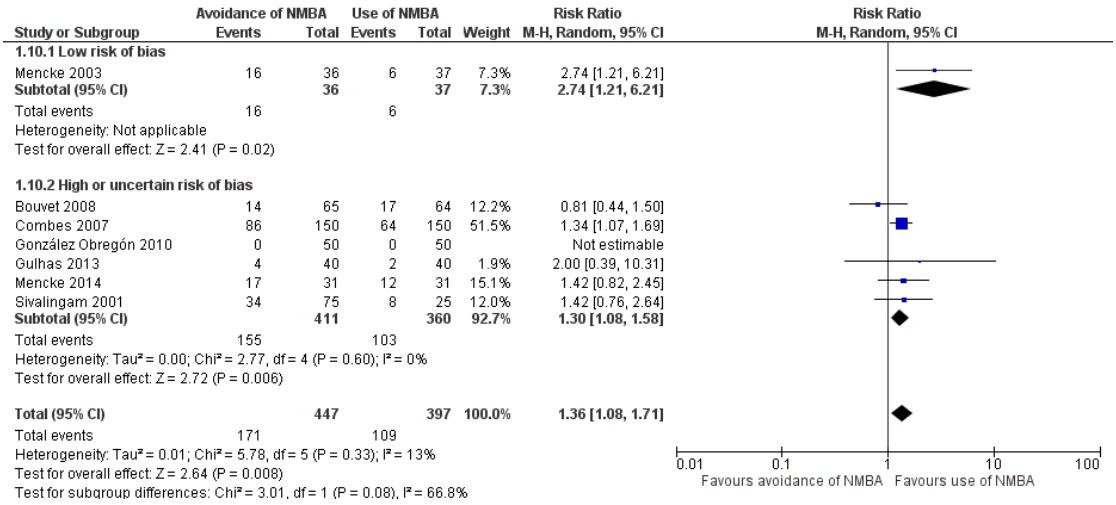
None of the trials provided data on mortality.

Primary outcome: one or more events of upper airway discomfort or injury

One or more events of upper airway discomfort or injury in trials with lower risk of bias (Analysis 1.10)

One trial with low risk of bias described events of upper airway discomfort or injury (Mencke 2003). This trial found a significant association between avoidance of NMBA and upper airway discomfort or injury (RR 2.74, 95% CI 1.21 to 6.21; P = 0.02). A random-effects model among trials with high or uncertain risk of bias revealed a significant association between no use of NMBA and risk of upper airway discomfort or injury (RR 1.30, 95% CI 1.08 to 1.58; P = 0.006; NNTH = 9.7, I^2 = 0%). Because we identified only one low risk of bias trial, we performed no quality of evidence (GRADE) assessment (Analysis 1.10; Figure 5).

Figure 5.



One or more events of upper airway discomfort or injury in all trials (Analysis 1.10)

Subgroup analyses of one or more events of upper airway discomfort or injury

Seven trials representing 846 participants described events of upper airway discomfort or injury (Bouvet 2008; Combes 2007; González Obregón 2010; Gulhas 2013; Mencke 2003; Mencke 2014; Sivalingam 2001). However, one trial (González Obregón 2010) described no events of upper airway discomfort or injury. The crude prevalence was 33.1% (n = 280; 95% CI 30.4% to 36.3%). Among 447 participants undergoing tracheal intubation without the use of NMBA, a proportion of 38.2% (n = 171; 95% CI 34.4% to 42.8%) with upper airway discomfort or injury were identified. Among 399 participants intubated with the use of NMBA, the proportion of upper airway discomfort or injury was 27.3% (n = 109; 95% CI 23.5% to 31.7%). Risk of upper airway discomfort or injury was significant with avoidance of NMBA (RR 1.37, 95% CI 1.09 to 1.74; P = 0.008; NNTH = 9.1, I^2 = 13%). Our TSA of non-NMBA versus NMBA using a D^2-adjusted required information size of 1981 participants to detect or reject a 20% relative risk reduction with power of 80% and overall type 1 error of 5%. The cumulative z-curve crossed the TSMB for harm, and the TSA-adjusted CI for the RR was 1.00 to 1.85. Thus, we provided firm evidence on the proportion of upper airway discomfort or injury for the least possible harmful effect in the traditional meta-analysis of avoiding NMBA compared with using NMBA, even when the significance level was adjusted for repetitive testing and sparse data in a cumulative meta-analysis. We downgraded the quality of the evidence (GRADE) one level to moderate because of high or uncertain risk of bias (Analysis 1.10; Figure 5).

Depolarizing versus non-depolarizing NMBA (Analysis 1.11)

The two trials in which investigators used depolarizing NMBA showed no significant association between avoidance of NMBA and upper airway discomfort or injury (RR 1.48, 95% CI 0.83 to 2.65; P = 0.19; I^2 = 0%) (Gulhas 2013; Sivalingam 2001). Likewise, in the subgroup of five trials using non-depolarizing NMBA, results revealed no significant association (RR 1.37, 95% CI 0.97 to 1.94;, P = 0.07; I^2 = 15%) (Bouvet 2008; Combes 2007; González Obregón 2010; Mencke 2003; Mencke 2014) and no significant subgroup differences (P = 0.83) (Analysis 1.11) .

Remifentanil versus other opioids (Analysis 1.12)

The two trials (Bouvet 2008; Mencke 2014) that used remifentanil showed no significant association between avoidance of NMBA and upper airway discomfort or injury (RR 1.12, 95% CI 0.61 to 2.08; P = 0.14; I^2 = 55%). The five trials using opioids other than remifentanil revealed a significant association between avoidance of NMBA and upper airway discomfort or injury (RR 1.42, 95% CI 1.16 to 1.75; P = 0.0009; NNTH = 7.5, I^2 = 0%) (Combes 2007; González Obregón 2010; Gulhas 2013; Mencke 2003; Sivalingam 2001) and no significant subgroup differences (P = 0.47) (Analysis 1.12).

Alfentanil versus other opioids (Analysis 1.13)

In two trials, the amount of alfentanil used in the intervention group exceeded the amount used in the control group; thus we excluded these trials from the meta-analysis (Combes 2007; Sivalingam 2001). The remaining trials used opioids other than alfentanil (Bouvet 2008; González Obregón 2010; Gulhas 2013; Mencke 2003; Mencke 2014), and results showed no significant association between no use of NMBA and the presence of upper airway discomfort or injury (RR 1.47, 95% CI 0.85 to 2.53; P = 0.17; I^2 = 49%) (Analysis 1.13).

Local anaesthetic versus no use of local anaesthetic

None of the trials reporting upper airway discomfort or injury used local anaesthetic.

Exclusion of patients with expected DTI versus no exclusion of patients with expected DTI (Analysis 1.14)

Six of the trials reporting upper airway discomfort or injury excluded patients with anticipated difficult airway management (Bouvet 2008; Combes 2007; González Obregón 2010; Mencke 2003; Mencke 2014; Sivalingam 2001). Results showed significantly increased risk of upper airway discomfort or injury when the patient was not relaxed (RR 1.37, 95% CI 1.05 to 1.79; P = 0.02; NNTH = 8.9, I^2 = 29%). One trial included participants with expected difficult airway management (Gulhas 2013). Results showed no significant association between avoidance of NMBA and upper airway discomfort or injury (RR 2.00, 95% CI 0.39 to 10.31; P = 0.41) and no significant subgroup differences (Analysis 1.14).

Secondary outcome: one or more major serious adverse events

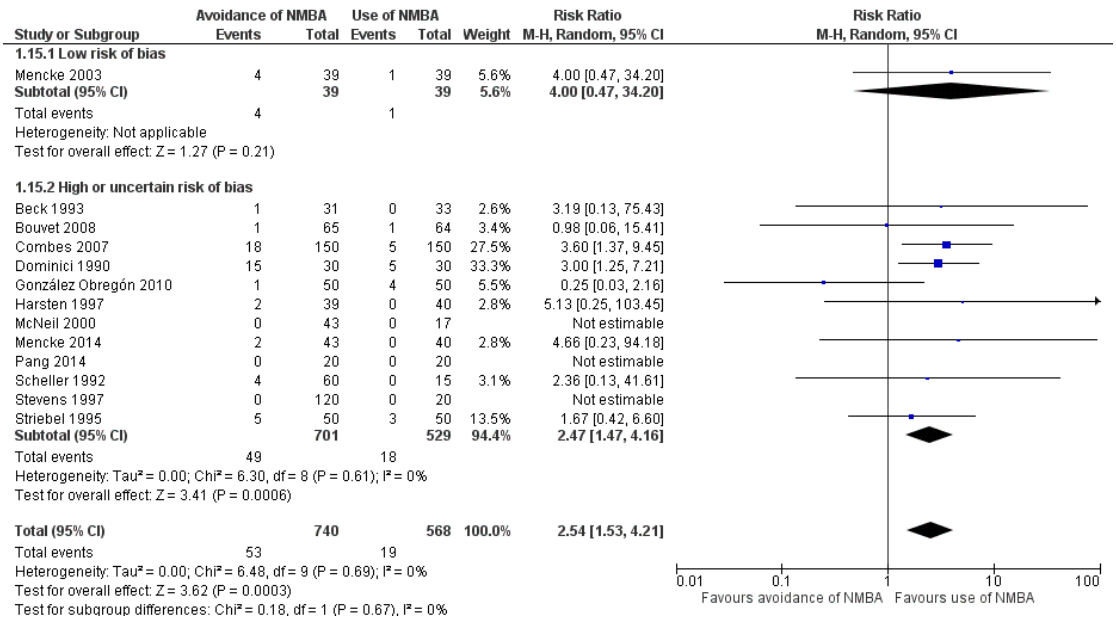
One study reported serious adverse events (Kahwaji 1997). A 29-year-old man, weighing 100 kg, with ASA physical status of I, experienced two of these events (tachycardia with heart rate from 85 to 150 bpm and bronchospasm) within 30 seconds of administration of 2.0 mg/ kg ORG 9487 (rapacuronium); these events were followed by erythema of the arms, shoulders, and face. Bronchospasm was treated with salbutamol, and all symptoms gradually subsided.

Secondary outcome: difficult laryngoscopy

Difficult laryngoscopy in trials with low risk of bias (Analysis 1.15)

We categorized one trial as having low risk of bias (Mencke 2003). This trial found no significant association between conditions for laryngoscopy and use of NMBA (RR 4.00, 95% CI 0.47 to 34.20; P = 0.21). Comparison with the subgroup of trials with high or uncertain risk of bias revealed significantly increased risk of difficult laryngoscopy in a random-effects model when NMBA was avoided (RR 2.47, 95% CI 1.47 to 4.16; P = 0.0006; NNTH = 27.9, I^2 = 0%) (Analysis 1.15; Figure 6).

Figure 6.



Difficult laryngoscopy in all trials (Analysis 1.15)

Thirteen trials representing 1308 participants reported the conditions for laryngoscopy (Beck 1993; Bouvet 2008; Combes 2007; Dominici 1990; González Obregón 2010; Harsten 1997; McNeil 2000; Mencke 2003; Mencke 2014; Pang 2014; Scheller 1992; Stevens 1997; Striebel 1995). Among 740 participants undergoing tracheal intubation without the use of NMBA, a crude proportion of 7.2% (n = 53; 95% CI 5.6% to 9.0%) had a difficult laryngoscopy. Among 568 participants intubated with use of NMBA, the proportion of difficult laryngoscopy was 3.3% (n = 19; 95% CI 2.1% to 4.8%). Avoidance of NMBA significantly increased the risk of a difficult laryngoscopy (RR 2.54, 95% CI 1.53 to 4.21; P = 0.0003; NNTH = 25.6, I^2 = 0%, D^2 =0%). In a fixed-effect model, RR was 2.46 (95% CI 1.52 to 3.97; P = 0.0002). Trial sequential analysis of avoiding versus using NMBA, with a D^2 - adjusted required information size, showed that only 6% of the information size required to detect or reject a 20% relative risk reduction was accrued and the TMSB was not crossed. The TSA-adjusted 95% CI for the RR was 0.27 to 21.75, meaning that firm evidence could not be established (Analysis 1.15; Figure 6).

In our subgroup analyses on DTI, use of remifentanil, alfentanil, or local anaesthesia did not change our primary finding, as avoidance of NMBA was significantly associated with a DTI. However, our subgroup analysis suggests that local anaesthetics may have a protective effect, as results showed a statistically significant subgroup difference between trials using and trials avoiding local anaesthesia in relation to tracheal intubation. Likewise, in the subgroup analysis of trials excluding participants with expected difficult intubation, avoiding NMBA increased the risk of a difficult intubation. Fixed-effect meta-analyses did not noticeably change results of the subgroup analyses.

Our analysis of seven trials suggests that avoidance of NMBA is associated with increased risk of upper airway discomfort or injury (RR = 1.37, 95% CI 1.09 to 1.74; P = 0.008; NNTH = 9.1, I^2 = 13%). Only one trial reporting this outcome had low risk of bias, but results revealed a significant association between avoidance of NMBA and upper airway discomfort or injury (Mencke 2003). Our TSA provided firm evidence for a harmful effect on the proportion of upper airway discomfort and injury in the traditional meta-analysis when the significance level is adjusted for repetitive testing and sparse data in a cumulative meta-analysis.

For 13 trials describing conditions for laryngoscopy, our meta-analysis showed that avoiding NMBA was associated with a difficult laryngoscopy, with RR of 2.54 (95% CI 1.53 to 4.21; P = 0.0003; NNTH = 14.6) (Beck 1993; Bouvet 2008; Combes 2007; Dominici 1990; González Obregón 2010; Harsten 1997; McNeil 2000; Mencke 2003; Mencke 2014; Pang 2014; Scheller 1992; Stevens 1997; Striebel 1995). Only one trial categorized as having low risk of bias reported this outcome (Mencke 2003). Results show no significant association between avoidance of NMBA and difficult laryngoscopy. Because information size was inadequate, our TSA of all 13 trials provided no firm evidence for a harmful effect of avoiding NMBA on upper airway discomfort or injury.

No trials reported mortality, and only one trial reported one episode of a serious adverse event (SAE) related to the use of NMBA (Kahwaji 1997).

DISCUSSION

Summary of main results

Our systematic review reveals several important findings. Analysis of 34 trials reporting on conditions regarding tracheal intubation suggests that avoidance of neuromuscular blocking agents (NMBA) is associated with increased risk of a difficult tracheal intubation (DTI) (Summary of findings for the main comparison). We confirmed this in our assessment of the four trials categorized as having low risk of bias (Analysis 1.1). Here, avoidance of NMBA was associated with DTI with a risk ratio (RR) of 13.27 (95% confidence interval (CI) 8.19 to 21.49; P < 0.00001; number needed to treat for an additional harmful outcome (NNTH) =1.9, I^2 = 0%). Results showed a significant subgroup difference between trials with low and high or uncertain risk of bias, as avoiding NMBA exceeded the risk ratio of a difficult intubation among trials with low risk of bias compared with trials with high or uncertain risk of bias. Fixed-effect meta-analyses did not noticeably change the conclusions. Our trial sequential analysis (TSA) provided firm evidence for the least possible harmful effect on the proportion of DTI in the traditional meta-analysis of avoiding NMBA compared with using NMBA, even when the significance level was adjusted for repetitive testing and sparse data in a cumulative meta-analysis.

Overall completeness and applicability of evidence

The plan to analyse effects of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in randomized clinical trials in adults followed our published protocol to a great extent. We included all eligible randomized clinical trials up to January 2017. Most of these trials were conducted in high-income countries, and most participants were undergoing elective surgery. We included participants of both gen-

ders, and most participants were American Society of Anesthesiologists (ASA) class I or II and non-obese, without expected airway management difficulties. Studies showed a high degree of clinical diversity as included combinations of different adjuvant drugs and NMBA were substantial.

About half of the included trials used a (modified) intubation score according to "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Fuchs-Buder 2007; Viby-Mogensen 1996). Further, a major portion of the remaining trials used intubation scores that incorporated many of the elements described by the GCRP score. Thus, to some extent, included trials showed some agreement on how DTI should be defined. Although trials used a defined outcome in accordance with recommendations for research regarding NMBA, definitions used differ from those traditionally used in research dealing with difficult airway management (Adnet 1997; Lundstrøm 2011b). Although the literature lacks consensus, these definitions often describe multiple (unsuccessful) attempts at intubation and/or shift to more advanced intubation techniques and/or other personnel performing airway management. One must therefore bear in mind that our primary outcome may not reflect a situation that most clinicians consider a truly difficult intubation that threatens the patient's life or health. Thus, one may observe a substantial degree of indirectness concerning our primary outcome describing DTI. Thirteen trials used the difficult laryngoscopy score of Cormack and Lehane (Cormack 1984) as a surrogate measure of a difficult intubation. This outcome measure is often used in studies on difficult airway management; thus it seems reasonable to interpret our findings on difficult laryngoscopy in a traditionally difficult airway management context. Most trials excluded patients expected to have difficult airway management. This may have a significant impact on the applicability of evidence, but subgroup analysis of 'Exclusion of patients with expected DTI versus no exclusion of expected DTI' (Analysis 1.6) showed no significant subgroup differences. Further, several studies have demonstrated that prediction of a DTI is difficult (Lundstrøm 2011b; Nørskov 2015; Nørskov 2016) and involves low sensitivity and specificity; thus the impact of these exclusions is uncertain.

Selected outcome measures varied among trials dealing with sore throat, upper airway discomfort, and injury. Further, by whom, how, or when the outcome measure was evaluated differed or was not clearly defined by some of these trials - a fact that must be taken into account when our results are interpreted in a clinical context.

Of specific notice is the fact that evaluation of the effect on occurrence of serious adverse events (SAE) of avoidance of NMBA compared with use of NMBA is virtually absent, as none of the included trials evaluated effects on mortality (short-term or long-term), and only one trial evaluated effects on other types of SAEs, reporting one SAE.

Quality of the evidence

We present our main results on all investigated outcomes in Summary of findings for the main comparison, which shows grading of the quality of evidence, including imprecision, according to the GRADE approach (Guyatt 2013; Guyatt 2011) and stresses results of meta-analyses originating from trials with overall low risk of bias. Our review follows the overall plan of a published, peer-reviewed Cochrane protocol (Lundstrøm 2011a). It represents a comprehensive review of the topic, including meta-analyses of results from 34 randomized trials with a total of 3565 participants. To our knowledge, no previous meta-analyses have included trials comparing use or avoidance of NMBA for tracheal intubation. We conducted a thorough review in accordance with methods of the Cochrane Collaboration (Higgins 2011). Between-trial heterogeneity varied from absent to substantial among the various meta-analyses in terms of our different outcomes. This may emphasize the diversity of the dose-finding regimens used in different trials that used substantially different combinations of adjuvant drugs and NMBA. Further, minor differences among definitions of a DTI in some degree may contribute to the heterogeneity. In contrast, we noted no between-trial heterogeneity regarding our secondary outcome describing conditions needed for direct laryngoscopy, which may be explained by a well-defined outcome measure (Cormack 1984) that was retrievable from all 13 trials.

We performed trial sequential analyses and calculated TSA-adjusted confidence intervals reflecting sparse data and multiple testing due to potentially repeated updates of cumulative meta-analyses to control risk of random errors and to prevent premature statements of superiority of one intervention over another (Brok 2008; Brok 2009; Thorlund 2009;Thorlund 2011; Wetterslev 2008; Wetterslev 2009). TSA revealed that all of our meta-analyses including the primary outcomes have a very low degree of imprecision, indicating low risk of random error. The finding of an insignificant TSA-adjusted association between avoidance of NMBA and difficult laryngoscopy may be due to a type II error, that is, a false-negative finding, exemplified by the cumulative z-curve not crossing the trial sequential monitoring boundary (TSMB) for futility. However, such an analysis cannot remove risks of bias - detected or undetected. It is worth discussing how much evidence is required when one is dealing with potential benefit or harm. On the other hand, beneficial or harmful effects can occur as the result of random errors; therefore, sufficient information must be assessed to demonstrate benefit or harm beyond reasonable doubt.

Because actual airway management was evaluated just after induction of anaesthesia, no cases were lost to follow-up. However, cases with upper airway discomfort and/or injury were lost to follow-up in three trials (Combes 2007; Mencke 2003; Mencke 2014). We therefore performed post hoc "best- and worst-case" sensitivity analyses. We included participants who were lost to follow-up with or without upper airway discomfort and/or injury. These explorative analyses did not alter our primary findings derived both

from all trials and from trials with low risk of bias.

Potential biases in the review process

We strived to reduce bias by identifying all relevant trials through a comprehensive systematic search of the literature. We contacted study authors to retrieve unpublished data, when possible. However, it was difficult to obtain updated contact information for authors of the oldest published trials. This may have introduced bias, as it was generally easier to retrieve additional data from more recently published trials, which also were more likely to be categorized as having low risk of bias. Two review authors assessed trials for inclusion or eligibility and extracted all data in duplicate, thereby reaching a high level of agreement. We did not conduct quality assessments or data extractions while blinded to review authors and bias risks.

Most included trials clearly stated cut-off values defining a DTI. However, five trials (Beck 1993; Gulhas 2013; McNeil 2000; Scheller 1992; Stevens 1997) used different composite scores without defined cut-offs. We used underlying references or comparable scores to define cut-off values, enabling us to include these trials in our meta-analyses. The Characteristics of included studies section provides detailed explanations. In these cases, some degree of interpretation of outcome measures was necessary, and our assessments may have introduced bias as a consequence. Nevertheless, we believe that this categorization was evident when compared with the existing literature, and we therefore consider risk of introducing bias as low.

The authors of six trials (Harsten 1997; Jiao 2014; Mencke 2003; Mencke 2014; Nimmo 1995; Sivalingam 2001) excluded a few participants from their assessments when tracheal intubation failed. We consider these patients as truly difficult to intubate and thus chose to include them in our meta-analyses. This may have introduced bias; however, a sensitivity analysis excluding these participants from our meta-analyses did not change the conclusion.

Agreements and disagreements with other studies or reviews

To our knowledge, no previous systematic review has included meta-analyses of trials comparing use or avoidance of NMBA for tracheal intubation. However, a narrative review (Woods 2005) concluded that the literature describes successful techniques to intubate the trachea without the use of neuromuscular blocking agents with the patient under general anaesthesia. Further, those review authors concluded that these techniques offer a useful alternative when drugs are contraindicated or undesirable. Another narrative review (Fotopouloua 2012) concluded that induction of anaesthesia without the use of NMBA but in combination with remifentanil provides acceptable conditions for tracheal intubation. Both reviews include several dose-finding trials in which none of the participants in the different intervention groups were administered NMBA. Thus, it was impossible to compare avoiding versus using NMBA for tracheal intubation. On the basis of findings related to specific drug combinations and concentrations, the review authors concluded that induction without the use of NMBA may offer (almost) perfect or good conditions for intubation.

In large observational studies and reviews on difficult airway management, fractions of DTI range from 2% to 7% (Lundstrøm 2011b; Nørskov 2015; Shiga 2005), which is consistent with our findings on the overall proportion of difficult intubation in patients who are intubated with use of NMBA. The crude proportion was 4.7% in trials with low risk of bias and 8.1% in all trials. However, among participants undergoing tracheal intubation without the use of NMBA, corresponding crude proportions were tremendously higher, at 56.3% in trials with low risk of bias and 24.2% in all trials. These latter proportions are not consistent with those reported in experiences from everyday clinical practice, and several trials may therefore include suboptimal dosing regimens. Thus, we speculate that some of the dose-finding trials may include control groups with clinically unacceptable dosing regimens that may contribute to an unrealistically increased risk of DTI. As an example, one trial concluded that the optimal remifentanil dose used for intubation with propofol and without NMBA is 4 µg/kg administered in 60 seconds (Bouvet 2009). However in our review, only two of the included trials actually used equivalent or larger doses of remifentanil (Hanna 2010; McNeil 2000). Therefore, we performed a post hoc sensitivity analysis of a best-case scenario (Analysis 1.7). Dose-finding trials were represented only by control and intervention groups with the lowest incidence of difficult intubation. Results showed a crude proportion of 25.0% DTI among participants anaesthetized without the use of NMBA, and this again significantly increased the risk of DTI, with a risk ratio of 5.99. Finally, in our attempt to exclude comparisons of suboptimal anaesthetic dosing regimens, we performed a post hoc sensitivity analysis while excluding all dose-finding trials (Analysis 1.8). We included in our meta-analysis 16 trials with a single intervention group and a single control group. The crude proportion of DTI among participants anaesthetized without the use of NMBA decreased to 15.4%. However, avoiding NMBA still significantly increased the risk of DTI, with a risk ratio of 3.40. Another possible explanation for the increased crude proportion of DTI among participants induced without NMBA may be that most included trials used a (modified) intubation score according to "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Fuchs-Buder 2007; Viby-Mogensen 1996). Assessment of intubation conditions included information on jaw mobility and/or reactions to insertion of the tracheal tube and cuff inflation (diaphragmatic movement/coughing). These are reasonable elements for describing ideal conditions for intubation, although they may be affected even when everyday clinical airway management is successful without "true"

difficulties. Thus, the GCRP score may be highly sensitive and may be used to enforce the difference between the ideal procedure and a clinically acceptable intubation. Trials reporting conditions for laryngoscopy (described by Cormack 1984) report an outcome measure traditionally used in studies dealing with difficult airway management. In our assessment, the crude proportions of difficult laryngoscopy reported among intervention groups may reflect a more clinically acceptable situation, as 4.2% among all trials and 7.2% in trials with low risk of bias who were intubated without NMBA had a difficult laryngoscopy.

In the literature, one review reported on various causes for postoperative sore throat (El-Boghdadly 2016). These review authors state that tracheal intubation without the use of NMBA is a potential risk factor for sore throat. Although this study is presented as a systematic review, review authors included only one study (Combes 2007) reporting on upper airway discomfort or injury, review authors performed no bias assessment, and the review included no meta-analyses. Other conditions such as tube size (Jaensson 2010; Jaensson 2012; Stout 1987; Xu 2012) and use of corticosteroids (Sumathi 2007; Thomas 2007) may play an important role in the postoperative sore throat. In our review, we did not evaluate the impact of these factors in subgroup analyses. The review of EL-Boghdadly reports postoperative sore throat with a prevalence of up to 62% following general anaesthesia. In a Cochrane review on lidocaine for preventing postoperative sore throat (Tanaka 2015), the crude prevalence of sore throat was 20% to 30% pending the use of lidocaine. In our assessment, the crude prevalence was 33%.

AUTHORS' CONCLUSIONS

Implications for practice

This review supports that use of NMBA may create better conditions for tracheal intubation in clinical practice than are provided by avoidance of NMBA. Revuew results are characterized by indirectness regarding our primary outcome describing DTI. Given defined outcomes in the included trials, our primary outcome may not reflect a situation that most clinicians consider to show a clinically important DTI by which the patient's life or health may be threatened. Thus, we could not conclude with certainty that avoidance of NMBA was associated with a clinically important or seriously difficult intubation. A difficult laryngoscopy as defined by Cormack and Lehane may be a reasonable surrogate for a clinically serious difficult airway. Our results indicate that avoiding NMBA increases the risk of a difficult laryngoscopy, but after adjustments for required information size, firm evidence could not be established.

In terms of our other primary outcome - events of upper airway discomfort or injury - data on low risk of bias trials are sparse. Among all trials, evidence shows a firm and significant risk of upper airway discomfort or injury when NMBA is avoided. Of specific notice is the fact that evaluation of the effects of avoidance of NMBA compared with use of NMBA on the occurrence of serious adverse events (SAEs) is virtually absent, as none of these trials evaluated effects on mortality (short-term or long-term), and only one trial evaluated effects on other types of SAEs, reporting one SAE.

In conclusion, in a clinical context, one must have weighty arguments for using or not using NMBA when performing tracheal intubation.

Implications for research

Our assessments show some degree of indirectness for our primary outcome of describing difficult intubation. Insufficient information size led to uncertainty regarding our assessment of the effects of avoiding NMBA on the frequency of a difficult laryngoscopy and implications for future research focusing on the impact of avoiding NMBA on the prevalence of severe intubation difficulties and difficult laryngoscopy as categorized by Cormack and Lehane. In addition, large trials with low risk of bias undertaken to describe upper airway injury and discomfort, as well as other serious adverse events and mortality, are needed.

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References to other published versions of this review

Lundstrøm 2011a

Lundstrøm LH, Strande S, Møller AM, Wetterslev J. Use versus avoidance of neuromuscular blocking agent for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents. *Cochrane Database of Systematic Reviews* 2011, Issue 7. [DOI: 10.1002/14651858.CD009237]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Alexander 1999

Methods	Parallel-group RCT Settings: single centre Country: UK Language: English Number of control groups = 1/Number of Intervention groups = 2 Number of participants in control group = 20/Number of participants in intervention groups = 20/20 Randomized: N = 60 Analysed: N = 60 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA physical status I or II Scheduled for elective surgery **Exclusion criteria** Oesophageal reflux or hiatal hernia Previous difficulty with intubation or a suspected difficult airway Allergies to any of the study drugs Administration of sedative or opioid drugs in the previous 24 hours Renal or hepatic impairment
Interventions	**NMBA** Control group S: suxamethonium 1 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Intervention group A: alfentanil 50 μg/kg Intervention group R: remifentanil 2 μg/kg Control group S: none **Local anaesthetic** None **Other** Premedicated with midazolam 0.03 mg/kg, 10 minutes before induction
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	One patient in both control group R and control group A had closed vocal cords requiring administration of suxamethonium. Tracheal intubation occurred 60 seconds after administration of the study drug **Funding source:** not specified **Declarations of interest:** not specified
Risk of bias	*Risk of bias*

Alexander 1999 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated with a computer-generated table to 1 of 3 groups
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The anaesthetist who intubated the participant was unaware of the study drug and was instructed to face away from the participant; the sound of the pulse oximeter was temporarily turned off to avoid recognition of the study drug by observation of fasciculations or a decrease in heart rate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Barclay 1997

Methods	Parallel-group RCT Settings: single centre Country: UK Language: English Number of control groups = 2/Number of Intervention groups = 1 Number of participants in control groups = 20/20/Number of participants in intervention group = 20 Randomized: N = 60 Analysed: N = 60 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Aged 18 to 50 years **Exclusion criteria** Obese Risk of pulmonary aspiration Smoked more than 10 cigarettes per day Tracheas known to be difficult to intubate or coughing or straining after tracheal intubation

Barclay 1997 (*Continued*)

Interventions	**NMBA** Control group 1: rocuronium 0.1 mg/kg Control group 2: rocuronium 0.3 mg/kg **Hypnotic** Propofol 2.5 mg/kg **Opioid** Alfentanil 10 μg/kg **Local anaesthetic** Lidocaine 10 mg IV **Other** Premedicated with temazepam 20 to 30 mg per os 1 hour before induction
Outcomes	**1. Intubation conditions:** modified version of "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) . The investigator assessed 3 factors: ease of jaw opening and laryngoscopy (1 easy; 2 fair; 3 difficult), position of the vocal cords and their movement (1 open; 2 moving; 3 closing), and degree of straining ("bucking") after tracheal intubation and cuff inflation (1 none; 2 with diaphragm; 3 with abdominal muscles). The occurrence of any significant complication was recorded. Overall conditions for tracheal intubation were scored by 3 grades: optimal, suboptimal, and failure. Tracheal intubation was judged as optimal when all scores were 1 or 2, and was judged as suboptimal if any scores were 3. Failure to intubate was scored as a failure
Notes	**Funding source:** "We also thank Organa Teknika for their generous supply of rocuronium" **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	....an investigator, who was blinded as to the allocation....
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described

Barclay 1997 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Beck 1993

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 1/Number of Intervention groups = 1 Number of participants in control group = 33/Number of participants in intervention group = 31 Randomized: N = 64 Analysed: N = 64 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Aged 18 to 60 years Elective surgery lasting > 20 minutes **Exclusion criteria** Neurosurgical, obstetrical, or ophthalmological procedures
Interventions	**NMBA** Suxamethonium 1 mg/kg **Hypnotic** Control group: thiopenthal 5 mg/kg Intervention group: propofol 2 mg/mL **Opioid** Control group: none Intervention group: alfentanil 50 μg/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation condition:** VAS 0 to 100, intubation condition: 0 = perfect, 100 = terrible. No defined cut-off value indicating acceptable intubation condition **2. Laryngoscopy condition:** Cormack and Lehane score (Cormack 1984) In our meta-analyses, we categorized Cormack and Lehane scores I and II as acceptable intubation condition, and scores III and IV as unacceptable condition
Notes	**Funding source:** not specified **Declarations of interest:** not specified

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Beck 1993 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not specified how
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The anaesthetist performing the intubation was independent from the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Bouvet 2008

Methods	Parallel-group RCT Settings: single centre Country: France Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 64/Number of participants in intervention group = 65 Randomized: N = 130 Analysed: N = 129 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Elective gynaecological surgery ASA class I or II Aged > 18 years **Exclusion criteria** History or evidence of a difficult airway (combination of Mallampati score 3 or 4, thyromental distance < 60 mm, mouth opening < 35 mm) Contraindication to use of NMBA
Interventions	**NMBA** Cisatracurium 0.15 $mg \cdot kg^{-1}$ **Hypnotic** Propofol 2.5 $mg \cdot kg^{-1}$ **Opioid** Remifentanil 2 $\mu g \cdot kg^{-1}$ **Local anaesthetic**

Bouvet 2008 (*Continued*)

	None **Other** Premedication when appropriate: alprazolam 0.5 mg and/or hydroxyzine 0.5 to 2 mg·kg-1 PO
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) **2. Laryngoscopy condition:** Cormack and Lehane score (Cormack 1984) **3. Postoperative laryngeal symptoms and vocal cord injury:** 24 hours, 48 hours, 1 month postoperative
Notes	One participant in group cisatracurium was excluded because of non-observance of the anaesthetic protocol, leaving 129 clinically evaluable participants. Time from induction to start of tracheal intubation: 270 seconds **Funding source:** "Financial support for this study was provided solely from institutional sources" **Declarations of interest:** "none declared"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer
Allocation concealment (selection bias)	Low risk	Allocation concealment was ensured by the use of coded, sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	In our protocol, only the study physician (performing all tracheal intubations) was blinded to intervention allocations (along with the participant). Other personnel were aware because they had to await the disappearance of all 4 twitches in response to train-of-four stimulation at the adductor pollicis muscle before allowing arrival of the study physician into the operating room (contacted study author)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The same experienced senior physician, blinded to the anaesthetic regimen, performed all tracheal intubations..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant in group cisatracurium was excluded because of non-observance of the anaesthetic protocol

Bouvet 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Combes 2007

Methods	Parallel-group RCT Settings: single centre Country: France Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 150/Number of participants in intervention group = 150 Randomized: N = 300 Analysed: N = 299 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA status I or II Elective surgery **Exclusion criteria** Predictive of difficult intubation BMI above 30 $kg{\cdot}m^{-2}$ Allergy to muscle relaxants Need for a nasogastric tube Ear-nose-and-throat surgery. Preoperative sore throat or hoarseness at history taking
Interventions	**NMBA** Rocuronium 0.6 $mg{\cdot}kg^{-1}$ **Hypnotic** Propofol 2.5 $mg{\cdot}kg^{-1}$ **Opioid** Control group: alfentanil 15 µg/kg Intervention group: alfentanil 40 µg/kg **Local anaesthetic** None **Other** Premedication: hydroxyzine 50 to 100 mg PO
Outcomes	**1. Intubation condition:** Intubation Difficulty Scale (IDS) (Adnet 1997) and "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) **2. Laryngoscopy condition:** Cormack and Lehane score (Cormack 1984) **3. Post-intubation pharyngolaryngeal symptoms:** 2 hours and 24 hours after extubation. Methods not specified

Notes	Intubation 90 seconds after rocuronium/saline One participant left the hospital before questioning a second time on their pharyngolaryngeal symptoms. This participant (from the rocuronium arm) could not be reached **Funding source:** "Support was from departmental sources only" **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method not specified
Allocation concealment (selection bias)	Low risk	"Patients were randomly assigned to one of the two groups by a physician not involved in the patient's care, using numbered sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All drugs were prepared by an independent staff anaesthetist not involved in the study. The muscle relaxant (rocuronium) and the saline solution were prepared in identical syringes and in identical volumes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All drugs were prepared by an independent staff anaesthetist not involved in the study. The muscle relaxant (rocuronium) and the saline solution were prepared in identical syringes and in identical volumes"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) dropouts and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Dominici 1990

Methods	Parallel-group RCT Settings: single centre Country: France Language: French Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 30/Number of participants in intervention group = 30 Randomized: N = 60 Analysed: N = 60 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Aged > 18 years ASA I, II, or III Endoscopies with or without laser, tonsillectomies, nose-fracture surgeries, adenectomies, meatotomies and tympanoplastics Surgeries with duration < 90 minutes **Exclusion criteria** Known allergies Severe arterial hypertension, unstable heart failure Sickness related to conduction and excitability of ventricles Potassium levels above 5 mmol/L Renal failure Epilepsy
Interventions	**NMBA** Suxamethonium 1.5 mg/kg **Hypnotic** Propofol 3 mg/mL **Opioid** Alfentanil 7 to 10µg/kg **Local anaesthetic** Lidocaine (2%): 1 mL injected before administration of propofol. Topical lidocaine 5% used in larynx before intubation **Other** Midazolam 0.1 mg/kg was given 30 minutes before induction
Outcomes	**1. Intubation condition:** quality of intubation measured by (1) position of the glottis (open or semi-open on 1 part and closed or not visualized); (2) presence or absence of bucking; or (3) number of intubation attempts necessary for successful intubation **2. Laryngoscopy condition:** position of the glottis (open or semi-open on 1 part and closed or not visualized). Closed or not visualized defined as difficult
Notes	Intubation 60 seconds after induction **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias	***Risk of bias***

Dominici 1990 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"...are distributed according to a randomised list into two groups of 30"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...waits outside the operation room for 1 minute (to make sure fasciculations are not seen), before performing the laryngoscopy"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

González Obregón 2010

Methods	Parallel-group RCT Settings: single centre Country: Columbia Language: Spanish Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 50/Number of participants in intervention group = 50 Randomized: N = 100 Analysed: N = 100 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Ambulatory surgery ASA physical status I or II **Exclusion criteria** Aged < 15 or > 60 years Expected difficult airway Full stomach Rapid sequence induction indicated Pregnant or neuromuscular disease
Interventions	**NMBA** Rocuronium 0.6 mg/kg **Hypnotic** Intervention group A: oxygen 3 L/min + sevoflurane 3%; after 3 minutes, bolus of

González Obregón 2010 (*Continued*)

	propofol 2 mg/kg Control group B: bolus of propofol of 1 to 2 mg/kg (not standardized) for a minute **Opioid** Intervention group A: remifentanil 0,6 microg/kg/min for 5 minutes, hereafter remifentanil dose is halved until intubation Control group B: bolus of remifentanil 1 to 2 microg/kg (not standardized) for a minute, followed by infusion of 0,15 microg/kg/min for 1 minute **Local anaesthetic** None **Other** None
Outcomes	**1. Difficult laryngoscopy** (Cormack 1984) **2. Post-intubation pharyngolaryngeal symptoms:** postoperative hoarseness, not further specified
Notes	Difficult laryngoscopy was included as a surrogate for difficult intubation in our meta-analysis **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	50 random numbers between 00 and 99 are selected by a manual/hand calculator. These numbers constitute group A, the rest group B. The group that will receive NMBA is then determined by randomization
Allocation concealment (selection bias)	Low risk	The result of randomization is kept in a sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	The investigator or other anaesthetist who is administering the induction according to randomization is not blinded but is not the one assessing outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The anaesthesiologist who performs tracheal intubation does not participate in randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Gulhas 2013

Methods	Parallel-group RCT Settings: single centre Country: Turkey Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 40/Number of participants in intervention group = 40 Randomized: N = 80 Analysed: N = 80 Dates when the study was conducted: between November 2009 and July 2010
Participants	**Inclusion criteria** ASA physical status I and II Mallampati scores of I and II Aged 18 to 65 years Selective microlaryngoscopy **Exclusion criteria** History of head and neck Previous surgery or scheduled to undergo head and neck surgery Severe cardiovascular and pulmonary disease Neuromuscular disease Medications affecting neuromuscular junctions Strained patients
Interventions	**NMBA** Succinylcholine 1 mg/kg **Hypnotic** Control group: propofol 2 mg/kg over 30 seconds Intervention group: propofol 2 mg/kg over 30 seconds **Opioid** Control group: remifentanil 1 μg/kg over 90 seconds Intervention group: remifentanil 4 μg/kg over 90 seconds **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation conditions:** categorized by (1) jaw relaxation (complete; tone; stiff; rigid) , (2) laryngoscopy (easy; fair; difficult; impossible), (3) vocal cords (open; moving; closing; closed), (4) coughing (none; slight; moderate; severe), (5) movement (none; slight; moderate; severe) (Hellbo-Hansen 1988). In this study, no accumulated score was presented, and laryngoscopy was categorized as difficult; it was impossible to define a difficult intubation **2. Post-intubation pharyngolaryngeal symptoms:** sore throat and hoarseness evaluated. Methods and timing not described
Notes	**Funding source:** not specified **Declarations of interest:** "none"

Risk of bias	*Risk of bias*

Gulhas 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization and allocation of participants into intervention groups using computerized numbers
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both care providers on the ward and anaesthesiologists assessing outcomes were blinded to study groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Both care providers on the ward and anaesthesiologists assessing outcomes were blinded to study groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Hanna 2010

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 24/Number of participants in intervention group = 23 Randomized: N = 50 Analysed: N = 47 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Aged 18 to 75 years Elective non-ophthalmic surgery **Exclusion criteria** Anticipated difficult airway management GI reflux, hiatal hernia Ocular surgery within 6 months Long-term opioid use Allergy to study drugs

Hanna 2010 (*Continued*)

Interventions	**NMBA** Rocuronium 0.06 mg/kg (defasciculation) + succinylcholine 1.5 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Control group: none Intervention group: remifentanil 4 μg/kg **Local anaesthetic** Lidocaine 0.5 mg/kg IV **Other** Premedication: midazolam 2 mg and glycopyrrolate 0.2 mg IV
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	"...Three patients were excluded from the study due to IOP tonometer malfunction...." Intubation 60 seconds after induction **Funding source:** "supported in part by Aspect Medical Systems, Inc., Norwood, MA, USA, who provided bispectral index (BIStm) electrodes for the study. Otherwise, the study was supported by funds from the Department of Anesthesiology, Loyola University Medical Center, Maywood, IL, USA" **Declarations of interest:** "none"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	"...each consecutive patient contained in a sealed envelope..."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"....two attending anesthesiologists and nurse anesthetist, blinded to patient group assignment entered the operation room."
Incomplete outcome data (attrition bias) All outcomes	Low risk	"...Three patients were excluded from the study due to IOP tonometer malfunction. ..."
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Harsten 1997

Methods	Parallel-group RCT Settings: single centre Country: Sweden Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 40/Number of participants in intervention group = 39 Randomized: N = 80 Analysed: N = 79 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Age ranging from 18 to 76 years **Exclusion criteria** Not specified
Interventions	**NMBA** Suxamethonium 1 mg/kg **Hypnotic** Control group: thiopental 5 mg/kg Intervention group: propofol 2,5 mg/kg **Opioid** Alfentanil 10 μg/kg **Local anaesthetic** None **Other** Premedication: 0.25 mg triazolam 45 to 60 minutes before induction
Outcomes	**1. Intubation condition:** "Intubating conditions were assessed on the basis of jaw relaxation (0 = no relaxation, impossible to open mouth, 1 = moderate relaxation, 2 = complete relaxation), ease of the insertion of the tube (0 = vigorous movements of the vocal cords and difficult or impossible to insert tracheal tube, 1 = slight movements of the vocal cords, 2 = relaxed vocal cords without any movements) and coughing on intubation (0 = vigorous coughing, 1 = slight coughing, 2 = no coughing) (9)" In this RCT, study authors did not define any cut-off value for acceptable intubation. For the meta-analysis, we defined an accumulated score = 4 as clinically unacceptable. We dichotomized the score on the basis of the definition presented in "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) **2. Laryngoscopy condition:** Further, patients in whom the vocal cords were not visible (equals Cormach and Lehane grade III and IV) were categorized as clinically unacceptable
Notes	In the PA group, 1 patient was excluded because the induction dose of propofol was not sufficient to produce anaesthesia, and a further 2 patients because the vocal cords were not visible. In our meta-analysis, we included the last 2 patients as "difficult to intubation" and "difficult to laryngoscope" **Funding source:** "The authors wish to thank Zeneca, Sweden, for the supply of propofol. This study was supported by grants from the Local Fund for Medical Research and

	Development of the Kristianstad County Council" **Declarations of interest:** not specified

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to a computer generated randomisation list, patients were assigned to receive either…"
Allocation concealment (selection bias)	Low risk	"we used sealed non-transparent envelopes containing a slip of paper with a description of which of the two induction methods was being used" (mail contact with study author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Apart from the drug administering doctor no one else knew which drugs were given" (mail contact with study author)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The intubating anaesthetist was not present during the induction of anaesthesia but was waiting outside the operating room. He was allowed to enter the room when the eyelash reflex or the muscle fasciculations had disappeared and was unaware of which drugs had been used"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) dropouts and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Iamaroon 2001

Methods	Parallel-group RCT Settings: single centre Country: Thailand Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in intervention group = 60/Number of participants in control group = 60 Randomized: N = 120 Analysed: N = 120 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I and II Aged 20 to 60 years Elective non-cardiothoracic surgery **Exclusion criteria** Obesity, body mass index > 30 kg/m^2 Pregnancy, small bowel obstruction, history of oesophageal reflux, or hiatal hernia Difficult airway problems Hyperkalaemia Suspected malignant hyperthermia Cardiac, pulmonary, or renal disease
Interventions	**NMBA** Suxamentonium 1.5 mg/kg **Hypnotic** Control group: thiopenthal 5 mg/kg + 4 L/min (N_2O) and 2 L/min O_2 Intervention group: sevoflurane 8% in 66% N_2O and 33% O_2 mixture **Opioid** Fentanyl 1.5 μg/kg **Local anaesthetic** None **Other** Diazepam 5 or 10 mg orally 1 to 2 hours before induction
Outcomes	**1. Intubating conditions:** Jaw relaxation was described as fully relaxed (score = 1), mildly resistant (score = 2), tight but open (score = 3), and impossible (score = 4). Vocal cord position was described as widely open (score = 1), mid position (score = 2), moving but open (score = 3), and closed (score = 4). Intubating responses were described as none (score = 1), diaphragmatic movement (score = 2), mild/moderate coughing (score = 3) , and severe coughing (score = 4). Intubating conditions were graded as excellent (total score (TS) = 3), good (TS = 4 to 6), poor (TS = 7 to 9), or impossible (TS = 10 to 12). Total score of 6 or less was classified as an acceptable intubation condition, otherwise as an unacceptable condition
Notes	**Funding source:** supported by Mahidol University research fund. Sevoflurane was supported by Abbott Laboratories Limited **Declarations of interest:** not specified

Iamaroon 2001 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"..... anaesthetic residents blindly participated as the intubators and the nurse anesthetists blindly participated as the observers...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Isesele 2012

Methods	Parallel-group RCT Settings: single centre Country: Nigeria Language: English/French Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 48/Number of participants in intervention group = 48 Randomized: N = 96 Analysed: N = 88 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Aged 18 to 45 years Mallampati class I and II Elective surgery **Exclusion criteria** Inability to understand written or verbal information Presence of dental crowns Past history of difficult intubation Obvious signs of expected difficult intubation Intercurrent chronic ailments such as valvular heart disease and asthma

	Overt or risk of raised intracranial or intraocular pressure Risk of regurgitation and aspiration of gastric contents Antipsychotic therapy Opioid therapy
Interventions	**NMBA** Suxamentonium 1.5 mg/kg **Hypnotic** Propofol 2mg/kg **Opioid** None **Local anaesthetic** Intervention group: 1.5 mg/kg intravenous lidocaine **Other** Diazepam 10 mg orally the morning of surgery
Outcomes	**1. Intubation conditions:** With the intubating condition scoring system, 3 parameters were assessed and scored on a scale of 0 to 2. These included jaw relaxation, ease of insertion of endotracheal tube, and response to intubation. Thus, a total intubating condition score could range from 0 (worst) to 6 (best). A score of 5 to 6 = good, 3 to 4 = moderate, and 0 to 2 = poor. Scoring system from Saarnivaara 1991
Notes	**Funding source:** none **Declarations of interest:** none

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	All eligible participants were randomly assigned to the 2 study groups with sealed unmarked envelopes
Allocation concealment (selection bias)	Low risk	All eligible participants were randomly assigned to the 2 study groups with sealed unmarked envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Eight participants, however, were excluded from further participation in the study for various reasons: 5 of these for improper documentation of the data collection form,

Isesele 2012 (*Continued*)

		2 for electrocardiographic abnormalities, and 1 for abnormal haemodynamic values before induction of anaesthesia
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Jiao 2014

Methods	Parallel-group RCT Settings: single centre Country: China Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 27/Number of participants in intervention group = 28 Randomized: N = 55 Analysed: N = 55 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Aged 18 to 60 years Elective gynaecological laparoscopic **Exclusion criteria** BMI mass index > 30 Mallampati airway grade 2 to 4 Known allergy to propofol, egg, or opioids Alcohol or drug abuse History of gastro-oesophageal reflux disease Neuromuscular disease History of upper respiratory tract infection or other airway hyperactivity disease in the recent 2 weeks
Interventions	**NMBA** Suxamentonium 0.6 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Control group: remifentanil 1.0 μg/kg Intervention group: remifentanil 1.5 μg/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)

Notes	1 participant in group C was graded as 4 by Cormach-Lehane grading and was not improved in laryngeal exposure after addition of succinylcholine, then was transferred for video laryngoscopic intubation. We included this participant as difficult to intubate in our meta-analyses. Additional succinylcholine was administered for 1 participant in the control group before intubation. This participant was included int the meta-analyses as difficult to intubate **Funding source:** not specified **Declarations of interest:** "none"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	...with random number table
Allocation concealment (selection bias)	Low risk	...given random numbers by a study co-ordinator, who also encodes the drugs with matching random numbers. The study co-ordinator also prepared all drugs..... (contact with study author)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Remifentanil in each group was diluted with normal saline to 10 mL, and injectors were labelled with "2". The injectors were infused with succinylcholine (diluted with normal saline to 10 mL) in group S and with normal saline 10 mL in group C (labelled with "3")
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Intubation was attempted by an experienced anaesthesiologist blinded to grouping of the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Kahwaji 1997

Methods	Parallel-group RCT Settings: multi-centre Country: USA Language: English Number of control groups = 5/Number of intervention groups = 1 Number of participants in control group = 30/27/32/28/29/Number of participants in intervention group = 30 Randomized: N = 181 Analysed: N = 178 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Aged 19 to 85 years ASA physical status I to III Elective surgical procedures with anticipated duration ≥ 1 hour **Exclusion criteria** Significant neurological, renal, or hepatic disease Receiving drugs that could interfere with normal neuromuscular function Preoperative evaluation indicated that difficult tracheal intubation was anticipated
Interventions	**NMBA** Type: ORG 9487 (rapacuronium) Control group 1: 0.5 mg/kg Control group 2: 1.0 mg/kg Control group 3: 1.5 mg/kg Control group 4: 2.0 mg/kg Control group 5: 2.5 mg/kg **Hypnotic** Thiopental (3 to 6 mg/kg) **Opioid** Fentanyl 0.5 to 3 μg/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation conditions:** Intubating conditions were assessed by a blind observer, using a 4-point scale (excellent, good, poor, impossible) - modification of "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) **2. Serious adverse experience:** defined as an adverse effect that was fatal, life-threatening, or permanently disabling, and required prolonged hospitalization, or was an overdose. Investigators stated whether they considered the adverse effect to be related to administration of ORG 9487
Notes	Three elderly participants were excluded before administration of the study drug owing to equipment failure, contraindicated drug administration, or clinical decision Time from induction to start of tracheal intubation: 90 seconds **Adverse event:** Two of these events (tachycardia, with heart rate from 85 to 150 bpm, and bronchospasm) occurred in one 29-year-old, 100-kg, ASA physical status I male

Kahwaji 1997 (*Continued*)

	participant within 30 seconds of administration of 2.0 mg/kg ORG 9487 and were followed by erythema of the arms, shoulders, and face. The bronchospasm was treated with salbutamol, and all symptoms gradually subsided. These events were considered to meet the criteria for serious adverse experiences **Funding source:** supported by Organon Inc., Akzo Nobel Inc., West Orange, NJ **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...before injection of one of five doses of ORG 9487 (0.5, 1.0, 1.5, 2.0, 2.5 mg/ kg) or placebo given in a randomized, blind sequence..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	".....Violations included administration of isoflurane for induction before administration of ORG 9487, administration of enflurane before TOF had returned to 0. 7, administration of an incorrect dose of ORG 9487, or allocation to the incorrect age group....."
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Kirkegaard-Nielsen 1999

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 3/Number of intervention groups = 1 Number of participants in control group = 20/20/20/Number of participants in intervention group = 20 Randomized: N = 80 Analysed: N = 80 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Adults ASA class I and II Elective surgical procedures **Exclusion criteria** Aged > 60 yr or < 18 years Gastro-oesophageal reflux Weighing > 30% more than ideal body weight Neuromuscular disease, or undergoing treatment with drugs known to interfere with neuromuscular transmission
Interventions	**NMBA** Control group 1: rocuronium 0.4 mg/kg Control group 2: rocuronium 0.8 mg/kg Control group 3: rocuronium 1.2 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Fentanyl 2 μg/kg **Local anaesthetic** None **Other** Premedication: midazolam 2 mg IV
Outcomes	**1. Intubation condition:** "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996). Further, if the endotracheal tube was not passed successfully within 30 seconds, i.e. 70 seconds after rocuronium or saline solution administration, this was recorded as a failed intubation
Notes	Intubation 40 seconds after induction **Funding source:** Support was provided solely by institutional and/or departmental sources **Declarations of interest:** not specified

Risk of bias			***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**	

Kirkegaard-Nielsen 1999 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	The dose each participant received was decided on a random basis by selection of an unmarked envelope containing details of the dose
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator performing the intubation and assessing conditions was blinded to the dose of rocuronium administered
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Kopman 2001

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 3/Number of intervention groups = 1 Number of participants in control group = 30/30/30/Number of participants in intervention group = 10 Randomized: N = 100 Analysed: N = 100 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA physical status I or II Aged 18 to 65 years Elective surgical procedures Body mass index $\geq$ 17.5 and $\leq$ 27.5 **Exclusion criteria** Neuromuscular disease
Interventions	**NMBA** Intervention group 1: rapacuronium 1.0 mg/kg Intervention group 2: rapacuronium 1.2 mg/kg Intervention group 3: rocuronium 0.50 mg/kg **Hypnotic**

Kopman 2001 (*Continued*)

	Propofol 2.0 mg/kg IV **Opioid** Alfentanil 12.5 μg/kg **Local anaesthetic** None **Other** Midazolam (maximum 2 mg) for induction
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	Tracheal Intubation 75 seconds after induction After 10 participants had been recruited into the saline group, it became obvious that the induction sequence in this group produced conditions for intubation that were clinically unacceptable in most patients. As a consequence, no further participants were added to this group. Each of the other 3 groups consisted of 30 participants **Funding source:** supported, in part, by an unrestricted grant from Organon, Inc., of West Orange, NJ **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...I generated the random number sequence using a Microsoft Excel spreadsheet. " (contacted study author by mail)
Allocation concealment (selection bias)	High risk	After 10 participants had been recruited into the saline group, it became obvious that the induction sequence in this group produced conditions for intubation that were clinically unacceptable in most patients. As a consequence, no further participants were added to this group. Each of the other 3 groups consisted of 30 participant
Blinding of participants and personnel (performance bias) All outcomes	High risk	After 10 participants had been recruited into the saline group, it became obvious that the induction sequence in this group produced conditions for intubation that were clinically unacceptable in most patients. As a consequence, no further participants were added to this group. Each of the other 3 groups consisted of 30 participants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All attempts at intubation were performed by AFK, who was not informed which test drug was administered"

Kopman 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Lieutaud 2003

Methods	Parallel-group RCT Settings: single centre Country: France Language: English Number of control groups = 3/Number of intervention groups = 1 Number of participants in control group = 45/48/47/Number of participants in intervention group = 20 Randomized: N = 160 Analysed: N = 160 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA physical status I or II Aged 18 to 65 years Scheduled for abdominal or breast surgery **Exclusion criteria** Abnormal airway Significant cardiovascular, respiratory, hepatic, neuromuscular, or renal disease Administration of any drug known or suspected to interact with neuromuscular transmission
Interventions	**NMBA** Control groups 'L', 'M', 'H' (atracurium 0.5 mg/kg) **Hypnotic** Control group 'L' (propofol 1.5 mg/kg) Control group 'M' (propofol 2.0 mg/kg) Control group 'H' (propofol 2.5 mg/kg) Intervention group 'WA' (propofol 2.5 mg/kg) **Opioid** Fentanyl 3 μm/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation conditions:** The scale distributes intubating conditions into 4 classes (excellent, good, poor, impossible). Intubating conditions were pooled as "clinically acceptable" (excellent or good) or "not clinically acceptable" (poor or impossible) (Krieg 1980). The scoring scale is a composite score based on scores of laryngoscopy, cough, and position of vocal cords

Notes	Intubation 240 after induction in control group and in intervention groups based upon TOF response **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of randomization (4 groups) was designed to assign 2 participants in each group every 8 inclusions
Allocation concealment (selection bias)	Low risk	Allocation of the participant was sealed in an opaque envelope, which was opened upon arrival in the operating room
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...Laryngoscopy and intubation were performed when all train-of-four responses were abolished at the orbicularis oculi in groups high (H), medium (M) and low (L)....." Hereby, personnel performing the treatment were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Same physician, blinded to the anaesthetic procedure, performed all intubations
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study was discontinued in group WA after the first intermediate analysis because the incidence of "clinically not acceptable" (poor and impossible) intubating conditions was unacceptable (13 of 20 patients, 65%)
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Lowry 1999

Methods	Parallel-group RCT Settings: single centre Country: UK Language: English Number of control groups = 6/Number of intervention groups = 2 Number of participants in control groups = 20/20/20/20/20/10/Number of participants in intervention groups = 10/10 Randomized: N = 140 Analysed: N = 140 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Aged 18 to 65 years ASA classes I and II Udergoing elective surgery **Exclusion criteria** Concurrent medication known to interfere with neuromuscular transmission Weighing > 30% outside the ideal for height Patients with anticipated difficult intubation
Interventions	**NMBA** Control group 1: rocuronium 0.3 mg/kg Control group 2: rocuronium 0.45 mg/kg Control group 3: rocuronium 0.6 mg/kg Control group 4: rocuronium 0.3 mg/kg Control group 5: rocuronium 0.45 mg/kg Control group 6: rocuronium 0.6 mg/kg **Hypnotic** Control groups 1 to 3 and intervention group 1: propofol 2 to 3 mg/kg Control groups 4 to 6 and Intervention group 2: sevoflurane 8% in oxygen, via a vital capacity technique **Opioid** Fentanyl 1 μm/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	Intubation 60 seconds after induction **Funding source:** This study was supported by a grant from Abbott (UK) Ltd. Dr Lowry was in receipt of a DHSS (Northern Ireland) Clinical Research Fellowship **Declarations of interest:** not specified

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**

Lowry 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	"....according to prior computer-generated random allocation...."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...Propofol was administered at a rate of 10-15 mg/sec until the loss of eyelash reflex. Patients in the sevoflurane group were asked to take vital capacity breaths of sevoflurane 8%...."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	".....by an experienced anaesthetist blinded to both the method of induction used and the dose of rocuronium administered. In order to achieve this the intubator did not enter the operating room until 45 sec after the administration of the muscle relaxant.. .."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

McNeil 2000

Methods	Parallel-group RCT Settings: single centre Country: UK Language: English Number of control groups = 1/Number of intervention groups = 2 Number of participants in control groups = 17/Number of participants in intervention groups = 20/23 Randomized: N = 60 Analysed: N = 60 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA 1 or 2 Non-obese Elective surgery Aged 18 to 65 years **Exclusion criteria** Obstetrical, neurosurgical, ophthalmic patients Mallampati score > 2 Gastro-oesophageal reflux

Interventions	**NMBA** Succinylcholine 1 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Control group: none Intervention group 1: remifentanil 2 μg/kg Intervention group 2: remifentanil 4 μg/kg **Local anaesthetic** None **Other** After induction, participants were mask ventilated with Sevo 2% + 50% N_2O until end of fasciculation and before laryngoscopy
Outcomes	**1. Intubation conditions:** Scoring system included jaw mobility, mask ventilation, vocal cord visibility, vocal cord position, and participant movement during intubation (all assessed by a 3-grade grading system) In this RCT, study authors did not define any cut-off value for acceptable intubation. In our meta-analyses, intubation condition was categorized as acceptable if the vocal cords were open or in mid-position. If the vocal cords were closed, it was categorized as unacceptable **2. Difficult laryngoscopy:** Vocal cord visibility was categorized as (1) vocal cords and arytenoids completely visible, (2) vocal cords and arytenoids partly visible, or (3) vocal cords and arytenoids not seen. Score = 3 was defined as a difficult laryngoscopy
Notes	In all patients, vocal cord was visible (Coemack and Lehane score = 1 and 2) Intubation 30 seconds after induction of remifentanil and after fasciculation in intervention group **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Participants were randomized into 3 groups by opening unmarked envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	"....was initiated with 2% sevoflurane in 50% nitrous oxide in oxygen at a total flow 8 litres min-1 and continued in group PS until fasciculation had ceased....."
Blinding of outcome assessment (detection bias)	Low risk	An experienced blinded anaesthetist took over airway control and attempted tracheal

McNeil 2000 (*Continued*)

All outcomes		intubation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Mencke 2003

Methods	Parallel-group RCT Settings: single centre Country: Germany Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 39(37)/Number of participants in intervention group = 39(36) Randomized: N = 80 Analysed: N = 78 for laryngoscpy conditions and N = 73 for intubation condition and post-intubation pharyngolaryngeal symptoms Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA status I or II Aged 18 to 76 years Elective surgery of the ear **Exclusion criteria** Obesity (defined as weight exceeding 20% of normal weight) Pregnancy Suspected to have a difficult airway (i.e. abnormal airway anatomy (Mallampati score 3 or 4); and mouth opening < 3.5 cm or cervical spine disease, difficult intubation (i.e. Cormack and Lehane score ≥ 3)) Pathological findings of the larynx revealed by initial stroboscopic examination the day before surgery
Interventions	**NMBA** Attracurium 0.5 mg/kg **Hypnotic** Propofol 2.5 to 3 mg/kg **Opioid** Fentanyl 2 to 3 μg/kg **Local anaesthetic** None **Other** Premedication: -midazolam 7.5 mg 1 hour before, as requested
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996) **2. Post-intubation pharyngolaryngeal symptoms:** Postoperative hoarseness was as-

Mencke 2003 (*Continued*)

	sessed at 24, 48, and 72 hours by a standardized interview. Vocal cords were examined by stroboscopy before and 24 and 72 hours after surgery **3. Laryngoscopy condition:** It was possible to retrieve information on the laryngoscopy categorized by Cormack and Lehane (Cormack 1984)
Notes	Five participants were excluded from analyses of intubation conditions and post-intubation upper airway symptoms because of a Cormack grade of 3 or greater (1 in the atracurium group and 4 in the saline group). Moreover, 1 participant in each group had unexpected surgery of the pharynx and therefore had to be excluded Time from induction to start of tracheal intubation: 180 seconds **Funding source:** Support was provided solely by institutional and departmental sources **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized to 2 groups of 40 participants each, via random number draws
Allocation concealment (selection bias)	Low risk	Concealment was ensured. The investigator in the operating theatre was blinded; the investigator performing the interview concerning hoarseness was blinded, too. The ENT physician, who performed the stroboscopy, did not know the participant's group. Participants were blinded throughout the study (contacted study author)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The study drugs were administered in a double-blind fashion, and syringes were prepared (adjusted to a 5-ml volume) by an investigator who did not participate in the evaluation of intubating conditions, intubating score, and assessment.."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The study drugs were administered in a double-blind fashion, and syringes were prepared (adjusted to a 5-ml volume) by an investigator who did not participate in the evaluation of intubating conditions, intubating score, and assessment .."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described

Mencke 2003 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Mencke 2014

Methods	Parallel-group RCT Settings: single centre Country: Germany Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 40(40)/Number of participants in intervention group = 43(39) Randomized: N = 83 Analysed: N = 83 for laryngoscopy conditions and N = 79 for intubation condition and post-intubation pharyngolaryngeal symptoms Dates when the study was conducted: Between April 2012 and January 2013
Participants	**Inclusion criteria** ASA status I or II Aged 18 to 80 years Surgery of the ear **Exclusion criteria** Known or suspected difficult airway, such as mouth opening < 3.5 cm or Mallampati score 4 or Cormack grade 3 or 4 Obesity Disease of the larynx or vocal cords Hoarseness before surgery Preexisting severe vocal cord pathology
Interventions	**NMBA** Rocuronium 0.45 $mg \cdot kg^{-1}$ **Hypnotic** Control group: propofol 1.5 $mg \cdot kg^{-1}$ was given (if necessary, 30 mg was supplemented) Intervention group: propofol 1.5 $mg \cdot kg^{-1}$ was given (if necessary, 30 mg was supplemented). After propofol, the SEVO group received sevoflurane at an inspired concentration of 3.0 to 3.5 Vol% (fresh gas flow 8 $L \cdot min^{-1}$). After 2 to 3 minutes, when the end-tidal sevoflurane concentration reached 1.0 MAC (stable for 20 seconds), intubation was performed **Opioid** Remifentanil 0.30 $\mu g \cdot kg \cdot min^{-1}$ for 3 minutes **Local anaesthetic** None **Other** Midazolam 7.5 mg orally before arrival in the anaesthetic room
Outcomes	**1. Intubation conditions:** "Good clinical research practice in pharmacodynamic studies of neuromuscular blocking agents II: the Stockholm revision" (Fuchs-Buder 2007) **2. Post-intubation vocal cord injury:** All participants underwent laryngoscopy by an

	ENT physician who was blinded to the participant's group. Slight changes, such as erythema, and vocal cord injuries, such as oedema, haematoma, and granuloma, were noted by videolaryngoscopy **3. Laryngoscopy condition:** It was possible to retrieve information on the laryngoscopy categorized by Cormack and Lehane (Cormack 1984)
Notes	Two participants from the intervention (SEVO) group could be intubated only after administration of rocuronium. The vocal cords were closed and did not open after propofol 30 mg IV; to avoid vocal cord injury, rocuronium 0.45 $mg \cdot kg^{-1}$ was given. These 2 participants were included in our meta-analyses as difficult to intubate. Other participants from the intervention (SEVO) group had a Cormack and Lehane score of 3. These participants were included in our meta-analyses as difficult to intubate All participants received dexamethasone 4.0 mg IV. This may have reduced the prevalence of postoperative upper airway discomfort/injury **Funding source: "**There was no funding for any of the authors and there was no funding for the manuscript preparation" **Declarations of interest:** "None of the authors has any conflict of interest"

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"....a randomization program was used..."
Allocation concealment (selection bias)	Low risk	Concealment was ensured. The investigator in the operating theatre was blinded when assessing intubating conditions. The investigator who performed the interview regarding hoarseness was blinded. The ENT physician, who performed the endoscopy, did not know the participant's group. Participants were blinded throughout the study (contacted study author)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Anaesthetists and nurses responsible for treatment were aware of the intervention to ensure a safe general anaesthesia if problems had occurred (contacted study author)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All intubating variables and scores were blinded for randomization (contacted study author) Assessment of upper airway injury was blinded to participants' group assignment (direct from paper)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described

Mencke 2014 (*Continued*)

Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Naguib 2003

Methods	Parallel-group RCT Settings: single centre Country: Saudi Arabia Language: English Number of control groups = 3/Number of intervention groups = 1 Number of participants in control group = 50/50/50/Number of participants in intervention group = 50 Randomized: N = 200 Analysed: N = 200 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I status Elective procedures **Exclusion criteria** Neuromuscular, renal, hepatic, or cardiovascular disease Taking any drug known to interfere with neuromuscular function Drug or alcohol abuse Gastro-oesophageal reflux or hiatus hernia Reactive airway disease Allergies to any of the study drugs Administration of sedative or narcotic drugs in the previous 24 hours Renal or hepatic impairment Anticipated difficult intubation
Interventions	**NMBA** Control group I: succinylcholine 0.3 mg/kg Control group II: succinylcholine 0.5 mg/kg Control group III: succinylcholine 1.0 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Fentanyl 2 μg/kg **Local anaesthetic** None **Other** Premedication: 2 mg oral lorazepam 90 minutes before operation
Outcomes	**1. Intubation conditions:** acceptable vs unacceptable "GCRP in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)

Notes	Intubation 60 seconds after induction **Funding source:** Support was provided solely by institutional and/or departmental sources **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number generation (contacted study author by mail)
Allocation concealment (selection bias)	Low risk	Yes (contacted study author by mail)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes (contacted study author by mail)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Because observation of fasciculations would identify the drug administered as succinylcholine, the anaesthesiologist performing and grading intubation was positioned with his back to the participant until just before beginning the intubation sequence
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Naguib 2006

Methods	Parallel-group RCT Settings: single centre Country: Saudi Arabia Language: English Number of control groups = 5/Number of intervention groups = 1 Number of participants in control group = 30/30/30/30/30/Number of participants in intervention group = 30 Randomized: N = 180 Analysed: N = 180 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA physical status I Participants underwent elective procedures

	Exclusion criteria Neuromuscular, renal, cardiovascular, or hepatic disease Patient was taking any drug known to interfere with neuromuscular function History of drug or alcohol abuse Gastro-oesophageal reflux or hiatal hernia Reactive airway disease Allergies to any of the study drugs Administration of sedative or narcotic drugs in the previous 24 hours Anticipated difficult intubation
Interventions	**NMBA** Control group 1: succinylcholine 0.3 mg/kg Control group 2: succinylcholine 0.5 mg/kg Control group 3: succinylcholine 1.0 mg/kg Control group 4: succinylcholine 1.5 mg/kg Control group 5: succinylcholine 2.0 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Fentanyl 2 μm/kg **Local anaesthetic** None **Other** None
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	Intubation was subsequently performed 60 seconds after succinylcholine administration **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization schedule provided in sealed envelopes according to a computer-generated list
Allocation concealment (selection bias)	Low risk	Randomization schedule provided in sealed envelopes according to a computer-generated list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Yes (contacted study author by mail)

Naguib 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The anaesthesiologist performing and grading the intubation was positioned with his back to the participant until just before beginning the intubation sequence
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Nimmo 1995

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 2/Number of intervention groups = 1 Number of participants in control group = 20/20/Number of participants in intervention group = 20 Randomized: N = 60 Analysed: N = 60 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Elective oral surgery under general anaesthesia necessitating nasal intubation **Exclusion criteria** Aged < 16 years or > 50 years Appeared clinically to present difficulty in intubation Anaesthetic technique was unsuitable
Interventions	**NMBA** Control group 1: suxamethonium 0.25 mg/kg Control group 2: suxamethonium 0.5 mg/kg **Hypnotic** Propofol 2.5 mg/kg **Opioid** Alfentanil 15 μg/kg **Local anaesthetic** None **Other** Premedication: temazepam 10 mg 1 hour before operation
Outcomes	**1. Intubation conditions:** jaw and cord relaxation (Young, Clarke & Dundee). Overall intubation conditions (three grade assessment.Incidence of coughing on intubation (four grade assessment), duration of apnoea (Lund 1969) **2. Postoperative myalgia and sore throat:** incidence of postoperative myalgia (four

	grade assessment). Later on the day of operation (day 1), participants were interviewed by one of the investigators (not participating in the anaesthetic) regarding muscle pain and sore throat and were given a questionnaire to return 5 days after the operation (day 5) with the same questions. Muscle pain and sore throat were scored as none, mild, moderate, or severe
Notes	In the Intervention group, intubation was unsuccessful in 2 participants because of a combination of poor vision and poor cord relaxation. In both participants, the trachea was successfully intubated after a dose of suxamethonium 50 mg. These two participants were included in the meta-analysis as patients difficult to intubate Postoperative sore throat was present in more than 50% of participants in all 3 groups at both 1 and 5 days after operation. Investigators noted no significant difference in the incidence of sore throat between the 3 groups. However, they did not report the specific number of participants in the 2 groups. Therefore, we did not include this study in the meta-analysis **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Syringes with medicine were prepared by one of the investigators not participating in the anaesthetic, and 20 participants were allocated randomly to each of the 3 groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Unclear risk	The exact incidence of sore throat was not reported

Pang 2014

Methods	Parallel-group RCT Settings: single centre Country: China Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 20/Number of participants in intervention group = 20 Randomized: N = 40 Analysed: N = 40 Dates when the study was conducted: between July 2010 and January 2011
Participants	**Inclusion criteria** Aged 18 to 65 years Body mass index 18.5 to 25 kg/m^2 ASA class I or II Mallampati class I or II Elective suspension laryngoscopic excision under intubation without muscular relaxation **Exclusion criteria** Medical history of myopathy Known allergy to study drugs Drug abuse History of upper respiratory tract infection within 3 weeks of enrolment Gastrointestinal reflux Intracranial pathology Suspected difficult airway Serious cardiopulmonary or hepatorenal insufficiency
Interventions	**NMBA** Control group: cisatracurium 0.1 mg/kg **Hypnotic** Propofol target control **Opioid** Remifentanil target control **Local anaesthetic** Superficial anaesthesia with 10 mg/mL tetracaine **Other** Midazolam (0.03 mg/kg) was administered for induction of anaesthesia
Outcomes	**1. Intubation condition:** Hellbo-Hansen 1988 **2. Laryngoscopy condition:** Cormack-Lehane classification (Cormack 1984)
Notes	**Funding source:** This work was supported by Jilin Provincial Department of Science and Technology under the International Collaborative Initiative (#20110759) **Declarations of interest:** none declared

Risk of bias			*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**	

Pang 2014 (*Continued*)

Random sequence generation (selection bias)	Low risk	A computer- generated random number table was used to randomly and equally assign participants
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding of personnel performing drug administration. Participants were blinded to treatment assignment throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent anaesthetist performed tracheal intubation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Pino 1998

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 5/Number of intervention groups = 1 Number of participants in control group = 30/15/14/14/15/Number of participants in intervention group = 10 Randomized: N = 100 Analysed: N = 98 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Normal upper airway anatomy Aged 18 to 65 years Within 30% of ideal body weight **Exclusion criteria** History of malignant hyperthermia Abnormal plasma cholinesterase levels Neuromuscular, neurological, hepatic, and renal conditions that might influence neuromuscular function Use of drugs that might alter the response to neuromuscular blockade or might affect histamine release

Pino 1998 (*Continued*)

Interventions	**NMBA** Control group 1: mivacurium 0.25 mg/kg Control group 2: rocuronium 0.45 mg/kg Control group 3: rocuronium 0.6 mg/kg Control group 4: rocuronium 0.9 mg/kg Control group 5: rocuronium 1.2 mg/kg **Hypnotic** Propofol 2 mg/kg **Opioid** Fentanyl 2 μm/kg **Local anaesthetic** None **Other** Midazolam 1 to 2 mg for induction
Outcomes	**1. Intubation conditions** - Excellent: easy passage of endotracheal tube without coughing; vocal cords relaxed and abducted - Good: passage of endotracheal tube with slight coughing or bucking; vocal cords relaxed and abducted - Poor: passage of endotracheal tube with moderate coughing or bucking; vocal cords moderately abducted - Not possible: unable to intubate
Notes	Two participants were excluded from analysis because they were mistakenly entered into the study twice Intubation 90 seconds after administration of midazolam **Funding source:** supported by a grant from GlaxoWellcome **Declarations of interest:** Affiliated GlaxoWellcome Company, Research Triangle Park, North Carolina

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of assessor: intubator not involved in protocol; waited outside OP room until last minute before intubation attempt

Pino 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were excluded from analysis because they were mistakenly entered into the study twice
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Rousseau 1995

Methods	Parallel-group RCT Settings: single centre Country: France Language: French Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group (77)/Number of participants in intervention group = 75 Randomized: N = 152 Analysed: N = 152 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** > 18 years of age ASA I Mallampati I Elective surgery not needing relaxant **Exclusion criteria** Suspect difficult intubation Former allergies Abnormal ECG Bradycardia < 50 Urgent surgery
Interventions	**NMBA** Vecuronium 0.08 mg/kg **Hypnotic** Propofol 2.5 mg/kg **Opioid** Alfentanil 0.03 mg/kg **Local anaesthetic** Intervention group: lidocaine 1.5 mg/kg **Other** Premedication: prazepam 40 mg and hydroxyzine 100 mg (1 hour before induction)
Outcomes	**1. Intubation conditions:** Physician performing the intubation evaluated mouth opening, opening of the glottis, and the occurrence of coughing (Saarnivaara 1991) Mouth opening: impossible 3, medium 2, complete 0; opening of the glottis: moving or closed 3, half closed 2, open 0; cough at intubation: significant ("Importante") 3, a little 1, absent 0. Total score < 3 considered good intubating conditions. A score is calculated

Rousseau 1995 (*Continued*)

	for each intubation attempt
Notes	107 oral intubations, 45 nasal intubations, all intubations by direct laryngoscopy Intubation after induction: 60 seconds in control group and 180 seconds in intervention group **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Using a random number table
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Different times from infusion to intubation in the 2 groups (1 minute for Vecu0 and 3 minutes for Vecu+) make it easy to discern the 2 groups from each other;no mention of measures of concealment of allocation towards assessor, who might have been present from infusion to finish (not mentioned)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Different times from infusion to intubation in the 2 groups (1 minute for Vecu0 and 3 minutes for Vecu+) make it easy to discern the 2 groups from each other; no mention of measures of concealment of allocation towards assessor, who might have been present from infusion to finish (not mentioned)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Scheller 1992

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 1/Number of intervention groups = 4 Number of participants in control group (15)/Number of participants in intervention group = 15/15/15/15 Randomized: N = 75 Analysed: N = 75 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** Same-day surgery for a variety of surgical procedures ASA physical status I or II Mallampati class I airway anatomy **Exclusion criteria** History of intravenous drug use, alcohol addiction Full stomach Coronary artery disease Reactive airway disease
Interventions	**NMBA** d-Tubocurarine 3 mg and succinylcholine 1 mg/kg **Hypnotic** Control group 1: thiamylal 4 mg/kg Intervention groups 1 to 4: propofol 2 mg/kg **Opioid** Control group: no opioids Intervention group 1: alfentanil 30 µg/kg Intervention group 2: alfentanil 40 µg/kg Intervention group 3: alfentanil 50 µg/kg Intervention group 4: alfentanil 60 µg/kg **Local anaesthetic** None **Other** All participants received midazolam 1 mg IV before induction
Outcomes	**1. Intubation conditions:** Vocal cords, position of vocal cards, jaw mobility, and participant movement during and within 1 minute of attempted intubation of the trachea. Participants whose tracheas could not be intubated after receiving assigned induction drugs were so noted, and succinylcholine (1 mg/kg IV) was administered. Tracheal intubation was then re-attempted, and exposure of the larynx and outcome of intubation attempt were recorded In this RCT, study authors did not define any cut-off value for acceptable intubation and provided no composite measure of the 4 variables. For the meta-analysis, we defined complete or partial exposure of the vocal cords as clinically acceptable. Vocal cord exposure was categorized as: (1) vocal cords and arytenoids completely visible; (2) vocal cords or arytenoids partially visible; or (3) vocal cords or arytenoids not seen **2. Laryngoscopy condition:** vocal cords or arytenoids not seen defined as difficult

Scheller 1992 (*Continued*)

	laryngoscopy
Notes	Induction after 90 seconds **Funding source:** Dr Scheller is a recipient of a B.B. Sankey Foundation Award. This work was supported in part by a grant from Janssen Pharmaceutica, Piscataway, NJ **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	".....randomized to one of five groups by having an assistant pick one of five cards describing the induction sequence....."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	"...Note that we were not able to be completely blinded as to group because we could generally distinguish the thiamylal/succinylcholine group from the others..."
Blinding of outcome assessment (detection bias) All outcomes	High risk	"...Note that we were not able to be completely blinded as to group because we could generally distinguish the thiamylal/succinylcholine group from the others..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Schlaich 2000

Methods	Parallel-group RCT Settings: single centre Country: Germany Language: English Number of control groups = 3/Number of intervention groups = 1 Number of participants in control group = 30/30/30/Number of participants in intervention group = 30 Randomized: N = 120 Analysed: N = 120 Dates when the study was conducted: not specified

Schlaich 2000 (*Continued*)

Participants	**Inclusion criteria** ASA status I or II Adult Scheduled for elective ambulatory surgery up to 90 minutes **Exclusion criteria** Pregnancy Neuromuscular disorder or receiving medications known to interact with neuromuscular function Suspected to have a difficult airway
Interventions	**NMBA** Control group 1 (0.6 mg/kg rocuronium) Control group 2 (0.45 mg/kg rocuronium) Control group 3 (0.3 mg/kg rocuronium) **Hypnotic** Propofol 2 to 2.5 mg/kg **Opioid** Remifentanil 0.5 µg/kg/min **Local anaesthetic** None **Other** Premedication: midazolam 7.5 mg orally 1 hour before
Outcomes	**1. Intubation condition: "**Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996)
Notes	Time from induction to start of tracheal intubation: 180 seconds **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"....All patients were intubated by the same experienced anaesthetist blinded to the treatment...."

Schlaich 2000 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Sivalingam 2001

Methods	Parallel-group RCT Settings: single centre Country: New Zealand Language: English Number of control groups = 1/Number of intervention groups = 3 Number of participants in control group = 25/Number of participants in intervention group = 25/25/25/25 Randomized: N = 100 Analysed: N = 100 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Aged 18 to 65 years Mixed surgery **Exclusion criteria** Smokers Known or anticipated difficult tracheaI intubation Risk of aspiration Adverse effects of coughing or straining Taking beta-blocker with absolute contraindication to use of sevoflurane, suxamethonium, and alfentanil
Interventions	**NMBA** Suxamethonium 1 mg/kg **Hypnotic** Sevoflurane 7% and nitrous oxide 60% **Opioid** Control group 1: alfentanil 10 μg/kg Intervention group 1: alfentanil 20 μg/kg Intervention group 2: alfentanil 25 μg/kg Intervention group 3: alfentanil 30 μg/kg **Local anaesthetic** None **Other** Atropine 0.3 mg
Outcomes	**1) Intubation conditions:** modified version of Saarnivaara L, Klemola UM (Saarnivaara 1991). The scoring scale is a composite score based on scores of jaw relaxation, movement of limbs, movement of vocal cords, and coughing. Based on a score ranging from 3 to

Sivalingam 2001 (*Continued*)

	12 points Intubation conditions were categorized as excellent = 12 points, satisfactory = 10 to 11 points, poor < 10 points or failed **2) Sore throat:** postoperative, self-reporting, time and method of reporting not defined
Notes	One participant from intervention group 1 was intubated by rescue suxamethonium. We included this participant in our meta-analyses as difficult to intubate **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly allocated to receive…"; method not specified
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes, opened immediately before induction
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"...one of the investigators who was blinded to the group allocation, entered the operation room to perform direct laryngoscopy. ..."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Stevens 1997

Methods	Parallel-group RCT Settings: single centre Country: USA Language: English Number of control groups = 1/Number of intervention groups = 6 Number of participants in control group = 20/Number of participants in intervention group = 20/20/20/20/20/20 Randomized: N = 140 Analysed: N = 140 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Outpatients Aged 18 to 60 years Scheduled for elective surgery All enrolled participants had Mallampati class I or II airway anatomy **Exclusion criteria** Coronary artery disease, hypertension, reactive airway disease Obesity > 30% above ideal body weight History of drug or alcohol abuse, or gastro-oesophageal reflux Taking narcotics or drugs known to interfere with neuromuscular transmission
Interventions	**NMBA** Control group: d-tubocurarine 3 mg and succinylcholine 1 mg/kg **Hypnotic** Control group: thiopental 4 mg/kg Intervention groups 1 and 2: etomidate 0.3 mg/kg Intervention groups 3 and 4: propofol 2 mg/kg Intervention groups 5 and 6: thiopental 4 mg/kg **Opioid** Control group: none Intervention groups 1 to 6: alfentanil 40 μg/kg **Local anaesthetic** Lidocaine 1 mg/kg (intervention groups 2, 4, 6) **Other** Premedication: midazolam 0.03 mg/kg IV 5 minutes before induction
Outcomes	**1. Intubation conditions:** "The intubating anaesthesiologist, assessed each patient on four variables: jaw relaxation, exposure of the vocal cords, vocal cord position, and patient response to intubation and slow (5-s) inflation of the endotracheal tube cuff" Participants who could not be intubated on the first attempt were given succinylcholine 1 mg/kg, and intubation was completed In this RCT, study authors did not define any cut-off value for acceptable intubation and provided no composite measure of the 4 variables. For the meta-analysis, we defined closed vocal cords as difficult intubation, and open or midline as acceptable intubation conditions **2. Laryngoscopy conditions:** Exposure of the vocal cords was defined as 'complete', 'partial', or 'not seen'. Difficult laryngoscopy was defined as 'not seen'

Stevens 1997 (*Continued*)

Notes	For all participants, it was possible to expose the vocal cords. In the various alfentanil groups, 17 required succinylcholine to complete intubation. Thirty-five percent of participants (7 of 20) in intervention group 5 (alfentanil/ thiopental) required succinylcholine to complete intubation compared with 3 of 20 (15%), 2 of 20 (10%), 2 of 20 (10%), and 0% and 3 of 20 (15%) in Intervention groups 1 to 4 and 6, respectively. It was not possible to identify specific participants who had closed vocal cords and therefore required succinyl chloride Intubation was performed 90 seconds after induction **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Participants were randomly allocated to 1 of 7 groups (n = 20/group) by means of previously prepared envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The induction sequence was conducted using four prepared syringes in all patients". ..."Opaque tape was applied to Syringe 3 to disguise the color of the hypnotic drug". ... "Injection of all syringes was performed by an assistant behind a drape so that the intubating anesthesiologist (one of three of the authors) was blinded to the color and volume of the IV drugs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The induction sequence was conducted using four prepared syringes in all patients". ..."Opaque tape was applied to Syringe 3 to disguise the color of the hypnotic drug". ... "Injection of all syringes was performed by an assistant behind a drape so that the intubating anesthesiologist (one of three of the authors) was blinded to the color and volume of the IV drugs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Striebel 1995

Methods	Parallel-group RCT Settings: single centre Country: Germany Language: German Number of control groups = 2/Number of intervention groups = 2 Number of participants in control group = 25/25/Number of participants in intervention group = 25/25 Randomized: N = 100 Analysed: N = 100 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Gynaecological surgery **Exclusion criteria** Not specified
Interventions	**NMBA** Control groups 1 and 2: vecuronium 1 mg + succinylcholine 1 mg/kg **Hypnotic** Control group 1: demand-adapted thiopental (5.5 ± 3.14 mg/kg) Control group 2: demand-adapted propofol (2.2 ± 0.48 mg/kg) Intervention group 1: demand-adapted propofol (2.4 ± 0.63 mg/kg) Intervention group 2: demand-adapted propofol (2.2 ± 0.48 mg/kg) **Opioid** Control group 1: fentanyl 0.1 mg Control group 2: fentanyl 0.1 mg Intervention group 1: fentanyl 0.1 mg Intervention group 2: fentanyl 0.2 mg **Local anaesthetic** None **Other** Premedication: midazolam 7.5 mg
Outcomes	**1) Intubation conditions:** (1) very good, (2) good, (3) satisfactory, (4) sufficient, (5) inadequate, (6) insufficient. Acceptable conditions 1 to 4, unacceptable conditions 5 and 6 **2) Laryngoscopy conditions:** Comack & Lehane (Cormack 1984). Unproblematic laryngoscopy: grades I and II. Difficult laryngoscopy: grades III and IV
Notes	**Funding source:** not specified **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified

Striebel 1995 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All medicaments were blinded to personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Anaesthetist performing the intubation was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Wong 1996

Methods	Parallel-group RCT Settings: single centre Country: Malaysia Language: English Number of control groups = 1/Number of intervention groups = 3 Number of participants in control group = 30/Number of participants in intervention group = 30/30/30 Randomized: N = 120 Analysed: N = 120 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Elective surgery Aged 18 to 60 years **Exclusion criteria** Expected difficult airway Aspiration risk Head and neck surgery Suxamethonium contraindicated
Interventions	**NMBA** Control group: succinylcholine 1 mg/kg **Hypnotic** Propofol 200 mg/min until loss of verbal response **Opioid** Control group: none Intervention group 1: alfentanil 15 μg/kg Intervention group 2: alfentanil 30 μg/kg Intervention group 3: none

Wong 1996 (*Continued*)

	Local anaesthetic None **Other** Premedication: midazolam 7 mg 1 hour before induction
Outcomes	**1. Intubation conditions:** The scoring scale is a composite score based on scores of jaw relaxation, movement of the vocal cords, and coughing. Based on a score ranging from 0 to 6 points. Intubation conditions were categorized as good = 5 to 6 points, moderate = 3 to 4 points, poor = 1 to 2 points or failed (Saarnivaara 1991)
Notes	One participant in intervention group 3 was excluded because of an unanticipated difficult intubation. We included this participant in our meta-analysis as a difficult tracheal intubation patient The mean dose requirement for induction by propofol was higher in groups without alfentanil (3 mg/kg vs 2.5 mg/kg) **Funding source:** "....Janssen Pharmaceutica for supplying the alfentanil" **Declarations of interest:** not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"....The drug was given by an anaesthetic trainee who was unaware of the drugs before its administration....."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	".....who was unaware of the randomisation process entered the operating room 30 seconds after completion of drug administration....."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

Yazdi 2016

Methods	Parallel-group RCT Settings: single centre Country: Iran Language: English Number of control groups = 1/Number of intervention groups = 1 Number of participants in control group = 31/Number of participants in intervention group = 35 Randomized: N = 66 Analysed: N = 66 Dates when the study was conducted: not specified
Participants	**Inclusion criteria** ASA I or II Elective surgery Aged 15 to 65 years **Exclusion criteria** Expected difficult airway (Mallampati score III or IV) Chronic alcohol or opioid use Allergy to study medications
Interventions	**NMBA** Control group: atracurium 0.5 mg/kg **Hypnotic** Propofol 2.5 mg/kg **Opioid** Control group: none Intervention group: remifentanil 2 μg/kg IV over 30 seconds **Local anaesthetic** None **Other** Atropine 0.5 mg
Outcomes	**1. Intubation conditions:** "...anaesthesiologist checked the intubation condition using criteria based on jaw relaxation, vocal cord movement and bucking on tracheal tube as primary measurements of comparison (Table 1). Intubation condition defined as optimal (score 1 or 2 in all categories), suboptimal (score 3 in at least 1 of the 3 categories), or fail (fail to intubation)
Notes	"Unsuccessful intubation due to closed vocal cords were seen in 2 patients in remifentanil group, the patients ventilated and received atracurium and intubation was applied again" These two participants were categorized as failed intubation in the intervention (remifentanil) group **Funding source:** not specified **Declarations of interest:** not specified

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Yazdi 2016 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study was categorized as "double-blinded". However, no detailed description was provided in the manuscript
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was categorized as "double-blinded". However, no detailed description was provided in the manuscript
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers and reasons for (possible) drop-outs and withdrawals are described
Selective reporting (reporting bias)	Low risk	Relevant and reasonably expected outcomes are reported

ASA = American Society of Anesthesiologists ASA physical status classification system; BMI = body mass index; ECG = electrocardiography; ENT= ear, nose, and throat; GCRP = "Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents" (Viby-Mogensen 1996); GI = gastrointestinal; IV = intravenous; kg = kilogram; mg = milligram; mmol/L = millimoles per litre; N = number of cases; NMBA = neuromuscular blocking agent; PO = per os; RCT = randomized controlled trial; sec = second; TOF = 'train of four'; TS = total score; µg = microgram; VAS = visual analogue scale.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alcock 1993	An unspecified number of participants were intubated blind nasal
Baumgarten 1988	Study was terminated for the control group because of unacceptable intubation conditions. Thus, randomization and blinding were violated
Ide 2015	Participants were intubated blind nasal. No evaluation of direct laryngoscopy was performed

DATA AND ANALYSES

Comparison 1. Avoidance vs use of NMBA

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Difficult tracheal intubation: low risk of bias vs high or uncertain risk of bias	34	3565	Risk Ratio (M-H, Random, 95% CI)	5.00 [3.49, 7.15]
1.1 Low risk of bias	4	508	Risk Ratio (M-H, Random, 95% CI)	13.27 [8.19, 21.49]
1.2 High or uncertain risk of bias	30	3057	Risk Ratio (M-H, Random, 95% CI)	4.14 [2.92, 5.87]
2 Difficult tracheal intubation: depolarizing vs non-depolarizing NMBA	32	3413	Risk Ratio (M-H, Random, 95% CI)	5.25 [3.61, 7.63]
2.1 Depolarizing NMBA	16	1540	Risk Ratio (M-H, Random, 95% CI)	5.79 [2.64, 12.72]
2.2 Non-depolarizing NMBA	16	1873	Risk Ratio (M-H, Random, 95% CI)	4.72 [3.17, 7.02]
3 Difficult tracheal intubation: remifentanil vs no remifentanil	26	3008	Risk Ratio (M-H, Random, 95% CI)	5.64 [3.82, 8.31]
3.1 Remifentanil	4	372	Risk Ratio (M-H, Random, 95% CI)	15.86 [4.43, 56.71]
3.2 No remifentanil	22	2636	Risk Ratio (M-H, Random, 95% CI)	5.23 [3.54, 7.74]
4 Difficult tracheal intubation: alfentanil vs no alfentanil	26	2618	Risk Ratio (M-H, Random, 95% CI)	4.77 [3.25, 7.01]
4.1 Alfentanil	6	511	Risk Ratio (M-H, Random, 95% CI)	4.46 [1.66, 11.98]
4.2 No alfentanil	20	2107	Risk Ratio (M-H, Random, 95% CI)	5.10 [3.34, 7.79]
5 Difficult tracheal intubation: local anaesthesia vs no local anaesthesia	31	3184	Risk Ratio (M-H, Random, 95% CI)	5.04 [3.48, 7.29]
5.1 Local anaesthesia	5	307	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.14, 3.18]
5.2 No local anaesthesia	26	2877	Risk Ratio (M-H, Random, 95% CI)	6.26 [4.15, 9.44]
6 Difficult tracheal intubation: excluded anticipated DTI vs included anticipated DTI	34	3564	Risk Ratio (M-H, Random, 95% CI)	5.00 [3.50, 7.16]
6.1 Exclusion of patients with anticipated difficult intubation	25	2886	Risk Ratio (M-H, Random, 95% CI)	5.32 [3.54, 8.00]
6.2 No exclusion of patients with anticipated difficult intubation	9	678	Risk Ratio (M-H, Random, 95% CI)	4.40 [1.71, 11.29]
7 Difficult tracheal intubation: ”best-case scenario”	34	2410	Risk Ratio (M-H, Random, 95% CI)	5.99 [3.46, 10.38]
8 Difficult tracheal intubation excluding dose-finding studies	16	1536	Risk Ratio (M-H, Random, 95% CI)	3.40 [1.63, 7.10]
9 Difficult tracheal intubation: funding from pharmaceutical industry	34	3565	Risk Ratio (M-H, Random, 95% CI)	5.00 [3.49, 7.15]
9.1 No funding from pharmaceutical industry	24	2550	Risk Ratio (M-H, Random, 95% CI)	5.33 [3.16, 8.98]
9.2 Funding from pharmaceutical industry	10	1015	Risk Ratio (M-H, Random, 95% CI)	4.10 [2.67, 6.31]

10 One or more events of upper airway discomfort or injury: low risk of bias vs high or uncertain risk of bias	7	844	Risk Ratio (M-H, Random, 95% CI)	1.36 [1.08, 1.71]
10.1 Low risk of bias	1	73	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.21, 6.21]
10.2 High or uncertain risk of bias	6	771	Risk Ratio (M-H, Random, 95% CI)	1.30 [1.08, 1.58]
11 One or more events of upper airway discomfort or injury: depolarizing vs non-depolarizing NMBA	7	846	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.09, 1.74]
11.1 Depolarizing NMBA	2	180	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.83, 2.65]
11.2 Non-depolarizing NMBA	5	666	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.97, 1.94]
12 One or more events of upper airway discomfort or injury: remifentanil vs no remifentanil	7	846	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.09, 1.74]
12.1 Remifentanil	2	193	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.61, 2.08]
12.2 No remifentanil	5	653	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.16, 1.75]
13 One or more events of upper airway discomfort or injury: alfentanil vs no alfentanil	5	446	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.85, 2.53]
13.1 No alfentanil	5	446	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.85, 2.53]
14 One or more events of upper airway discomfort or injury: excluded anticipated DTI vs included anticipated DTI	7	846	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.09, 1.74]
14.1 Excluded anticipated DTI	6	766	Risk Ratio (M-H, Random, 95% CI)	1.37 [1.05, 1.79]
14.2 Included anticipated DTI	1	80	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.39, 10.31]
15 Difficult laryngoscopy: low risk of bias vs high or uncertain risk of bias	13	1308	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.53, 4.21]
15.1 Low risk of bias	1	78	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.47, 34.20]
15.2 High or uncertain risk of bias	12	1230	Risk Ratio (M-H, Random, 95% CI)	2.47 [1.47, 4.16]

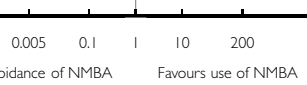
Analysis 1.1. Comparison 1 Avoidance vs use of NMBA, Outcome 1 Difficult tracheal intubation: low risk of bias vs high or uncertain risk of bias.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 1 Difficult tracheal intubation: low risk of bias vs high or uncertain risk of bias

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Jiao 2014	13/28	1/27		2.2 %	12.54 [1.76, 89.36]
Mencke 2003	12/36	2/37		3.2 %	6.17 [1.48, 25.64]
Naguib 2003	35/50	8/150		5.3 %	13.13 [6.53, 26.38]
Naguib 2006	21/30	6/150		4.9 %	17.50 [7.72, 39.66]
Subtotal (95% CI)	**144**	**364**		**15.7 %**	**13.27 [8.19, 21.49]**
Total events: 81 (Avoidance of NMBA), 17 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.61$, df = 3 (P = 0.66); $I^2 = 0.0\%$					
Test for overall effect: Z = 10.50 (P < 0.00001)					
2 High or uncertain risk of bias					
Alexander 1999	16/40	0/20		1.3 %	16.90 [1.07, 268.10]
Barclay 1997	19/20	16/40		6.2 %	2.38 [1.60, 3.52]
Beck 1993	1/31	0/33		1.1 %	3.19 [0.13, 75.43]
Bouvet 2008	3/65	0/64		1.2 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		2.2 %	18.00 [2.43, 133.12]
Dominici 1990	11/30	10/30		5.3 %	1.10 [0.55, 2.19]
Gonz lez Obreg n 2010	1/50	4/50		2.0 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		1.3 %	0.09 [0.01, 1.59]
Hanna 2010	3/23	2/24		2.7 %	1.57 [0.29, 8.53]
Harsten 1997	6/39	0/40		1.3 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		1.2 %	9.00 [0.50, 163.58]
Isesele 2012	18/44	0/44		1.3 %	37.00 [2.30, 595.49]
Kahwaji 1997	18/30	17/146		5.8 %	5.15 [3.02, 8.79]
Kirkegaard-Nielsen 1999	13/20	12/60		5.6 %	3.25 [1.78, 5.92]
Kopman 2001	7/10	2/90		3.2 %	31.50 [7.54, 131.53]
Lieutaud 2003	13/20	10/140		5.4 %	9.10 [4.62, 17.93]



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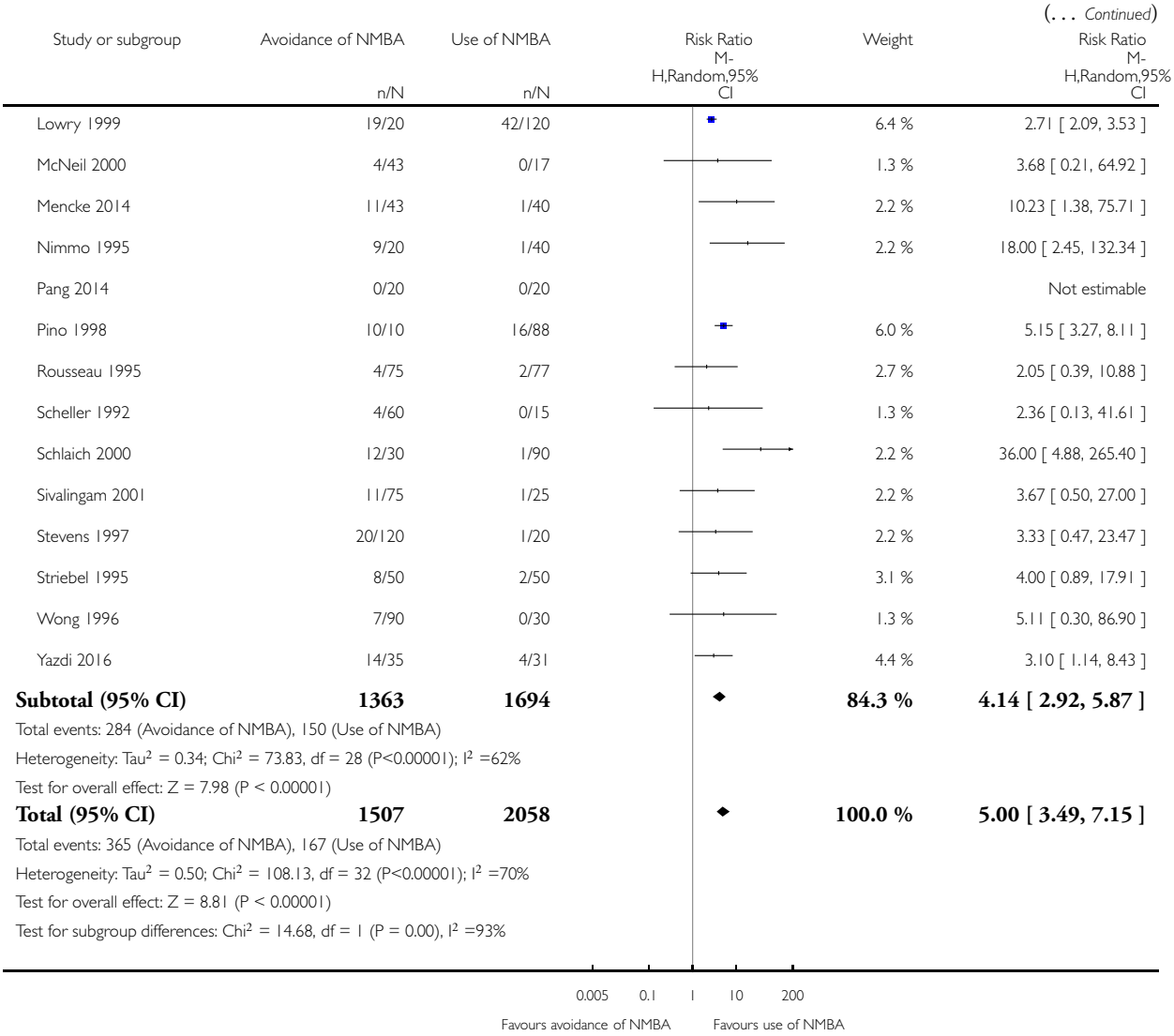
Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lowry 1999	19/20	42/120		6.4 %	2.71 [2.09, 3.53]
McNeil 2000	4/43	0/17		1.3 %	3.68 [0.21, 64.92]
Mencke 2014	11/43	1/40		2.2 %	10.23 [1.38, 75.71]
Nimmo 1995	9/20	1/40		2.2 %	18.00 [2.45, 132.34]
Pang 2014	0/20	0/20			Not estimable
Pino 1998	10/10	16/88		6.0 %	5.15 [3.27, 8.11]
Rousseau 1995	4/75	2/77		2.7 %	2.05 [0.39, 10.88]
Scheller 1992	4/60	0/15		1.3 %	2.36 [0.13, 41.61]
Schlaich 2000	12/30	1/90		2.2 %	36.00 [4.88, 265.40]
Sivalingam 2001	11/75	1/25		2.2 %	3.67 [0.50, 27.00]
Stevens 1997	20/120	1/20		2.2 %	3.33 [0.47, 23.47]
Striebel 1995	8/50	2/50		3.1 %	4.00 [0.89, 17.91]
Wong 1996	7/90	0/30		1.3 %	5.11 [0.30, 86.90]
Yazdi 2016	14/35	4/31		4.4 %	3.10 [1.14, 8.43]
Subtotal (95% CI)	**1363**	**1694**		**84.3 %**	**4.14 [2.92, 5.87]**
Total events: 284 (Avoidance of NMBA), 150 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.34; Chi^2 = 73.83, df = 28 (P<0.00001); I^2 =62%					
Test for overall effect: Z = 7.98 (P < 0.00001)					
Total (95% CI)	**1507**	**2058**		**100.0 %**	**5.00 [3.49, 7.15]**
Total events: 365 (Avoidance of NMBA), 167 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 108.13, df = 32 (P<0.00001); I^2 =70%					
Test for overall effect: Z = 8.81 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 14.68, df = 1 (P = 0.00), I^2 =93%					



Analysis 1.2. Comparison 1 Avoidance vs use of NMBA, Outcome 2 Difficult tracheal intubation: depolarizing vs non-depolarizing NMBA.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 2 Difficult tracheal intubation: depolarizing vs non-depolarizing NMBA

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Depolarizing NMBA					
Alexander 1999	16/40	0/20		1.4 %	16.90 [1.07, 268.10]
Beck 1993	1/31	0/33		1.2 %	3.19 [0.13, 75.43]
Dominici 1990	11/30	10/30		5.6 %	1.10 [0.55, 2.19]
Gulhas 2013	0/40	5/40		1.4 %	0.09 [0.01, 1.59]
Harsten 1997	6/39	0/40		1.4 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		1.3 %	9.00 [0.50, 163.58]
Isesele 2012	18/44	0/44		1.4 %	37.00 [2.30, 595.49]
Jiao 2014	13/28	1/27		2.4 %	12.54 [1.76, 89.36]
McNeil 2000	4/43	0/17		1.4 %	3.68 [0.21, 64.92]
Naguib 2003	35/50	8/150		5.6 %	13.13 [6.53, 26.38]
Naguib 2006	21/30	6/150		5.2 %	17.50 [7.72, 39.66]
Nimmo 1995	9/20	1/40		2.3 %	18.00 [2.45, 132.34]
Scheller 1992	4/60	0/15		1.4 %	2.36 [0.13, 41.61]
Sivalingam 2001	11/74	1/25		2.3 %	3.72 [0.50, 27.36]
Stevens 1997	20/120	1/20		2.4 %	3.33 [0.47, 23.47]
Wong 1996	7/90	0/30		1.4 %	5.11 [0.30, 86.90]
Subtotal (95% CI)	**799**	**741**		**38.1 %**	**5.79 [2.64, 12.72]**
Total events: 180 (Avoidance of NMBA), 33 (Use of NMBA)					
Heterogeneity: $Tau^2 = 1.37$; $Chi^2 = 48.29$, df = 15 (P = 0.00002); $I^2 = 69\%$					
Test for overall effect: Z = 4.38 (P = 0.000012)					
2 Non-depolarizing NMBA					
Barclay 1997	19/20	16/40		6.4 %	2.38 [1.60, 3.52]
Bouvet 2008	3/65	0/64		1.3 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		2.3 %	18.00 [2.43, 133.12]
Gonz lez Obreg n 2010	1/50	4/50		2.1 %	0.25 [0.03, 2.16]

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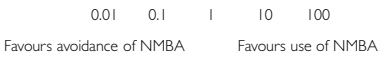
Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kahwaji 1997	18/30	17/146		6.1 %	5.15 [3.02, 8.79]
Kirkegaard-Nielsen 1999	13/20	12/60		5.9 %	3.25 [1.78, 5.92]
Kopman 2001	7/10	2/90		3.4 %	31.50 [7.54, 131.53]
Lieutaud 2003	13/20	10/140		5.6 %	9.10 [4.62, 17.93]
Lowry 1999	19/20	42/120		6.7 %	2.71 [2.09, 3.53]
Mencke 2003	12/36	2/37		3.5 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		2.3 %	10.23 [1.38, 75.71]
Pang 2014	0/20	0/20			Not estimable
Pino 1998	10/10	16/88		6.3 %	5.15 [3.27, 8.11]
Rousseau 1995	4/75	2/77		2.9 %	2.05 [0.39, 10.88]
Schlaich 2000	12/30	1/90		2.3 %	36.00 [4.88, 265.40]
Yazdi 2016	14/31	4/31		4.7 %	3.50 [1.30, 9.45]
Subtotal (95% CI)	**630**	**1243**		**61.9 %**	**4.72 [3.17, 7.02]**
Total events: 174 (Avoidance of NMBA), 130 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.32; Chi^2 = 49.91, df = 14 (P<0.00001); I^2 =72%					
Test for overall effect: Z = 7.62 (P < 0.00001)					
Total (95% CI)	**1429**	**1984**		**100.0 %**	**5.25 [3.61, 7.63]**
Total events: 354 (Avoidance of NMBA), 163 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.53; Chi^2 = 107.89, df = 30 (P<0.00001); I^2 =72%					
Test for overall effect: Z = 8.68 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.21, df = 1 (P = 0.65), I^2 =0.0%					

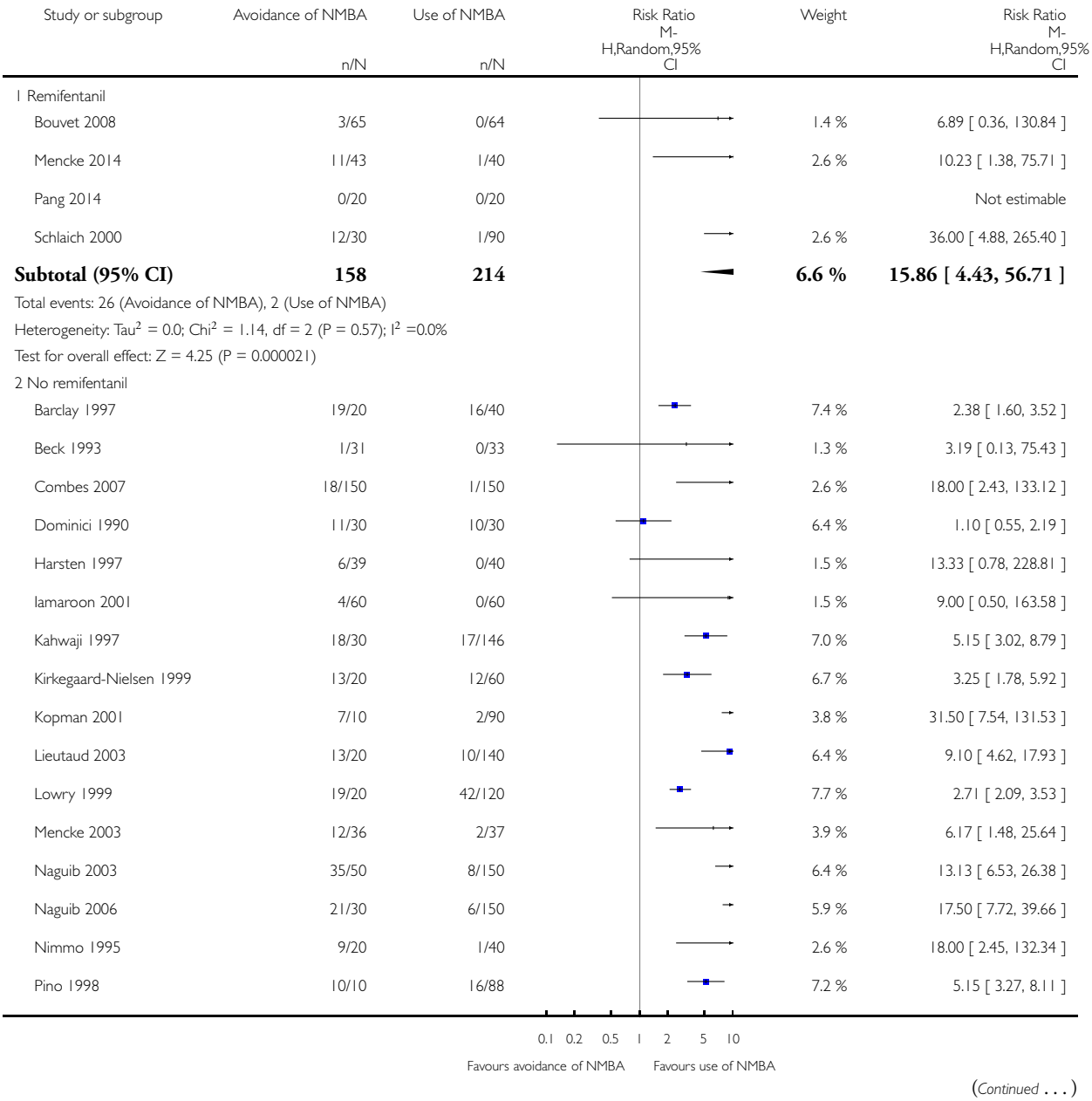


Analysis 1.3. Comparison 1 Avoidance vs use of NMBA, Outcome 3 Difficult tracheal intubation: remifentanil vs no remifentanil.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 3 Difficult tracheal intubation: remifentanil vs no remifentanil



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Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Rousseau 1995	4/75	2/77		3.2 %	2.05 [0.39, 10.88]
Scheller 1992	4/60	0/15		1.5 %	2.36 [0.13, 41.61]
Sivalingam 2001	11/74	1/25		2.6 %	3.72 [0.50, 27.36]
Stevens 1997	20/120	1/20		2.7 %	3.33 [0.47, 23.47]
Striebel 1995	8/50	2/50		3.7 %	4.00 [0.89, 17.91]
Wong 1996	7/90	0/30		1.5 %	5.11 [0.30, 86.90]
Subtotal (95% CI)	**1045**	**1591**		**93.4 %**	**5.23 [3.54, 7.74]**
Total events: 270 (Avoidance of NMBA), 149 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.45; Chi^2 = 83.70, df = 21 (P<0.00001); I^2 =75%					
Test for overall effect: Z = 8.29 (P < 0.00001)					
Total (95% CI)	**1203**	**1805**		**100.0 %**	**5.64 [3.82, 8.31]**
Total events: 296 (Avoidance of NMBA), 151 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 93.20, df = 24 (P<0.00001); I^2 =74%					
Test for overall effect: Z = 8.72 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 2.66, df = 1 (P = 0.10), I^2 =62%					

Analysis 1.4. Comparison 1 Avoidance vs use of NMBA, Outcome 4 Difficult tracheal intubation: alfentanil vs no alfentanil.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 4 Difficult tracheal intubation: alfentanil vs no alfentanil

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Alfentanil					
Barclay 1997	19/20	16/40		7.0 %	2.38 [1.60, 3.52]
Dominici 1990	11/30	10/30		6.1 %	1.10 [0.55, 2.19]
Harsten 1997	6/39	0/40		1.5 %	13.33 [0.78, 228.81]
Kopman 2001	7/10	2/90		3.7 %	31.50 [7.54, 131.53]
Nimmo 1995	9/20	1/40		2.5 %	18.00 [2.45, 132.34]
Rousseau 1995	4/75	2/77		3.1 %	2.05 [0.39, 10.88]
Subtotal (95% CI)	**194**	**317**		**24.0 %**	**4.46 [1.66, 11.98]**
Total events: 56 (Avoidance of NMBA), 31 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.99$; $Chi^2 = 24.00$, df = 5 (P = 0.00022); $I^2 = 79\%$					
Test for overall effect: Z = 2.97 (P = 0.0030)					
2 No alfentanil					
Bouvet 2008	3/65	0/64		1.4 %	6.89 [0.36, 130.84]
Gonz lez Obreg n 2010	1/50	4/50		2.2 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		1.5 %	0.09 [0.01, 1.59]
Hanna 2010	3/23	2/24		3.1 %	1.57 [0.29, 8.53]
Iamaroon 2001	4/60	0/60		1.4 %	9.00 [0.50, 163.58]
Jiao 2014	13/28	1/27		2.6 %	12.54 [1.76, 89.36]
Kahwaji 1997	18/30	17/146		6.6 %	5.15 [3.02, 8.79]
Kirkegaard-Nielsen 1999	13/20	12/60		6.4 %	3.25 [1.78, 5.92]
Lieutaud 2003	13/20	10/140		6.2 %	9.10 [4.62, 17.93]
Lowry 1999	19/20	42/120		7.3 %	2.71 [2.09, 3.53]
McNeil 2000	4/43	0/17		1.5 %	3.68 [0.21, 64.92]
Mencke 2003	12/36	2/37		3.7 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		2.5 %	10.23 [1.38, 75.71]
Naguib 2003	35/50	8/150		6.1 %	13.13 [6.53, 26.38]

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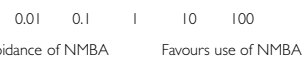
Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Naguib 2006	21/30	6/150		5.7 %	17.50 [7.72, 39.66]
Pang 2014	0/20	0/20			Not estimable
Pino 1998	10/10	16/88		6.9 %	5.15 [3.27, 8.11]
Schlaich 2000	12/30	1/90		2.5 %	36.00 [4.88, 265.40]
Striebel 1995	8/50	2/50		3.5 %	4.00 [0.89, 17.91]
Yazdi 2016	14/35	4/31		5.0 %	3.10 [1.14, 8.43]
Subtotal (95% CI)	**703**	**1404**		**76.0 %**	**5.10 [3.34, 7.79]**
Total events: 214 (Avoidance of NMBA), 133 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.45; Chi^2 = 65.29, df = 18 (P<0.00001); I^2 =72%					
Test for overall effect: Z = 7.53 (P < 0.00001)					
Total (95% CI)	**897**	**1721**		**100.0 %**	**4.77 [3.25, 7.01]**
Total events: 270 (Avoidance of NMBA), 164 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.51; Chi^2 = 97.65, df = 24 (P<0.00001); I^2 =75%					
Test for overall effect: Z = 7.96 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.06, df = 1 (P = 0.81), I^2 =0.0%					



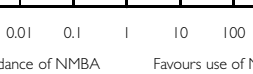
Analysis 1.5. Comparison 1 Avoidance vs use of NMBA, Outcome 5 Difficult tracheal intubation: local anaesthesia vs no local anaesthesia.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 5 Difficult tracheal intubation: local anaesthesia vs no local anaesthesia

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Local anaesthesia					
Barclay 1997	19/20	16/40		6.6 %	2.38 [1.60, 3.52]
Dominici 1990	11/30	10/30		5.7 %	1.10 [0.55, 2.19]
Hanna 2010	3/23	2/24		2.8 %	1.57 [0.29, 8.53]
Pang 2014	0/20	0/20			Not estimable
Striebel 1995	8/50	2/50		3.3 %	4.00 [0.89, 17.91]
Subtotal (95% CI)	**143**	**164**		**18.4 %**	**1.90 [1.14, 3.18]**
Total events: 41 (Avoidance of NMBA), 30 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.09; Chi^2 = 4.59, df = 3 (P = 0.20); I^2 =35%					
Test for overall effect: Z = 2.46 (P = 0.014)					
2 No local anaesthesia					
Alexander 1999	16/40	0/20		1.4 %	16.90 [1.07, 268.10]
Beck 1993	1/31	0/33		1.1 %	3.19 [0.13, 75.43]
Bouvet 2008	3/65	0/64		1.3 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		2.3 %	18.00 [2.43, 133.12]
Gonz lez Obreg n 2010	1/50	4/50		2.1 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		1.4 %	0.09 [0.01, 1.59]
Harsten 1997	6/39	0/40		1.4 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		1.3 %	9.00 [0.50, 163.58]
Jiao 2014	13/28	1/27		2.4 %	12.54 [1.76, 89.36]
Kahwaji 1997	18/30	17/146		6.2 %	5.15 [3.02, 8.79]
Kirkegaard-Nielsen 1999	13/20	12/60		6.0 %	3.25 [1.78, 5.92]
Kopman 2001	7/10	2/90		3.4 %	31.50 [7.54, 131.53]
Lieutaud 2003	13/20	10/140		5.7 %	9.10 [4.62, 17.93]
Lowry 1999	19/20	42/120		6.8 %	2.71 [2.09, 3.53]
McNeil 2000	4/43	0/17		1.3 %	3.68 [0.21, 64.92]



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Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Mencke 2003	12/36	2/37		3.5 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		2.3 %	10.23 [1.38, 75.71]
Naguib 2003	35/50	8/150		5.7 %	13.13 [6.53, 26.38]
Naguib 2006	21/30	6/150		5.3 %	17.50 [7.72, 39.66]
Nimmo 1995	9/20	1/40		2.3 %	18.00 [2.45, 132.34]
Pino 1998	10/10	16/88		6.4 %	5.15 [3.27, 8.11]
Scheller 1992	4/60	0/15		1.3 %	2.36 [0.13, 41.61]
Schlaich 2000	12/30	1/90		2.3 %	36.00 [4.88, 265.40]
Sivalingam 2001	11/74	1/25		2.3 %	3.72 [0.50, 27.36]
Wong 1996	7/90	0/30		1.4 %	5.11 [0.30, 86.90]
Yazdi 2016	14/35	4/31		4.7 %	3.10 [1.14, 8.43]
Subtotal (95% CI)	**1124**	**1753**		**81.6 %**	**6.26 [4.15, 9.44]**
Total events: 282 (Avoidance of NMBA), 134 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.51; Chi^2 = 81.28, df = 25 (P<0.00001); I^2 =69%					
Test for overall effect: Z = 8.73 (P < 0.00001)					
Total (95% CI)	**1267**	**1917**		**100.0 %**	**5.04 [3.48, 7.29]**
Total events: 323 (Avoidance of NMBA), 164 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 103.47, df = 29 (P<0.00001); I^2 =72%					
Test for overall effect: Z = 8.56 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 12.61, df = 1 (P = 0.00), I^2 =92%					

Analysis 1.6. Comparison 1 Avoidance vs use of NMBA, Outcome 6 Difficult tracheal intubation: excluded anticipated DTI vs included anticipated DTI.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 6 Difficult tracheal intubation: excluded anticipated DTI vs included anticipated DTI

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Exclusion of patients with anticipated difficult intubation					
Alexander 1999	16/40	0/20		1.3 %	16.90 [1.07, 268.10]
Barclay 1997	19/20	16/40		6.2 %	2.38 [1.60, 3.52]
Bouvet 2008	3/65	0/64		1.2 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		2.2 %	18.00 [2.43, 133.12]
Gonz lez Obreg n 2010	1/50	4/50		2.0 %	0.25 [0.03, 2.16]
Hanna 2010	3/23	2/24		2.7 %	1.57 [0.29, 8.53]
Iamaroon 2001	4/60	0/60		1.2 %	9.00 [0.50, 163.58]
Isesele 2012	18/44	0/44		1.3 %	37.00 [2.30, 595.49]
Kahwaji 1997	18/30	17/146		5.8 %	5.15 [3.02, 8.79]
Lieutaud 2003	13/20	10/140		5.4 %	9.10 [4.62, 17.93]
Lowry 1999	19/20	42/120		6.4 %	2.71 [2.09, 3.53]
McNeil 2000	4/43	0/17		1.3 %	3.68 [0.21, 64.92]
Mencke 2003	12/36	2/37		3.2 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		2.2 %	10.23 [1.38, 75.71]
Naguib 2003	35/50	8/150		5.3 %	13.13 [6.53, 26.38]
Naguib 2006	21/30	6/150		4.9 %	17.50 [7.72, 39.66]
Pang 2014	0/20	0/20			Not estimable
Pino 1998	10/10	16/88		6.0 %	5.15 [3.27, 8.11]
Rousseau 1995	4/75	2/77		2.7 %	2.05 [0.39, 10.88]
Scheller 1992	4/60	0/15		1.3 %	2.36 [0.13, 41.61]
Schlaich 2000	12/30	1/90		2.2 %	36.00 [4.88, 265.40]
Sivalingam 2001	11/74	1/25		2.2 %	3.72 [0.50, 27.36]
Stevens 1997	20/120	1/20		2.2 %	3.33 [0.47, 23.47]

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Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wong 1996	7/90	0/30		1.3 %	5.11 [0.30, 86.90]
Yazdi 2016	14/35	4/31		4.4 %	3.10 [1.14, 8.43]
Subtotal (95% CI)	**1238**	**1648**		**74.8 %**	**5.32 [3.54, 8.00]**
Total events: 297 (Avoidance of NMBA), 134 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 81.36$, df = 23 (P<0.00001); $I^2 = 72\%$					
Test for overall effect: Z = 8.05 (P < 0.00001)					
2 No exclusion of patients with anticipated difficult intubation					
Beck 1993	1/31	0/33		1.1 %	3.19 [0.13, 75.43]
Dominici 1990	11/30	10/30		5.3 %	1.10 [0.55, 2.19]
Gulhas 2013	0/40	5/40		1.3 %	0.09 [0.01, 1.59]
Harsten 1997	6/39	0/40		1.3 %	13.33 [0.78, 228.81]
Jiao 2014	13/28	1/27		2.2 %	12.54 [1.76, 89.36]
Kirkegaard-Nielsen 1999	13/20	12/60		5.6 %	3.25 [1.78, 5.92]
Kopman 2001	7/10	2/90		3.2 %	31.50 [7.54, 131.53]
Nimmo 1995	9/20	1/40		2.2 %	18.00 [2.45, 132.34]
Striebel 1995	8/50	2/50		3.1 %	4.00 [0.89, 17.91]
Subtotal (95% CI)	**268**	**410**		**25.2 %**	**4.40 [1.71, 11.29]**
Total events: 68 (Avoidance of NMBA), 33 (Use of NMBA)					
Heterogeneity: $Tau^2 = 1.24$; $Chi^2 = 30.73$, df = 8 (P = 0.00016); $I^2 = 74\%$					
Test for overall effect: Z = 3.08 (P = 0.0021)					
Total (95% CI)	**1506**	**2058**		**100.0 %**	**5.00 [3.50, 7.16]**
Total events: 365 (Avoidance of NMBA), 167 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 108.14$, df = 32 (P<0.00001); $I^2 = 70\%$					
Test for overall effect: Z = 8.81 (P < 0.00001)					
Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.72), $I^2 = 0.0\%$					

Analysis 1.7. Comparison 1 Avoidance vs use of NMBA, Outcome 7 Difficult tracheal intubation: "best-case scenario".

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 7 Difficult tracheal intubation: "best-case scenario"

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Alexander 1999	3/20	0/20		2.3 %	7.00 [0.38, 127.32]
Barclay 1997	19/20	2/20		4.7 %	9.50 [2.54, 35.51]
Beck 1993	1/31	0/33		2.0 %	3.19 [0.13, 75.43]
Bouvet 2008	3/65	0/64		2.3 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		3.5 %	18.00 [2.43, 133.12]
Dominici 1990	11/30	10/30		5.8 %	1.10 [0.55, 2.19]
Gonz lez Obreg n 2010	1/50	4/50		3.2 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		2.3 %	0.09 [0.01, 1.59]
Hanna 2010	3/23	2/24		4.0 %	1.57 [0.29, 8.53]
Harsten 1997	6/39	0/40		2.4 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		2.3 %	9.00 [0.50, 163.58]
Isesele 2012	18/44	0/44		2.4 %	37.00 [2.30, 595.49]
Jiao 2014	13/28	1/27		3.5 %	12.54 [1.76, 89.36]
Kahwaji 1997	18/30	0/28		2.4 %	34.61 [2.18, 548.52]
Kirkegaard-Nielsen 1999	13/20	1/20		3.6 %	13.00 [1.87, 90.21]
Kopman 2001	7/10	0/30		2.4 %	42.27 [2.63, 680.61]
Lieutaud 2003	13/20	1/48		3.5 %	31.20 [4.37, 222.81]
Lowry 1999	9/10	2/20		4.6 %	9.00 [2.38, 34.06]
McNeil 2000	2/23	0/17		2.2 %	3.75 [0.19, 73.40]
Mencke 2003	12/36	2/37		4.5 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		3.5 %	10.23 [1.38, 75.71]
Naguib 2003	35/50	1/50		3.5 %	35.00 [4.99, 245.69]
Naguib 2006	21/30	0/30		2.4 %	43.00 [2.72, 678.92]
Nimmo 1995	9/20	0/20		2.4 %	19.00 [1.18, 305.88]
Pang 2014	0/20	0/20			Not estimable

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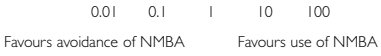
Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Pino 1998	10/10	0/15		2.5 %	30.55 [1.99, 468.91]
Rousseau 1995	4/75	2/77		4.0 %	2.05 [0.39, 10.88]
Scheller 1992	1/15	0/15		2.1 %	3.00 [0.13, 68.26]
Schlaich 2000	12/30	0/30		2.4 %	25.00 [1.55, 403.99]
Sivalingam 2001	2/25	1/25		3.0 %	2.00 [0.19, 20.67]
Stevens 1997	1/20	1/20		2.5 %	1.00 [0.07, 14.90]
Striebel 1995	1/28	1/25		2.5 %	0.89 [0.06, 13.54]
Wong 1996	0/30	0/30			Not estimable
Yazdi 2016	14/35	4/31		5.3 %	3.10 [1.14, 8.43]
Total (95% CI)	**1180**	**1230**		**100.0 %**	**5.99 [3.46, 10.38]**

Total events: 295 (Avoidance of NMBA), 42 (Use of NMBA)

Heterogeneity: $Tau^2 = 1.23$; $Chi^2 = 72.19$, df = 31 (P = 0.00004); $I^2 = 57\%$

Test for overall effect: Z = 6.39 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1 Avoidance vs use of NMBA, Outcome 8 Difficult tracheal intubation excluding dose-finding studies.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 8 Difficult tracheal intubation excluding dose-finding studies

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Beck 1993	1/31	0/33		3.9 %	3.19 [0.13, 75.43]
Bouvet 2008	3/65	0/64		4.3 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		6.7 %	18.00 [2.43, 133.12]
Dominici 1990	11/30	10/30		12.0 %	1.10 [0.55, 2.19]
Gonz lez Obreg n 2010	1/50	4/50		6.2 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		4.4 %	0.09 [0.01, 1.59]
Hanna 2010	3/23	2/24		7.8 %	1.57 [0.29, 8.53]
Harsten 1997	6/39	0/40		4.5 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		4.4 %	9.00 [0.50, 163.58]
Isesele 2012	18/44	0/44		4.6 %	37.00 [2.30, 595.49]
Jiao 2014	13/28	1/27		6.9 %	12.54 [1.76, 89.36]
Mencke 2003	12/36	2/37		8.9 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		6.7 %	10.23 [1.38, 75.71]
Pang 2014	0/20	0/20			Not estimable
Rousseau 1995	4/75	2/77		7.9 %	2.05 [0.39, 10.88]
Yazdi 2016	14/35	4/31		10.7 %	3.10 [1.14, 8.43]
Total (95% CI)	**769**	**767**		**100.0 %**	**3.40 [1.63, 7.10]**

Total events: 119 (Avoidance of NMBA), 32 (Use of NMBA)

Heterogeneity: $Tau^2 = 1.05$; $Chi^2 = 33.95$, df = 14 (P = 0.002); $I^2 = 59\%$

Test for overall effect: Z = 3.26 (P = 0.0011)

Test for subgroup differences: Not applicable

Analysis 1.9. Comparison 1 Avoidance vs use of NMBA, Outcome 9 Difficult tracheal intubation: funding from pharmaceutical industry.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 9 Difficult tracheal intubation: funding from pharmaceutical industry

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 No funding from pharmaceutical industry					
Alexander 1999	16/40	0/20		1.3 %	16.90 [1.07, 268.10]
Beck 1993	1/31	0/33		1.1 %	3.19 [0.13, 75.43]
Bouvet 2008	3/65	0/64		1.2 %	6.89 [0.36, 130.84]
Combes 2007	18/150	1/150		2.2 %	18.00 [2.43, 133.12]
Dominici 1990	11/30	10/30		5.3 %	1.10 [0.55, 2.19]
Gonz lez Obreg n 2010	1/50	4/50		2.0 %	0.25 [0.03, 2.16]
Gulhas 2013	0/40	5/40		1.3 %	0.09 [0.01, 1.59]
Isesele 2012	18/44	0/44		1.3 %	37.00 [2.30, 595.49]
Jiao 2014	13/28	1/27		2.2 %	12.54 [1.76, 89.36]
Kirkegaard-Nielsen 1999	13/20	12/60		5.6 %	3.25 [1.78, 5.92]
Lieutaud 2003	13/20	10/140		5.4 %	9.10 [4.62, 17.93]
McNeil 2000	4/43	0/17		1.3 %	3.68 [0.21, 64.92]
Mencke 2003	12/36	2/37		3.2 %	6.17 [1.48, 25.64]
Mencke 2014	11/43	1/40		2.2 %	10.23 [1.38, 75.71]
Naguib 2003	35/50	8/150		5.3 %	13.13 [6.53, 26.38]
Naguib 2006	21/30	6/150		4.9 %	17.50 [7.72, 39.66]
Nimmo 1995	9/20	1/40		2.2 %	18.00 [2.45, 132.34]
Pang 2014	0/20	0/20			Not estimable
Rousseau 1995	4/75	2/77		2.7 %	2.05 [0.39, 10.88]
Schlaich 2000	12/30	1/90		2.2 %	36.00 [4.88, 265.40]
Sivalingam 2001	11/75	1/25		2.2 %	3.67 [0.50, 27.00]
Stevens 1997	20/120	1/20		2.2 %	3.33 [0.47, 23.47]
Striebel 1995	8/50	2/50		3.1 %	4.00 [0.89, 17.91]

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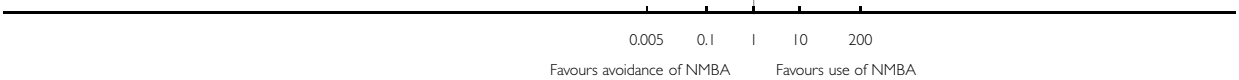
Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Yazdi 2016	14/35	4/31		4.4 %	3.10 [1.14, 8.43]
Subtotal (95% CI)	**1145**	**1405**		**64.7 %**	**5.33 [3.16, 8.98]**
Total events: 268 (Avoidance of NMBA), 72 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.86; Chi^2 = 68.37, df = 22 (P<0.00001); I^2 =68%					
Test for overall effect: Z = 6.29 (P < 0.00001)					
2 Funding from pharmaceutical industry					
Barclay 1997	19/20	16/40		6.2 %	2.38 [1.60, 3.52]
Hanna 2010	3/23	2/24		2.7 %	1.57 [0.29, 8.53]
Harsten 1997	6/39	0/40		1.3 %	13.33 [0.78, 228.81]
Iamaroon 2001	4/60	0/60		1.2 %	9.00 [0.50, 163.58]
Kahwaji 1997	18/30	17/146		5.8 %	5.15 [3.02, 8.79]
Kopman 2001	7/10	2/90		3.2 %	31.50 [7.54, 131.53]
Lowry 1999	19/20	42/120		6.4 %	2.71 [2.09, 3.53]
Pino 1998	10/10	16/88		6.0 %	5.15 [3.27, 8.11]
Scheller 1992	4/60	0/15		1.3 %	2.36 [0.13, 41.61]
Wong 1996	7/90	0/30		1.3 %	5.11 [0.30, 86.90]
Subtotal (95% CI)	**362**	**653**		**35.3 %**	**4.10 [2.67, 6.31]**
Total events: 97 (Avoidance of NMBA), 95 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.20; Chi^2 = 25.04, df = 9 (P = 0.003); I^2 =64%					
Test for overall effect: Z = 6.42 (P < 0.00001)					
Total (95% CI)	**1507**	**2058**		**100.0 %**	**5.00 [3.49, 7.15]**
Total events: 365 (Avoidance of NMBA), 167 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.50; Chi^2 = 108.13, df = 32 (P<0.00001); I^2 =70%					
Test for overall effect: Z = 8.81 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.57, df = 1 (P = 0.45), I^2 =0.0%					



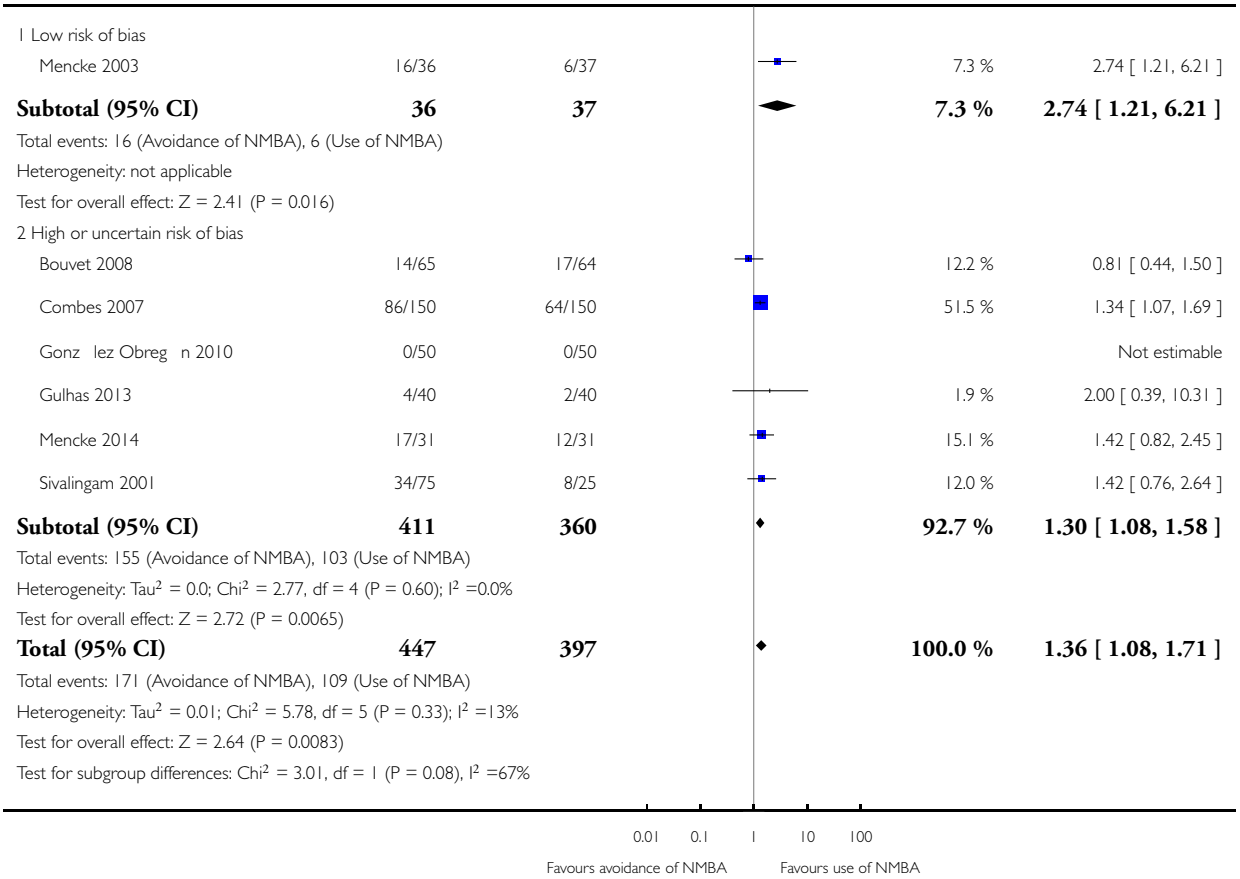
Analysis 1.10. Comparison 1 Avoidance vs use of NMBA, Outcome 10 One or more events of upper airway discomfort or injury: low risk of bias vs high or uncertain risk of bias.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 10 One or more events of upper airway discomfort or injury: low risk of bias vs high or uncertain risk of bias

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Mencke 2003	16/36	6/37		7.3 %	2.74 [1.21, 6.21]
Subtotal (95% CI)	**36**	**37**		**7.3 %**	**2.74 [1.21, 6.21]**
Total events: 16 (Avoidance of NMBA), 6 (Use of NMBA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.41 (P = 0.016)					
2 High or uncertain risk of bias					
Bouvet 2008	14/65	17/64		12.2 %	0.81 [0.44, 1.50]
Combes 2007	86/150	64/150		51.5 %	1.34 [1.07, 1.69]
Gonz lez Obreg n 2010	0/50	0/50			Not estimable
Gulhas 2013	4/40	2/40		1.9 %	2.00 [0.39, 10.31]
Mencke 2014	17/31	12/31		15.1 %	1.42 [0.82, 2.45]
Sivalingam 2001	34/75	8/25		12.0 %	1.42 [0.76, 2.64]
Subtotal (95% CI)	**411**	**360**		**92.7 %**	**1.30 [1.08, 1.58]**
Total events: 155 (Avoidance of NMBA), 103 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.77, df = 4 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 2.72 (P = 0.0065)					
Total (95% CI)	**447**	**397**		**100.0 %**	**1.36 [1.08, 1.71]**
Total events: 171 (Avoidance of NMBA), 109 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 5.78, df = 5 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 2.64 (P = 0.0083)					
Test for subgroup differences: Chi^2 = 3.01, df = 1 (P = 0.08), I^2 =67%					



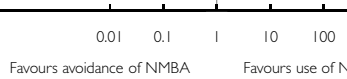
Analysis 1.11. Comparison 1 Avoidance vs use of NMBA, Outcome 11 One or more events of upper airway discomfort or injury: depolarizing vs non-depolarizing NMBA.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 11 One or more events of upper airway discomfort or injury: depolarizing vs non-depolarizing NMBA

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Depolarizing NMBA					
Gulhas 2013	4/40	2/40		2.0 %	2.00 [0.39, 10.31]
Sivalingam 2001	34/75	8/25		12.4 %	1.42 [0.76, 2.64]
Subtotal (95% CI)	**115**	**65**		**14.4 %**	**1.48 [0.83, 2.65]**
Total events: 38 (Avoidance of NMBA), 10 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.15$, df = 1 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.32 (P = 0.19)					
2 Non-depolarizing NMBA					
Bouvet 2008	14/65	17/64		12.6 %	0.81 [0.44, 1.50]
Combes 2007	86/150	64/150		50.4 %	1.34 [1.07, 1.69]
Gonz lez Obreg n 2010	0/50	0/50			Not estimable
Mencke 2003	16/36	6/37		7.6 %	2.74 [1.21, 6.21]
Mencke 2014	17/31	12/33		15.2 %	1.51 [0.87, 2.62]
Subtotal (95% CI)	**332**	**334**		**85.6 %**	**1.37 [0.97, 1.94]**
Total events: 133 (Avoidance of NMBA), 99 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 5.65$, df = 3 (P = 0.13); $I^2 = 47\%$					
Test for overall effect: Z = 1.79 (P = 0.073)					
Total (95% CI)	**447**	**399**		**100.0 %**	**1.37 [1.09, 1.74]**
Total events: 171 (Avoidance of NMBA), 109 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.89$, df = 5 (P = 0.32); $I^2 = 15\%$					
Test for overall effect: Z = 2.66 (P = 0.0078)					
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), $I^2 = 0.0\%$					

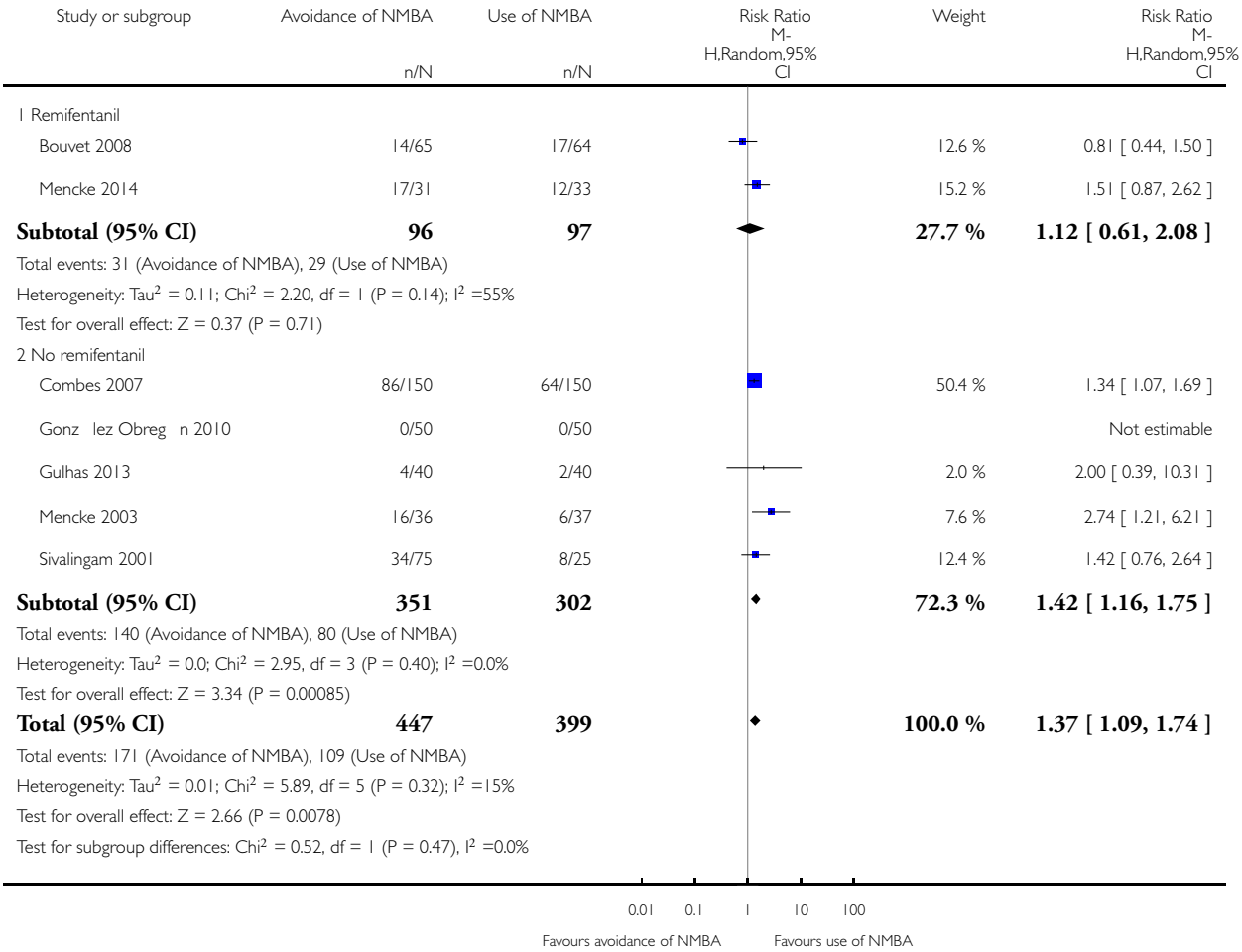


Analysis 1.12. Comparison 1 Avoidance vs use of NMBA, Outcome 12 One or more events of upper airway discomfort or injury: remifentanil vs no remifentanil.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 12 One or more events of upper airway discomfort or injury: remifentanil vs no remifentanil

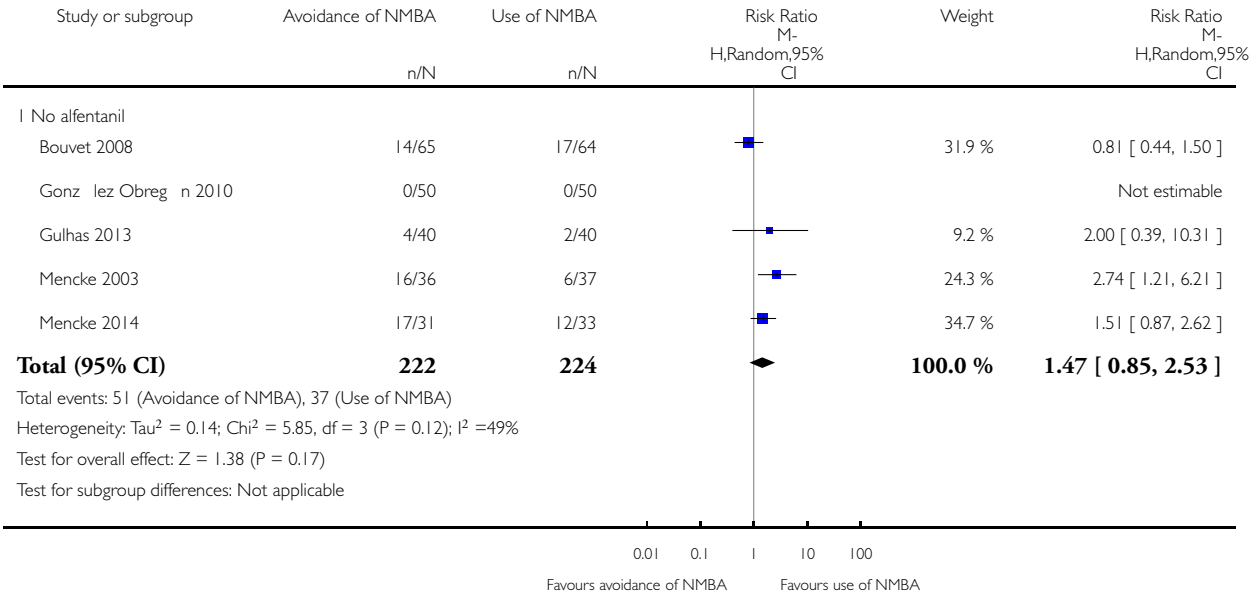


Analysis 1.13. Comparison 1 Avoidance vs use of NMBA, Outcome 13 One or more events of upper airway discomfort or injury: alfentanil vs no alfentanil.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 13 One or more events of upper airway discomfort or injury: alfentanil vs no alfentanil



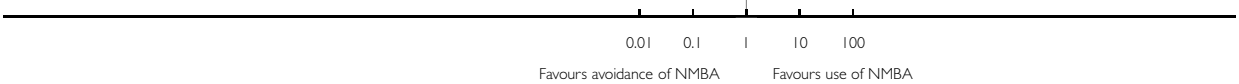
Analysis 1.14. Comparison 1 Avoidance vs use of NMBA, Outcome 14 One or more events of upper airway discomfort or injury: excluded anticipated DTI vs included anticipated DTI.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 14 One or more events of upper airway discomfort or injury: excluded anticipated DTI vs included anticipated DTI

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Excluded anticipated DTI					
Bouvet 2008	14/65	17/64		12.6 %	0.81 [0.44, 1.50]
Combes 2007	86/150	64/150		50.4 %	1.34 [1.07, 1.69]
Gonz lez Obreg n 2010	0/50	0/50			Not estimable
Mencke 2003	16/36	6/37		7.6 %	2.74 [1.21, 6.21]
Mencke 2014	17/31	12/33		15.2 %	1.51 [0.87, 2.62]
Sivalingam 2001	34/75	8/25		12.4 %	1.42 [0.76, 2.64]
Subtotal (95% CI)	**407**	**359**		**98.0 %**	**1.37 [1.05, 1.79]**
Total events: 167 (Avoidance of NMBA), 107 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.67$, df = 4 (P = 0.22); $I^2 = 29\%$					
Test for overall effect: Z = 2.31 (P = 0.021)					
2 Included anticipated DTI					
Gulhas 2013	4/40	2/40		2.0 %	2.00 [0.39, 10.31]
Subtotal (95% CI)	**40**	**40**		**2.0 %**	**2.00 [0.39, 10.31]**
Total events: 4 (Avoidance of NMBA), 2 (Use of NMBA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.83 (P = 0.41)					
Total (95% CI)	**447**	**399**		**100.0 %**	**1.37 [1.09, 1.74]**
Total events: 171 (Avoidance of NMBA), 109 (Use of NMBA)					
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 5.89$, df = 5 (P = 0.32); $I^2 = 15\%$					
Test for overall effect: Z = 2.66 (P = 0.0078)					
Test for subgroup differences: $Chi^2 = 0.20$, df = 1 (P = 0.66), $I^2 = 0.0\%$					



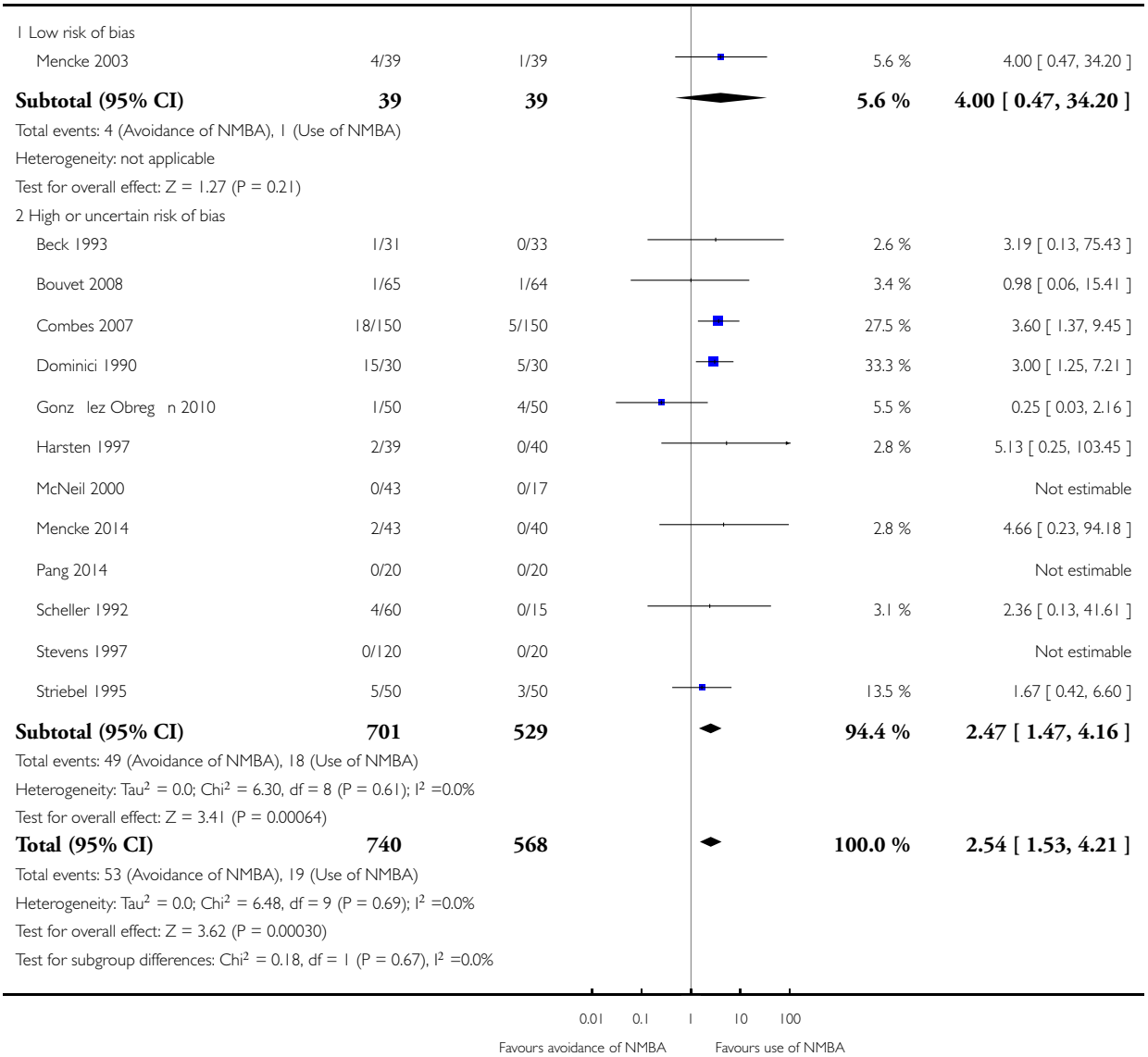
Analysis 1.15. Comparison 1 Avoidance vs use of NMBA, Outcome 15 Difficult laryngoscopy: low risk of bias vs high or uncertain risk of bias.

Review: Avoidance versus use of neuromuscular blocking agents for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents

Comparison: 1 Avoidance vs use of NMBA

Outcome: 15 Difficult laryngoscopy: low risk of bias vs high or uncertain risk of bias

Study or subgroup	Avoidance of NMBA n/N	Use of NMBA n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Low risk of bias					
Mencke 2003	4/39	1/39		5.6 %	4.00 [0.47, 34.20]
Subtotal (95% CI)	**39**	**39**		**5.6 %**	**4.00 [0.47, 34.20]**
Total events: 4 (Avoidance of NMBA), 1 (Use of NMBA)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.27 (P = 0.21)					
2 High or uncertain risk of bias					
Beck 1993	1/31	0/33		2.6 %	3.19 [0.13, 75.43]
Bouvet 2008	1/65	1/64		3.4 %	0.98 [0.06, 15.41]
Combes 2007	18/150	5/150		27.5 %	3.60 [1.37, 9.45]
Dominici 1990	15/30	5/30		33.3 %	3.00 [1.25, 7.21]
Gonz lez Obreg n 2010	1/50	4/50		5.5 %	0.25 [0.03, 2.16]
Harsten 1997	2/39	0/40		2.8 %	5.13 [0.25, 103.45]
McNeil 2000	0/43	0/17			Not estimable
Mencke 2014	2/43	0/40		2.8 %	4.66 [0.23, 94.18]
Pang 2014	0/20	0/20			Not estimable
Scheller 1992	4/60	0/15		3.1 %	2.36 [0.13, 41.61]
Stevens 1997	0/120	0/20			Not estimable
Striebel 1995	5/50	3/50		13.5 %	1.67 [0.42, 6.60]
Subtotal (95% CI)	**701**	**529**		**94.4 %**	**2.47 [1.47, 4.16]**
Total events: 49 (Avoidance of NMBA), 18 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.30, df = 8 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 3.41 (P = 0.00064)					
Total (95% CI)	**740**	**568**		**100.0 %**	**2.54 [1.53, 4.21]**
Total events: 53 (Avoidance of NMBA), 19 (Use of NMBA)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.48, df = 9 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 3.62 (P = 0.00030)					
Test for subgroup differences: Chi^2 = 0.18, df = 1 (P = 0.67), I^2 =0.0%					



ADDITIONAL TABLES

Table 1. Baseline

Study ID	NMBA	Country	Language	Randomized	Sex	Age, years	Weight, kg	BMI	ASA class included	Expected difficult airway excluded	Overweight excluded
Alexander 1999	C1: suxamethonium 1 mg/kg	UK	English	60	C: 12F/8M I1: 11F/9M I2: 11F/9M	C: 41.7 (17.4) I1: 40.3 (10.6) I2: 44.2 (15.0)	C: 76.3 (15.0) I1: 75.5 (15.1) I2: 76.6 (16.8)	ns	I-II	yes	
Barclay 1997	C1: rocuronium 0.1 mg/kg C2: rocuronium 0.13 mg/kg	UK	English	60	ns	C1: 30 C2: 29 I1: 27	C1: 74 C2: 72 I1: 64	ns	ns	yes	yes
Beck 1993	C1: suxamethonium 1 mg/kg	USA	English	64	C1: 22F/11M I1: 21F/10M	C1: 34 (11) I1: 35 (11)	C1: 69 (14) I1: 65 (13)		I-II		
Bouvet 2008	C1: cisatracuri 0.15 mg/kg	France	English	130	C1: 65F I1: 65F	C1: 41.5 (12.9) I1: 40.7 (15.2)	ns	C1: 24.6 (5.4) I1: 23.0 (3.5)	I-II	yes	
Combes 2007	C1: rocuronium 0.6 mg/kg	France	English	300	C1: 73F/77M I1: 69F/81M	C1: 41 (18-70) I1: 43 (18-66)	C1: 73 (13) I1: 70 (13)	ns	I-II	yes	yes
Dominici 1990	C1: suxamethonium 1.5 mg/kg	France	French	60	C1: 9F/21M I1: 9F/21M	C1: 48.4 (3.4) I1: 50.1 (2.9)	C1: 62.8 (2.5) I1: 61.6 (2.1)	ns	I-III		

Table 1. Baseline (*Continued*)

González Obregón 2010	C1: rocuronium 0.6 mg/kg	Columbia	Spanish	100	C1: 33F/17M I1: 33F/17M	C1: 34.7 (11.0) I1: 32.8 (12.3)	ns	ns	I-II	yes	
Gulhas 2013	C1: succinylcholine 1 mg/kg	Turkey	English	80	C1: 19F/21M I1: 22F/18M	C1: 49.6 (8.4) I1: 47.9 (8.7)	C1: 77.3 (13.1) I1: 73.2 (14.4)	ns	I-II		
Hanna 2010	C1: rocuronium 0.06 mg/kg + succinylcholine 1.5 mg/kg	USA	English	50	C1: 15F/9M I1: 5F/18M	C1: 39.0 (13.3) I1: 43.0 (14.5)	C1: 75.0 (15.0) I1: 81.0 (13.0)	C1: 25.9 (4.6) I1: 26.5 (2.9)	I-II	yes	
Harsten 1997	C1: suxamethonium 1 mg/kg	Sweden	English	80	C1: 26F/13M I1: 23F/14M	C1: 41.8 (13) I1: 39.5 (14)	ns	ns	I-II		
Iamaroon 2001	C1: suxamethonium 1.5 mg/kg	Thailand	English	120	C1: 54F/6M I1: 54F/6M	C1: 40.6 (9.1) I1: 39.7 (9.2)	C1: 55.8 (10.8) I1: 55.1 (9.1)	ns	I-II	yes	yes
Isesele 2012	C1: suxamethonium 1.5 mg/kg	Nigeria	English	96	C1: 12F/32M I1: 21F/23M	C1: 30.8 (9.0) I1: 32.6 (8.0)	C1. 69.0 (7.4) I1: 68.3 (6.6)		I-II	yes	
Jiao 2014	C1: suxamethonium 0.6 mg/kg	China	English	55	C1: 27F/0M I1: 28F/0M	C1: 38.4 (10.9) I2: 36.3 (9.9)	C1: 58.1 (7.0) I2: 58.2 (7.9)	ns	I-II		yes
Kahwaji 1997	C1: ORG 9487 (ra-	USA	English	181	C1: 20F/10M C2:	C1: 51.3 C2: 49.6 C3: 52.0	C1: 67.3 C2: 70.5 C3: 68.6	ns	I-III	yes	

Table 1. Baseline (*Continued*)

	pacuronium) 0.5 mg/kg C2: ORG 9487 (rapacuronium) 1.0 mg/kg C3: ORG 9487 (rapacuronium) 1.5 mg/kg C4: ORG 9487 (rapacuronium) 2.0 mg/kg C5: ORG 9487 (rapacuronium) 2.5 mg/kg				18F/9M C3: 17F/15M C4: 15F/13M C5: 22F/9M I1: 19F/11M	C4: 50.6 C5: 50.2 I1: 52.6	C4: 71.3 C5: 75.9 I1: 69.7				
Kirkegaard Nielsen 1999	C1: rocuronium 0.4 mg/kg C2: rocuronium 0.8 mg/kg C3: rocuronium 1.2 mg/kg	USA	English	80	C1: 2F/18M C2: 6F/14M C3: 10F/10M I1: 5F/15M	C1: 39.7 (7.5) C2: 39.5 (14.3) C3: 39.2 (10.5) I1: 39.3 (11.8)	C1: 75.0 (16.9) C2: 78.6 (15.8) C3: 67.4 (14.8) I1: 73.4 (16.6)	ns	I-II		yes
Kopman 2001	C1: rapacuronium 1.0 mg/kg	USA	English	100	ns	range: 18-65	ns	range: 17.5-27.5	I-II		yes

Table 1. Baseline (*Continued*)

	C2: rapacuronium 1.2 mg/kg C3: rocuronium 0.50 mg/kg										
Lieutaud 2003	C1: atracurium 0.5 mg/kg C2: atracurium 0.5 mg/kg C3: atracurium 0.5 mg/kg	France	English	170	C1: 3F/42M C2: 7F/41M C3: 8F/39M I1: 2F/18M	C1: 52.9 (11.8) C2: 51.3 (12.6) C3: 56.3 (11.9) I1: 50.4 (10.7)	ns	C1: 23.7 (3.2) C2: 23.1 (3.2) C3: 23.6 (3.4) I1: 23.3 (3.9)	I-II	yes	
Lowry 1999	C1: rocuronium 0.3 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.6 mg/kg C4: rocuronium 0.3 mg/kg C5: rocuronium 0.45 mg/kg C6: rocuronium 0.6 mg/kg	UK	English	140	C1: 4F/16M C2: 7F/13M C3: 12F/8M C4: 9F/11M C5: 9F/11M C6: 4F/16M I1: 2F/8M I2: 4F/6M	C1: 29 (11) C2: 40 (14) C3: 36 (12) C4: 33 (12) C5: 30 (12) C6: 33 (13) I1: 29 (11) I2: 30 (9)	C1: 77 (16) C2: 75 (14) C3: 69 (14) C4: 72 (12) C5: 73 (14) C6: 74 (14) I1: 72 (12) I2: 73 (15)	ns	I-II	yes	yes

Table 1. Baseline (*Continued*)

McNeil 2000	C1: succinylcholine 1 mg/kg	UK	English	60	ns	C1: 44 (15) I1: 39 (11) I2: 40 (13)	C1: 75 (10) I1: 76 (15) I2: 71 (12)	ns	I-II	yes	yes
Mencke 2003	C1: atracurium 0.5 mg/kg	Germany	English	80	C1: 19F/18M I1: 18F/18M	C1: 47.2 (13.2) I1: 47.7 (14.3)	C1: 77.7 (16) I1: 74.2 (15)		I-II	yes	yes
Mencke 2014	I1: rocuronium 0.45 $mg \cdot kg^{-1}$	Germany	English	83	C1: 16F/24M I1: 16F/23M	C1: 50 (16) I1: 48 (17)	C1: 83.8 (16) I1: 79.6 (15)	C1: 28.2 (4.3) I1: 26.5 (3.7)	I-III	yes	yes
Naguib 2003	C1: succinylcholine 0.3 mg/kg C2: succinylcholine 0.5 mg/kg C3: succinylcholine 1.0 mg/kg	Saudi Arabia	English	200	C1: 25F/25M C2: 23F/27M C3: 28F/22M I1: 23F/27M	C1: 30.9 (28-34) C2: 30.5 (27-34) C3: 30.0 (28-32) I1: 29.5 (27-32)	C1: 66.6 (64-70) C2: 67.4 (64-71) C3: 67.8 (65-71) I1: 67.4 (64-71)	ns	I	yes	
Naguib 2006	C1: succinylcholine 0.3 mg/kg C2: succinylcholine 0.5 mg/kg C3: succinylcholine	Saudi Arabia	English	180	C1: 17F13M C2: 19F/11M C3: 13F/17M C4: 14F/16M C5:	C1: 33.5 (8.7) C2: 29.7 (8.8) C3: 28.3 (7.9) C4: 31.5 (9.6) C5: 33.8 (14.8) I1: 20.1 (8.8)	C1: 67.8 (10.3) C2: 67.3 (10.8) C3: 71.1 (14.2) C4: 72.9 (12.5) C5: 70.9 (14.5) I1: 67.4 (10.7)	C1: 25.6 (2.8) C2: 25.6 (3.2) C3: 25.9 (3.9) C4: 26.2 (3.2) C5: 25.7 (3.9) I1: 25.7 (3.4)	I	yes	

Table 1. Baseline (*Continued*)

	1.0 mg/kg C4: succinylcholine 1.5 mg/kg C5: succinylcholine 2.0 mg/kg				18F/12M I1: 19F/11M						
Nimmo 1995	C1: suxamethonium 0.25 mg/kg C2: suxamethonium 0.5 mg/kg	USA	English	60	C1: 12F/8M C2: 12F/8M I1: 14F/6M	C1: 28.6 (17-55) C2: 29.0 (16-53) I1: 27.0 (18-53)	C1: 66.2 (13.6) C2: 64.4 (11.2) I1: 68.1 (13.6)	ns	I-II		
Pang 2014	C1: cisatracuri 0.1 mg/kg	China	English	40	C1: 14F/6M I1: 9F/11M	C1: 45.2 (7.4) I1: 43.3 (6.7)	C1: 63.8 (9.5) I1: 64.6 (7.9)	C1: 23.7 (2.8) I1: 23.3 (3.1)	I-II	yes	yes
Pino 1998	C1: mivacurium 0.25 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.6 mg/kg C4: rocuronium 0.9 mg/kg C5: rocuronium 1.	USA	English	100	ns	ns	ns	ns	I-II	yes	yes

Table 1. Baseline (*Continued*)

	2 mg/kg										
Rousseau 1995	C1: vecuronium 0.08 mg/kg	France	French	152	ns	C1: 23 (5) I1: 25 (8)	C1: 71 (10) I1: 71 (11)	ns	I	yes	
Scheller 1992	C1: d-tubocurarine 3 mg and succinylcholine 1 mg/kg	USA	English	75	C1: 8F/7M I1: 10F/5M I2: 11F/4M I3: 13F/2M I4: 10F/5M	C1: 37 (10) I1: 33 (9) I2: 30 (10) I3: 35 (11) I4: 36 (16)	C1: 77 (20) I1: 65 (11) I2: 66 (15) I3: 66 (12) I4: 68 (16)	ns	I	yes	
Schlaich 2000	C1: rocuronium 0.6 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.3 mg/kg	Germany	English	120	C1: 13F/17M C2: 13F/17M C3: 14F/16M I1: 14F/16M	C1: 37 (11) C2: 35 (11) C3: 36 (12) I1: 37 (11)	C1: 72 (14) C2: 75 (13) C3: 75 (12) I1: 70 (14)	ns	I-II	yes	
Sivalingan 2001	C1: suxamethonium 1 mg/kg	New Zealand	English	100	C1: 7F/18M I1: 9F/16M I2: 8F/17M I3: 10F/15M	C1: 34.3 (14.0) I1: 36.8 (12.6) I2: 29.6 (9.7) I3: 37.7 (12)	C1: 66 (10) I1: 62 (11) I2: 63 (15) I3: 61 (11)	ns	I-II	yes	
Stevens 1997	C1: d-tubocurarine 3 mg and succinylcholine	USA	English	140	C1: 12F/8M I1: 12F/8M I2: 15F/5M I3: 17F/	C1: 35 (9) I1: 38 (12) I2: 34 (11) I3: 37	C1: 70 (8) I1: 72 (17) I2: 70 (14)	ns	I-II	yes	yes

Table 1. Baseline (*Continued*)

	1 mg/kg				3M I4: 17F/ 3M I5: 15F/ 5M I6: 14F/ 6M	(10) I4: 34 (9) I5: 33 (11) I6: 37 (14)	I3: 72 (10) I4: 72 (13) I5: 72 (18) I6: 70 (13)				
Striebel 1995	C1: vecuronium 1 mg + succinylcholine 1 mg/kg C2: vecuronium 1 mg + succinylcholine 1 mg/kg	Germany	German	100	C1: 25F C2: 25F I1: 25F I2: 25F	C1: 47.8 (11.7) C2: 43.8 (9.5) I1: 46.5 (12.7) I2: 46.0 (12.4)	C1: 62.6 (9.4) C2: 68.2 (14) I1: 64.9 (10.1) I2: 70.8 (14.6)	ns	I-II		
Wong 1996	C1: succinylcholine 1 mg/kg	Malaysia	English	120	C1: 16F/ 14M I1: 13F/ 17M I2: 18F/ 12M I3: 12F/ 17M	C1: 35.7 (16) I1: 35.5 (12) I2: 35.4 (13) I3: 35.7 (11)	C1: 60.2 (8.9) I1: 66.0 (13.1) I2: 63.4 (12.9) I3: 60.1 (10.8)	ns	I-II	yes	
Yazdi 2016	C1: atracurium 0.5 mg/kg	Iran	English	66	69.7% M	31.6 (13)	ns	ns	I-II	yes	

ns = not specified; The values in parentheses are standard deviation or range

Table 2. Intervention

Study ID	NMBA	Randomized/ Analysed	Hypnotic	Opioid	Local anaesthetic	Difficult intubation events/ total	Difficult laryngoscopy events/ total	Upper airway discomfort or injury events/total
Alexander 1999	C1: suxamethonium 1 mg/kg	60/60	C1: propofol 2 mg/kg I1: propofol 2 mg/kg I2: propofol 2 mg/kg	C1: none I1: alfentanil 50 μg/kg I2: remifentanil 2 μg/kg	None	C1: 0/20 I1: 3/20 I2: 13/20	ns	ns
Barclay 1997	C1: rocuronium 0.1 mg/kg C2: rocuronium 0.3 mg/kg	60/60	C1: propofol 2.5 mg/kg C2: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: alfentanil 10 μg/kg C2: alfentanil 10 μg/kg I1: alfentanil 10 μg/kg	Lidocaine 10 mg IV	C1: 14/20 C2: 2/20 I1: 19/20	ns	ns
Beck 1993	C1: suxamethonium 1 mg/kg	64/64	C1: thiopenthal 5 mg/kg I1: propofol 2 mg/mL	C1: none I1: alfentanil 50 μg/kg	None	C1: 0/33 I1: 1/31	C1: 0/33 I1: 1/31	ns
Bouvet 2008	C1: cisatracurium 0.15 mg/kg	130/129	C1: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: remifentanil 2 μg/kg I1: remifentanil 2 μg/kg	None	C1: 0/64 I1: 3/65	C1: 1/64 I1: 1/65	C1: 17/64 I1: 14/65
Combes 2007	C1: rocuronium 0.6 mg/kg	300/300	C1: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: alfentanil 15 μg/kg I1: alfentanil 40 μg/kg	None	C1: 1/150 I1: 18/150	C1: 5/150 I1: 18/150	C1: 64/150 I1: 86/150
Dominici 1990	C1: suxamethonium 1.5 mg/kg	60	C1: propofol 3 mg/mL I1: propofol 3 mg/mL	C1: alfentanil 7-10 μg/kg I1: alfentanil 7-10 μg/kg	Lidocaine (2%): IV + topical Lidocaine 5%	C1: 10/30 I1: 11/30	C1: 5/30 I1: 15/30	ns

Table 2. Intervention (*Continued*)

González Obregón 2010	C1: rocuronium 0.6 mg/kg	100/100	C1: propofol 1-2 mg/kg I1: Sevoflurane 3% + propofol 2 mg/kg	C1: remifentanil 1-2 μg/kg in 1 min + 0.15 μ/kg/min in1 min I1: remifentanil 0.6 μ/kg/min for 5 min	None	C1: 4/50 I1: 1/50	C1: 4/50 I1: 1/50	C1: 0/50 I1: 0/50
Gulhas 2013	C1: succinylcholine 1 mg/kg	80/80	C1: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: remifentanil 1 μg/kg I1: remifentanil 4 μg/kg	None	C1: 5/40 I1: 0/40	ns	C1: 2/40 I1: 4/40
Hanna 2010	C1: rocuronium 0.06 mg/kg + succinylcholine 1.5 mg/kg	50/47	C1: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: none I1: remifentanil 4 μg/kg	Lidocaine 0.5 mg/kg IV	C1: 2/24 I1: 3/23	ns	ns
Harsten 1997	C1: suxamethonium 1 mg/kg	80/79	C1: thiopental 5 mg/kg I1: propofol 2.5 mg/kg	C1: alfentanil 10 μg/kg I1: alfentanil 10 μg/kg	None	C1: 0/40 I1: 6/39	C1: 0/40 I1: 2/39	ns
Iamaroon 2001	C1: suxamentonium 1.5 mg/kg	120/120	C1: thiopenthal 5 mg/kg + (N_2O) I1: sevoflurane 8%	C1: fentanyl 1.5 μg/kg I1: fentanyl 1.5 μg/kg	None	C1: 0/60 I1: 4/60	ns	ns
Isesele 2012	C1: suxamethonium 1.5 mg/kg	96/88	C1: propofol 2.0 mg/kg I1: propofol 2.0 mg/kg	None	C1: none I1: lidocaine IV 1.5 mg/kg	C1: 0/44 I1: 18/44	ns	ns
Jiao 2014	C1: suxamethonium 0.6 mg/kg	55/55	C1: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: remifentanil 1 μg/kg	None	C1: 1/27 I2: 13/28	ns	ns

Table 2. Intervention (*Continued*)

				I1: remifentanil 1.5 μg/kg				
Kahwaji 1997	C1: ORG 9487 (rapacuronium) 0.5 mg/kg C2: ORG 9487 (rapacuronium) 1.0 mg/kg C3: ORG 9487 (rapacuronium) 1.5 mg/kg C4: ORG 9487 (rapacuronium) 2.0 mg/kg C5: ORG 9487 (rapacuronium) 2.5 mg/kg	181/176	C1: thiopental 3-6 mg/kg C2: thiopental 3-6 mg/kg C3: thiopental 3-6 mg/kg C4: thiopental 3-6 mg/kg C5: thiopental 3-6 mg/kg I1: thiopental 3-6 mg/kg	C1: fentanyl 0.5-3 μm/kg C2: fentanyl 0.5-3 μm/kg C3: fentanyl 0.5-3 μm/kg C4: fentanyl 0.5-3 μm/kg C5: fentanyl 0.5-3 μm/kg I1: fentanyl 0.5-3 μm/kg	None	C1: 9/30 C2: 6/27 C3: 1/32 C4: 0/28 C5: 1/29 I1: 18/30	ns	ns
Kirkegaard-Nielsen 1999	C1: rocuronium 0.4 mg/kg C2: rocuronium 0.8 mg/kg C3: rocuronium 1.2 mg/kg	80/80	C1: propofol 2 mg/kg C2: propofol 2 mg/kg C3: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: fentanyl 2 μm/kg C2: fentanyl 2 μm/kg C3: fentanyl 2 μm/kg I1: fentanyl 2 μm/kg	None	C1: 9/20 C2: 2/20 C3: 1/20 I1: 13/20	ns	ns
Kopman 2001	C1: rapacuronium 1.0 mg/kg C2: rapacuronium 1.2 mg/kg C3: rocuronium 0.50 mg/kg	100/100	C1: propofol 2.0 mg/kg IV C2: propofol 2.0 mg/kg IV C3: propofol 2.0 mg/kg IV	C1: alfentanil 12.5 μg/kg C2: alfentanil 12.5 μg/kg C3: alfentanil 12.5 μg/kg	None	C1: 2/30 C2: 0/30 C3: 0/30 I1: 7/10		

Table 2. Intervention (*Continued*)

			I1: propofol 2.0 mg/kg IV	I1: alfentanil 12.5 μg/kg				
Lieutaud 2003	C1: atracurium 0.5 mg/kg C2: atracurium 0.5 mg/kg C3: atracurium 0.5 mg/kg	170/160	C1: propofol 1.5 mg/kg C2: propofol 2.0 mg/kg C3: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: fentanyl 3 μm/kg C2: fentanyl 3 μm/kg C3: fentanyl 3 μm/kg I1: fentanyl 3 μm/kg	None	C1: 7/47 C2: 1/48 C3: 2/45 I1: 13/20	ns	ns
Lowry 1999	C1: rocuronium 0.3 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.6 mg/kg C4: rocuronium 0.3 mg/kg C5: rocuronium 0.45 mg/kg C6: rocuronium 0.6 mg/kg	140/140	C1: propofol 2-3 mg/kg C2: propofol 2-3 mg/kg C3: propofol 2-3 mg/kg C4: sevoflurane 8% C5: sevoflurane 8% C6: sevoflurane 8% I1: propofol 2-3 mg/kg I2: sevoflurane 8%	C1: fentanyl 1 μm/kg C2: fentanyl 1 μm/kg C3: fentanyl 1 μm/kg C4: fentanyl 1 μm/kg C5: fentanyl 1 μm/kg C6: fentanyl 1 μm/kg I1: fentanyl 1 μm/kg I2: fentanyl 1 μm/kg	None	C1: 11/20 C2: 4/20 C3: 2/20 C4:14/20 C5: 9/20 C6: 2/20 I1:10/10 I2: 9/10	ns	ns
McNeil 2000	C1: succinylcholine 1 mg/kg	60/60	C1: propofol 2 mg/kg I1: propofol 2 mg/kg I2: propofol 2 mg/kg	C1: none I1: remifentanil 2 μg/kg I2: remifentanil 4 μg/kg	None	C1: 0/17 I1: 2/23 I2: 2/20	C1: 0/17 I1: 0/23 I2: 0/20	ns
Mencke 2003	C1: atracurium 0.5 mg/kg	80/73	C1: propofol 2.5-3 mg/kg I1: propofol 2.5-3 mg/kg	C1: fentanyl 2-3 μg/kg I1: fentanyl 2-3 μg/kg	None	C1: 2/37 I1: 12/36	C1: 1/39 I1: 4/39	C1: 6/37 I1: 16/36

Table 2. Intervention (*Continued*)

Mencke 2014	C1: rocuronium 0.45 mg·kg/kg	83/83	C1: propofol 1.5 mg·kg^{-1} + sevoflurane 3.0-3.5 Vol%, 8 l·min^{-1} in 2-3 minutes I1: propofol 1.5 mg/kg	C1: remifentanil 0.30 μg/kg/min for 3 minutes I1: remifentanil 0.30 μg/kg/min for 3 minutes	None	C1: 1/40 I1: 11/43	C1: 0/40 I1: 2/43	C1: 12/33 I1: 17/31
Naguib 2003	C1: succinylcholine 0.3 mg/kg C2: succinylcholine 0.5 mg/kg C3: succinylcholine 1.0 mg/kg	200/200	C1: propofol 2 mg/kg C2: propofol 2 mg/kg C3: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: fentanyl 2 μg/kg C2: fentanyl 2 μg/kg C3: fentanyl 2 μg/kg I1: fentanyl 2 μg/kg	None	C1: 4/50 C2: 3/50 C3: 1/50 I1: 15/50	ns	ns
Naguib 2006	C1: succinylcholine 0.3 mg/kg C2: succinylcholine 0.5 mg/kg C3: succinylcholine 1.0 mg/kg C4: succinylcholine 1.5 mg/kg C5: succinylcholine 2.0 mg/kg	180/180	C1: propofol 2 mg/kg C2: propofol 2 mg/kg C3: propofol 2 mg/kg C4: propofol 2 mg/kg C5: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: fentanyl 2 μm/kg C2: fentanyl 2 μm/kg C3: fentanyl 2 μm/kg C4: fentanyl 2 μm/kg C5: fentanyl 2 μm/kg I1: fentanyl 2 μm/kg	None	C1: 2/30 C2: 2/30 C3: 1/30 C4: 1/30 C5: 0/30 I1: 21/30	ns	ns
Nimmo 1995	C1: suxamethonium 0.25 mg/kg C2: suxamethonium 0.5 mg/kg	60/60	C1: propofol 2.5 mg/kg C2: propofol 2.5 mg/kg I1: Propofol 2.5 mg/kg	C1: alfentanil 15 μg/kg C2: alfentanil 15 μg/kg I1: alfentanil 15 μg/kg	None	C1: 0/20 C2: 1/20 I1: 9/20	ns	ns
Pang 2014	C1: cisatracurium 0.1 mg/kg	20/20	C1: propofol tar-	C1: remifen-	C1: tetracaine 10 mg/	C1: 0/20 I1: 0/20	C1: 0/20 I1: 0/20	ns

Table 2. Intervention (*Continued*)

			get control I1: propofol target control	tanil target control I1: remifentanil target control	mL I1: tetracaine 10 mg/mL			
Pino 1998	C1: mivacurium 0.25 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.6 mg/kg C4: rocuronium 0.9 mg/kg C5: rocuronium 1.2 mg/kg	100/98	C1: propofol 2 mg/kg C2: propofol 2 mg/kg C3: propofol 2 mg/kg C4: propofol 2 mg/kg C5: propofol 2 mg/kg I1: propofol 2 mg/kg	C1: fentanyl 2 μm/kg C2: fentanyl 2 μm/kg C3: fentanyl 2 μm/kg C4: fentanyl 2 μm/kg C5: fentanyl 2 μm/kg I1: fentanyl 2 μm/kg	None	C1: 2/30 IC2: 9/15 C3: 4/14 C4: 1/14 C5: 0/15 I1: 10/10	ns	ns
Rousseau 1995	C1: vecuronium 0.08 mg/kg	152/152	C1: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: alfentanil 0.03 mg/kg I1: alfentanil 0.03 mg/kg	C1: none I1: lidocaine 1.5 mg/kg	C1: 2/77 I1: 4/75	ns	ns
Scheller 1992	C1: d-tubocurarine 3 mg and succinylcholine 1 mg/kg	75/75	C1: thiamylal 4 mg/kg I1: propofol 2 mg/kg I2: propofol 2 mg/kg I3: propofol 2 mg/kg I4: propofol 2 mg/kg	C1: none I1: alfentanil 30 µg/kg I2: alfentanil 40 µg/kg I3: alfentanil 50 µg/kg I4: alfentanil 60 µg/kg	None	C1: 0/15 I1: 1/15 I2: 1/15 I3: 1/15 I4: 1/15	C1: 0/15 I1: 1/15 I2: 1/15 I3: 1/15 I4: 1/15	ns
Schlaich 2000	C1: rocuronium 0.6 mg/kg C2: rocuronium 0.45 mg/kg C3: rocuronium 0.3 mg/kg	120/120	C1: propofol 2-2.5 mg/kg C2: propofol 2-2.5 mg/kg C3: propofol 2-2.5 mg/kg I1: propofol	C1: remifentanil 0.5 µg/kg/min C2: remifentanil 0.5 µg/kg/min IC3: remifen-	None	C1: 0/30 C2: 1/30 C3: 0/30 I1: 12/30	ns	ns

Table 2. Intervention (*Continued*)

			2-2.5 mg/kg	tanil 0.5 µg/kg/min I1: remifentanil 0.5 µg/kg/min				
Sivalingam 2001	C1: suxamethonium 1 mg/kg	100/100	C1: Sevoflu 7% + N_2O60% I1: Sevoflu 7% + N_2O60% I2: Sevoflu 7% + N_2O60% I3: Sevoflu 7% + N_2O60%	C1: alfentanil 10 µg/kg I1: alfentanil 20 µg/kg I2: alfentanil 25 µg/kg I3: alfentanil 30 µg/kg	None	C1: 1/25 I1: 4/25 I2: 5/25 I3: 2/25	ns	C1: 8/25 I1: 12/25 I2: 13/25 I3: 9/25
Stevens 1997	C1: d-tubocurarine 3 mg and succinylcholine 1 mg/kg	140/140	C1: thiopental 4 mg/kg I1: etomidate 0.3 mg/kg I2: etomidate 0.3 mg/kg I3: propofol 2 mg/kg I4: propofol 2 mg/kg I5: thiopental 4 mg/kg I6: thiopental 4 mg/kg	C1: none I1: alfentanil 40 µg/kg I2: alfentanil 40 µg/kg I3: alfentanil 40 µg/kg I4: alfentanil 40 µg/kg I5: alfentanil 40 µg/kg I6: alfentanil 40 µg/kg	C1: none I1: none I2: lidocaine 1 mg/kg I3: none I4: lidocaine 1 mg/kg I5: none I6: lidocaine1 mg/kg	C1: 1/20 I1: 3/20 I2: 1/20 I3: 3/20 I4: 2/20 I5: 8/20 I6: 3/20	C1: 0/20 I1: 0/20 I2: 0/20 I3: 0/20 I4: 0/20 I5: 0/20 I6: 0/20	ns
Striebel 1995	C1: vecuronium 1 mg + succinylcholine 1 mg/kg C2: vecuronium 1 mg + succinylcholine 1 mg/kg	100/100	C1: thiopental 5.5 mg/kg C2: propofol 2.2 mg/kg I1: propofol 2.4 mg/kg I2: propofol 2.2 mg/kg	C1: fentanyl 0.1 mg C2: fentanyl 0.1 mg I1: fentanyl 0.1 mg I2: fentanyl 0.2 mg	2 mL lidocaine 1% IV	C1: 1/25 C2: 1/25 I1: 3/25 I2: 5/25	C1: 2/25 C2: 1/25 I1: 1/28 I2: 4/25	ns

Table 2. Intervention (*Continued*)

Wong 1996	C1: succinylcholine 1 mg/kg	120/120	C1: propofol 3.0 mg/kg I1: propofol 2.6 mg/kg I2: propofol 2.6 mg/kg I3: propofol 3.1 mg/kg	C1: none I1: alfentanil 15 μg/kg I2: alfentanil 30 μg/kg I3: none	None	C1: 0/30 I1: 1/30 I2: 0/30 I3: 6/30	ns	ns
Yazdi 2016	C1: atracurium 0.5 mg/kg	66/66	C1: propofol 2.5 mg/kg I1: propofol 2.5 mg/kg	C1: none I1: remifentanil 2 μg/kg	None	C1: 4/31 I1: 14/35	ns	ns

ns = not specified

APPENDICES

Appendix 1. Cormack and Lehane classification

Difficult laryngoscopy

Cormack and Lehane (Cormack 1984) classification

Grade 1: full view of the glottis.
Grade 2: partial view of the glottis or arytenoids.
Grade 3: only epiglottis visible.
Grade 4: neither glottis nor epiglottis visible.
Laryngoscopy grade 3 and 4 define a difficult laryngoscopy.

Modified Cormack and Lehane (Yentis 1998) classification

Grade 1: full view of the glottis.
Grade 2a: partial view of the glottis.
Grade 2b: arytenoids or posterior part of the vocal cords only just visible.
Grade 3: only epiglottis visible.
Grade 4: neither glottis nor epiglottis visible.
Laryngoscopy grades 2b, 3, and 4 define a difficult laryngoscopy.

Appendix 2. CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Neuromuscular Blocking Agents] explode all trees
#2 MeSH descriptor: [Muscle Relaxants, Central] explode all trees
#3 (suxameton or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium):ti,ab)
#4 #1 or #2 or #3
#5 MeSH descriptor: [Laryngoscopy] explode all trees
#6 MeSH descriptor: [Intubation, Intratracheal] explode all trees
#7 (difficult near (intubat* or laryngoscopy or airway))
#8 (Intubation near (score or scale))
#9 Cormack or Lehane
#10 ((tracheal near intub*) or airway or laryngoscopy):ti
#11 #5 or #6 or #7 or #8 or #9 or #10
#12 #4 and #11

Appendix 3. MEDLINE (Ovid SP) search strategy

1 exp Neuromuscular Blocking Agents/ or Muscle Relaxants, Central/ or (suxamethonium or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium).ti,ab.
2 Laryngoscopy/ or Intubation, Intratracheal/ or (difficult adj3 (intubat* or laryngoscopy or airway)).mp. or ((Intubation adj3 (score or scale)) or (Cormack or Lehane)).mp. or ((tracheal adj3 intub*) or airway or laryngoscopy).ti.
3 1 and 2
4 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.
5 3 and 4

Appendix 4. Embase (Ovid SP) search strategy

1. exp neuromuscular blocking agent/ or central muscle relaxant/ or (suxameton or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium).ti,ab.
2. laryngoscopy/ or endotracheal intubation/ or (difficult adj3 (intubat* or laryngoscopy or airway)).mp. or ((Intubation adj3 (score or scale)) or (Cormack or Lehane)).mp. or ((tracheal adj3 intub*) or airway or laryngoscopy).ti.
3. 1 and 2
4. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 5. BIOSIS Citation Index

#1 TS=Neuromuscular Blocking or TS=Muscle Relaxant* or TS=(suxameton or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium)
#2 TS=(Cormack or Lehane) or TS=(difficult SAME (intubat* or laryngoscopy or airway)) or TS=(Intubation SAME (score or scale)) or TI=((tracheal and intub*) or airway or laryngoscopy)
#3 #2 AND #1
#4 TS=(random* or (controlled SAME (study or trial*)) or prospective or placebo or multicenter) or TS=((mask* or blind*) SAME (single or double or triple or treble))
#5 #3 and #4

Appendix 6. CINAHL (EBSCO) search strategy

S1 ((MH "Neuromuscular Blocking Agents") OR (MH "Muscle Relaxants, Central")) OR AB (suxameton or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium)
S2 ((MH "Laryngoscopy") OR (MH "Intubation, Intratracheal")) OR ((difficult and (intubat* or laryngoscopy or airway))) OR ((Intubation and (score or scale))) OR (Cormack or Lehane) OR TI ((tracheal and intub*) or airway or laryngoscopy)
S3 S2 and S1

Appendix 7. LILACS (BIREME) serach strategy

((Neuromuscular Blocking Agent$) or Muscle Relaxant$ or (suxameton or rapacuronium or mivacurium or atracurium or doxacurium or cisatracurium or vecuronium or rocuronium or pancuronium or tubocurarine or gallamine or pipecuronium)) and ((Cormack or Lehane) or (difficult and (intubate$ or laryngoscopy or airway)) or (Intubation and (score or scale)) or ((tracheal and intub$) or airway or laryngoscopy))

Appendix 8. Data extraction form

Study selection, quality assessment, and data extraction form

First study author	Journal/Conference proceedings, etc.	Year

Study eligibility

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No*/Unclear

Issue relates to selective reporting when study authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Review authors should contact trialists for information on possible non-reported outcomes and reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.

Do not proceed if any of the above answers are 'No'. If study is to be included in 'Excluded studies' section of the review, record below the information to be inserted into the 'Table of excluded studies'

Freehand space for comments on study design and treatment:

References to trial

Check other references identified in searches. If further references to this trial are available, link the papers now and list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Study author(s)	Journal/Conference proceedings, etc.	Year
A	*The paper listed above*		
B	*Further papers*		
C			
D			
E			

Participants and trial characteristics

Participant characteristics	**Participant cha**
Covariate	Further details
Age (mean, median, range, etc.)	
Sex of participants (numbers/%, etc.)	
BMI (mean, median, range, etc.)	

Trial characteristics

Methodological quality

Random sequence generation		Random sequen
State here method used to generate random sequence and reasons for grading	Grade (circle)	
	Low risk of bias (random)	
	High risk of bias (e.g. alternate)	
	Unclear	

Allocation concealment **Process used to prevent foreknowledge of group assignment in an RCT, which should be seen as distinct from blinding**		Allocation conce **Process used to distinct from bl**
State here method used to conceal allocation and reasons for grading	Grade (circle)	
	Low risk of bias	
	High risk of bias	
	Unclear	

Blinding		
Person responsible for participant care	Low risk/High risk/Unclear risk	
Participant	Low risk/High risk/Unclear risk	
Outcome assessor	Low risk/High risk/Unclear risk	
Other (please specify)	Low risk/High risk/Unclear risk	
Incomplete outcome data		

(*Continued*)

Low risk, if numbers and reasons for dropouts and withdrawals in the intervention groups were described, or if it was specified that no dropouts or withdrawals occurred	Yes/No	
High risk, if numbers or reasons for dropouts and withdrawals were not described	Yes/No	
Unclear, if the report gave the impression that no dropouts or withdrawals had occurred, but did not specifically state this	Yes/No	
Selective reporting		
Low risk, if predefined or clinically relevant and reasonably expected outcomes are reported	Yes/No	
High risk, if one or more clinically relevant and reasonably expected outcomes were not reported; data on these outcomes were likely to have been recorded	Yes/No	
Unclear, if not all predefined or clinically relevant and reasonably expected outcomes are reported, or if they are not reported fully, or if it is unclear whether data on these outcomes were recorded	Yes/No	
Baseline imbalance		
Low risk, if no baseline imbalance in important characteristics is evident	Yes/No	
High risk, if a baseline imbalance is due to chance or is due to imbalanced exclusion after randomization	Yes/No	
Unclear, if baseline characteristics were not reported	Yes/No	
Early stopping		
Low risk, if sample size calculation was reported and the trial was not stopped, or if the trial was stopped early by formal stopping rules at a point when the likelihood of observing an extreme intervention effect due to chance was low	Yes/No	

(*Continued*)

High risk, if the trial was stopped early owing to informal stopping rules, or if the trial was stopped early by a formal stopping rule at a point when the likelihood of observing an extreme intervention effect due to chance was high	Yes/No	
Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early	Yes/No	

Other bias		
Low risk of bias, if the trial appears to be free of other components that could put it at risk of bias	Yes/No	
High risk of bias, if other factors in the trial could put it at risk of bias (e.g. 'for-profit' involvement, authors have conducted trials on the same topic)	Yes/No	
Unclear, if the trial may or may not be free of other components that could put it at risk of bias	Yes/No	
Modified intention-to-treat A modified intention-to-treat analysis is one in which all participants in a trial are operated and analysed according to the intervention to which they were allocated, whether or not they received it		
All participants entering trial after surgery		
15% or fewer excluded		
More than 15% excluded		
Not analysed as modified 'intention-to-treat'		
Unclear		

(*Continued*)

Were withdrawals described? **Yes ?** **No ?** **Not clear ?**

Discuss if appropriate

Trial characteristics	**Trial characteris**
	Further details
Single-centre/Multi-centre	
Country/Countries	
How was participant eligibility defined?	
How many participants were randomized?	
Number of intervention groups/number of control groups	
Number of participants in each intervention group/Number of participants in each control group	
Number of participants who received intended intervention (per-protocol population)	
Number of participants who were analysed	
Type of outcome measure (DTI/DL?)	
NMBA: type and dose?	
Hypnotic: type and dose	
Opioid: type and dose	
Local anaesthetic: type and dose	

(*Continued*)

Other	

* If cross-over design, please refer to the Cochrane Editorial Office for further advice on how to analyse these data

Other design characteristics of the trial

1. Mallampati score (predicts DTI/DL Yes/No??)
2. Thyromental distance (predicts DTI/DL Yes/No??) or (cm)
3. Neck extension (predicts DTI/DL Yes/No??) or (degrees)
4. Mouth opening/Interincisor gap (predicts DTI/DL Yes/No??) or (cm)
5. Mandible subluxation (predicts DTI/DL Yes/No??)
6. Time from induction to start of tracheal intubation (seconds)

Data extraction

Outcomes	**Available for the trial**
1.1 Difficult tracheal intubation	Yes/No
1.2 Overall mortality. We will use the maximal follow-up data from each trial	Yes/No
1.3. One or more events of upper airway discomfort/injury (e.g. sore throat, hoarseness, vocal cord lesion, minor pharyngeal injury)	Yes/No
2.1. One or more major serious events: gastric aspiration, brain and heart injuries (e.g. caused by anoxia, hypotension, bradycardia/tachycardia during tracheal intubation)	Yes/No
2.2 Difficult laryngoscopy	Yes/No

For continuous data							**For continuous**
Code of paper	Outcomes (rename)	Unit of measurement	Intervention group		Control group		Details if outcome described only in text
			n	Mean (SD)	n	Mean (SD)	
A	**1.1 Difficulty of tracheal intubation**	Score					

For dichotomous data				For dichotomou
Code of paper	Outcomes	Intervention group E/N E = number of events N = number of participants	Control group E/N E = number of events N = number of participants	
A	1.1 Difficult tracheal intubation			
	1.2 Overall mortality. We will use the maximal follow-up data from each trial			
	1.3. One or more events of upper airway discomfort/injury (e.g. sore throat, hoarseness, vocal cord lesion, minor pharyngeal injury)			
	2.1. One or more major serious events: gastric aspiration, brain and heart injuries (e.g. caused by anoxia, hypotension, bradycardia/tachycardia during tracheal intubation)			
	2.2 Difficult laryngoscopy			

Other information that you believe is relevant to the results Indicate if any data were obtained from the primary author; if results were estimated from graphs, etc. or were calculated by using a formula (this should be stated and the formula given). In general, if results not reported in paper(s) are obtained, this should be made clear here to be cited in the review			Other informat Indicate if any d formula (this sho clear here to be c
Mallampati score	Predicts DTI/DL (numbers/% of participants)		
Thyromental distance	Predicts DTI/DL (numbers/% of participants)	cm (mean, median, range, etc.)	
Neck extension	Predicts DTI/DL (numbers/% of participants)	degrees (mean, median, range, etc.)	
Mouth opening/Interincisor gap	Predicts DTI/DL (numbers/% of participants)	cm (mean, median, range, etc.)	

(*Continued*)

Mandible subluxation	Predicts DTI/DL (numbers/% of participants)	
Time from induction to start of tracheal intubation		seconds (mean, median, range, etc.)

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports of potentially eligible trials not already identified for this review?			Did this report i
First study author	Journal/Conference	Year of publication	

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, list contact names and details	Did this report i this review? If ye

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: LHL, SS, AMM, JW.

Designing the review: LHL, JW, AMM, SS.

Co-ordinating the review: LHL.

Undertaking manual searches: LHL.

Screening search results: LHL, CD, AN.

Organizing retrieval of papers: LHL, CD, AN.

Screening retrieved papers against inclusion criteria: LHL, CD, AN, CVR, JT.

Appraising the quality of papers: LHL, CD, AN, CVR, JT.

Abstracting data from papers: LHL, CD, AN, CVR, JT.

Writing to authors of papers for additional information: LHL.

Providing additional data about papers: LHL.

Obtaining and screening data on unpublished studies: LHL, AN.

Managing data for the review: LHL, CD, AN.

Entering data into Review Manager (RevMan 5.3): LHL, AN.

Analysing RevMan statistical data: LHL, JW.

Performing other statistical analysis not using RevMan: LHL, JW.

Performing double entry of data: data entered by person one: LHL; data entered by person two: AN.

Interpreting data: LHL, AMM, JW.

Making statistical inferences: LHL, JW.

Writing the review: LHL, CD, AN, CR, JT, SS, AMM, JW.

Securing funding for the review: Copenhagen Trial Unit, Rigshospitalet, Copenhagen, Denmark, and Department of Anaesthesiology, Herlev Hospital, University of Copenhagen, Herlev, Denmark.

Serving as guarantor for the review (one review author): LHL.

Taking responsibility for reading and checking the review before submission: LHL.

DECLARATIONS OF INTEREST

LHL, AMM, CR, and JW were co-authors of an observational study entitled "Avoidance of neuromuscular blocking agents may increase the risk of difficult tracheal intubation: a cohort study of 103,812 consecutive adult patients recorded in the Danish Anaesthesia Database" (Lundstrom 2009a).

JW is a member of the task force in the Copenhagen Trial Unit, which develops theory, software, and manuals for trial sequential analysis (TSA).

AMM is a Co-ordinating Editor for the Cochrane Anaesthesia, Critical and Emergency Care Group.

JT received grants for two studies in 2016 through the Merck Investigator Studies Program. The aims of the two studies were (1) to assess the use of neuromuscular monitoring and the incidence of residual neuromuscular blockade in six Danish anaesthesia departments, and (2) to assess the effect of an e-learning course in neuromuscular monitoring.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol (Lundstrøm 2011a).

1. Christophe HV Duez, Anders K Nørskov, Charlotte V Rosenstock, and Jakob L Thomsen joined as review authors after publication of the protocol.

2. We considered avoiding NMBA as the intervention, thus we changed the title from "Use versus avoidance of neuromuscular blocking agent for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents" to "Avoidance versus use of neuromuscular blocking agent for improving conditions during tracheal intubation or direct laryngoscopy in adults and adolescents".

3. We did not consider stopping early for benefit, harm, or futility on inadequate stopping rules (or no reporting of sample size at all), as risk of bias in the accomplished review was high. In the protocol, we considered this a risk of bias component, but after the 11th Cochrane Symposium in Keystone, Colorado, early stopping was changed from constituting a bias risk to constituting increased risk of random error.

4. We did not consider baseline imbalance or lack of reporting of baseline characteristics as introducing high risk of bias. After the 11th Cochrane Symposium in Keystone, Colorado, baseline imbalance or lack of reporting of baseline characteristics changed from constituting a bias risk to constituting increased risk of random error.

5. We did not report on 'other bias' as suggested in the protocol.

6. In our protocol, we stated, "We will exclude trials using quasi-randomization and observational studies with regard to benefits, but not harms". In the review, we stated, "We excluded trials using quasi-randomization as well as observational studies". Thus we did not identify any quasi-randomized trials and did not include any observational studies examining harms.

7. Under 'Data extraction and management' in the protocol, we stated, "We will include each pair-wise comparison separately but with shared intervention groups divided out approximately evenly among the comparisons. For example if multiple intervention groups share a common control group the number of patients and the number of events of the control group will be divided equally, thereby the number of subgroups of the control group will match the number of intervention groups (Higgins 2011)" and "We will combine all relevant experimental intervention groups of the trials into a single intervention group, and combined all relevant control intervention groups into a single control group" (Higgins 2011). However, during the review process, we decided to perform only the latter (recommended) method when handling studies with multiple intervention or control groups. Thus, in the review, we have stated the following: "Some trials randomized participants to multiple intervention and/or control groups (more than two groups, as in dose-finding studies)". In the review, we combined all relevant experimental intervention groups from trials into a single intervention group, and we combined all relevant control intervention groups into a single control group, as recommended (Higgins 2011).

8. As conditions for tracheal intubation were not reported as a continuous outcome in any of the included trials, we did not calculate risk differences or mean differences with 95% confidence intervals.

9. We added two explorative outcomes: (1) a best-case scenario, whereby dose-finding studies were represented only by control and intervention groups with the lowest prevalence of difficult intubation; and (2) exclusion of dose-finding studies.

10. We did not explore selective outcome reporting by comparing publications with their protocols, if the latter were available.