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# Review Article

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## Rocuronium vs. succinylcholine for rapid sequence intubation: a Cochrane systematic review*

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### Summary

This systemic review was performed to determine whether rocuronium creates intubating conditions comparable to those of succinylcholine during rapid sequence intubation of the trachea. We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 2), MEDLINE (1966 to February Week 2 2015), and EMBASE (1988 to February 14 2015) for any randomised controlled trials or controlled clinical trials that reported intubating conditions comparing rocuronium and succinylcholine for rapid or modified rapid sequence intubation. The dose of rocuronium was at least 0.6 $mg.kg^{-1}$ and succinylcholine was at least 1 $mg.kg^{-1}$. Sixty-six studies were identified and 50 included, representing 4151 participants. Overall, succinylcholine was superior to rocuronium for achieving excellent intubating conditions (risk ratio (95%CI) 0.86 (0.81 to 0.92), n = 4151) and clinically acceptable intubation conditions (risk ratio (95%CI) 0.97 (0.95–0.99), n = 3992). A high incidence of detection bias amongst the trials coupled with significant heterogeneity means that the quality of evidence was moderate for these conclusions. Succinylcholine was more likely to produce excellent intubating conditions when using thiopental as the induction agent: risk ratio (95%CI) 0.81 (0.73–0.88), n = 2302) with or without the use of opioids (risk ratio (95%CI) 0.85 (0.78–0.93), n = 2292 or 0.85 (0.76–0.95), n = 1428).

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**This review is an abridged version of a Cochrane Review published in the Cochrane Database of Systematic Reviews (CDSR) 2015, Issue 10, DOI:10.1002/14651858.CD002788. (see www.cochranelibrary.com for information). Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and the CDSR should be consulted for the most recent version of the review.*

## Introduction

Patients who need tracheal intubation in the emergency department or the operating room often require a rapid sequence induction technique to protect against aspiration of gastric contents or to facilitate urgent airway protection in cases of imminent airway closure, haemodynamic instability, failing gas exchange and surgical emergencies [1–4]. The rapid sequence intubation technique involves the prompt sequential administration of a predetermined dose of hypnotic agent and muscle relaxant followed by tracheal intubation within 1 min of giving the muscle relaxant [5]. Frequently, modifications of this sequence are made, such as: titration of the hypnotic agent in situations of haemodynamic instability; the addition of an opioid to attenuate airway reflexes; and the addition of sedatives to induce amnesia (all hereafter termed 'modified' rapid sequence intubation).

Succinylcholine, a depolarising neuromuscular blocking agent, has traditionally been the most commonly used drug for a rapid sequence intubation technique in both the routine and emergency settings [6]. Its rapid onset (40–60 s) and short duration of action (6–10 min) are advantages that have to be balanced against the risk of hyperkalemia, variable increases in intracranial pressure [7] and, to a lesser extent, intra-ocular pressure [8]. As a result, succinylcholine is contra-indicated in major burns or crush injuries, severe abdominal sepsis, denervation syndromes, muscular dystrophy, malignant hyperthermia or in the presence of a previous allergic reaction to succinylcholine [9–13].

Alternative agents include pancuronium, vecuronium, atracurium and cisatracurium; however, none achieve acceptable intubating conditions as rapidly as succinylcholine. Rocuronium is a steroid-based non-depolarising muscle relaxant, which has been used to create intubating conditions similar to those of succinylcholine. The duration of action is longer (37–72 min with standard doses [14]). The only absolute contra-indication to rocuronium is allergy. Care must be taken with people who have myasthenia gravis or myasthenic syndrome, hepatic disease, neuromuscular disease, carcinomatosis, or severe cachexia, as the duration of action may be profoundly increased [3].

There have been many studies comparing rocuronium and succinylcholine; these have produced conflicting outcomes. It has been suggested that variation in the use of opioids, the hypnotic agent used (propofol, thiopental, etomidate), or the dose of rocuronium given may have accounted for these differences [14]. The intentions of this review are to determine whether rocuronium creates intubating conditions comparable to those of succinylcholine during rapid sequence intubation, and to perform subgroup analyses to assess for sources of inconsistency between studies. This review is important as rocuronium is becoming more widely used as a substitute for succinylcholine in rapid sequence intubation, especially with the introduction of a specific reversal agent, sugammadex [15, 16].

## Methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 2), MEDLINE (1966 to February 14th 2015), and EMBASE (1988 to February 14th 2015) to identify all clinical trials directly comparing rocuronium and succinylcholine during rapid sequence intubation, with no language, sex or age restrictions. We used the validated randomised controlled trial filter for the search [17]. Please refer to the Appendices in the full Cochrane review [18] for the exact search terms and strategy used. We included all randomised clinical trials (RCTs) and controlled clinical trials (CCTs) meeting the following criteria: a score of intubation conditions was reported as one of the main outcomes; rocuronium was compared with succinylcholine; and the dose of rocuronium administered was at least 0.6 $mg.kg^{-1}$ and succinylcholine was at least 1 $mg.kg^{-1}$ [19]. We hand searched the reference lists of included trials to add any citations missed by the electronic searches. Two independent appraisers (any two of JP, JL, VM, EN or DT) reviewed titles and abstracts using the inclusion criteria to assess relevance. We measured inter-rater agreement regarding article extraction using the kappa statistic. We resolved all disagreements by consensus. If we could not reach consensus, then a third author (GW or JP) was available to give a final decision. Once the final list of included studies was confirmed, data were independently extracted by two authors (JP, JL, VM, EN, or DT) using

 

standardised data collection forms. Disagreements were settled by consensus, with both extractors referring to the original text together, or by consulting a third author (JP). All data presented were from published literature only, with the exception of one report where the authors provided the exact numbers for intubating conditions [20]. To minimise introduction of bias, DT and EN reviewed and assessed all trials included in the review using the 'Risk of bias' tool.

The induction sequence could be either a standard rapid sequence intubation or 'modified' rapid sequence intubation performed electively or as an emergency. Our definition of a 'modified' rapid sequence intubation was the use of both a hypnotic agent and a muscle relaxant with changes which might include: a delay between giving the two drugs; the addition of drugs before the hypnotic agent; or an elapsed time of more than 60 s between the administration of the muscle relaxant and the intubation attempt. The hypnotics used for the induction of anaesthesia were thiopental, propofol, ketamine or etomidate. Additional medications allowed in this review were the use of pretreatment sedatives and opioids.

We assessed intubating conditions using the Goldberg scale [6, 21] (Table 1). This is a widely used scale (although not always attributed to Goldberg et al.) that allocates a score for each of: ease of intubation, vocal cord movement, and patient response to intubation (diaphragmatic movement, coughing or bucking). This scale gives a total value of 12, in which three represents excellent; four to six represents good; seven to nine represents poor, and 10 to 12 represents impossible or inadequate intubation conditions. Thus, for example, a score of three denotes good conditions recorded by the operator, open, immobile vocal cords, and no patient response to intubation. We only included trials if they reported intubating conditions as a scale or in components which could be converted to the Goldberg scale. For trials comparing multiple drugs, we used only data involving succinylcholine and rocuronium with the same induction agents. The primary outcome assessed was the proportion of excellent intubation conditions created during standard or modified rapid sequence intubation comparing rocuronium with succinylcholine. The secondary outcome assessed was the proportion of clinically acceptable (excellent or good) intubation conditions created during rapid or modified rapid sequence intubation comparing rocuronium with succinylcholine.

**Table 1** Goldberg scale used to describe intubation conditions

| Score | Ease of laryngoscopy | Vocal cords | Intubation response |
|---|---|---|---|
| 1. Excellent | Good | Open | None |
| 2. Good | Fair | Open | Diaphragmatic movement |
| 3. Poor | Difficult | Movement | Moderate coughing |
| 4. Impossible | Poor | Closed | Severe coughing or bucking |

We used Review Manager (RevMan) software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) to perform all the analyses in this study. Treatment effect was measured using dichotomous variables as risk ratios (RR) for both excellent and acceptable intubation conditions, with 95%CI, in a random-effects model. The unit of analysis was the intubation scores provided by each of the included trials. Sometimes the distribution of scores was provided only in graphical format, in which case we estimated data by reading the graphs directly. We performed analysis on an intention-to-treat basis.

Statistical heterogeneity was assessed by using the $I^2$ statistic with thresholds of 25%, 50% and 75% to indicate mild, moderate and high degrees of heterogeneity respectively [22]. Visual inspection was performed of the graphical representation of the trials with their 95%CIs. We explored the causes of significant heterogeneity with subgroup analyses. Reporting bias was assessed by visual inspection of a funnel plot of the included trials.

A priori subgroup analyses for the outcome of excellent intubation conditions compared the following groups: standard rapid sequence intubation vs. modified rapid sequence intubation; induction agent; use vs. non-use of an opioids; doses of rocuronium (0.6, 0.9, or 1.2 $mg.kg^{-1}$); adults vs. children; and emergency intubations. After we completed the assessment of bias, we conducted subgroup analyses according to categorisation of

 

blinding of outcome assessment to further identify the source of heterogeneity. In order to assess their impact on the effect direction, size and precision of the summary estimate, we conducted sensitivity analyses excluding trials in turn that: contributed most to heterogeneity; were most heavily weighted; and showed marked differences in intubation sequence (such as very short time between delivery of muscle relaxant and intubation).

## Results

Using our search protocol, 66 studies in total were identified, of which 50 trials [2, 6, 8, 14, 20, 23–67] were analysed, representing 4151 patients (Fig. 1). The inter-observer agreement regarding article selection had a κ statistic of 0.9. A detailed summary of the included and excluded studies can be found in the full Cochrane review [18]; the included studies are also available as online supplementary material on this journal's website. Two studies were excluded because the outcome could not be converted to the Goldberg scale. Intubation scores had to be extracted from bar graphs in 12 (24%) of the studies. Forty-five (90%) of the included studies involved adults; 30 (60%) studied patients with an ASA physical status classification of 1

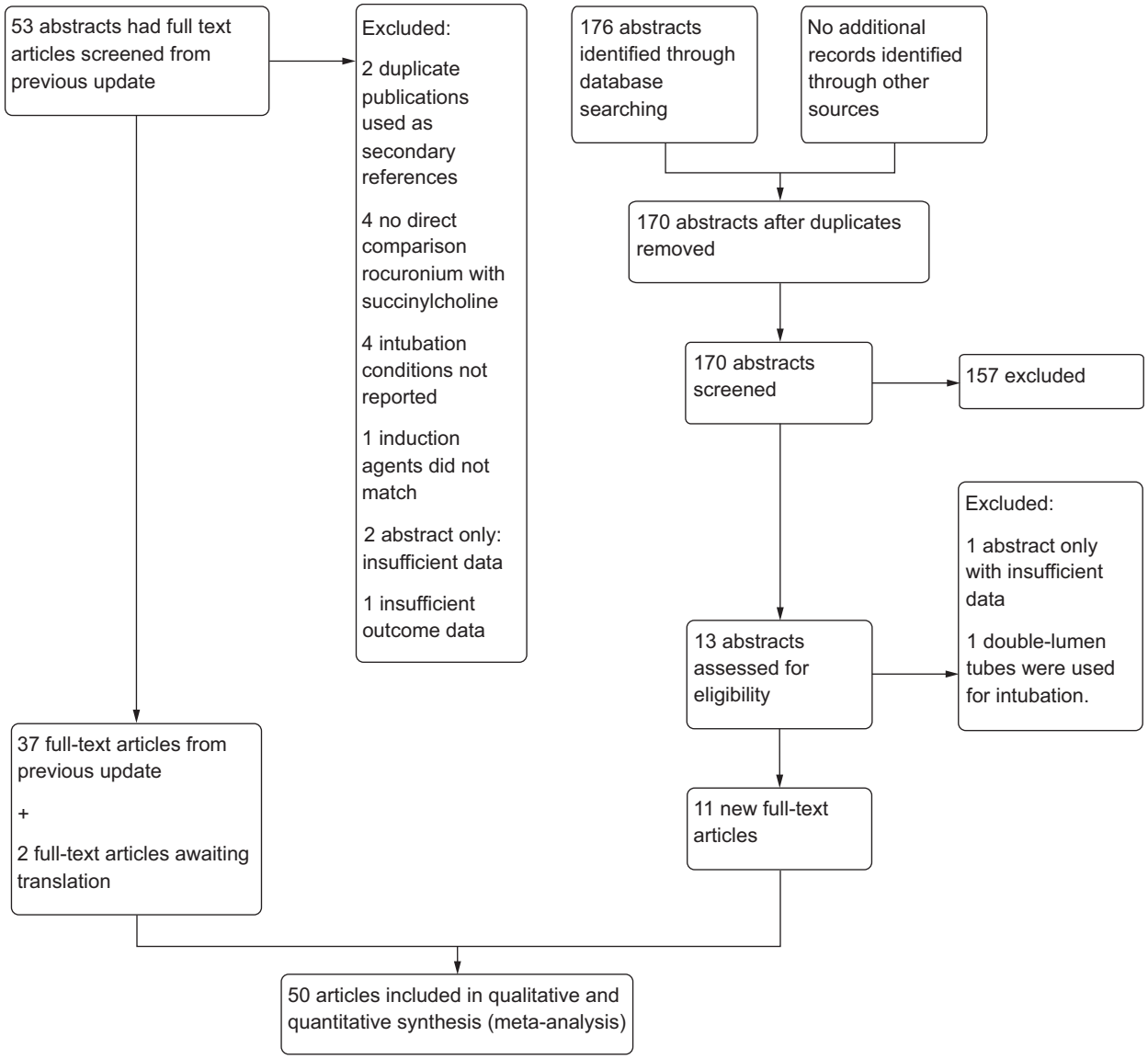


**Figure 1** Search flow diagram combining results from previous (left hand side) search (July 2007) and this update (February 2015).

and 2; 35 (70%) evaluated a modified rapid sequence intubation and 45 (90%) were conducted in an elective operating room environment.

Several studies only had part of published data included in the meta-analysis. The studies by Andrews [2] and McCourt [28] are two of the largest trials conducted to date. Both trials had to drop the lower dose rocuronium after the interim analysis, as it was found to be inferior to the larger dose [35]. Neither trial reported the results of the low-dose control groups and thus they are not included in this meta-analysis. Sparr used four different rocuronium treatment groups with only one succinylcholine control group [58]; we have therefore not included the rocuronium groups with propofol or alfentanil in this meta-analysis (no control group). Belyamani performed a trial assessing the benefit of ephedrine on intubating conditions with either succinylcholine or rocuronium [29]. Of the four treatment groups, only data from the two control groups were included in this analysis. De Almeida enrolled morbidly obese participants who were given different doses of muscle relaxant based on ideal body weight versus total body weight [34]. Only data for the two groups dosed for total body weight were included in this analysis, because the ideal body weight groups would have received lower drug doses than those specified in the inclusion criteria for the review. The second trial to involve emergency intubations [46] compared propofol with etomidate as the induction agent. The authors did not provide separate data for the two groups of participants, so this trial was not in the induction agent analysis. The figures and tables in Türkmen were unavailable, so only data points for excellent intubation conditions were used for the meta-analysis [66].

For each study, methodological details were assessed for risk of bias (Fig. 2). With regard to study allocation, all but one of the trials was described as a randomised controlled trial [34]. However, the exact method of randomisation was not always described. We rated two of the 50 included trials at high risk of bias for allocation, due to lack of randomisation [34] and randomisation by arrival sequence for surgery [38]. The most prevalent area of high risk of bias was blinding of outcome assessment, resulting in downgrading of the evidence in the review to 'moderate'.

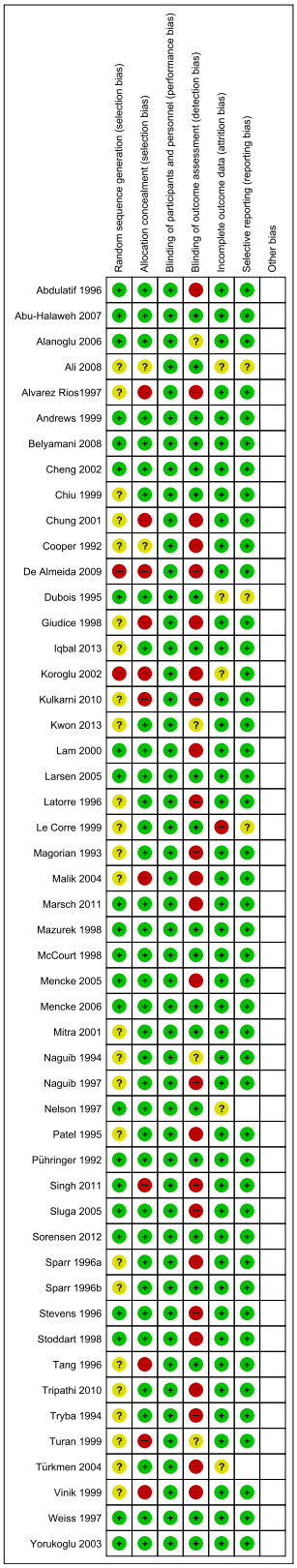


**Figure 2** Risk of bias summary: review authors' judgements about each risk of bias item for each included trial.

Although many investigators blinded the intubator to the medication injected, 50% did not blind the assessor. As succinylcholine causes very discernible fasciculations visible to the intubator, this 'unblinds' the study drug and could bias assessment of the primary outcome. Incomplete outcome data and selective reporting were almost uniformly low-risk in the included trials. We also assessed publication bias with a funnel plot. Visual inspection revealed an equal number of trials on either side of the effect estimate, although there was more scatter to the left, possibly indicating a paucity of trials in the lower right quadrant representing small unpublished trials favouring the use of rocuronium (Fig. 3).

For the primary outcome, when analysed for all patients, succinylcholine was more likely to provide excellent intubating conditions, RR (95%CI) 0.86 (0.81–0.92), 50 studies, 4151 participants, $I^2$ = 72%. The number needed to treat (95%CI) for an additional harmful outcome (NNTH) was 8 (12–6). There was heterogeneity present in this comparison, as demonstrated graphically with the 95% CIs for each trial. The chi² test for heterogeneity was significant (Fig. 4). For the secondary outcome of clinically acceptable intubating conditions ('excellent' or 'good') with a risk ratio (95%CI) 0.97 (0.95–0.99), 48 studies, 3992 patients, $I^2$ = 68%). An analysis of the influence on heterogeneity demonstrated that no single trial, regardless of size, significantly altered the I² statistic, with the exception

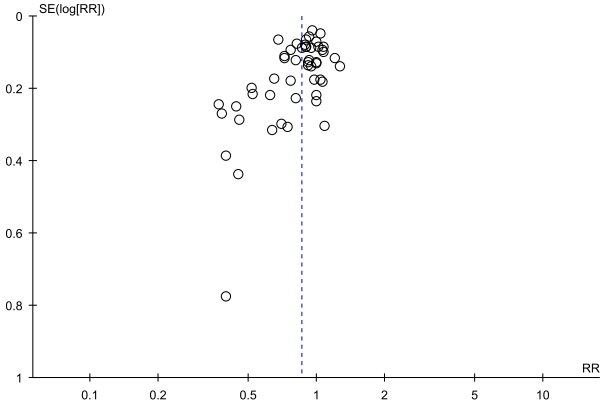


**Figure 3** Funnel plot of studies included comparing intubation conditions using rocuronium any dose versus succinylcholine. RSI, rapid sequence induction.

of Kulkarni et al. for the subgroup of modified rapid sequence intubation [39]. These assessments and the following subgroup analyses did not explain the heterogeneity in the trials. However, we did not downgrade the quality of the evidence because we felt that the sources of heterogeneity were clinical variables which contributed to the generalisability of these results. Detailed results for the subgroup analyses can be found in the full review [18].

Subgroup analysis comparing standard and 'modified' rapid sequence intubation for the primary outcome demonstrated that succinylcholine produced a higher proportion of excellent intubating conditions with both standard rapid sequence intubation (RR (95%CI) 0.80 (0.72–0.89), 23 studies, 2535 participants, $I^2$ = 77%, NNTH (95%CI) 8 (12–6) and modified rapid sequence intubation (RR (95%CI) 0.92 (0.85–0.99), 25 studies, 1468 participants, $I^2$ = 60%; NNTH (95%CI) 8 (11–5). There was significant heterogeneity present for both subgroups.

The influence of rocuronium dose was explored for the primary outcome of excellent intubation conditions; this showed that a dose of rocuronium of 0.6–0.7 $mg.kg^{-1}$ was less effective than succinylcholine (RR (95%CI) 0.80 (0.72–0.88), 39 studies, 2808 participants, $I^2$ = 77%; NNTH (95%CI) 6 (7–5). There were no statistical differences for excellent or acceptable intubation conditions in the group that received 0.9–1.0 $mg.kg^{-1}$ of rocuronium or the group that received 1.2 $mg.kg^{-1}$ of rocuronium.

When analysed by induction agent (thiopental vs. propofol), the thiopental subgroup displayed a preference for succinylcholine over rocuronium to produce excellent intubation conditions (RR (95%CI) 0.81 (0.73–0.88), 28 studies, 2302 participants, $I^2$ = 81%; NNTH (95%CI) 6 (7–5) (Fig. 5). Further analysis comparing the effect of thiopental when used with or without an opioid found that succinylcholine created significantly better outcomes both with opioids ((RR (95%CI) 0.82 (0.73–0.92), 17 studies, 1300 participants, $I^2$ = 79%) and without (RR (95%CI) 0.80 (0.69–0.94), 12 studies, 1002 participants, $I^2$ = 84%) in sequence with thiopental. There were no trials that used benzodiazepines for induction, comparing rocuronium with succinylcholine.

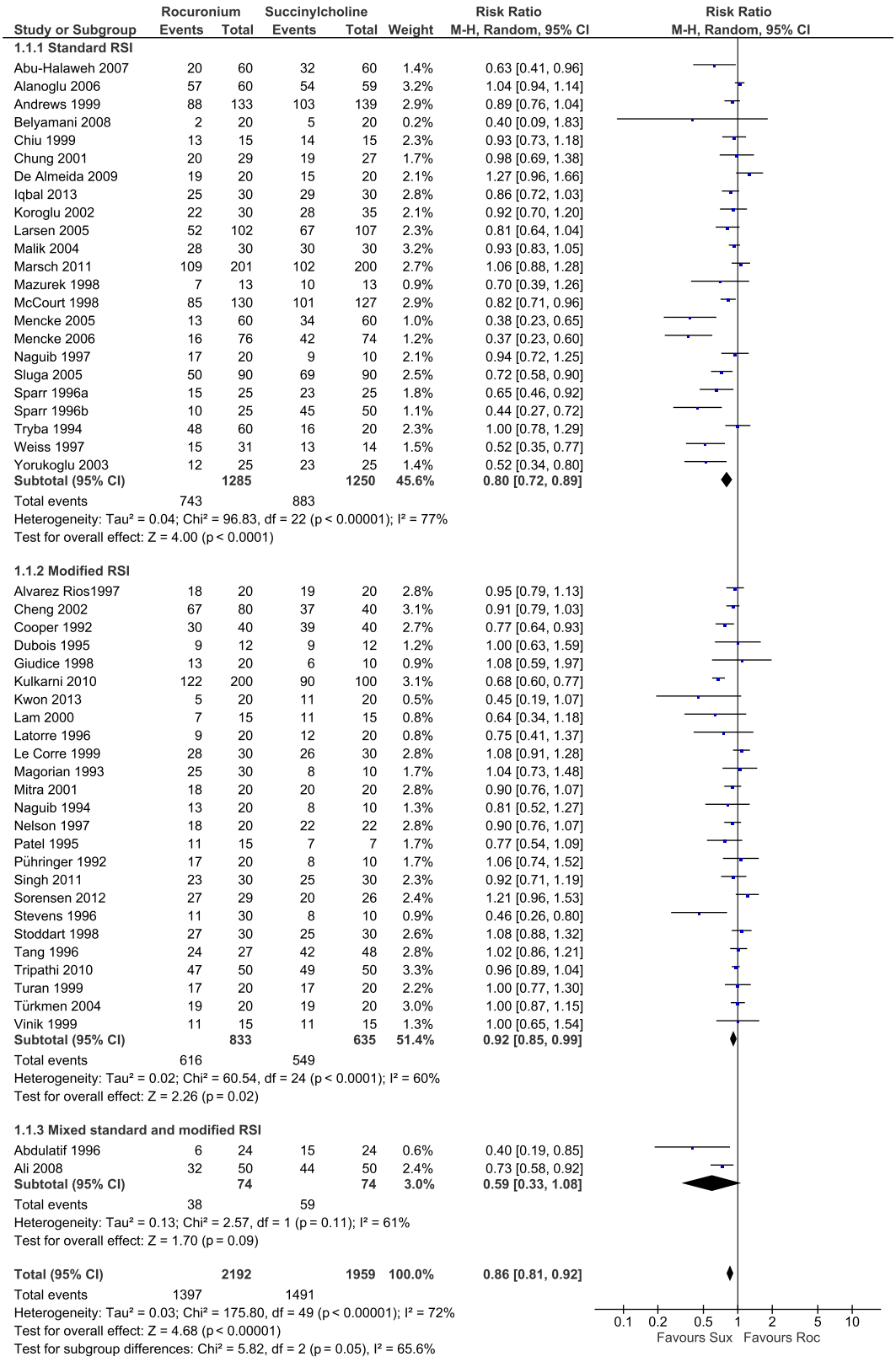


**Figure 4** Forest plot comparing rocuronium (any dose) with succinylcholine for outcome 'excellent' vs. other intubation conditions. RSI, rapid sequence induction; sux, succinylcholine; roc, rocuronium.

 

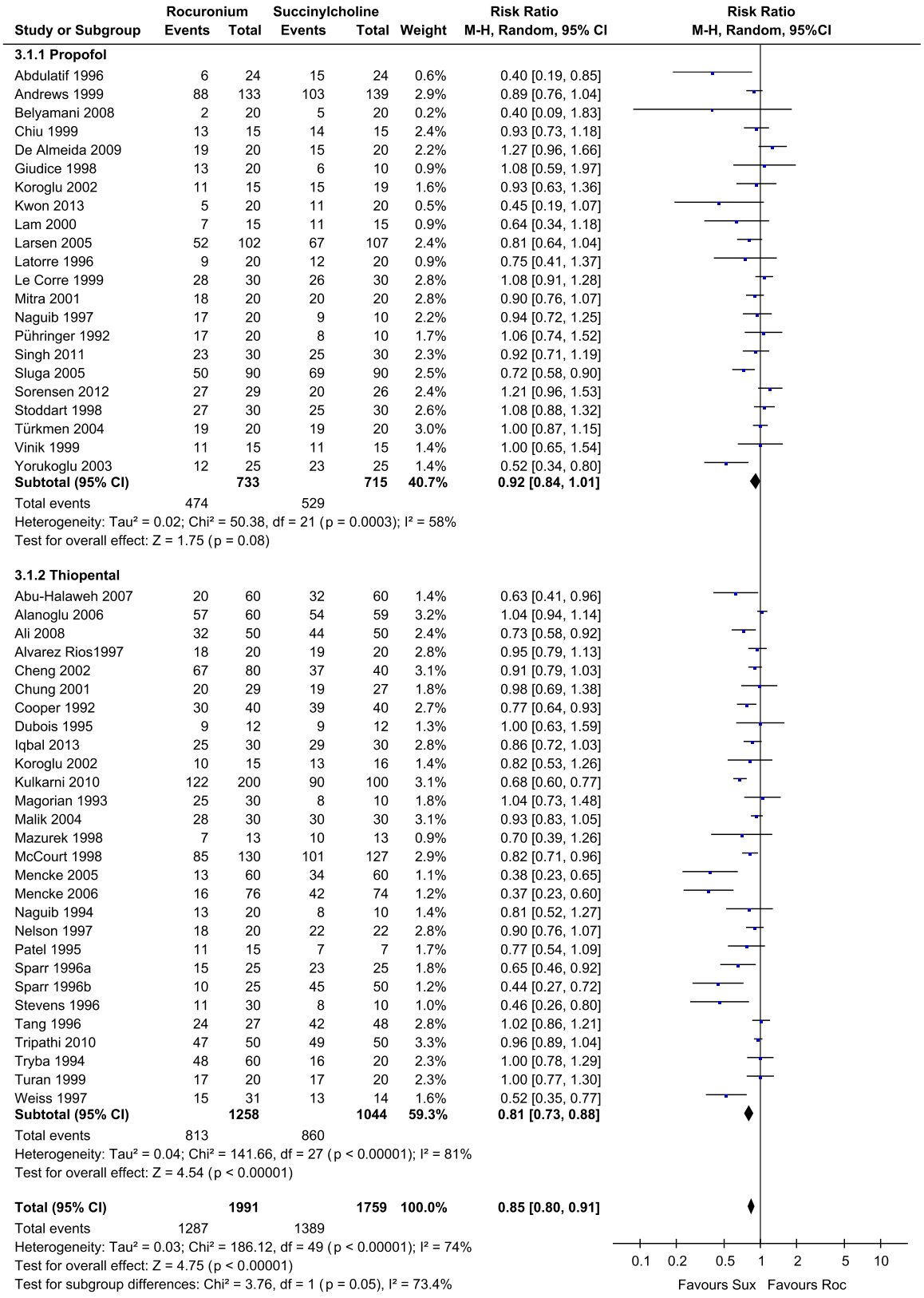


**Figure 5** Forest plot comparing rocuronium with succinylcholine by induction agent for outcome 'excellent' vs. other intubation conditions. RSI, rapid sequence induction; sux, succinylcholine; roc, rocuronium.

Succinylcholine also provided better intubating conditions whether opioids were used or not. The subgroup of trials using an opioid favoured the succinylcholine group (RR (95%CI) 0.85 (0.78–0.93), 34 studies, 2292 participants, $I^2$ = 74%, NNTH (95%CI) 7 (10–6). The subgroup without an opioid also demonstrated an advantage for succinylcholine (RR (95%CI) 0.85 (0.76–0.95), 16 studies, 1428 participants, $I^2$ = 76%; NNTH (95%CI) 6 (9–5).

The paediatric subgroup demonstrated no statistically significant difference between rocuronium and succinylcholine with regard to excellent intubation conditions (RR (95%CI) 0.86 (0.70–1.06), 5 studies, 536 participants, $I^2$ = 81%). There was significant heterogeneity amongst the five paediatric trials.

For the subgroup comparing rocuronium and succinylcholine in emergency participants (one study in the intensive care unit and four in the operating room), there was a statistically significant risk ratio favouring succinylcholine for excellent intubation conditions (RR (95%CI) 0.84 (0.73–0.98), 5 studies, 1073 participants, $I^2$ = 53%; NNTH (95%CI) 12 (38–7) and there was no significant heterogeneity between trials.

## Discussion

This review summarises the results of 50 trials in 4151 participants [2, 6, 8, 14, 20, 23–67], demonstrating moderate-quality evidence that succinylcholine creates better intubation circumstances than rocuronium. However, if an alternative agent is required, rocuronium 1 mg.kg$^{-1}$ can be used to create acceptable intubation conditions but should only be used as a second-line treatment because paralysis will be significantly prolonged. The introduction of sugammadex to facilitate reversal of rocuronium allows this problem to be overcome, but this drug is not currently widely available [68].

We have demonstrated that succinylcholine is superior to rocuronium when either a standard or modified rapid sequence intubation technique is used. Interestingly, thiopental was found to provide superior intubating conditions with or without the use of an opioid. Unfortunately, this finding will have limited clinical applicability in North America, where the availability of thiopental has become very limited. The failure of opioids to make a difference to the quality of intubation conditions is contrary to other research [59]. The dose of rocuronium has been thought to be important in creating intubation conditions equivalent to succinylcholine. Succinylcholine created significantly more excellent intubation conditions than rocuronium at doses of 0.6–0.7 mg.kg$^{-1}$. There was no statistically significant difference for the 0.9 to 1.0 mg.kg$^{-1}$ or 1.2 mg.kg$^{-1}$ groups, reaffirming the current practice of using 1 mg.kg$^{-1}$ of rocuronium for rapid sequence intubation when succinylcholine is not clinically indicated. It is difficult to draw conclusions regarding the higher doses of rocuronium, as there are relatively few studies which have examined the higher dose (1.2 mg.kg$^{-1}$) of rocuronium (n = 86). At this high dose, the duration of action of rocuronium becomes 73 min on average [8] which can result in an increased incidence of adverse outcomes. The relatively recent introduction of a reversal agent for non-depolarising muscle relaxants [16] may ameliorate the features of prolonged muscle blockade, but it has not been tested in emergency situations [15].

We included a subgroup analysis for participants undergoing emergency intubation demonstrating that succinylcholine is superior to rocuronium in creating excellent intubation conditions. This is consistent with our findings in the < 60-second time delay subgroup. There was, however, no significant difference between groups for the outcome of clinically acceptable intubation, indicating that in emergency patients for whom succinylcholine is contraindicated, rocuronium can still be used to reliably create acceptable intubating conditions.

There was no evidence of a difference in our primary outcome in the five paediatric trials [30, 39, 47, 51, 61]. However, these had very little power to demonstrate any statistically significant difference due to the small sample size (n = 536). In addition, two of the trials [51, 61] used propofol in the sequence, while a third [47] used a high dose of rocuronium (1.2 mg.kg$^{-1}$) which may have confounded the results. Another trial used ketamine in addition to a benzodiazepine as a premedication for particularly young children, further confounding the comparison [39].

This review has identified trials involving participants from a wide age range (1–77 years) in a variety of clinical settings, including both elective and

 

emergency intubations in the operating room and intensive care unit. The funnel plot of the included trials indicates a lack of trials in the right lower quadrant, which may represent small unpublished trials favouring the use of rocuronium (Fig. 3). The reason for such trials not being reported is not evident. Another reason for the asymmetric funnel plot is heterogeneous study effects that can be seen with varying study sizes, intubation sequences and study populations. It is also possible that despite the inclusive search strategy, we have missed research not included in the databases accessible to the English-speaking community.

With regard to the quality of the evidence presented, we found a significant amount of heterogeneity in the analysis of the primary outcome, which we tried to explore with subgroup analyses by: age; urgency; dose of rocuronium; timing of muscle relaxant; induction agent; and opioid use. The $I^2$ statistical value never fell below the 50% thresholds with these sensitivity analyses, nor did the direction or size of the summary estimate. As a result, we did not down-grade the quality of evidence, but suggest that the heterogeneity may be explained by variation in: patient populations; clinical settings (e.g. elective limb surgery, gastric bypass, emergency intensive care intubations); medications in induction sequences; and timing of intubation. All of these contribute to the generalisability of our results, and to reducing concerns about indirectness of evidence.

Assessments of the risk of biases demonstrate that the series of trials included in this review are at low risk of selection and attrition bias. All but one trial was described as a randomised controlled trial, with 11% of trials being at high risk for lack of allocation concealment. The area of most concern was the high incidence of detection bias due to lack of blinding of the outcome assessor, which led us to downgrade the quality of evidence to 'moderate'. Succinylcholine will cause significant fasciculations, and intubators who are not blinded to this effect may assign biased scores to the intubating conditions. We conducted a subgroup analysis based on the blinding of the outcome assessor which failed to explain the source of the heterogeneity in the meta-analysis.

Contrary to the primary findings of our review, a retrospective review of 327 rapid sequence intubation intubations using etomidate with rocuronium or succinylcholine in the emergency department showed equivalent success at first intubation attempts [69]. Median doses of rocuronium were 1.19 $mg.kg^{-1}$ and 1.5 $mg.kg^{-1}$ of succinylcholine. Herbstritt et al. performed a short review looking at use of equivalent doses of rocuronium and succinylcholine (1 $mg.kg^{-1}$) for rapid sequence intubation [70]. They included seven papers of varying quality (retrospective review, RCT and meta-analysis), and concluded that there are no differences in intubating conditions between the two. This is consistent with our finding in the 0.9–1.0 $mg.kg^{-1}$ dose range (RR (95%CI) 0.95 (0.89–1.00), 1458 participants). When using doses of 0.6 $mg.kg^{-1}$ of rocuronium, Larsen et al. used alfentanil and propofol as their induction agents and found no difference between rocuronium and succinylcholine 1 $mg.kg^{-1}$ in achieving clinically acceptable intubating conditions [42]. These results are also consistent with those reported in this review for the secondary outcome (RR (95%CI) 0.99 (0.96–1.02), 952 participants).

Any further trials comparing succinylcholine and rocuronium should make certain to blind the outcome assessor to the fasciculations triggered by succinylcholine. Most of the included trials assessed intubation conditions using ease of laryngoscopy, vocal cord motion and diaphragmatic movement. These measures should be maintained to allow for consistent comparison between trials. Although there are now five trials [2, 20, 42, 46, 47] involving emergency participants, further trials in this patient population may reveal differences in results because etomidate is more often used as an induction agent than in the operating room. Finally, there was a lack of reporting of adverse outcomes in the trials, which should be addressed in any trials performed in the future.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Included studies that compared intubating conditions between rocuronium and succinylcholine for rapid sequence intubation.

 