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Short title: Mivacurium systematic review

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:

$$\text{logit } (P_i) = a_0 + a_1 X_{1i} + a_2 X_{2i} + ... + a_n X_{ni} + \varepsilon \qquad (1)$$

where: P_i is the proportion of participants with excellent intubation conditions in group 'i'; logit $(P_i) = \ln (P_i/(1-P_i)) = \ln (\text{odds } P_i)$, 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:

$$\text{logit}(P) = a0 + (a_1 X_1) + (a_2 X_2) + (a_3 X_3) + (a_4 X_4) + (a_5 X_3 \times X_4) \qquad (3)$$

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

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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

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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	N₂O	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

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

Study	Dose	Induction agent	Opioid				
	150*				103	36	5/10
	150				188	38	6/10
Pendeville et al. [37]	170	thiopentone	fentanyl	yes	220	36	7/10
	190				159	35	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	thiopentone	fentanyl	yes	120	45	17/36
	250				120	41	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
	110				75	40	4/19
Van Aken et al. [43]	150	propofol	alfentanil	no	75	43	5/20
	190				75	38	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	propofol	alfentanil	yes	120	30	5/16
	150				150	30	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].

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessor to treatment (detection bias)	Blinding of outcome assessor to NM block (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ali et al. [19]	+	+	+	+	+	+	+
Alvarez-Ríos et al. [20]	?	?	+	?	+	+	+
Brandom et al. [21]	?	?	?	-	+	+	+
Dahaba et al. [22]	+	+	+	?	+	+	+
Demiroluk et al. [23]	?	?	?	-	+	+	?
Fuentes et al. [24]	?	?	?	?	+	+	?
Geldner et al. [25]	?	?	?	-	+	+	+
Giudice et al. [26]	?	?	?	?	+	+	+
Giudice et al. [27]	?	?	?	-	+	+	+
Goldberg et al. [11]	?	?	+	?	+	+	+
Goldhill et al. [28]	?	?	?	?	+	+	+
Hofmockel et al. [29]	?	?	?	-	+	+	+
Le Corre et al. [30]	?	?	+	-	+	?	?
Lee et al. [31]	?	?	?	-	+	+	+
Lin et al. [32]	?	?	?	-	+	+	+
Maddineni et al. [33]	?	?	?	?	+	+	+
Molbegott et al. [34]	?	?	+	+	+	+	+
Motamed et al. [35]	?	?	+	?	+	+	+
Naguib et al. [36]	?	+	+	-	+	+	+
Pendeville et al. [37]	?	?	+	-	+	+	?
Pendeville et al. [38]	?	?	?	-	+	+	?
Pino et al. [39]	+	?	+	+	+	+	+
Shanks et al. [40]	+	?	?	?	+	+	?
Tang et al. [41]	?	?	?	+	+	+	+
Türkmen et al. [42]	?	?	+	-	+	+	+
Vanacker et al. [43]	?	?	+	-	+	+	+
Van Aken et al. [44]	?	?	+	?	+	+	?
Wierda et al. [45]	?	?	+	?	+	+	+
Wrigley et al. [46]	?	?	?	?	+	+	+

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

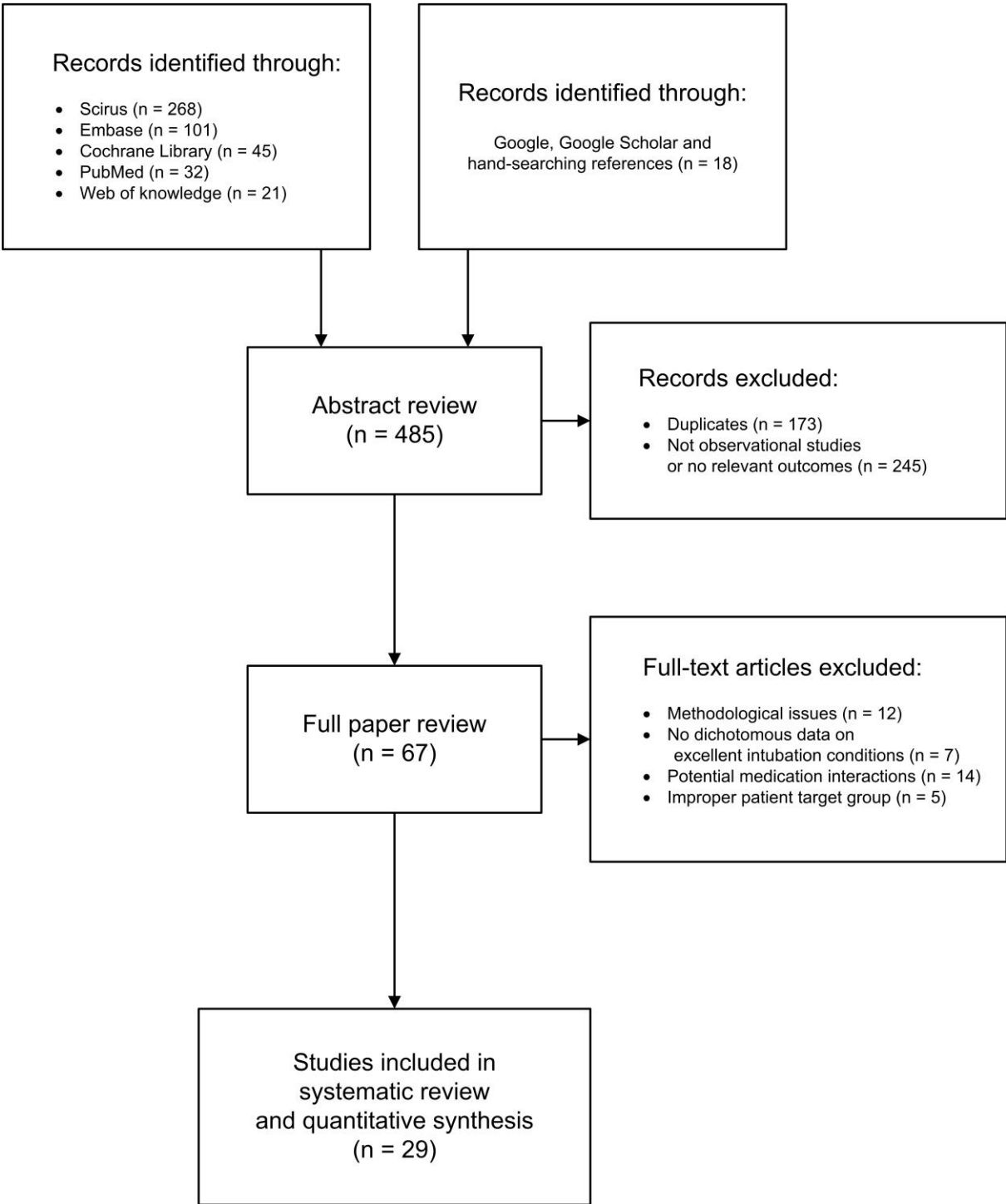| Variable	Coefficient	Coefficient value		p
		Bayesian	**Classical parametric**	
Constant	a_0	-13.02 (2.57) [-18.06 to -8.92]	-15.01 (4.96) [-24.93 to -5.09]	0.002
ln(dose of mivacurium); mg.kg^{-1}	a_1	1.57 (0.47) [0.72-2.52]	1.51 (0.53) [0.87-2.15]	< 0.001
Use of opioids; 'yes' = 1 'no' = 0	a_2	1.67 (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.

Records identified through:
- Scirus (n = 268)
- Embase (n = 101)
- Cochrane Library (n = 45)
- PubMed (n = 32)
- Web of knowledge (n = 21)

Records identified through:

Google, Google Scholar and
hand-searching references (n = 18)

Abstract review
(n = 485)

Records excluded:
- Duplicates (n = 173)
- Not observational studies
  or no relevant outcomes (n = 245)

Full paper review
(n = 67)

Full-text articles excluded:
- Methodological issues (n = 12)
- No dichotomous data on
  excellent intubation conditions (n = 7)
- Potential medication interactions (n = 14)
- Improper patient target group (n = 5)

Studies included in
systematic review
and quantitative synthesis
(n = 29)

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.
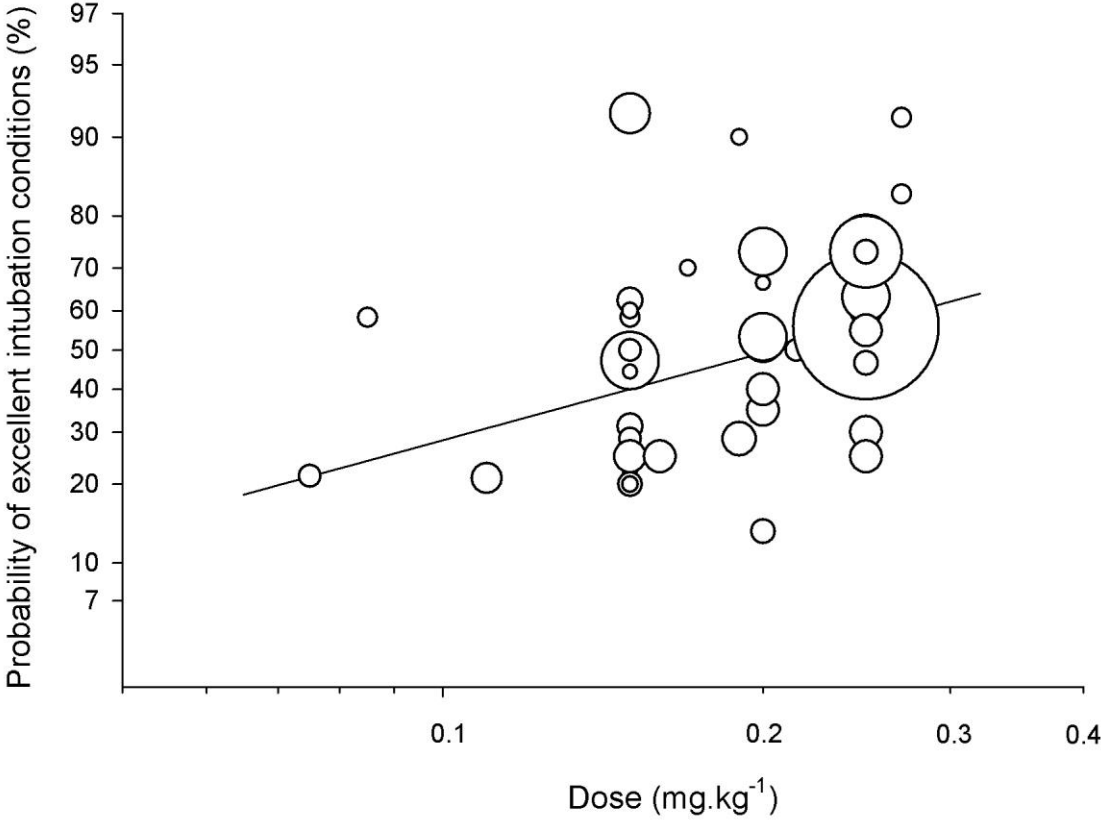
Figure 3 Scatter plot comparing the number of excellent intubation conditions observed versus that expected from the meta-regression model (log scale) in 57 treatment groups. Equal numbers of observed and expected are plotted on the line of identity (diagonal). Some of the treatment groups are not displayed as they are overlapped by others.
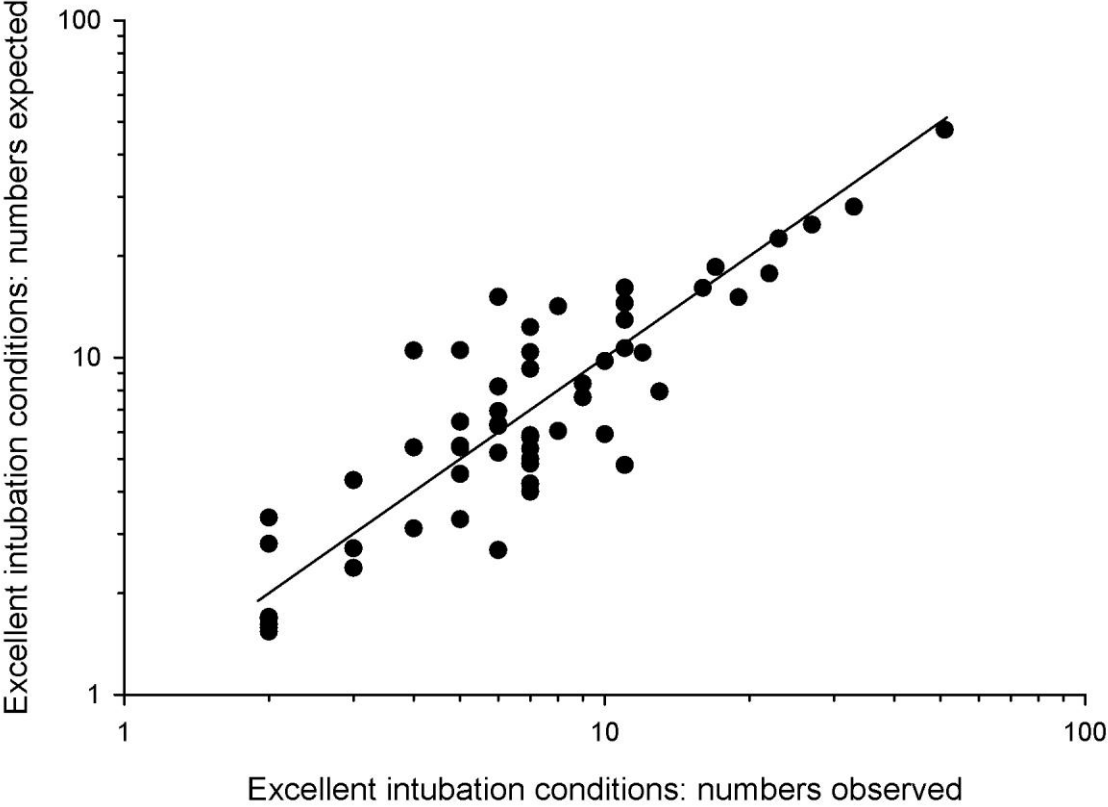
Figure 4 Simulation of the effect of opioids on the relationship between mivacurium dose (mg.kg^{-1}, log scale) and the probability of excellent intubation conditions (%, logit scale) in 45 yr old subjects intubated two minutes after mivacurium injection. Dose-response curves without (━ · · ━ · ·) and with an opioid (━━━━━). The grey areas are their 95% CIs.
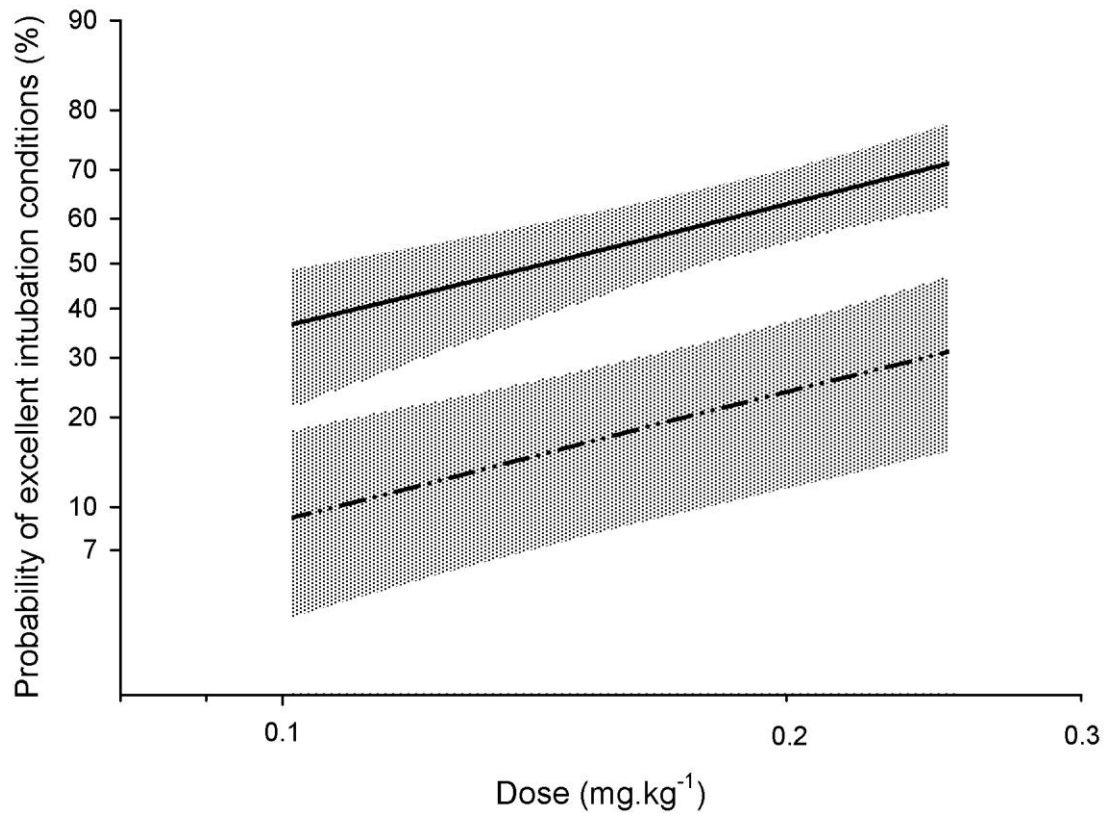
Figure 5 Relationship between mivacurium dose (mg.kg^{-1}, log scale) and the mean probabilities of excellent intubation conditions (%, logit scale) one and two minutes after mivacurium injection: for 25 year old subjects, — · · — · · and ——————, respectively; and for 74 year old subjects, — · — · — · and — — — — —, respectively. The 95% CIs have been omitted for clarity.