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REVIEW ARTICLE

Neuromuscular monitoring and postoperative residual curarization: a meta-analysis

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We conducted a meta-analysis to examine the effect of intraoperative monitoring of neuromuscular function on the incidence of postoperative residual curarization (PORC). PORC has been considered present when a patient has a train-of-four (TOF) ratio of <0.7 or <0.9. We analysed data from 24 trials (3375 patients) that were published between 1979 and 2005. We excluded data on mivacurium from this meta-analysis because only three studies had examined the incidence of PORC associated with its use. Long- and intermediate-acting neuromuscular blocking drugs had been given to 662 and 2713 patients, respectively. Neuromuscular function was monitored in 823 patients (24.4%). A simple peripheral nerve stimulator was used in 543 patients, and an objective monitor was used in 280. The incidence of PORC was found to be significantly lower after the use of intermediate neuromuscular blocking drugs. We could not demonstrate that the use of an intraoperative neuromuscular function monitor decreased the incidence of PORC.

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Incomplete recovery from non-depolarizing neuromuscular blocking agents [postoperative residual curarization (PORC)[17]] continues to be a common problem in modern post-anaesthesia care units (PACUs).[3 11 15 27 29 36 43] Given that PORC is a potentially preventable patient safety problem,[20 22] it is important to find ways to reduce its incidence. Editorial opinion has suggested that the most salient factor contributing to PORC is failing to use objective or quantitative intraoperative monitoring of neuromuscular function.[21 53]

The proposition that the proper use of an intraoperative neuromuscular monitor should prevent or at least reduce the incidence of PORC appears reasonable. Unfortunately, objective monitors that can measure the train-of-four (TOF) ratio in real time are not available in most operating rooms. Subjective evaluation of the evoked muscular response to TOF stimulation is extremely inaccurate.[54] In addition, many practitioners are unclear about the current standards that define adequate recovery from neuromuscular blockade.[51] There is also conflicting evidence as to the utility of conventional peripheral nerve stimulators (PNSs) in preventing PORC.[24 26 27 29 43 45 48 50 52] In fact, several studies have suggested that the use of a PNS is not associated with a reduced incidence of PORC.[24 29 43 48]

In view of the heterogeneity of the findings in published reports, we conducted a meta-analysis and review of studies to better understand the impact of intraoperative monitoring of neuromuscular function on the incidence of PORC. We combined the results from multiple small and moderate sized studies to increase the statistical power[28] of our study and also analysed the potentially confounding factors in these studies.

Methods

We conducted an electronic search of the literature in the National Library of Medicine's PubMed database (from 1964 to June 2006), the Cochrane Controlled Trials

† *Declaration of interest*. Drs Naguib and Kopman have worked as consultants on an *ad hoc* basis with Organon Pharmaceuticals (Roseland, NJ, USA) and Avera Pharmaceuticals (San Diego, CA, USA). They are currently involved with multicentre phase IIIa studies of sugammadex.

Register, and the ISI Web of Knowledge (from 1975 to 2006). For our search, we used combinations of the following key and text words: curarization, postoperative, neuromuscular blockers, muscle relaxants, and residual block. We also manually searched the references cited in published papers. All potentially relevant reports were reviewed independently by two investigators (M.N. and A.F.K.).

The primary outcome used for the meta-analysis was the incidence of PORC. PORC has been considered present when a patient has a TOF ratio of <0.7 or <0.9. Historically, a TOF ratio of 0.7 was used as an indication of adequate recovery of neuromuscular blockade. Current evidence indicates that we need to ensure a recovery of TOF ratio to 0.9 rather than to 0.7.[20 22 40] We included all human adult studies published in English, peer-reviewed literature in which the outcome was rendered as the fraction of patients who had PORC. We initially identified 50 potentially relevant studies and 26 studies were subsequently excluded from meta-analysis. We did not include abstracts, editorials, studies of cardiac or paediatric patients, or studies in which primary outcome variables could not be determined. No duplicate population was included in the analysis.

The quality of individual studies was graded according to the criteria that make up the previously validated Jadad 5-point scale.[34] These criteria are randomization (0–2 points), double-blinding (0–2 points), and a description of withdrawals or dropouts (0–1 point). The maximum score that can be assigned to any study is 5 and the minimum is 0. The scores for all studies included in this meta-analysis ranged from 1 to 4. Detailed information for each study was entered into an Excel spreadsheet (Microsoft Corporation, Redmond, WA) by one investigator (M.N.) and independently checked by another (A.F.K.). Disagreements regarding the correct categorization of data were resolved by discussion.

The data extracted from each article were the first author's name, year of article's publication, Jadad score,[34] number of patients, body weights, the type of neuromuscular blocker used (long-, intermediate, or short-acting), total dose of neuromuscular blocking drugs used, duration of anaesthesia, types of anaesthesia (total intravenous anaesthesia, inhalational anaesthesia, or both), the use of an intraoperative neuromuscular function monitor, type of the neuromuscular function monitor used (objective or simple), the use of antagonism, and the incidence of PORC (in patients with a TOF ratio of <0.7 or <0.9). We converted the dose of each neuromuscular blocker to its respective 95% effective dose and expressed them as ED_{95} (mg) kg^{-1} h^{-1}.

Statistical analyses

As noted by Etzel and Guerra,[23] 'The concept of the combination of results from significance tests, across studies, to obtain consensus is not new'. However, the synthesis of estimates published in the literature of non-comparative studies is less prevalent. The methods of Wolfe, Mantel-Haenszel, and Peto are popular for performing fixed effects meta-analyses, but these methods are not structured to accommodate non-comparative studies. The purpose of this analysis is to combine, in a systematic fashion, the estimated incidence rates of PORC from the available literature including both comparative and non-comparative studies. Separate analyses were conducted to combine the findings of studies defining this incidence rate by a TOF ratio of <0.70 and for studies defining the rate as a TOF ratio of <0.90.

Egger and colleagues[18] state 'In meta-analysis the weight given to each study generally reflects the statistical power of the study, the larger the study, the greater the weight'. However, it has been shown that combining the study findings by weighting each estimate by the inverse of the sampling variance of the estimate is optimal, and weighting in general provides more precise results.[30 31] The Freeman–Tukey double-arcsine variance-stabilizing transformation[25] was used to normalize the study findings before combining the data.

This analysis relies heavily on the findings of cohort studies. Sackett[49] maintains that confounding is the most important threat to the validity of results from cohort studies. We acknowledge that a confounding factor such as patient population could produce significant between-studies variability. An important aspect of any meta-analysis is an investigation of the inconsistency of the published findings. With the normalized data, study heterogeneity was assessed using both Cochran's Q χ^2 test[14] and the inconsistency measure I^2 suggested by Higgins[32] which measures the proportion of between-studies variability that cannot be explained by chance. In the presence of significant heterogeneity, we used the random effects model approach to combine estimates to explicitly account for said inconsistency; otherwise, a fixed effects model was employed. The pooled incidence rate estimates and the corresponding 95% confidence intervals were achieved using the inverse of the Freeman–Tukey double arcsine transformation suggested by Miller.[44] Confidence intervals within studies were achieved using the exact binomial method. Group differences were assessed using a two-tailed pooled *t*-test on the basis of the normalized data and the weights derived from random-effects model. The relationship of TOF ratio recovery with the use of intraoperative neuromuscular monitor adjusted for other covariates such as anaesthetic technique was assessed by random-effects weighted regression models. Random-effects weighted regression models were also employed to investigate changes in the reported incidence of PORC over time. All analyses were conducted using SAS Release 9.1 (SAS Institute Inc., Cary, NC, USA). The appendix contains the equations used to conduct this analysis.

Results

We analysed data from 24 studies (13 randomized and 11 observational studies) that were published between 1979 and 2005[1–4 8 10 11 15 24 26 27 29 33 36 38 39 41 42 45 46 48 50 52 55] (Table 1). A total of 3375 patients were included in these studies.

We excluded mivacurium from this meta-analysis because only three studies[6 12 39] had reported an incidence of PORC with its use. Cammu and colleagues[12] did not present an overall incidence of PORC after mivacurium in their report. The weighted rate of PORC of mivacurium defined as a TOF ratio <0.7 as reported in the two remaining studies was 5.9%.[6 39] Bevan and coauthors[6] did not report the incidence of PORC for TOF<0.9. The incidence of PORC defined as a TOF ratio <0.9 was 5.7% as reported by Kopman and colleagues.[39]

Long- and intermediate-acting neuromuscular blocking drugs were given to 662 and 2713 patients, respectively. TIVA was the sole anaesthetic technique used in seven trials; different inhalational anaesthetics were the sole technique in another 10 trials; and both techniques were used in the remaining 7 trials.

In 23 studies, 524 patients received TIVA as the sole anaesthetic technique compared with 2779 patients who received only inhalational anaesthetics. These details were not provided in one study.[55] Anticholinesterases were administered to a subset of patients in 23 studies. Antagonism of neuromuscular blockade was used in 2095 patients (62.1%) in the form of neostigmine (1493 patients) and pyridostigmine (602 patients), respectively. Neuromuscular function was monitored in 823 patients (24.4%). A conventional PNS unit (subjective visual/tactile evaluation of responses to evoked stimulation) was used in 543 patients, and an objective monitor (the TOF ratio is displayed digitally in real time) was used in 280 patients. The incidence of PORC defined as a TOF ratio <0.7 was reported in 23 trials, whereas a TOF ratio of <0.9 was reported in 15 trials.

The pooled estimated incidence of PORC (TOF<0.7 or TOF<0.9) by the type of muscle relaxant (long- or intermediate-acting) (Table 2) shows that within each sub-population, significant heterogeneity exists, and the differences between trials were very large (Higgins' inconsistency is $>85\%$ for each sub-population). Thus, we used a random-effects model to pool our study findings.

The results show that the use of neuromuscular function monitoring did not have any significant effect on the incidence of PORC for any of the sub-population comparisons (Table 3, Figs 1 and 2). Although the pooled rate of PORC is always higher if the patient is not monitored, the difference was not statistically significant from that in the patient who is monitored (Table 3).

A weighted random-effects linear model was fitted to the normalized data to investigate the effect of using intraoperative neuromuscular monitors on the incidence of PORC, while adjusting for the effects of neuromuscular blocker type (long or intermediate) as well as anaesthetic technique (TIVA, inhalational, or both). The weighted random-effects linear model disclosed that for patients who had a TOF of <0.7 ($R^2=0.28$), only the use of intermediate neuromuscular blocking drugs was associated with a significantly lower incidence of PORC compared with that seen with long-acting drugs ($P=0.0082$). Neither the use of an intraoperative neuromuscular monitor ($P=0.3100$) nor the anaesthetic technique (TIVA or inhalation) had any significant effect on the incidence of PORC ($P=0.7894$). For patients who had a TOF ratio of <0.9 ($R^2=0.70$), the use of both intermediate neuromuscular blocking drugs ($P=0.0003$) and TIVA ($P=0.0007$) was associated with a low incidence of PORC. However, the use of an intraoperative neuromuscular monitor ($P=0.2173$) was also an insignificant factor in predicting the incidence of PORC.

When analysed by year of study, with PORC defined by a TOF ratio of <0.7, neither long-acting ($P=0.52$) nor intermediate-acting ($P=0.97$) neuromuscular blocking drugs exhibited a significant relationship with the incidence of PORC (Fig. 3). The average incidence of PORC in studies involving long-acting neuromuscular blocking drugs decreased insignificantly over time whereas the average incidence of PORC in the studies involving intermediate-acting neuromuscular blocking drugs was almost constant over time. For studies in which PORC was defined by a TOF ratio of <0.9, the use of intermediate-acting muscle was associated with an insignificant ($P=0.09$) decrease in PORC incidence over time possibly due to an outlier (study L)[38] (Fig. 3). If we were to exclude this study, the P-value would be <0.002. Almost no change in the incidence over time was seen for the studies of long-acting neuromuscular blocking drugs ($P=0.69$).

A sensitivity analysis comparing monitored *vs* non-monitored patients in controlled studies showed that the incidence of PORC (at TOF$<70\%$) was significantly lower in the monitored patients who received long-acting neuromuscular blocking drugs compared with those who were not monitored (Table 4). No significant differences were found with other comparisons. For instance, there were three controlled trials that reported the use of intermediate neuromuscular blocking drugs including that of Pedersen and colleagues[48] which reported an incidence of PORC of 40% in monitored patients compared with an incidence of 15% in non-monitored patients. This anomaly could explain the absence of significant results in patients who received intermediate neuromuscular blocking drugs (Table 4).

A sensitivity analysis comparing the 13 randomized with the 11 observational studies demonstrated a tendency for randomized studies to report a higher incidence of PORC compared with observational studies (six out of the eight comparisons) and it was significantly different in

Table 1 Description of the studies included in the meta-analysis. PORC, postoperative residual curarization; TOF, train-of-four; NR, not reported; NEO, neostigmine. *Data from the year 2004. [§]Intermediate=atracurium and vecuronium. [†]Randomized study

Study	*N*	Neuromuscular blocker	Dose (ED_{95} equivalent kg^{-1} h^{-1})	Intraoperative NM monitoring	Antagonism	Incidence of PORC number (%)		Jadad score[34]
						TOF<0.7	TOF<0.9	
Viby-Mogensen, 1979[55]	11	d-tubocurarine	0.397	None	NEO	30 (41.7)	52 (72.2)	1
	28	Gallamine	0.439	None	NEO			
	33	Pancuronium	0.806	None	NEO			
Lennmarken, 1984[42]	48	Pancuronium	0.645	None	NEO	12 (25)	NR	2
Beemer, 1986[4]	100	Different long-acting	NR	None	NEO	21 (21)	40 (40)	2
[†]Andersen, 1988[1]	30	Atracurium	2.320	None	NEO	0 (0)	NR	4
	30	Pancuronium	0.968	None	NEO	6 (20)		
[†]Howardy-Hansen[33]	9	Atracurium	1.401	NR	NEO	0 (0)	NR	3
	10	Gallamine	0.557	NR	NEO	5 (50)	NR	
[†]Pedersen, 1990[48]	20	Pancuronium	0.645	Conventional	NEO	12 (60)	NR	3
	20	Pancuronium	0.597	None	NEO	12 (60)	NR	
	20	Vecuronium	1.169	Conventional	NEO	8 (40)	NR	
	20	Vecuronium	1.101	None	NEO	3 (15)	NR	
[†]Brull, 1991[10]	29	Pancuronium	NR	Conventional	NEO	13 (45)	NR	4
	25	Vecuronium	NR	Conventional	NEO	2 (8)	NR	
[†]Ueda, 1991[52]	30	Pancuronium	0.548	None	NEO	25 (83)	28 (93)	1
	60	Pancuronium	0.613	Conventional	NEO	19 (32)	53 (88)	
[†]Shorten, 1995[50]	20	Pancuronium	0.613	Conventional	NEO	3 (15)	NR	2
	19	Pancuronium	0.726	None	NEO	9 (47)	NR	
Fawcett, 1995[24]	88	[§]Intermediate	NR	Conventional	NEO	14 (16)	74 (84)	3
	62	[§]Intermediate	NR	None	NEO	10 (16)	52 (84)	
[†]Mortensen, 1995[45]	21	Pancuronium	0.903	None	NEO	11 (52)	17 (81)	3
	19	Pancuronium	1.000	Quantitative	NEO	1 (5)	10 (53)	
Kopman, 1996[39]	56	Pancuronium	0.635	Conventional	NEO	2 (4)	36 (64)	2
[†]Fruergaard, 1998[26]	30	Pancuronium	0.694	None	NEO	17 (57)	25 (83)	3
	29	Pancuronium	0.645	Quantitative	NEO	7 (24)	20 (69)	

Continued

Table 1 Continued

Study	*N*	Neuromuscular blocker	Dose (ED_{95} equivalent kg^{-1} h^{-1})	Intraoperative NM monitoring	Antagonism	Incidence of PORC number (%)		Jadad score[34]
						TOF<0.7	TOF<0.9	
†Bissinger, 2000[8]	49	Pancuronium	0.887	None	NEO	10 (20)	NR	1
	27	Vecuronium	1.978	None	NEO	2 (7)	NR	
Baillard, 2000[3]	568	Vecuronium	NR	None (*n*=557) Conventional (*n*=11)	None (*n*=567) NEO (*n*=1)	239 (42)	NR	1
†Hayes, 2001[29]	19	Vecuronium	2.022	Conventional	None (*n*=47)	NR	13 (26)	3
	18	Atracurium	2.121	Conventional	NEO (*n*=101)		6 (12)	
	24	Rocuronium	1.301	Conventional			8 (17)	
	31	Vecuronium	2.022	None			19 (38)	
	32	Atracurium	2.121	None			20 (40)	
	24	Rocuronium	1.301	None			11 (23)	
Kim, 2002[36]	364	Vecuronium	NR	None	Pyridostigmine	90 (25)	NR	2
	238	Rocuronium	NR	None	Pyridostigmine	35 (15)	NR	
†Gatke, 2002[27]	60	Rocuronium	1.430	Quantitative	NEO	1 (2)	9 (15)	3
	60	Rocuronium	1.246	None	NEO	6 (10)	18 (30)	
Cammu, 2002[11]	15	Cisatracurium	1.360	Quantitative	NEO (*n*=11)	0 (0)	0 (0)	2
	15	Rocuronium	1.206	Quantitative	NEO (*n*=14)	1 (7)	1 (7)	
Debaene, 2003[15]	79	Atracurium	0.761	None	None	13 (17)	33 (42)	2
	47	Vecuronium	0.987	None	None	8 (17)	22 (47)	
	400	Rocuronium	0.958	None	None	64 (16)	180 (45)	
†Kopman, 2004[41]	30	Cisatracurium	1.758	Conventional	NEO	0 (0)	2 (7)	2
	30	Rocuronium	1.310	Conventional	NEO	0 (0)	5 (17)	
Murphy, 2005[46]	120	Rocuronium	1.033	Conventional	NEO	9 (8)	38 (32)	2
*Baillard, 2005[2]	218	Different intermediate	1.100	Quantitative (*n*=131)	NEO (*n*=92)	NR	8 (3.5)	1
†Kopman, 2005[38]	20	Cisatracurium	1.627	Quantitative	NEO	8 (40)	19 (95)	2
	20	Rocuronium	1.208	Quantitative	NEO	9 (45)	19 (95)	

Table 2 Pooled estimated incidence of PORC by muscle relaxant type and TOF ratio. MR, muscle relaxant; PORC, postoperative residual curarization; TOF, train-of-four. [§]Pooled rate of PORC is the weighted average. The weight in the random-effect model takes into account both between and within studies variation. [†]Inconsistency is the proportion of between studies variability that cannot be explained by chance

Sub-population	Pooled rate of PORC[§]	Confidence interval	Heterogeneity	
			P-value	Inconsistency[†] (%)
Long-acting MR (TOF<0.7)	0.351	(0.25–0.46)	<0.001	86.7
Intermediate-acting MR (TOF<0.7)	0.115	(0.07–0.17)	<0.001	85.9
Long-acting MR (TOF<0.9)	0.721	(0.59–0.84)	<0.001	88.1
Intermediate-acting MR (TOF <0.9)	0.413	(0.25–0.58)	<0.001	97.2

two comparisons at TOF<0.7 in patients who received intermediate- or long-acting neuromuscular blocking drugs (Table 5). However, the small number of the remaining studies yielded insignificant results.

Discussion

We found that the incidence of PORC was more frequent after the use of traditional long-acting neuromuscular blocking drugs (P=0.0082). However, the results of this meta-analysis indicated that neuromuscular monitoring did not decrease the incidence of PORC. For instance, the pooled rates of PORC (TOF<0.9) for intermediate neuromuscular blocking drugs were 0.348 and 0.544 for monitored and non-monitored patients, respectively (P=0.314). As this finding did not support our original hypothesis, a more detailed analysis of the studies[24 26 27 29 43 45 48 50 52] which compared clinical management by purely clinical criteria to cases where intraoperative neuromuscular monitoring was used may be instructive.

Studies which conclude that neuromuscular monitoring does not decrease the incidence of PORC

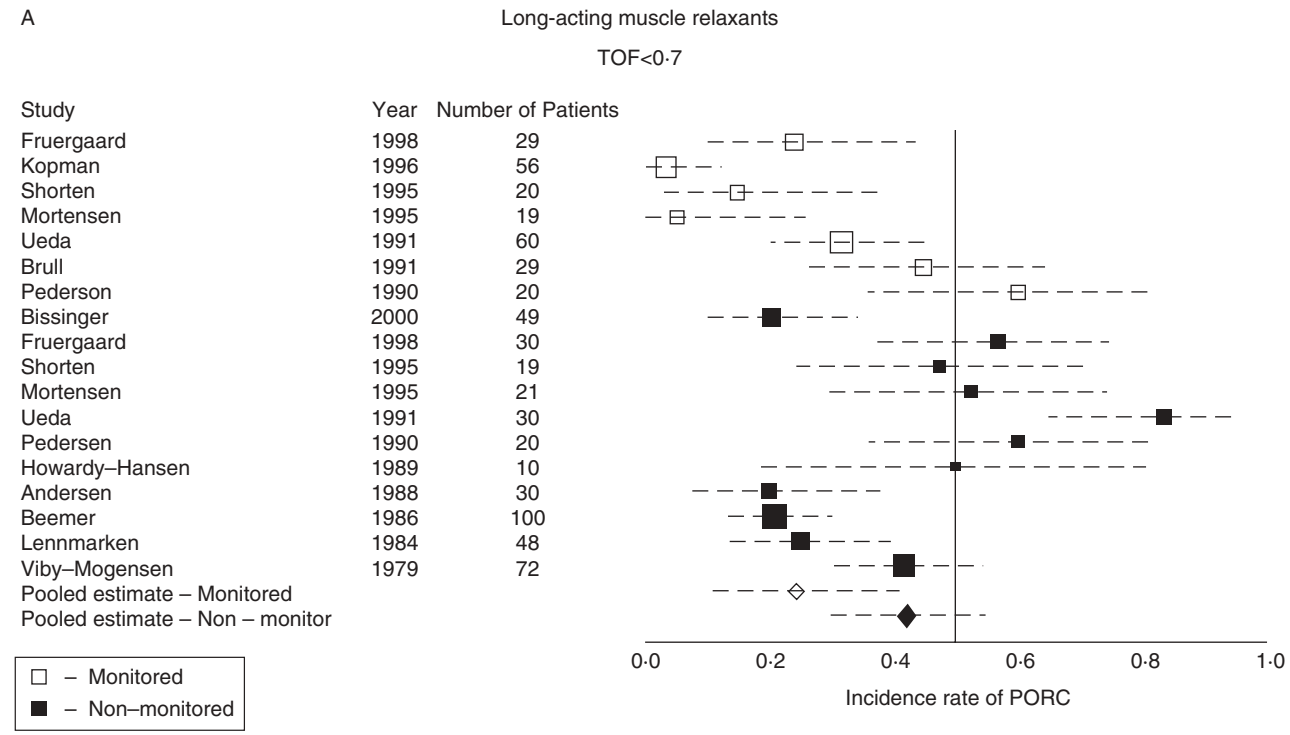
In a randomized clinical trial by Pedersen and colleagues,[48] 80 patients received either vecuronium or pancuronium. In half of the patients, the degree of intraoperative blockade was assessed by tactile evaluation of the TOF response at the thumb. In the other half, the degree of block was evaluated solely by clinical criteria. The use of a PNS had no effect on the dose of relaxant given during anaesthesia, on the need for supplementary doses of anticholinesterase in the recovery room, on the time from the end of surgery to the end of anaesthesia, or on the incidence of postoperative residual neuromuscular blockade evaluated clinically.

In the clinical criteria groups, reversal of residual paralysis was not attempted until spontaneous respiration or other indication of muscle activity was observed. However, the authors' protocol almost guaranteed that results in the monitored group would be less than optimal. Anaesthetists were instructed to maintain the TOF count at one or two detectable responses and antagonism of residual block with neostigmine was initiated at this level of block. There is ample evidence that prompt and satisfactory anticholinesterase-induced antagonism at this level of block is simply not a realistic goal.[36–38 41] Intraoperative neuromuscular monitoring should be used to help the anaesthetist titrate doses of relaxant to avoid this level of block at the end of surgery, not the converse.

In the study of Fawcett and colleagues,[24] 150 patients were given either an intermittent bolus or continuous infusion of atracurium or vecuronium. No attempt was made to influence the conduct of anaesthesia, the choice of blocking drug, or whether a neuromuscular function should be monitored. PNSs were used intraoperatively in 88 (59%) of the patients. TOF ratios upon arrival in the PACU were measured electromyographically. The incidence of PORC was not decreased in patients in whom a PNS device was used (TOF<0.70).

Table 3 Pooled estimated incidence of PORC by muscle relaxant, TOF ratio, and the use of an intraoperative neuromuscular function monitor. MR, muscle relaxant; PORC, postoperative residual curarization; TOF, train-of-four. [§]Pooled rate of PORC is the weighted average. The weight in the random-effect model takes into account both between and within studies variation. [†]Inconsistency is the proportion of between studies variability that cannot be explained by chance

Sub-population	Pooled rate of PORC[§]	Confidence interval	*t*-test *P*-value	Heterogeneity	
				Inconsistency[†] (%)	*P*-value
Long-acting MR (TOF<0.7) Monitored	0.246	(0.11–0.41)	0.109	86.7	<0.001
Long-acting MR (TOF <0.7) Non-monitored	0.422	(0.30–0.55)		85.3	<0.001
Intermediate-acting MR (TOF<0.7) Monitored	0.117	(0.04–0.23)	0.870	89.1	<0.001
Intermediate-acting MR (TOF<0.7) Non-monitored	0.128	(0.08–0.18)		73.5	0.0004
Long-acting MR (TOF<0.9) Monitored	0.701	(0.53–0.85)	0.745	79.7	0.002
Long-acting MR (TOF< 0.9) Non-monitored	0.741	(0.53–0.91)		91.9	<0.001
Intermediate-acting MR (TOF<0.9) Monitored	0.348	(0.13–0.61)	0.314	97.7	<0.001
Intermediate-acting MR (TOF<0.9) Non-monitored	0.544	(0.36–0.73)		94.1	<0.001



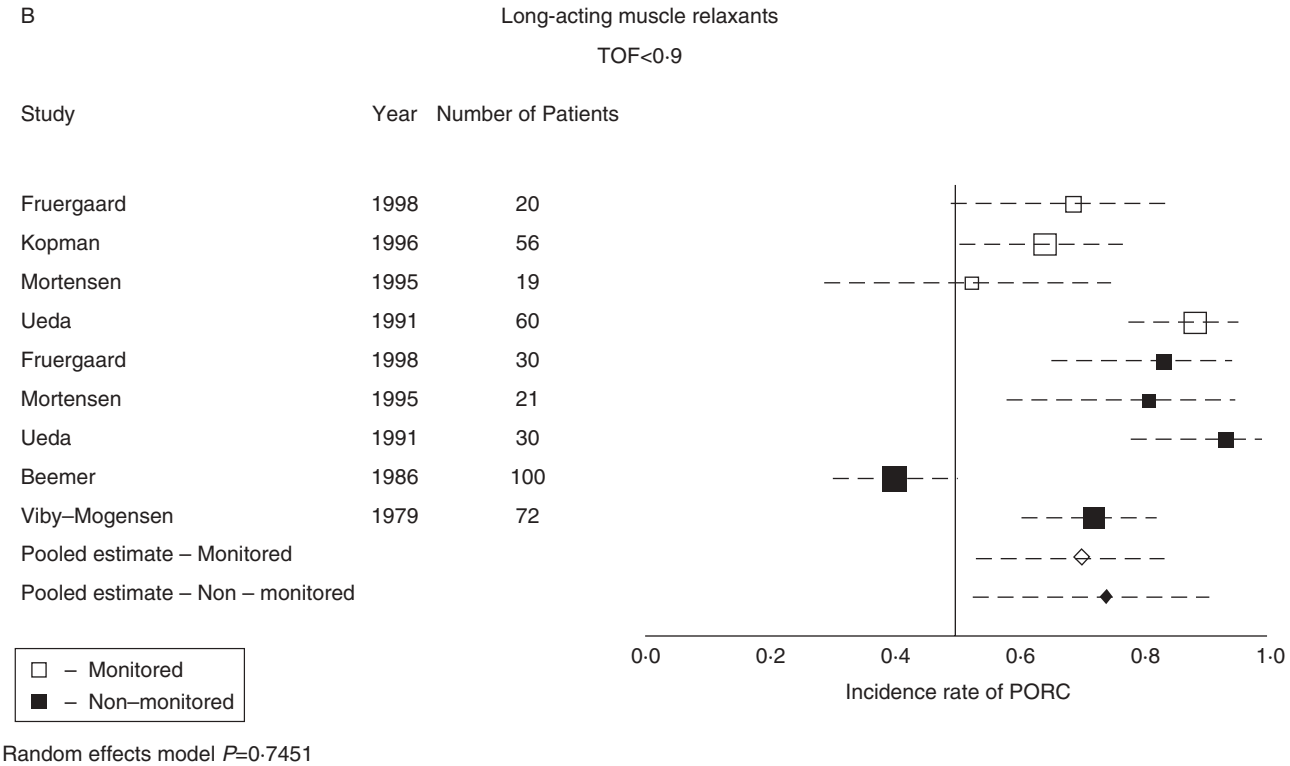


Fig 1 Effect of using an intraoperative neuromuscular function monitor on the incidence of PORC in patients who received long-acting neuromuscular blocking drugs. PORC is typically considered present in patients with a TOF ratio of <0.7 (A) or <0.9 (B). The position of each symbol indicates the incidence rate of PORC of each respective study. The horizontal dotted line indicates the 95% confidence interval of each study.

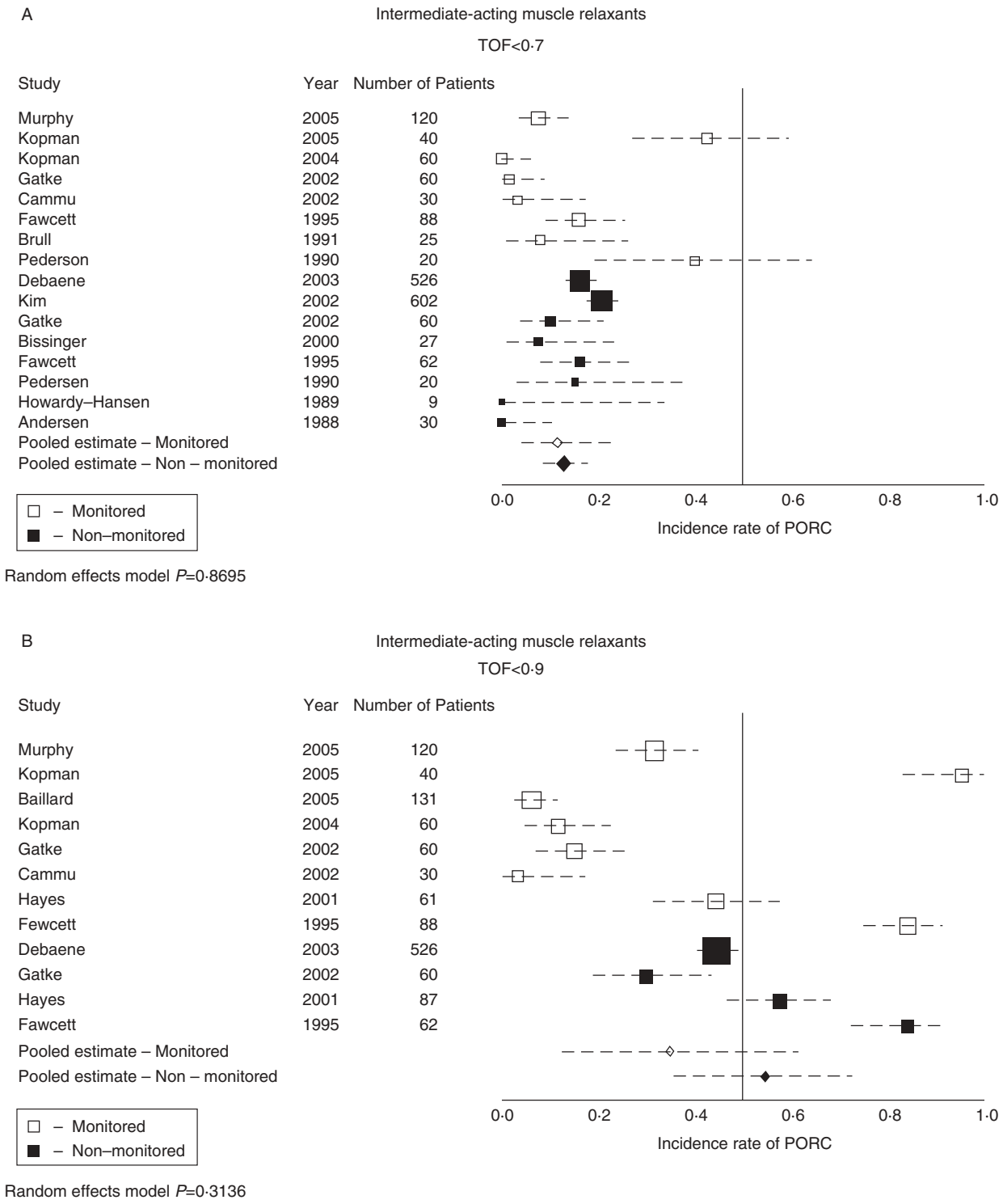


Fig 2 Effect of using an intraoperative neuromuscular function monitor on the incidence of PORC in patients who received intermediate-acting neuromuscular blocking drugs. PORC is typically considered present in patients with a TOF ratio of <0.7 (A) or <0.9 (B). The position of each symbol indicates the incidence rate of PORC of each respective study. The horizontal dotted line indicates the 95% confidence interval of each study.

The virtue of this study is that it probably accurately reflected the then-current clinical practice of the authors' department. Its weakness is that it gives the reader no insight into how clinical decisions were made. If monitored patients were routinely kept at TOF counts of two or fewer detectable responses, then one may argue that a PNS might be counterproductive in some circumstances. Relaxants might be given in response to a

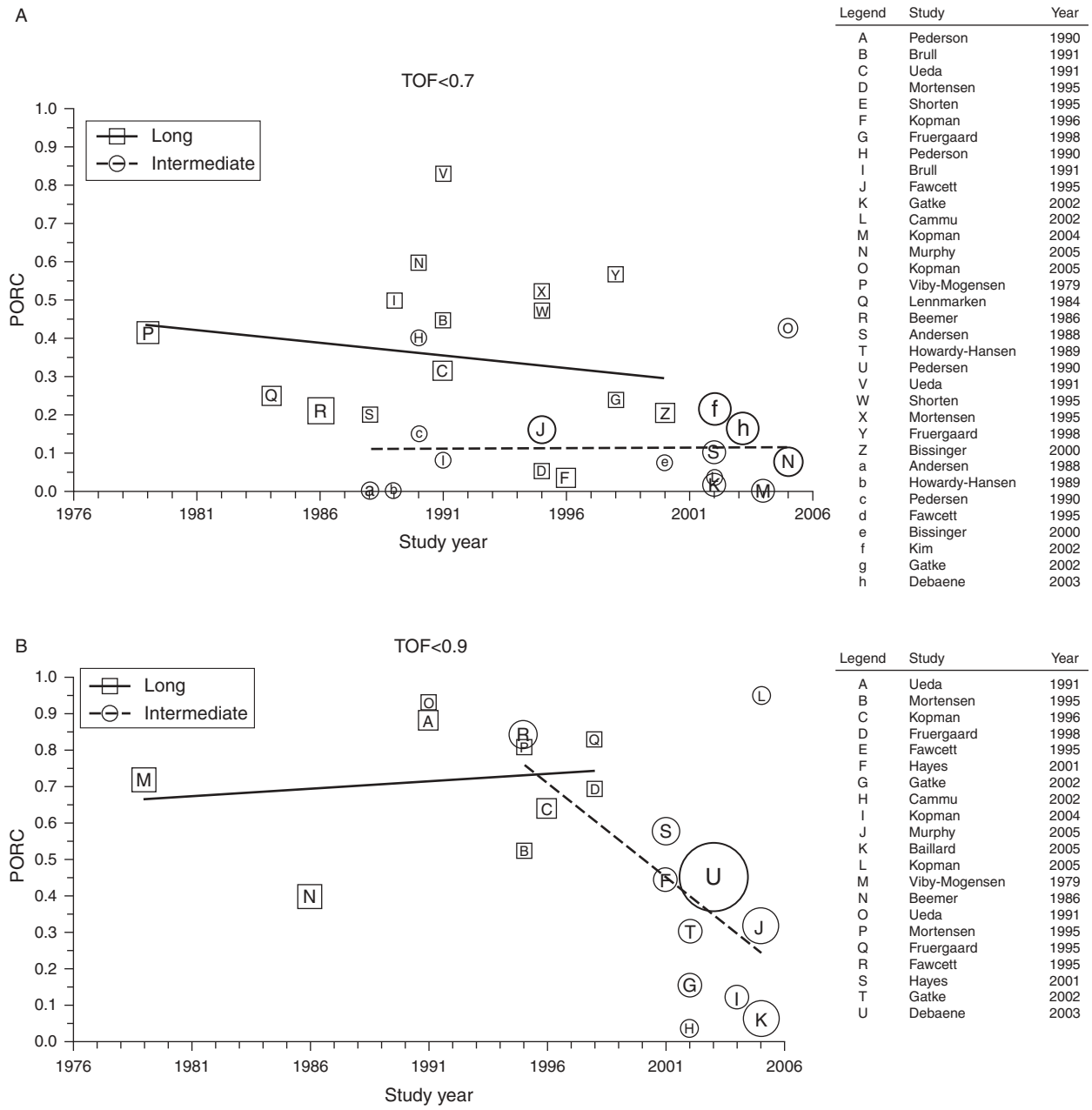


Fig 3 Random-effects weighted regression for the incidence of PORC by year of study. PORC is typically considered present in patients with a TOF ratio of <0.7 (A) or <0.9 (B). For studies associating PORC by a TOF of <0.7, neither long-acting (P=0.52) nor intermediate-acting (P=0.97) neuromuscular blocking drugs exhibited a significant relationship. For studies associating PORC by a TOF of <0.9, intermediate-acting muscle relaxants showed an insignificant (P=0.09) decrease in PORC incidence over time. There was no change in the average rates of PORC over time among studies of long-acting neuromuscular blocking drugs (P=0.69). The size of symbols reflects the size of study. The larger the symbol, the larger the number of patients included in the study.

perceived need for a specific evoked response rather on the basis of the clinical requirements of the moment.

Hayes and colleagues[29] focused on the frequency of PORC on arrival in the PACU in 150 patients who received vecuronium, atracurium, or rocuronium. Residual block was considered present in patients with a TOF ratio of <0.8. The overall incidence of PORC was 52% with no statistical difference between relaxants. Intraoperative neuromuscular monitoring was used in only 41% of patients and reversal of residual block was omitted in one third of the patients. The authors concluded that the use of intermediate-acting neuromuscular blocking drugs does not solve the problem of PORC.

The authors were not able to demonstrate that the incidence of PORC was significantly less in patients in whom a PNS was used. Nevertheless, as several of their patients

Table 4 Comparison of the rate of PORC for monitored *vs* non-monitored patients using only studies containing both sub-populations (controlled studies). *MR, muscle relaxant; PORC, postoperative residual curarization; TOF, train-of-four

Sub-population	Number of studies	PORC		*t*-test *P*-value
		Monitored	Non-monitored	
Long-acting MR (TOF<0.7)	5	0.265	0.609	0.017
Intermediate-acting MR (TOF<0.7)	3	0.155	0.137	0.865
Long-acting MR (TOF<0.9)	3	0.721	0.860	0.266
Intermediate-acting MR (TOF<0.9)	3	0.479	0.579	0.735

(who were not recorded as having used a PNS device) arrived in the PACU with TOF counts of less than four detectable responses, it is difficult to accept the premise that even rudimentary monitoring would not have been helpful.

McCaul and colleagues[43] examined the TOF ratio at tracheal extubation in 40 patients receiving atracurium. The TOF response was continuously measured mechanomyographically in all patients, but anaesthetists were not privy to the objective results. A conventional PNS unit was available to all clinicians but was used in only half of the cases. The TOF ratio was $\leq$0.70 in 26 of 40 patients at the time of tracheal extubation, and a PNS device had been used in 14. Clearly, the use of a PNS device was not associated with improved outcomes in this small sample of patients.

However, reversal of residual block was frequently attempted in the absence of any evoked response to TOF stimuli, and the average time interval between neostigmine administration and extubation in the 26 patients with a TOF ratio of <0.70 was only 6 min. The authors concluded that a high level of unwarranted complacency exists with regard to the ease of reversal of intermediate-acting neuromuscular blocking agents. Clinicians do not seem to believe that PORC is a clinical problem that may affect their patients. Certainly, the high incidence of disinclination to use even simple PNS devices suggests that many practitioners simply do not accept the premise that these devices are helpful. Thus, four decades after the first battery-operated nerve stimulators were described,[13 35] unacceptable levels of residual paresis in the PACU continue to be reported.[15 55]

Studies using conventional peripheral nerve stimulators that suggest that neuromuscular monitoring is helpful

In the study of Shorten and colleagues[50] patients were given an initial 70–100 $\mu g\,kg^{-1}$ dose of pancuronium. The requirement for incremental doses of pancuronium and the adequacy of recovery following reversal were assessed according to random allocation either with (Group A; n=20) or without (Group B; n=19) access to TOF monitoring. PORC was considered present in patients with a TOF ratio <0.70 in the PACU (measured by electromyography). On patient arrival in the recovery area, the incidence of PORC was greater in Group B (47%) than in Group A (15%) (P=0.029). The authors concluded that TOF monitoring decreases the incidence of pancuronium-induced PORC.

Fruergaard and colleagues[26] reported results very similar to those of Shorten and colleagues.[50] The TOF ratio, as measured immediately after tracheal extubation, was significantly lower in the clinical criteria group than in the group using TOF and double-burst stimulation (DBS) (means 0.68 and 0.78, respectively), and the incidence of residual neuromuscular block, considered present in patients with a TOF ratio of <0.7 was significantly higher in the clinical criteria group than in the TOF/DBS group (57% and 24%, respectively). However, no significant differences between the two groups of patients were found in the duration of anaesthesia, the times from the end of surgery to the injection of neostigmine, tracheal extubation, the TOF ratio of 0.8, or the dose of pancuronium administered.

Table 5 Comparison of the rate of PORC for randomized trials *vs* observational studies. MR, muscle relaxant; PORC, postoperative residual curarization; TOF, train-of-four. [§]R, randomized; O, observational

Sub-population	Number of studies (R, O)[§]	PORC		*t*-test *P*-value
		Randomized	Observational	
Long-acting MR (TOF <0.7) Monitored	6, 1	0.296	0.038	0.023
Intermediate-acting MR (TOF<0.7) Monitored	5, 3	0.137	0.096	0.677
Long-acting MR (TOF<0.9) Monitored	3, 1	0.721	0.643	0.594
Intermediate-acting MR (TOF<0.9) Monitored	4, 4	0.417	0.281	0.663
Long-acting MR (TOF<0.7) Non-monitored	8, 3	0.483	0.290	0.086
Intermediate-acting MR (TOF<0.7) Non-monitored	5, 3	0.068	0.183	0.029
Long-acting MR (TOF<0.9) Non-monitored	3, 2	0.860	0.562	0.148
Intermediate-acting MR (TOF<0.9) Non-monitored	2, 2	0.438	0.650	0.484

The results of Ueda and colleagues[52] were similar to the two previous studies.[26 50] The mean (SD) TOF ratio upon patient arrival in the PACU was 0.53 (SD 0.20) in patients in whom pancuronium requirements and the degree of recovery were guided solely by clinical criteria. When these criteria were assessed by intraoperative tactile evaluation of the response to TOF stimulation, the average TOF ratio in the PACU rose to 0.67, and when the response to DBS was also monitored, the PACU TOF ratio rose to 0.81. The authors concluded that the use of DBS enabled the anaesthetists to recognize significant residual block and thus reduce the incidence of postoperative residual neuromuscular blockade. However, as in the above-mentioned studies,[26 50] there were no differences in the doses of pancuronium administered to the three groups.

The three studies cited above raise a vexing question. The amount of pancuronium administered (total mg or mg kg^{-1} min^{-1}) was the same in both monitored and non-monitored groups. Why then was the incidence of PORC lower in the monitored patients? This was probably in part because the incremental doses given represented only a small fraction of the total dose administered, and hence, large differences in the total doses given would not be expected. Perhaps a different trend might have emerged if agents of intermediate-duration had been studied, but this is speculation.

Is it possible to decrease the incidence of PORC significantly with the intraoperative use of conventional (non-objective neuromuscular) monitors? Kopman and colleagues[39] reported a series of 56 patients given pancuronium. Clinicians were carefully instructed to keep the tactile TOF count as close to 2 as possible, and this protocol was rigidly adhered to. The average TOF count at reversal (with the use of neostigmine 0.05 mg kg^{-1}) was 2.1. However, this protocol represents a less than optimal scenario: a long-acting relaxant with relatively profound neuromuscular block. As a result, only 4 of 56 patients had a TOF ratio of $\geq$0.90 on discharge from the operating room, and 8 patients failed to attain this level of recovery within 90 min of receiving neostigmine. Nevertheless, the mean (SD) TOF ratio on patient arrival in the PACU [30 (8) min after reversal] was 0.85(0.08). Two patients ($<$4%) had a TOF ratio of $<$0.70 but $>$0.60. These results are considerably better than those in most reports of PORC following the use of pancuronium.[7, 55] Thus, it appears that even non-objective neuromuscular monitoring can decrease the incidence of clinically significant PORC, but not totally eliminate it.

Studies comparing clinical criteria to objective measurement of neuromuscular function

In the study of Mortensen and colleagues,[45] forty adult patients were randomized into two groups. Group A patients were managed without the use of a nerve stimulator; Group B patients were monitored using TOF nerve stimulation and acceleromyography. All received pancuronium 0.08–0.1 mg kg^{-1} for tracheal intubation and 1–2 mg for maintenance of neuromuscular block. Neostigmine 2.5 mg preceded by atropine 1 mg was administered for reversal. In Group A, the trachea was extubated when the anaesthetist judged the neuromuscular function to have recovered adequately for upper airway protection and spontaneous ventilation. In Group B, reversal was not initiated until the TOF count was at least 2 detectable responses and the trachea was extubated when the TOF ratio was $>$0.70. In all 40 patients, the TOF ratio was measured mechano-myographically immediately after tracheal extubation and the patients were evaluated for clinical signs of residual neuromuscular block.

Despite the fact that the dose of pancuronium administered did not differ between groups, at reversal, the number of patients with a TOF ratio $<$0.7 in the monitored group was significantly fewer compared with that in the non-monitored group (1 of 19 patients *vs* 11 of 21 patients, respectively). As acceleromyography slightly overestimates TOF recovery compared with mechanomyography, an occasional case of unacceptable recovery in Group B was not unexpected with the authors' protocol. The higher TOF ratios at extubation in the monitored patients reflected the fact that extubation frequently was delayed (as mandated by the protocol) in the monitored patients. Anaesthesia was not discontinued and extubation was not attempted until an adequate recovery had been objectively measured.

In the study of Gatke and colleagues,[27] during propofol/opioid anaesthesia, 120 adult patients were randomized to two 60-patient groups, one monitored acceleromyographically and the other monitored using only clinical criteria without a nerve stimulator. Postoperatively, the TOF ratio was measured mechano-myographically; a TOF ratio of $<$0.80 indicated residual muscle paralysis. The authors found no difference in the dose of rocuronium administered in the two groups. Nevertheless, at the time of tracheal extubation, residual muscle paralysis was found in 10 patients (16.7%) in the group without neuromuscular monitoring and in only two patients (3%) in the acceleromyographically monitored group. The control group consisted of clinicians who were very much aware of the goals of the study and were trying to avoid residual weakness. Thus results in the 'real world' might have been more dramatic.

The authors concluded that clinical evaluation of neuromuscular function does not exclude significant residual paralysis following the intermediate-acting muscle relaxant rocuronium, but the problem of residual block can be minimized by the use of accelero-myography.

Objective monitors in clinical practice

According to Baillard and colleagues:[2 3] Perhaps the most convincing evidence that the use of objective

neuromuscular monitors (combined with a strong educational effort at the departmental level) can decrease the incidence of PORC comes from two studies.[2 3] The first was a prospective study of the incidence of PORC following the administration of vecuronium in 568 consecutive patients over a 3 month period in 1995. As was customary in the authors' department, no anticholinesterase antagonists were used in this series of patients, and PNS devices were rarely used (<2.0%) intraoperatively. PORC (indicated by an accelero-myographic TOF ratio of <0.70) in the PACU was found in 42% of patients. Of 435 patients who had been extubated in the operating room, the incidence of PORC was 33%.

As a result of these rather alarming findings, their department placed accelero-myographic monitors in all operating rooms shortly after the completion of their 1995 study. In addition, the department instituted an educational programme about the use of neuromuscular monitoring and the indications for neostigmine administration. The results of their findings regarding the incidence of PORC were distributed to their staff. They then conducted repeated 3 month surveys of clinical practice in the years 2000 (n=130), 2002 (n=101), and 2004 (n=218) to determine the success of their educational efforts. In the 9 year interval between these studies, the use of intraoperative monitoring of neuromuscular function rose from 2% to 60%, and reversal of residual antagonism increased from 6% to 42% of cases.

One other notable change was in the choice of relaxant. In 1995, all patients received vecuronium, but this agent was gradually replaced by atracurium, which was used in 99% of cases in 2004. As a result of these changes in clinical practice, the incidence of PORC (acceleromyographic TOF ratio of <0.90) in their department decreased from 62% to <4%.

An interesting issue in this study, which was not addressed, is the low incidence of PORC reported in 2004 at a time when residual block was antagonized in less than half of the cases. Perhaps objective monitoring indicated that routine anticholinesterase administration was not indicated in many of these cases.

We noted that the point in time in which PORC was defined was variable. For instance, in Bevan's 1988 study[7] the average time from reversal to TOF measurement in the PACU was little more than 15 min. In contrast, Kopman's reversal time to the PACU was almost twice as long.[39] Fruergaard and colleagues[26] reported TOF values immediately after extubation in the operating room. Other reports simply failed to provide this information. This of course represents a weakness in our analysis for which we saw no possible correction.

Our original hypothesis was that intraoperative neuromuscular monitoring would reduce the incidence of PORC. It appears that substantiating this thesis from the peer-reviewed literature is a questionable proposition. Certainly, our current meta-analysis was unable to confirm the validity of this assumption. However, systematic evidence based reviews are limited by the quality of the individual trials analysed and reviewed. Nuances in protocol and apparently 'minor' variations in methodology may markedly affect outcome. Widely cited studies are often poorly designed to detect any advantages conferred by monitoring that might exist. For example, Pedersen and colleagues[48] instructed clinicians using clinical criteria to avoid neuromuscular antagonism until signs of muscle recovery had commenced. In the monitored group, however, block was kept at a TOFC of 1 to 2 and antagonism was initiated at this rather deep level of block. Finally, if antagonism with neostigmine is attempted in the absence of an evoked response to TOF stimulation and tracheal extubation follows 6 min later,[43] this does not indicate the failure of utility of neuromuscular monitoring as it does indicate a basic lack of knowledge on the part of the clinician. We believe that evidence based reviews are best read with some prior knowledge of the subject. The result of our statistical analysis notwithstanding, after a critical rereading of our cited studies, we are not yet ready to abandon our initial hypothesis.

In view of the continued high incidence of PORC reported from multiple academic centres, one must ask whether there is any realistic hope of eliminating, or at least markedly reducing, the current prevalence of PORC. We are not optimistic. Editorial comments such as 'it is time to … introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers and aficionados of muscle relaxants'[21] and that '…objective neuromuscular monitoring…should consequently be used whenever a non-depolarizing neuromuscular blocking agent is administered'[21] have been widely ignored. It is clear that large numbers of practitioners still fail to monitor neuromuscular function and fail to administer antagonists when appropriate. Despite intense educational campaigns,[2] there will always be some clinicians who fail to comply. In addition, marked regional differences in the 'usual and customary' management of residual neuromuscular block are prevalent. The routine administration of anticholinesterases as 'standard of care' is at least given lip service in North America, the United Kingdom, and Scandinavia. Anaesthetists in Germany and France are much less likely to administer reversal agents in the absence of clear signs of residual weakness. This reluctance appears to be based in large part on greater apprehension concerning potential side effects of neostigmine (postoperative nausea and vomiting, severe bradycardia, etc.).

Perhaps a new paradigm is called for. It is clear that reversal of competitive neuromuscular block by cholinesterase inhibitors has its limitations. Once inhibition of true acetylcholinesterase is complete, giving

additional neostigmine does not serve any useful purpose. If concentrations of blocking drug at the neuromuscular nicotinic receptors are high enough, recovery will be incomplete. Future progress in achieving rapid return of neuromuscular function will probably result from some form of 'chemical reversal' of residual block.[5 9 19 47] Binding of free drug molecules in plasma such as the encapsulation of rocuronium by sugammadex is one such example.[9 19] Another approach is exemplified by the rapid inactivation of gantacurium *via* cysteine adduction.[5] Although these approaches have the potential to virtually eliminate PORC from our recovery rooms, we remain cautious. Clinicians must first accept the fact that if they do not routinely antagonize non-depolarizing neuromuscular block, an unacceptably high proportion of patients will have clinically significant residual block in the immediate recovery period.

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Appendix

Freeman–Tukey double arcsine transformation

It is recommended that proportions be normalized when a significant number of the sample lies outside the range of 0.3–0.7. We used the Freeman–Tukey double arcsine transformation which for the *i*th study can be stated as

$$y_i = \sin^{-1}\sqrt{\frac{x_i}{n_i+1}} + \sin^{-1}\sqrt{\frac{x_i+1}{n_i+1}}$$

where x_i is the number of patients in the study suffering an incomplete recovery from non-depolarizing neuromuscular block and n_i is the size of the study.

Fixed effects weights

The inverse variance weights for the normalized data can be stated as

$$w_i^f = n_i + 1$$

Weighted mean

The fixed effects weighted mean for the normalized data can be stated as

$$\bar{y}_f = \frac{\sum_{i=1}^{m} y_i w_i^f}{\sum_{i=1}^{m} w_i^f}$$

where m is the number of studies. The weighted mean of the random effects model can be calculated similarly by substituting the random effects weights.

Inverse of the Freeman–Tukey double arcsine transformation

The fixed effects pooled incidence rate of PORC can be stated as

$$\hat{p}_f = \frac{1}{2}\left\{1 - \mathrm{sgn}(\cos(\bar{y}_f)) \times \left[1 - \left(\sin(\bar{y}_f) + \frac{(\sin(\bar{y}_f) - 1/\sin(\bar{y}_f))}{n}\right)^2\right]^{0.5}\right\}$$

where $n = \dfrac{m}{\sum_{i=1}^{m} 1/n_i}$

The random effects pooled incidence rate of PORC can be calculated similarly by substituting the random effects weighted mean for the normalized data.

Cochran's Q

The following χ^2 statistic with $m-1$ degrees of freedom can be used to test for between-studies heterogeneity within a systematic review of m studies.

$$Q = \sum_{i=1}^{m} w_i^f (y_i - \bar{y}_f)^2$$

Moment based estimate of between studies variance

The between studies variance can be estimated by

$$\tau^2 = \frac{Q - m + 1}{\sum_{i=1}^{m} w_i^f - [\sum_{i=1}^{m} (w_i^f)^2 / \sum_{i=1}^{m} w_i^f]}$$

Random effects weights

The random effects weights for the normalized data were derived by DerSimonian and Laird[16] and can be stated as

$$w_i^r = \frac{1}{\tau^2 + (1/w_i^f)}$$

Higgins inconsistency

The proportion of between studies variability that cannot be explained by chance can be measured by

$$I^2 = \frac{Q - m + 1}{Q}$$

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