A systematic review and meta-regression analysis of mivacurium for tracheal intubation

A systematic review and meta-regression analysis of mivacurium for tracheal intubation[1]

L.E.H. Vanlinthout,[1] S.H. Mesfin,[2] N. Hens,[3] B.F. Vanacker,[4] E.N. Robertson[1] and L.H.D.J. Booij[5]

1 Staff Anaesthesiologist, 5 Professor Department of Anaesthesiology, Radboud University Medical Centre Nijmegen, Nijmegen, The Netherlands

2 Statistician, 3 Professor of Biostatistics, Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BIOSTAT), Universities of Leuven and Hasselt, Leuven and Diepenbeek, Belgium

4 Professor of Anaesthesiology, Department of Anaesthesiology, University Hospitals Leuven, Leuven, Belgium

Short title: Mivacurium systematic review

[1] The study was presented at the 3rd joint Statistical Meeting, organised by the Deutsche Arbeitsgemeinschaft Statistik (DAGStat), March, 18-22, 2013, Freiburg, Germany

SUMMARY

We systematically reviewed factors associated with intubation conditions in randomised controlled trials of mivacurium, using random-effects meta-regression analysis. We included 29 studies of 1052 healthy participants. Four factors explained 72.9% of the variation in the probability of excellent intubation conditions: mivacurium dose, 24.4%; opioid use, 29.9%: time to intubation and age together, 18.6%. The odds ratio (95% CI) for excellent intubation was 3.14 (1.65-5.73) for doubling mivacurium dose, 5.99 (2.14-15.18) for adding opioids to the intubation sequence, 6.55 (6.01-7.74) for increasing the delay between mivacurium injection and airway insertion from one to two minutes in subjects aged 25 years and 2.17 (2.01-2.69) for subjects aged 70 years, $p < 0.001$ for all. We conclude that good conditions for tracheal intubation are more likely by delaying laryngoscopy after injecting a higher dose of mivacurium with an opioid, particularly in older people.

INTRODUCTION

Mivacurium is a short-acting non-depolarizing neuromuscular blocker with a combination of the bisbenzyltetrahydroisoquinolinium structure of atracurium and the enzymatically degradable ester linkage of suxamethonium. It therefore suffers from disadvantages of both of its constituents. As a structural analogue of atracurium it has a slow onset of action and anaphylactoid potential. Similar to suxamethonium, the rapid clearance of mivacurium by butyrylcholinesterase accounts for the short duration of its neuromuscular block. In the presence of butyrylcholinesterase deficiency, however, neuromuscular recovery may be prolonged [1].

In recent years other neuromuscular blocking drugs have offered fast onset with safe cardiovascular profiles when administered as a rapid bolus dose. Although mivacurium is used less often it may be preferred for short procedures, such as those performed in the ambulatory setting. It is often given to maintain neuromuscular blockade for longer procedures where easy alteration of depth of block and fast recovery are considered important [2-5].

A number of randomised controlled trials have compared the efficacy of mivacurium at different doses and versus other neuromuscular blocking drugs. The efficacy of mivacurium is unclear due to the variation in results between these studies. We have performed this systematic review to identify factors associated with excellent tracheal intubation conditions following mivacurium injection. We explored potential characteristics associated with variation between study outcomes using meta-regression analysis, which can uncover relationships in a set of trials that remain unnoticed at the level of individual studies [6].

METHODS

We followed the PRISMA guidance [7]. We searched for randomised controlled trials (RCTs) published in any language that compared different doses of intravenous mivacurium, or mivacurium versus an inactive control or another neuromuscular blocking agent, to September 2013 in five databases: CENTRAL; Embase; MEDLINE; SCIRUS (now retired); Web of Science. We combined the free text terms 'mivacurium', 'intubation conditions' and 'adults'. We manually searched the references of retrieved studies. We included RCTs that studied healthy men or women (ASA physical status 1 or 2) having elective or emergency surgery that required tracheal intubation. We excluded abstracts, doctoral dissertations, letters, reviews, as well as RCTs that were not peer-reviewed. We also excluded RCTs that induced anaesthesia with at least 0.5 MAC of volatile agent and those that gave intravenous local anaesthetic before induction: both interventions can increase neuromuscular blockade, potentially obscuring interactions of mivacurium with other variables [8-10]. The primary outcome was 'excellent conditions' during laryngoscopy and tracheal intubation, defined by three criteria: open vocal cords; easy tube insertion; no cough during laryngoscopy and endotracheal intubation. We converted reported categories to the Goldberg scale [11]. We included RCTs that failed to adequately report one of these criteria, but assessed the effect of their inclusion on the results.

Two authors (LEHV and SHM) independently assessed RCTs for risks of bias in six domains: sequence generation; allocation concealment; blinding; attrition; selective outcome reporting; other potential biases [12]. Risks were categorised as present, absent or unclear. Both authors independently used a structured form to extract: study design; risks of bias; participant characteristics; interventions; outcomes. Differences were resolved by a third reviewer (LHDJB). We analysed the interaction of 10 variables with the quality of intubation conditions: mivacurium dose; participant sex and mean age; anaesthetic agent; the use of opioids or nitrous oxide; the use of priming i.e. a small dose of mivacurium given 2-4 min before a second larger

dose; route of intubation (nasal vs oral); the continent of study; the year of publication. We used data from RCTs with complete results to impute missing values for RCTs with incomplete results [13].

The primary outcome was the proportion of participants in each RCT group with excellent intubation conditions, ranging from 0 to 1. We used a random-effects approach [14] to fit the following linear logistic multivariable meta-regression model to the data:

$$\text{logit}\,(P_i) = a_0 + a_1X_{1i} + a_2X_{2i} + ... + a_nX_{ni} + \varepsilon \qquad (1)$$

where: P_i is the proportion of participants with excellent intubation conditions in group 'i'; logit $(P_i) = \ln (P_i/(1-P_i)) = \ln$ (odds P_i), a_0, a_1, a_2, ... , a_n are the coefficients for the variables (X_1 etc); and ε is the sum of variation within and between groups. Conversely, the proportion of participants with excellent intubation conditions, P_i, can derived from the natural exponent for logit (P_i):

$$P_i = e^{\text{logit}\,(Pi)} / (1+ e^{\text{logit}\,(Pi)}) \qquad (2)$$

Variables associated with intubation conditions on univariable analysis (p value < 0.25) were included in a multivariable analysis, with terms for their pair-wise interactions [15]. We then sequentially excluded variables and terms from this initial multivariable model, using a stepwise elimination procedure [15]. The results of different RCTs were weighted by the precision (1/variance) of their association with intubation conditions. We defined substantial heterogeneity as $I^2 > 50\%$ [16].

We incorporated five sources of bias as covariates in the meta-regression: allocation sequence concealment; the number of participants; blinding of the outcomes assessors to group allocation; blinding of the outcomes assessors to the magnitude of neuromuscular block at laryngoscopy; complete reporting of intubation criteria [12]. We assessed the sensitivity of the results to the statistical method, classical parametric (frequentist) vs Bayesian inference.

Our intention was to include all RCTs that tested the effect of mivacurium on intubation conditions, leaving no external data against which to assess the predictive performance of our meta-regression equation. We therefore tested the performance of predictive equations generated by half the included RCTs on the outcomes reported by the other RCTs, and then reversed the process, generating a predictive equation with the second sample of RCTs on the first sample (cross validation). We repeated this four times, each time randomly sampling half the RCTs, to give a total of 10 sets (resulting from 5 cross validation rounds) of observed and predicted outcomes [17]. We combined these to produce one single file of validation results. The performance of the model, i.e. goodness of fit between observed and predicted outcomes, was tested with the Hosmer-Lemeshow chi-squared test [18].

We used Comprehensive Meta-Analysis (version 2, BioStat®, Englewood, New Jersey, USA), Stata (version 12, StatCorp®, College Drive, Texas, USA), Review Manager (version 5.2, The Nordic Cochrane Centre, Copenhagen, Denmark) and Winbugs (version 1.4.3, MRC Biostatistics Unit, Cambridge, UK). We considered a p value < 0.05 significant.

RESULTS

We included 29 RCTs of 1052 participants in 60 treatment groups (Figure 1 and Table 1). Table 2 summarises our assessments of bias risks.

We imputed missing age data for five RCTs [21, 25-27, 39]. One study excluded participants whose vocal cords were incompletely visualised or whose orbicularis oculi muscle was incompletely paralysed after 300 s [30]. One study did not report ASA physical status [40] and six provided insufficient detail to convert intubation conditions to the Goldberg scale [23, 24, 30, 37, 38, 43].

Studies excluded butyrylcholinesterase deficiency by direct measurement of enzyme activity [19, 21, 25, 26, 39] or by assessing mivacurium's pharmacodynamics, one of which excluded a participant when deficiency was detected [33]. The magnitude or duration of neuromuscular blockade was assessed qualitatively – visually [30, 34] or by touch [19, 25] – or quantitatively, with mechanomyography [11, 22, 29, 33, 34, 36, 39, 40, 43, 45, 46], electromyography [21, 26-28, 32, 37, 38, 41] or acceleromyography [20, 23, 24, 31, 35, 42, 44]. Two trials did not provide this information [30, 31]. Figure 2 shows the relationship between mivacurium dose and excellent intubation conditions. The treatment groups from three RCTs [26, 27, 33] are not represented as no participant exhibited excellent intubation conditions with mivacurium.

Six variables were not significantly associated with intubation conditions on univariable analyses: sex; thiopentone use; use of priming; route of intubation; continent and year of publication. Six other variables were initially included in multivariable analysis: propofol use; nitrous oxide use; dose of mivacurium; opioids; delay between mivacurium injection and laryngoscopy; the mean age of participants. The last four of these variables were included in the final model:

$$\text{logit}\,(P) = a0 + (a_1X_1) + (a_2X_2) + (a_3X_3) + (a_4X_4) + (a_5\,X_3 \times X_4) \qquad (3)$$

where: P, probability of excellent intubation conditions; X_1, ln [dose of mivacurium ($mg.kg^{-1}$)] ; X_2, use of opioids (1/0); X_3, mean time between mivacurium injection and laryngoscopy (min); and X_4, ln [mean age of participants who had mivacurium (yr)].

This model accounted for 72.9% of the variation in the probability of excellent intubation conditions: mivacurium dose (X_1), 24.4%; opioid use (X_2), 29.9%; and time to intubation (X_3) and age (X_4) together with their interaction (X_3 x X_4), 18.6% (Table 3). The results were similar with classical parametric (frequentist) and Bayesian methods.

To illustrate, consider laryngoscopy in a healthy 70 year old man two minutes after the injection of 0.2 $mg.kg^{-1}$ mivacurium and a dose of alfentanil. From the RCTs we reviewed his probability of excellent intubation conditions was:

logit (P) = -12.95 + (1.64 x ln(0.2)) + (1.72 x 1) + (5.05 x 2) + (3.10 x ln(70)) + (-0.99 x 2 x ln(70))

logit (P) = 1.03 with 95% CI (0.32-1.78)

$P = e^{1.03}/ (1+e^{1.03}) = 3.03 / (1+3.03) = 3.03 / 4.03 = 0.74$, or 74% with 95% CI (58-86%).

Table 4 shows the odds ratios for the associations between mivacurium dose, opioids, delay before intubation and the probability of excellent intubation conditions. In sensitivity analysis the intubation score was increased by failure to blind the intubation assessor to allocation or the dose of neuromuscular blocking drug, p = 0.023. Intubation conditions were not associated with: allocation concealment, p = 0.10; blinding the intubation assessor to the depth of neuromuscular block at the time of laryngoscopy, p = 0.07; the number of participants, p = 0.56; and the scoring system used to grade intubation conditions, p = 0.32.

Figure 3 shows the number of participants in each RCT with excellent intubation conditions against the median expected number. The treatment groups from three RCTs [26, 27, 33] are not represented as no participant exhibited excellent intubation conditions with mivacurium.

The cross-validations did not demonstrate any significant differences between observed and expected outcomes. The performance of the model is unknown outside the limits investigated by the RCTs included in this review: a mivacurium dose 0.075-0.27 $mg.kg^{-1}$; a time between mivacurium injection and intubation 1.00-3.52 min; and participants aged 25-74 yr. The relationship between the expected probability of excellent intubation conditions and mivacurium dose and the use of opioids is represented in Figure 4, whilst Figure 5 illustrates the effects of age and the time between mivacurium injection and airway insertion.

DISCUSSION

Excellent intubation conditions were more likely with more mivacurium, opioids, delayed intubation and older participants. The maximum safe dose of mivacurium will be limited by side effects, for instance those mediated by histamine release. Opioids reduce stimulation from intubation and cuff inflation by action at μ receptors which are abundantly present in the cell bodies of glossopharyngeal and vagal nerves that innervate muscles of the soft palate, the pharynx and larynx [47]. Furthermore, opioids are synergistic with hypnotics [48]. With adequate depth of anaesthesia, satisfactory intubation conditions can usually be obtained even before complete neuromuscular block is attained [49]. Waiting after mivacurium injection increases blockade through more relaxant at the neuromuscular junction, but too long a delay might allow the central nervous system to recover from the depression caused by induction. With inadequate anaesthesia smooth intubation cannot be ensured, even after two or three times the median dose of neuromuscular blocking drug that reduces maximal twitch response by 95%.

Contrary to what has been found for drugs acting upon the central nervous system, no difference in magnitude of neuromuscular block has been found between young and elderly participants [50]. Owing to circulatory changes associated with induction of anaesthesia onset of neuromuscular block can be 1-1.5 minutes slower in the elderly than the young [50, 51]. Therefore the association of intubation conditions with age [35, 52] might be due to more profound central nervous system depression after induction [53, 54], even before complete paralysis has been obtained.

Sex was not associated with intubation conditions after mivacurium, which is at odds with the greater action of mivacurium in young women [55, 56] and different potencies of aminosteroids relaxants in men and women [57]. However, women are less sensitive to hypnotic [58] and opioid [59] drugs, which might have obscured an association in the RCTs we included. We did not find an association of intubation conditions with the administration of a

small ‘priming’ dose of mivacurium, 2-4 min before a second larger dose that some investigators have found accelerated the onset of paralysis by 0.5 to 1 min, although others have not [60]. Mivacurium may be less likely to exhibit this characteristic as it is rapidly hydrolysed by butyrylcholinesterase. We did not find any geographical variation for mivacurium. This confirms earlier observations [61] and is different from vecuronium where transatlantic differences were seen [62].

Our meta-regression model did not account for 28% of the variation in the probability of excellent intubation conditions. One factor might be the subjective assessment of intubation conditions. There are large differences in susceptibility to mivacurium. Variations in butyrylcholinesterase activity would contribute to variation in the speed and magnitude of neuromuscular block after mivacurium. However, as with suxamethonium [63], butyrylcholinesterase activity needs to be significantly reduced before any increase in the effect of mivacurium can be demonstrated [64]. The ease with which intubation of the trachea can be accomplished depends upon the interplay of neuromuscular blockade, depth of anaesthesia and technical proficiency: deficiency in one can be compensated for by another [65].

Our meta-regression is limited in part by the characteristics of the included RCTs, a minority of which reported adequate methods for allocation concealment and blinding, increasing the risks of selection and observer biases. Most trials recruited few participants, which might account for the large variability in event rates. However, we did not demonstrate a difference in the effect of mivacurium in small vs larger studies. Participants were recruited by RCTs over a 28 year period and in many countries. We think that this might be a strength, as much as a weakness, in determining robust associations, supported by consistency across subgroup analyses. We only included peer-reviewed RCTs, which might limit weaknesses in study design and analysis.

The results of any meta-regression have to be interpreted with caution, as they are prone to aggregation bias, confounding and to lack of power [66]. Aggregation bias is the failure of study-level associations to properly reflect individual-level associations. If, however, the distribution of a characteristic is very different across studies, as compared to within studies, meta-regression is a powerful way to evaluate its association with treatment effect [66]. The range of participants' mean ages and time to intubation were 25-74 yr and 1.0-3.5 min, respectively, yet within individual RCTs the spread of participant's ages and intubation times were rather restricted. Meta-regression with mean values for participant characteristics is less powerful with individual patient data; therefore an association with mean values probably represents a large and significant effect [67]. Meta-regression is both retrospective and observational, with associations being confounded by known and unknown covariates.

Mivacurium has failed to replace suxamethonium as intubation conditions are often unsatisfactory [68]. We conclude that good conditions for tracheal intubation are more likely by delaying laryngoscopy after injecting a high dose of mivacurium with an opioid, particularly in older people. More profound anaesthesia after standard doses of induction agents in older people may explain better intubation conditions, even before complete paralysis is obtained.

Acknowledgement

No external funding and no competing interests declared. This study was supported by the Department of Anaesthesiology of the Radboud University Medical Centre at Nijmegen, the Netherlands.

References

1. Østergaard D, Viby-Mogensen J, Rasmussen SN, Gätke MR, Varin F. Pharmacokinetics and pharmacodynamics of mivacurium in patients phenotypically homozygous for the atypical plasma cholinesterase variant: effect of injection of human cholinesterase. *Anesthesiology* 2005; **102**: 1124-32.

2. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. *British Journal of Anaesthesia* 2014; **112**: 498-505.

3. González A, Benavides J, Lema G. Anesthesia and electroconvulsive therapy: when succinylcholine is contraindicated. *Journal of Electroconvulsive Therapy* 2013; **29**: 75-6.

4. Shchegolev AV, Levshankov AI, Bogomolov BN, Pereloma VI, Dumnov AG. Evaluation of muscle relaxant requirement for hospital anesthesia. *Voenno-Meditsinskii Zhurnal* 2013; **334**: 20-6.

5. Janda M, Simanski O, Bajorat J, Pohl B, Noeldge-Schomburg GF, Hofmockel R. Clinical evaluation of a simultaneous closed-loop anaesthesia control system for depth of anaesthesia and neuromuscular blockade. *Anaesthesia* 2011; **66**: 1112-20.

6. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *Journal of Health Services Research and Policy* 2002; **7**: 51-61.

7. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *British Medical Journal* 2009 Jul 21; **339**: b2535 doi: 10.1136/bmj.b2535

8. Motamed C, F. Sevoflurane and isoflurane, but not propofol, decrease mivacurium requirements over time. *Canadian Journal of Anesthesia* 2002; **49**: 907-12.

9. Matsuo S, Rao DB, Chaudry I, Foldes FF. Interaction of muscle relaxants and local anesthetics at the neuromuscular junction. *Anesthesia and Analgesia* 1978; **57**: 580-7.

10. Pandey CK, Raza M, Ranjan R, et al. Intravenous lidocaine suppresses fentanyl-induced coughing: a double-blind, prospective, randomized placebo-controlled study. *Anesthesia and Analgesia* 2004; **99**: 1695-8.

11. Goldberg ME, Larijani GE, Azad SS, et al. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. *Anesthesia and Analgesia* 1989; **69**: 93-9.

12. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *British Medical Journal* 2011; **343**: d5928 doi: 10.1136/bmj.d5928.
13. Donders AR, van der Heijden GJ, Stijnen T, Moons KG. Review: a gentle introduction to imputation of missing values. *Journal of Clinical Epidemiology* 2006; **59**:1087-91.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986; **7**: 177-88.
15. Hosmer DW, Lemeshaw S. Model-building strategies and methods for logistic regression. In: Cressie NAC, Fisher IN, Johnstone IM et al.; Applied logistic regression 2nd ed., New-York, John Wiley & Sons, Inc, 2000: 91-142.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003; **327**: 557-60.
17. Molinaro AM, Simon R, Pfeiffer RM. Prediction error estimation: a comparison of resampling methods. *Bioinformatics*. 2005; **21**: 3301-7.
18. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *American Journal of Epidemiology* 1982; **115**: 92-106.
19. Ali HH, Lien CA, Witkowski T, et al. Efficacy and safety of divided dose administration of mivacurium for a 90-second tracheal intubation. *Journal of Clinical Anesthesia* 1996; **8**: 276-81.
20. Alvarez Rios JJ, Hernandez MV, Baez L, Meza G, Higuera. E, Gomez B. Analysis of the effects of rocuronium**,** mivacurium and succinylcholine for endotracheal intubation**.** *Revista Mexicana de Anestesiología* 1997; **20**: 122-6.
21. Brandom BW, Woelfel SK, Cook DR, Weber S, Powers DM, Weakly JN. Comparison of mivacurium and suxamethonium administered by bolus and infusion. *British Journal of Anaesthesia* 1989; **62**: 488-93.
22. Dahaba AA, Schweitzer E, Fitzgerald RD, Schwarz S. Equi-lasting doses of rocuronium, compared to mivacurium, result in improved neuromuscular blockade in patients undergoing gynecological laparoscopy. *Canadian Journal of Anesthesia* 2001; **48**: 1084-90.
23. Demiroluk IS, Salihoğlu Z, Karaca S, Köse Y. Comparison of bolus or intermittent administration of mivacurium. *Anestezi Dergisi* 2002; **10**: 89-93.
24. Fuentes de Frutos AL, Muriel Villoria C, Romo Cortina MT. Conditions of intubation and neuromuscular block induced by mivacurium: comparison with succinylcholine. *Revista Española de Anestesiología y Reanimación* 1999; **46**: 143-8.

25. Geldner GF, Schweiger S, Hetz W, Rügheimer E. Intubation conditions and circulatory effects 90 seconds after a divided mivacurium dose with three different TIVA induction methods. *Der Anaesthesist* 1995; **44**: 334-8.
26. Giudice G, Tomassini G, Mercuri P, Baggianini A Intubating conditions after three different doses of Mivacurium. *Acta Anaesthesiologica Italica* 1996; **47**: 103-10.
27. Giudice, G, Tomassini, G, Baggianini, A, Sagredini, R. The best priming dose and priming interval for Mivacurium 0.15 mg/kg-1.
Acta Anaesthesiologica Italica 1998; **49**: 141-8
28. Goldhill DR, Whitehead JP, Emmott RS, Griffith AP, Bracey BJ, Flynn PJ. Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia. *British Journal of Anaesthesia* 1991; **67**: 289-95.
29. Hofmockel R, Benad G, Jantschulev S. Comparison of neuromuscular blockade by mivacurium and atracurium. *Anaesthesiologie und Reanimation* 1995; **20**: 4-11.
30. Le Corre F, Plaud B, Benhamou E, Debaene B. Visual estimation of onset time at the orbicularis oculi after five muscle relaxants: application to clinical monitoring of tracheal intubation. *Anesthesia and Analgesia* 1999; **89**: 1305-10.
31. Lee MA, Kim TY, Yang HS. Comparison of onset time of mivacurium by priming principle with succinylcholine during endotracheal intubation. *Korean Journal of Anesthesiology* 1997; **33**: 73-8.
32. Lin SM, Chu YC, Lur JY, et al. The neuromuscular effects of mivacurium in adults with priming technique during nitrous oxide-fentanyl anesthesia: a randomized comparative study with succinylcholine. *Acta Anaesthesiologica Sinica* 1998; **36**: 75-80.
33. Maddineni VR, Mirakhur RK, McCoy EP, Fee JP, Clarke RS. Neuromuscular effects and intubating conditions following mivacurium: a comparison with suxamethonium. *Anaesthesia* 1993; **48**: 940-5.
34. Molbegott L, Baker T. Speed and ease of tracheal intubation: priming with mivacurium compared with succinylcholine. *Canadian Journal of Anesthesia* 1995; **42**: 780-4.
35. Motamed C, Donati F. Intubating conditions and blockade after mivacurium, rocuronium and their combination in young and elderly adults. *Canadian Journal of Anesthesia* 2000; **47**: 225-31.
36. Naguib M. Different priming techniques, including mivacurium, accelerate the onset of rocuronium. *Canadian Journal of Anesthesia* 1994; **41**: 902-7.
37. Pendeville PE, Laloyaux P, Fraselle B, Van Boven MJ. Mivacurium chloride for short laparoscopic procedures. *Acta Anaesthesiologica Belgica* 1995 ; **46** : 161-8.

38. Pendeville PE, Lois F, Scholtes JL. A comparison of intubation conditions and time-course of action with rocuronium and mivacurium for day case anaesthesia. *European Journal of Anaesthesiology* 2007; **24**: 546-50.
39. Pino RM, Ali HH, Denman WT, Barrett PS, Schwartz A. A comparison of the intubation conditions between mivacurium and rocuronium during balanced anesthesia. *Anesthesiology* 1998; **88**: 673-8.
40. Shanks CA, Fragen RJ, Pemberton D, Katz JA, Risner ME. Mivacurium-induced neuromuscular blockade following single bolus doses and with continuous infusion during either balanced or enflurane anesthesia. *Anesthesiology* 1989; **71**: 362-6.
41. Tang J, Joshi GP, White PF. Comparison of rocuronium and mivacurium to succinylcholine during outpatient laparoscopic surgery. *Anesthesia and Analgesia* 1996; **82**: 994-8.
42. Türkmen A, Altan A, Turgut N, et al. Comparison of the clinical duration of action and the intubating conditions of mivacurium with succinylcholine and rocuronium during balanced anaesthesia. *Türk Anesteziyoloji ve Reanimasyon Derneği Dergisi* 2004; **32**: 85-90.
43. Van Aken H, Ory JP, Vandermeersch E, Vertommen JD, Crul JF. Intubating conditions and neuromuscular effects of mivacurium during propofol-alfentanil anaesthesia. *Acta Anaesthesiologica Scandinavica Supplementum* 1995;**106**: 26-9.
44. Vanacker BF, Geerts E, Coppens S, van Iersel M. A comparison of neuromuscular effects, tracheal intubating conditions, and reversibility of rapacuronium versus mivacurium in female patients. *Anesthesia and Analgesia* 2002; **94**: 876-8.
45. Wierda JM, Hommes FD, Nap HJ, van den Broek L. Time course of action and intubating conditions following vecuronium, rocuronium and mivacurium. *Anaesthesia*. 1995; **50**: 393-6.
46. Wrigley SR, Jones RM, Harrop-Griffiths AW, Platt MW. Mivacurium chloride: a study to evaluate its use during propofol-nitrous oxide anaesthesia. *Anaesthesia* 1992; **47**: 653-7.
47. Xia Y, Haddad GG. Ontogeny and distribution of opioid receptors in the rat brainstem. *Brain Research* 1991; **549**: 181-93.
48. Mertens MJ, Olofsen E, Engbers FH, Burm AG, Bovill JG, Vuyk J. Propofol reduces perioperative remifentanil requirements in a synergistic manner: response surface modeling of perioperative remifentanil-propofol interactions. *Anesthesiology* 2003; **99**: 347-59.
49. Abou-Arab MH, Heier T, Caldwell JE. Dose of alfentanil needed to obtain optimal intubation conditions during rapid-sequence induction of anaesthesia with thiopentone and rocuronium. *British Journal of Anaesthesia*

50. Vanlinthout LEH, Booij LDHJ, van Egmond J, Robertson EN. Age related differences in magnitude and complete recovery of mivacurium induced neuromuscular block. *Anesthesiology* 1995: **83**: A897.
51. Dahaba AA, Rehak PH, List WF. A comparison of mivacurium infusion requirements between young and elderly adult patients. *European Journal of Anaesthesiology* 1996; **13**: 43-8.
52. Meydan B, Çelik M, Orhon ZN, Devrim S. Pharmacodynamic features of atracurium, mivacurium and rocuronium in the elderly patients. *Türk Anesteziyoloji ve Reanimasyon Cemiyeti Mecmuası* 2002; **30**: 27-32
53. Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. *Anesthesiology* 1999; **90**: 1502-16.
54. Scott JC, Stanski DR. Decreased fentanyl and alfentanil dose requirements with age. A simultaneous pharmacokinetic and pharmacodynamic evaluation. *Journal of Pharmacology and Experimental Therapeutics* 1987; **240**: 159-66.
55. Vanlinthout LE, Booij LH, van Egmond J, Robrtson EN. The effect of aging on gender related differences in magnitude and onset of mivacurium induced neuromuscular block. *Anesthesiology* 1996; **85**: A819.
56. Heier T, Feiner JR, Wright PM, Ward T, Caldwell JE. Sex-related differences in the relationship between acceleromyographic adductor pollicis train-of-four ratio and clinical manifestations of residual neuromuscular block: a study in healthy volunteers during near steady-state infusion of mivacurium. *British Journal of Anaesthesia* 2012; **108**: 444-51.
57. Xue FS, Tong SY, Liao X, Liu JH, An G, Luo LK. Dose-response and time course of effect of rocuronium in male and female anesthetized patients. *Anesthesia and Analgesia* 1997; **85**: 667-71.
58. Glass PS, Bloom M, Kearse L, et al. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane and alfentanil in healthy volunteers. *Anesthesiology* 1997; **86**: 836–47.
59. Sarton E, Olofsen E, Romberg R, et al. Sex differences in morphine analgesia: an experimental study in healthy volunteers. *Anesthesiology* 2000; **93**:1245–54.
60. Silverman DG, Brull SJ. Depth of block after divided doses of mivacurium spaced 60 seconds apart. *Anesthesia and Analgesia* 1993; **77**: 164-7.
61. Brandom BW, Meretoja OA, Simhi E, et al. Age related variability in the effects of mivacurium in paediatric surgical patients. *Canadian Journal of Anesthesia* 1998; **45**: 410-6.
62. Fiset P, Donati F, Balendran P, Meistelman C, Lira E, Bevan DR. Vecuronium is more potent in Montreal than in Paris. *Anesthesia and Analgesia* 1991; **38**: 717-21.

63. Vanlinthout LE, van Egmond J, de Boo T, Lerou JG, Wevers RA, Booij LH. Factors affecting magnitude and time course of neuromuscular block produced by suxamethonium. *British Journal of Anaesthesia* 1992; **69**: 29-35.
64. Østergaard D, Ibsen M, Skovgaard L, Viby-Mogensen J. Plasma cholinesterase activity and duration of action of mivacurium in phenotypically normal patients. *Acta Anaesthesiologica Scandinavica* 2002; **46**: 679-83.
65. Gergis SD, Sokoll MD, Mehta M, Kemmotsu O, Rudd GD. Intubation conditions after atracurium and suxamethonium. *British Journal of Anaesthesia* 1983; **55 Suppl 1**: 83-6S.
66. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Statistics in Medicine* 2002; **21**:1559-73.
67. Lambert PC, Sutton AJ, Abrams KR, Jones DR. A comparison of summary patient-level covariates in meta-regression with individual patient data meta-analysis. *Journal of Clinical Epidemiology* 2002; **55**: 86-94.
68. Dieck T, Steffens J, Sander B, et al. Propofol, remifentanil and mivacurium: fast track surgery with poor intubating conditions. *Minerva Anestesiologica* 2011; **77**: 585-91.

Table 1 Variables in 29 included RCTs with 60 treatment groups of 1052 participants. Values are number, mean or [range].

Reference	Mivacurium dose (μg.kg^{-1})	Hypnotic	Opioid	N_2O	Time to intubation (s)	Age (years)	Excellent / total intubations
Ali et al. [19]	250	midazolam and propofol	fentanyl	no	92	39	51/91
Alvarez-Ríos et al. [20]	250	midazolam and thiopentone	none	no	90	34	6/20
Brandom et al. [21]	250	thiopentone	fentanyl	yes	120	[18-70]	9/14
Dahaba et al. [22]	200	propofol	fentanyl	no	114	37	16/30
Demiroluk et al. [23]	250	thiopentone	fentanyl	yes	138	38	6/20
	250*				134	35	10/20
Fuentes de Frutos et al. [24]	250	droperidol and thiopentone	fentanyl	no	60	49	33/45
Geldner et al. [25]	250	etomidate	alfentanil	yes	90	No data	7/12
	250	propofol			90		6/11
	250	metohexitone			90		8/12
Giudice et al. [26]	150	propofol	none	no	120	[19-53]	3/15
	200				102	[19-53]	2/15
	150*				78	[19-53]	0/15
Giudice et al. [27]	150*	propofol	none	yes	115	[16-63]	2/10
	150*				126	[16-63]	0/10
	150*				112	[16-63]	2/10
	150*				111	[16-63]	2/10
	150*				109	[16-63]	2/10
	150*				89	[16-63]	2/10

Goldberg et al. [11]	200 250	thiopentone	fentanyl	yes	120 120	32 28	7/10 7/10
Goldhill et al. [28]	150 150 200 200 200†	propofol	alfentanil	yes	150 120 150 120 120	28 27 28 26 28	4/9 2/9 6/9 3/9 5/9
Hofmockel et al. [29]	150 85*	propofol	alfentanil	yes	72 72	34 36	7/12 7/12
Le Corre et al. [30]	200	propofol	fentanyl	no	99	55	22/30
Lee et al. [31]	270* 270	midazolam	fentanyl	none	90 75	35 35	10/12 11/12
Lin et al. [32]	250 250*	thiopentone	fentanyl	yes	97 98	36 37	12/20 11/20
Maddineni et al. [33]	150 200 200	thiopentone	fentanyl	yes	120 120 150	28 30 29	0/9 7/20 8/20
Molbegott et al. [34]	75* 150* 215*	midazolam and thiopentone	fentanyl	yes	106 90 82	37 39 34	3/14 7/14 7/14
Motamed et al. [35]	150 200 200	propofol	fentanyl	no	170 150 150	40 44 74	4/14 7/14 11/15
Naguib et al. [36]	150	midazolam and thiopentone	fentanyl	yes	164	32	6/10

	150*				103	36	5/10
Pendeville et al. [37]	150 170 190	thiopentone	fentanyl	yes	188 220 159	38 36 35	6/10 7/10 9/10
Pendeville et al. [38]	150	thiopentone	sufentanil	yes	285	25	23/25
Pino et al. [39]	250*	midazolam and propofol	fentanyl	no	90	[16-65]	19/30
Shanks et al. [40]	150 250	thiopentone	fentanyl	yes	120 120	45 41	17/36 27/36
Tang et al. [41]	200	midazolam and thiopentone	fentanyl	no	90	30	13/25
Türkmen et al. [42]	250	propofol	fentanyl	no	146	44	11/20
Van Aken et al. [43]	110 150 190	propofol	alfentanil	no	75 75 75	40 43 38	4/19 5/20 6/21
Vanacker et al. [44]	200	propofol	alfentanil	no	108	30‡	5/20
Wierda et al. [45]	160	thiopentone	fentanyl	yes	90	33	5/20
Wrigley et al. [46]	150 150	propofol	alfentanil	yes	120 150	30 30	5/16 10/16

* mivacurium dose divided; † injected over 30s; ‡ data obtained from the author

Table 2 Assessments of risks of bias in seven methodological domains for the included studies. Scores for each item are ranked as yes (+), no (-) or unsure (?), reflecting low, high or unclear risk of bias. Other bias risks included unclear physical health status of participants and insufficient detail to use the Goldberg scale for intubation conditions [11].

Table 3 The coefficients for variables in the final model that estimated the probability of excellent intubation conditions, logit (P) = a_0 + (a_1 x ln (mivacurium dose)) + (a_2 x use of opioids) + (a_3 x time to intubation) + (a_4 x ln (age)) + a_5 (time to intubation x ln (age)). Values are mean (SD) [95% CI].

Variable	Coefficient	Coefficient value		p
		Bayesian	Classical parametric	
Constant	a_0	-13.02 (2.57) [-18.06 to -8.92]	-15.01 (4.96) [-24.93 to -5.09]	0.002
ln(dose of mivacurium); $mg.kg^{-1}$	a_1	1.57 (0.47) [0.72-2.52]	1.51 (0.53) [0.87-2.15]	< 0.001
Use of opioids; 'yes' = 1 'no' = 0	a_2	1.67 (0.49) [0.76-2.72]	1.79 (0.29) [1.21-2.37]	< 0.001
Time to intubation; min	a_3	5.05 (0.50) [4.07-6.04]	5.98 (1.35) [3.28-8.68]	0.001
ln(age); yr	a_4	3.10 (0.42) [2.28-3.81]	3.52 (0.87) [1.78-5.26]	< 0.001
Time to intubation x ln(age)	a_5	-0.99 (0.14) [-1.66 to -0.71]	-1.19 (0.43) [-2.05 to -0.33]	< 0.001
n		60	60	
I^2		Not applicable	34.23	
R^2		Not applicable	72.89	

I^2, heterogeneity across studies (%); n, number of treatment groups included in the analysis; R^2, coefficient of determination (%).

Table 4 Change in the logit (Δ logit) and odds ratios for the probability of excellent intubation conditions with doubling mivacurium dose, use of opioids and increasing the delay before intubation. Values are mean (SD) [95% CI] for the Δ logit and median (95% CI) for the odds ratio.

Change in variable	**Δ Logit (probability EIC)**	**Odds ratio**	**p**
Doubling mivacurium dose, e.g. from 0.1 to 0.2 $mg.kg^{-1}$	1.09 (0.32) [0.50-1.75]	3.14 (1.65-5.73)	< 0.001
Adding opioids to the induction sequence	1.67 (0.49) [0.76-2.72]	5.99 (2.14-15.18)	< 0.001
Doubling delay before intubation, from 1 to 2 min			
25 yr old	1.88 (0.07) [1.79-2.05]	6.55 (6.01-7.74)	< 0.001
70 yr old	0.79 (0.08) [0.70-0.99]	2.17 (2.01-2.69)	< 0.001

Figure 1 Flowchart of retrieved, excluded and analysed trials.

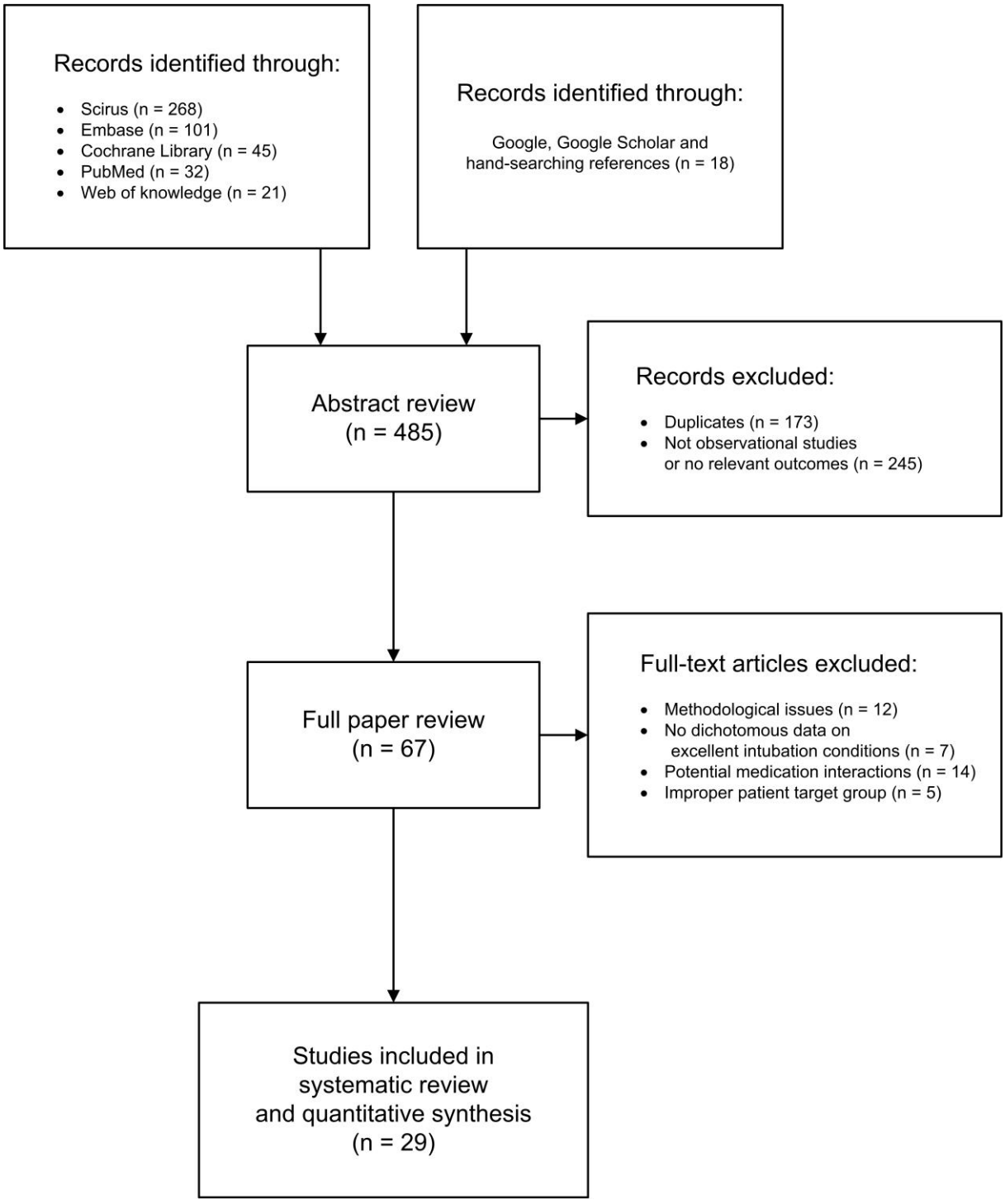

Figure 2 Relationship between mivacurium dose (mg.kg^{-1}, log scale) and the probability of excellent intubation conditions (%, logit scale) in 57 treatment groups. Each circle represents a treatment group, the diameter of which is proportional to the number of participants. Some of the treatment groups are not displayed as they are overlapped by others.

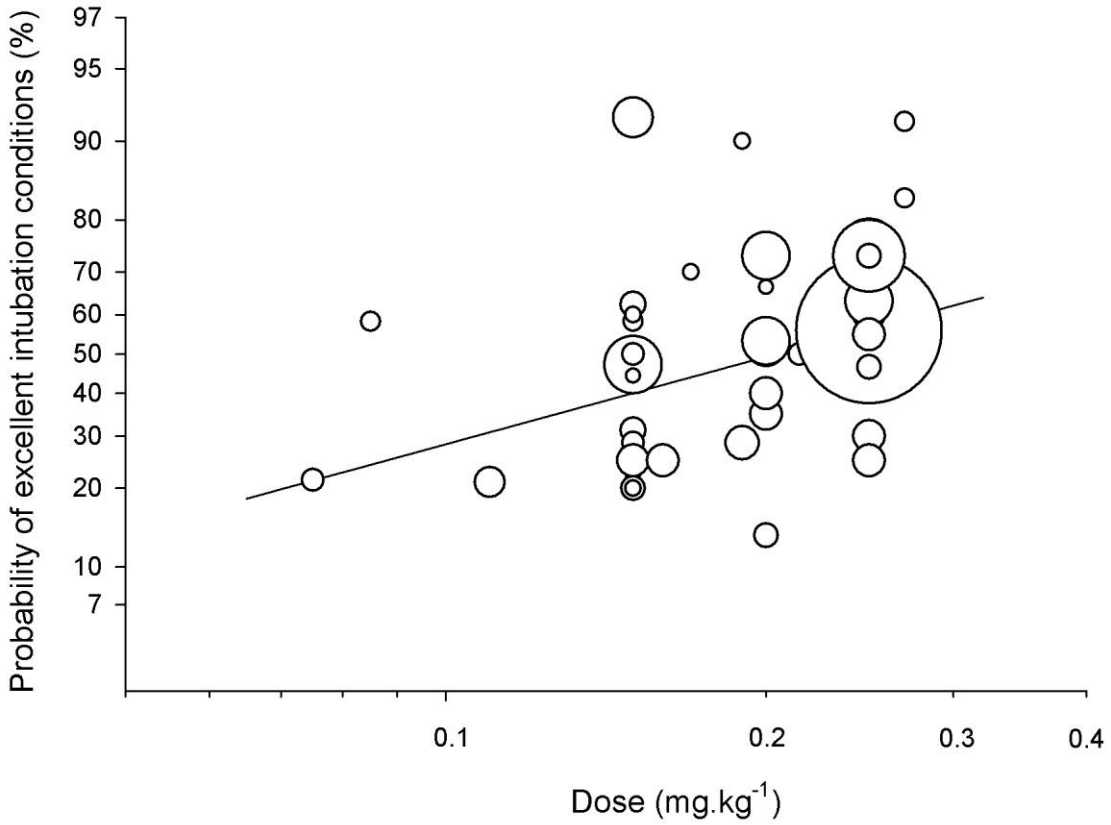

Figure 3 Scatter plot comparing the number of excellent intubation conditions observed versus that expected from the meta-regression model (log scale) in 57 treatment groups. Equal numbers of observed and expected are plotted on the line of identity (diagonal). Some of the treatment groups are not displayed as they are overlapped by others.

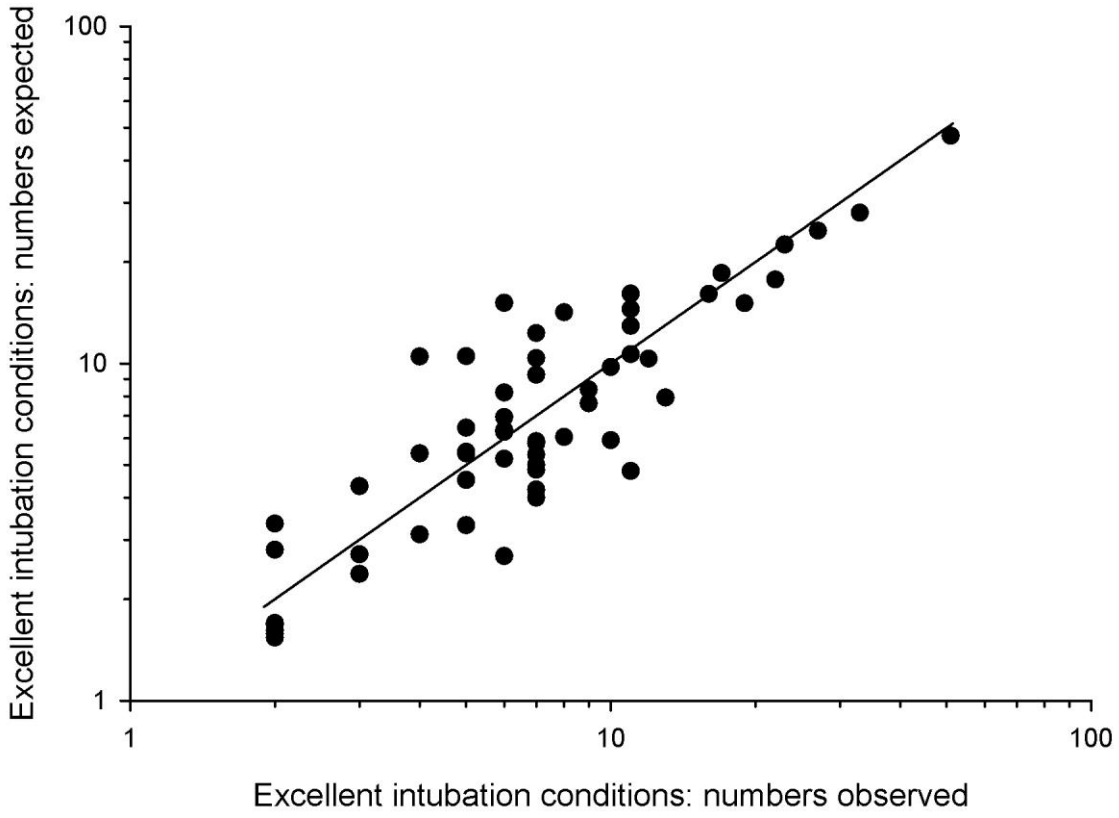

Figure 4 Simulation of the effect of opioids on the relationship between mivacurium dose ($mg.kg^{-1}$, log scale) and the probability of excellent intubation conditions (%, logit scale) in 45 yr old subjects intubated two minutes after mivacurium injection. Dose-response curves without (— · · — · ·) and with an opioid (————). The grey areas are their 95% CIs.

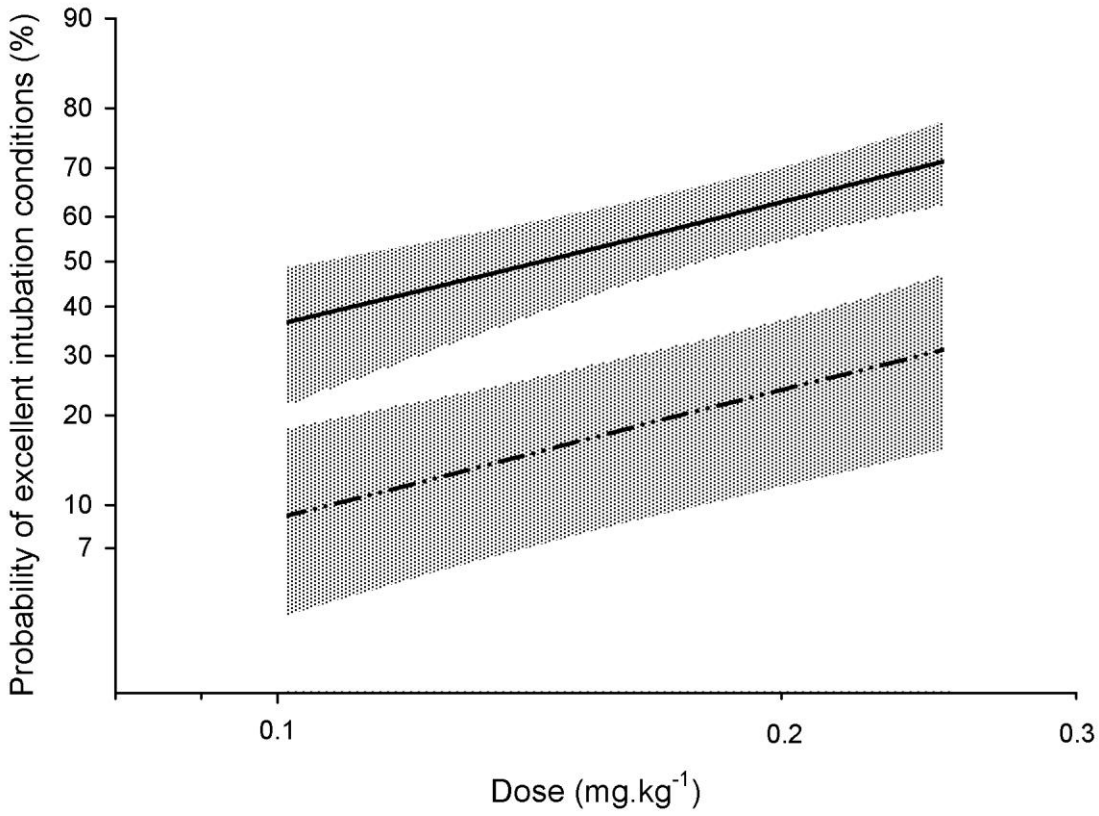

Figure 5 Relationship between mivacurium dose (mg.kg^{-1}, log scale) and the mean probabilities of excellent intubation conditions (%, logit scale) one and two minutes after mivacurium injection: for 25 year old subjects, ——·· and ————, respectively; and for 74 year old subjects, – · – · – · and – – – –, respectively. The 95% CIs have been omitted for clarity.