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REVIEW ARTICLE

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Reversal of mivacurium-induced neuromuscular blockade with a cholinesterase inhibitor: A systematic review

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Background: Mivacurium is a short-acting non-depolarizing muscle relaxant, which is hydrolyzed by butyrylcholinesterase. The neuromuscular block (NMB) can be antagonized with cholinesterase inhibitors (CHEI), but the short duration of action of mivacurium questions the need. This systematic review evaluated if the use of CHEIs (neostigmine, pyridostigmine or edrophonium) facilitates reversal of mivacurium-induced NMB.

Method: Randomized controlled trials and crossover-studies comparing spontaneous recovery with CHEI reversal in patients with mivacurium-induced NMB, assessed with quantitative neuromuscular monitoring, were included. Mean time from injection of the CHEI or allowing of spontaneous recovery to an endpoint representing full recovery was used as outcome. First response to train-of-four nerve stimulation (T_1) described the level of NMB for administration of the CHEI. Moderate NMB refers to $T_1 \geq 5\%$ and deeper NMB refers to $T_1 < 5\%$. Systematic critical appraisal was performed using the Scottish Intercollegiate Guidelines Network guidelines. Overall quality assessment was done using the Grading of Recommendations Assessment, Development and Evaluation approach.

Results: Sixteen studies with data from 546 patients were included. Low quality of evidence was found that neostigmine and edrophonium administered at moderate NMB accelerated recovery with up to approximately 5.5-6.5 and 6.5-9.0 minutes, respectively. At deeper NMB only edrophonium accelerated recovery. The effect of neostigmine was not clarified at deeper mivacurium-induced NMB. No studies with reversal by pyridostigmine were identified.

Conclusion: Low quality of evidence supports that neostigmine and edrophonium accelerate the recovery of mivacurium-induced NMB with 5-6.5 and 6-9.0 minutes respectively, when administered at moderate NMB. At deeper NMB only edrophonium accelerated the recovery.

1 | INTRODUCTION

During anaesthesia mivacurium and other non-depolarizing muscle relaxants (NMDR) may be used to facilitate tracheal intubation and establish muscle relaxation in surgical procedures. However, administration of NDMRs may cause postoperative residual neuromuscular block (NMB),[1,2] presumably causing respiratory complications[3-6] and higher morbidity and mortality.[7,8] The NMB induced by long-acting and intermediate-acting NDMR can be antagonized with

cholinesterase inhibitors such as neostigmine, pyridostigmine or edrophonium. Antagonism performed at the correct depth of NMB accelerates the muscle recovery,[9-13] thereby decreasing the incidence of residual block[4] and shortening the time to full recovery. Mivacurium is a short-acting NDMR which is hydrolyzed quickly by butyrylcholinesterase[14] (BChE, plasma cholinesterase). The rapid elimination of mivacurium ensures a clinical duration of 16.8 ± 1.1 minutes,[14] and thereby a short recovery time, why reversal with cholinesterase inhibitors may not be needed. Further, a paradox effect is seen when cholinesterase inhibitors are used for reversal of mivacurium-induced NMB. On one hand these drugs inhibit the acetylcholinesterase found at the neuromuscular junction resulting in increased acetylcholine concentration with the potential of accelerating the recovery. On the other hand a slower decrease in plasma concentration of mivacurium is seen. For neostigmine and pyridostigmine, this effect is due to inhibition of the BChE activity.[15-17] This is not the case for edrophonium.[18] The mechanism responsible of the altered decrease of mivacurium in plasma when edrophonium is administered is not known, but may be because of edrophonium displacing mivacurium from tissue into plasma.[19]

The short spontaneous recovery time of mivacurium and the altered decrease in plasma concentration, when cholinesterase inhibitors are given, elicit uncertainty whether the use of cholinesterase inhibitors facilitate the reversing process or not. As cholinesterase inhibitors have adverse effects including cardiovascular effects,[20-22] the potential beneficial effect of reversal should be of significance to justify the use.

The objective of this systematic review was to assess whether the use of cholinesterase inhibitors facilitates the reversal of mivacurium-induced NMB, and further evaluate if any time difference is seen between pyridostigmine, neostigmine or edrophonium.

The hypothesis was that cholinesterase inhibitors facilitate reversal of mivacurium-induced neuromuscular block.

Editorial Comment

In this systematic review, the authors set out to assess whether cholinesterase inhibitors accelerate reversal of mivacurium-induced neuromuscular blockade. The authors found low quality of evidence supporting this, and routine use of cholinesterase inhibitors for reversal of mivacurium-induced neuromuscular blockade does not seem justified.

2 | METHODS

2.1 | Protocol and registration

A protocol was published at the International prospective register of systematic reviews (PROSPERO) database, registration number CRD42016051195.[23]

2.2 | Eligibility criteria

The study population was patients receiving mivacurium. Only randomized controlled trials or crossover-studies comparing spontaneous reversal of NMB with either neostigmine, edrophonium or pyridostigmine facilitated reversal were included. The studies should report mean time of reversal measured from a specific time, assessed with quantitative neuromuscular monitoring, where either injection of the cholinesterase inhibitor was given or spontaneous recovery was allowed. The endpoint was a train-of-four (TOF) ratio of 0.9 or another level of NMB measured quantitatively representing full recovery. Studies comparing spontaneous reversal with one or more groups with cholinesterase inhibitors were included. The cholinesterase inhibitor could only be administered once, and had to be given after termination of mivacurium administration. Studies focusing on genetic variants of BChE were not included.

2.3 | Information sources

A specific search strategy was used on the databases Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) to identify relevant studies. Also, references in the included studies were screened.

2.4 | Search

The search at Medline, Embase and CENTRAL was conducted in September 2016, and repeated in August 2018 to ensure any new publications were included (Appendix S1).

2.5 | Study selection

Titles and abstracts of the studies found were read independently by two authors (JB and CMS) to identify studies that fulfilled the eligibility criteria. Any disagreements were discussed, and in case of disagreement a senior author (MRG or MVM) was consulted. The full text of the included studies was processed in the same manner (Figure 1).

2.6 | Data collection process and data item

Data extraction was performed on all included studies independently by two authors (JB and CMS), using a data extraction sheet (Table S1) comprising study purpose, type of study, number of included subjects, dropouts, premedication, type of anaesthesia, dose of mivacurium and type of administration, as well as dose, type and administration time of cholinesterase inhibitor, time to TOF 0.9, and type of neuromuscular monitoring device. The data extraction sheets were then compared to ensure full and correct data extraction. If more than one dose was investigated in a study (eg dose-response studies), only clinically relevant doses were extracted (edrophonium ≥0.5 mg/kg, neostigmine ≥0.02 mg/kg).

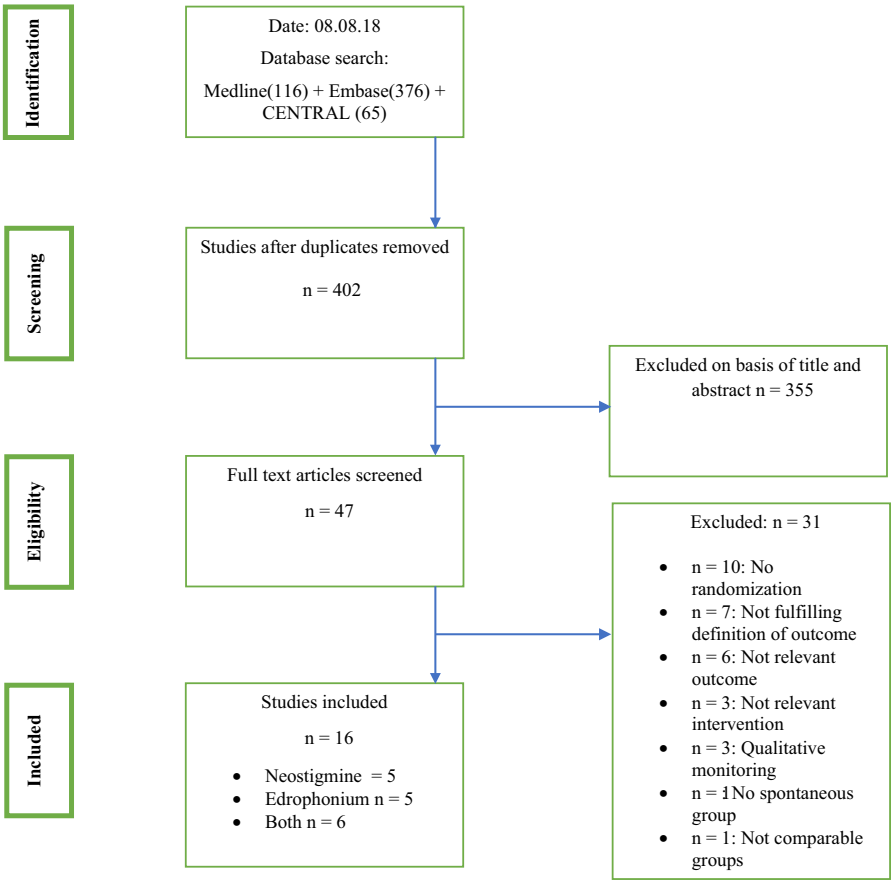

FIGURE 1 Flow diagram

2.7 | Risk of bias in individual studies

Checklists available from The Scottish Intercollegiate Guidelines Network (SIGN) website were used to assess the risk of bias.[24] The checklist consists of a series of questions among others description of adequate randomization, blinding, concealment of allocation, similarity of groups at the start of the trial, if the outcome is measured in a standardized and reliable way and number of dropouts. Each question could be answered with "Yes", "No", "Can´t say" or a short comment. The overall assessment of the risk of bias resulted in a grading of the quality of the individual study as High (++), Acceptable (+), Low (–) or Unacceptable (reject). The critical appraisal was done independently by two authors (JB and CMS). Discrepancy was discussed and if consensus could not be reached a senior author (MRG or MVM) was consulted.

2.8 | Summary measures, synthesis of results and risk of bias across studies

The mean times of reversal (T ± standard deviation) for the comparison group (spontaneous recovery) and the intervention group(s) (neostigmine, edrophonium or pyridostigmine) of each study were used to calculate the mean time difference of reversal (ΔT) ± confidence interval (CI) in minutes. CIs were calculated using *CI = difference * t-value * standard error(diff)*. Standard error (SE) values were calculated using the standard deviation (SD) given in the study. If the number of dropouts was unclear, 10% dropouts was used as a standard. No CI was calculated if the result was read from a graph. As a result of the broad eligibility criteria, it was expected to find differences in several variables (anaesthetics, doses of mivacurium, doses of cholinesterase inhibitor, time of administration) that could alter the recovery time. Accordingly, no meta-analyses were planned in the protocol. No attempt to contact study authors for additional information was done.

The first response (T_1) to TOF nerve stimulation was used to describe the level of NMB for administration of cholinesterase inhibitor. $T_1 \geq 5\%$ refers to moderate NMB, while $T_1 < 5\%$ refers to deeper NMB.

Because of heterogeneity of the studies a funnel plot was not made. The overall quality assessment was done using the Grading of Recommendations Assessment, Development and Evaluation working group methodology (GRADE).[25] The quality of evidence could be rated from high to very low (see Table S2 for further description), due to evaluation of study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations.

3 | RESULTS

The database searches resulted in 557 studies. After removal of duplicates, a total of 402 studies remained for assessment of title and abstract, which resulted in full-text assessment of 47 studies. Thirty-one studies were excluded (Figure 1).

Sixteen randomized controlled studies with data from 546 patients were included.[13,15,26-39] Six studies compared spontaneous recovery with both neostigmine and edrophonium reversal.[15,26,28,30,32,39] Five studies compared spontaneous recovery with neostigmine reversal[31,33,36-38] and five studies compared spontaneous recovery with edrophonium reversal[13,27,29,34,35] No studies on pyridostigmine were included. The overall assessment of the risk of bias for individual studies resulted in three studies judged as high quality, 11 as acceptable and two as low (Table S3).

3.1 | Reversal with neostigmine

A total of 11 studies compared spontaneous recovery with one or more group(s) receiving neostigmine.[15,26,28,30,33,36,39] Study characteristics, results and quality assessment are listed in Table 1.

The studies were heterogenic eg administration time of cholinesterase inhibitor, definition of endpoint (recovery as TOF ratio between 0.7 and 0.95), type of anaesthetics and doses of neostigmine. Two studies used our predefined endpoint TOF 0.9.[26,36] These studies also presented time to TOF 0.7.

Reversal times after neostigmine were compared to spontaneous recovery and ranged from prolonged recovery time up to 13.5 minutes,[26] to an accelerated recovery time of maximum 7.0 minutes[31] (significant) or 8.5 minutes[33] (non-significant). At reversal at $T_1 < 5\%$, three out of five studies showed prolonged mean reversal time when neostigmine had been administered. Only the results from Kao[26] was statistically significant. Two out of five studies showed a significant accelerated recovery time. When neostigmine was administered at $T_1 \geq 5\%$ NMB, a tendency to accelerated reversal was seen.

3.1.1 | Reversal when $T_1 < 5\%$ (5 studies)

The study by Naguib[28] was divided in two parts. Two groups met our inclusion criteria, one using edrophonium, and one using neostigmine. Neostigmine prolonged the recovery time to TOF 0.75 with 8.3 (−0.3; +16.9) min [+62%] as compared to spontaneous recovery. The result was insignificant. Neostigmine was administered at post-tetanic count (PTC) 1.

In Devcic[15] neostigmine was administrated at first detection of T_1 which resulted in significantly accelerated reversal by 3.3 (−5.4; −1.2) min [−21%] compared to spontaneous recovery.

In Nicolardot[31] only the group where neostigmine was administered at TOF count 1 met the inclusion criteria. Neostigmine significantly accelerated reversal to TOF 0.95 with 7 min (−3.2; −10.8) min [−35%].

In the study by Lien[36] neostigmine was administered 1 minute after discontinuation of mivacurium. Time to reach TOF 0.7 was accelerated with 3.0 (−7.9; +1.9) min [−18%] in the neostigmine group compared to spontaneous recovery. However, at TOF 0.9 the neostigmine group was 0.3 (−3.2; +3.8) min [+2%] slower than the spontaneous group. Both results were statistically insignificant.

In the study by Kao[26] neostigmine was administered at T_1 2%-3%. Time to TOF 0.7 was prolonged with 7.5 (−0.9; +15.9) min [+54%] in the neostigmine group compared to the spontaneous group. At TOF 0.9 the time gap had increased to 13.5 (+3.8; +23.2) min [+75%], only the latter result was significant.

3.1.2 | Reversal at $T_1 \geq 5\%$ (6 studies)

In Bartunek[30] neostigmine was administered in two groups; one group at T_1 5%, and one group at T_1 25%. In both groups, the reversal time was significantly accelerated compared to the spontaneous group, and to the same extent. When antagonizing at T_1 5%, the reversal was accelerated with 5.9 (−8.3; −3.5) min [−37%] compared to 5.6 (−7.6; −3.6) min [−52%] when done at T_1 25%.

In Lessard[37] neostigmine was administered at T_1 = 5%-10%. Two doses were given (0.02 and 0.04 mg/kg). Both significantly accelerated the recovery time compared to spontaneous recovery with 5.6 minutes (−8.1; −3.1) [−33%] and (−8,2; −3.0) [−33%] respectively.

In Jan[38] all patients were given suxamethonium before intubation. When T_1 had returned to 70% of the baseline twitch, a mivacurium bolus was given followed by an infusion titrated to T_1 10%. When infusion was stopped, neostigmine was administered or no reversal was given. Time to TOF 0.7 was similar in both groups, with the neostigmine group being 0.6 (−4.8; +3.6) min [−4%] faster.

Maddineni[39] administered neostigmine at approximately T_1 = 10%. Time to TOF 0.7 was significantly accelerated with 6.5 (−8.2; −4.8) min [−48%] in the neostigmine group compared to spontaneous recovery.

In Bevan[32] neostigmine doses of 0.02 and 0.05 mg/kg were given. TOF was measured every 10 seconds, but only noted every minute. This was done the first 10 minutes of recovery. The two doses accelerated recovery with 2.5 minutes [−31%] and 2.2 minutes [−27%], respectively compared to the spontaneous recovery.

Trévien[33] administered neostigmine at T_1 10%. The time to TOF 0.7 was not presented, but was calculated from mean times from other set points. Neostigmine accelerated reversal with 8.5 (−18.0; +1.0) min [−40%] compared to spontaneous recovery. No SD regarding our outcome was available, why the highest SD from the other mean times measured in each group, was used to calculate CI.

3.2 | Summary statement

There is low quality of evidence (Table 2) that neostigmine administered at moderate mivacurium-induced NMB ($T_1 \geq 5\%$) accelerates the reversal as compared to spontaneous recovery in adults.

The effect was not clarified at deeper mivacurium-induced NMB in adults.

3.3 | Reversal with edrophonium

A total of 11 studies reported on edrophonium. Of these four studies compared different doses of edrophonium[27,29,32,34] and one study compared the same dose of edrophonium given at two different levels of NMB.[30] The study characteristics varied considerably.

TABLE 1 Reversal with neostigmine: characteristics, results and quality assessment

References	Population n (dropouts)	Maintenance of anaesthesia and type of NM-monitoring	Groups (n)	Mivacurium mg/kg	NEO mg/kg	Start of reversal	Endpoint TOF	Duration of spontaneous reversal mean ±SD min	Duration of reversal with NEO mean ±SD min	Difference NEO-SP mean ΔT(CI) min %	Comments	Quality of study
Naguib[28]	Both sexes, 16-52 y 20 (0)	70% N_2O and 0.5%-1% isoflurane in O_2 NM: MMG AP	SP (10) NEO (10)	Bolus 0.15	- 0.06	After first detection of muscle contractions in response to PTC	0.75	13.3 ± 2.7	21.6 ± 12.7	+8.3 (−0.3; +16.9) +62%	Unclear method of randomizing in group SP/2	1−
Devcic[15]	Both sexes, adults 20 (0)	60% N_2O in O_2 + propofol infusion and bolus fentanyl EMG n. ulnaris (muscle not specified)	SP (10) NEO (10)	Bolus 0.2 followed by infusion to maintain T_1 = 1%-5%	- 0.07	At first detection of T_1 (T_1 = 1%-8%)	0.7	15.8 ± 0.9	12.5 ± 3.1	−3.3 (−5.4; −1.2) −21%	Actual administration time	1++
Nicolardot[31]	Adult NK (NK)	NK AMG AP	SP (16) NEO (16)	Bolus of 0.25	- 0.04	TOF count 1	0.95	20 ± 5	13 ± 5.5	−7.0 (−3.2; −10.8) −35%	Listed as 40, but probably a mistake	1+
Lien[36]	Male, adult 16 (NK)	70% N_2O in O_2 + fentanyl and thiopental as needed MMG AP	SP (8) NEO (8)	Bolus of 0.25 At T_1 = 25%, infusion was started and maintain at T_1 = 1%-5%	- 0.05	1 min after T_1 = 1%-5%	0.9 0.7	17.7 ± 1.3 16.3 ± 2.5	18.0 ± 4.4 13.3 ± 6.0	+0.3 (−3.2; +3.8) +2% −3.0 (−7.9; +1.9) −18%	Small deviation from eligibility criteria	1+
Kao[26]	Adult 20 (NK)	70% N_2O in O_2 + sufentanil and isoflurane (up to 1%) if required EMG AP	SP (NK) NEO (NK)	Bolus of 0.15 followed by infusion maintained at T_1 = 2%-3%	- 0.07	When infusion was stopped (T_1 = 2%-3%)	0.9 0.7	17.9 ± 6.4 13.8 ± 4.4	31.4 ± 12.1 21.3 ± 11.1	+13.5 (+3.8; +23.2) +75% +7.5 (−0.9; +15.9) +54%	Not mentioned if male is included. High SD Actual administration time	1+
Bartunek[30]	Both sexes, adult 29 (0)	N_2O in O_2 (2:1) + fentanyl and thiopental as needed MMG AP	SP (10) NEO T_1 = 5 (9) NEO T_1 = 25 (10)	Bolus 0.2	- 0.04	T_1 = 5% T_1 = 25%	0.7	15.9 ± 2.9 10.7 ± 2.2	10.0 ± 1.9 5.1 ± 2.0	−5.9 (−8.3; −3.5) −37% −5.6 (−7.6; −3.6) −52%	Uneven sex distribution. Mean BCHE activity similar. In germen. Listed as non-significant in the article	1+

(Continues)

TABLE 1 (Continued)

References	Population n (dropouts)	Maintenance of anaesthesia and type of NM-monitoring	Groups (n)	Mivacurium mg/kg	NEO mg/kg	Start of reversal	Endpoint TOF	Duration of spontaneous reversal mean ±SD min	Duration of reversal with NEO mean ±SD min	Difference NEO-SP mean ΔT(CI) min %	Comments	Quality of study
Lessard[37]	Both sexes, adult 75 (6)	70% N_2O in O_2 + propofol infusion +alfentanil as needed EMG AP	SP (24) NEO 0.02 (22) NEO 0.04 (23)	Bolus 0.2 At T_1 = 5%, infusion was started and maintained at T_1 = 5%-10%	- 0.02 0.04	Immediately after infusion stop (T_1 = 5%-10%)	0.7	17 ± 5.1	11.4 ± 3.0 11.4 ± 3.5	−5.6 (−8.1; −3.1) −33% −5.6 (−8.2; −.0) −33%		1++
Jan[38]	Female, adult 30 (0)	70% N_2O in O_2 + 0.4% enflurane AMG AP	SP (15) NEO (15)	Bolus 0.15 At T_1 = 10%, infusion was started and maintained at T_1 = 10%	- 0.05	Immediately after stop of infusion (T_1 = 10%)	0.7	16.7 ± 3.0	16.1 ± 7.4	−0.6 (−4.8; +3.6) −4%	Pregnant. Suxamethonium for intubation	1+
Maddineni[39]	Both sexes, adult 20 (0)	67% N_2O and 0.75%-1.0% halothane in O_2 + thiopentone and fentanyl as needed MMG AP	SP (10) NEO (10)	Bolus 0.2 At T_1 = 10%, infusion was started and adjusted to maintained at T_1 = 10%	- 0.04	When infusion was stopped (around T_1 = 10%, the exact is seen in the article)	0.7	13.5 ± 2.3	7.0 ± 1.2	−6.5 (−8.2; −4.8) −48%		1+
Bevan[32]	Both sexes, children Age 2-12 18(NK)	N_2O in O_2 + propofol infusion +fentanyl as needed EMG AP	SP (6) NEO 20 (6) NEO 50 (6)	Bolus 0.2, if necessary extra doses of 25% of initial dose were given. When T_1 = 5%-10% infusion was started and maintained at T_1 = 5%-10%	- 0.02 0.05	T_1 = 10%	0.7	8.2	5.7 6.0	−2.5 −31% −2.2 −27%	Secondary outcome. Read from graph. Same SP group for NEO and EDRO, but different reading	1−
Trévien[33]	Both sexes, adult 34(5)	60% N_2O in O_2 + 0.5%-1.0% endtidal enflurane +fentanyl as needed MMG AP	SP (15) NEO (14)	Bolus 0.15	- 0.04	T_1 = 10%	0.8	21.2 ± 14	12.7 ± 10.5	−8.5 (−18.0; +1.0) −40%	Time interval is calculated from mean times with other set points	1+

AMG, acceleromyography; AP, adductor pollicis muscle; EMG, electromyography; MMG, mechanomyography; NEO, neostigmine; NK, not known; NM, neuromuscular monitoring; PTC, post tetanic count; SP, spontaneous; TOF; train-of-four.

TABLE 2 Summery of findings: neostigmine and edrophonium compared to spontaneous for reversal of mivacurium-induced neuromuscular block (NMB)

Certainty assessment									
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty	Comments
Neostigmine									
10	Randomised trials	Not serious[a]	Not serious[b]	Serious[c]	Serious[d]	None	5-6.5 min	⨁⨁◯◯ LOW[e]	When administered at $T_1 \geq 5\%$ neostigmine accelerated the reversal with up to 6.5 min. Four out of six studies showed an effect of at least 5 min. The effect was not clarified at deeper mivacurium-induced NMB in adults.
Edrophonium									
11	Randomised trials	Not serious[a]	Not serious[b]	Serious[c]	Serious[f]	None	6-9 min	⨁⨁◯◯ LOW[e]	When administered at moderate and deeper mivacurium-induced NMB edrophonium accelerated the reversal time in adults with around 9 min. Six out of ten studies found an effect of at least 6 min. If administered at $T_1 \geq 5\%$ four out of seven studies found an effect of at least 6 min

[a]The risk of bias is low why potential limitations are unlikely to lower confidence in the estimate of effect.
[b]The inconsistency found in the results is believed to be explained for a large part by the big difference in when the cholinesterase inhibitor is administered, as well as other differences in the studies methodology. Borderline decision.
[c]Our outcome varied in both starting point (administration of CHEI or start of spontaneous recovery) and end point (definition of full recovery).
[d]The number of included patients for this outcome is less than 400 (301). Significant acceleration in reversal time is seen in half of the studies where neostigmine was administered at $T_1 \geq 5\%$, including the largest study. Borderline decision. Downgraded due to multiple borderline decisions.
[e]Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. See Table S2 for explanation.
[f]The number of included patients for this outcome is less than 400 (300). Most studies show significant acceleration in reversal time, including the largest study. Borderline decision. Downgraded due to multiple borderline decisions.

Study characteristics, results and quality assessment are listed in Table 3.

Two studies used the predefined endpoint TOF 0.9.[13,26] Both studies also presented time to TOF 0.7, which was the endpoint in all other studies, apart from two trials where TOF 0.75 was used as endpoint.[28,35]

The use of edrophonium accelerated the recovery of the NMB (from 1.1 minutes[28] to 9.2 minutes[27]) compared to spontaneous recovery in all groups presented (Table 3).

3.3.1 | Reversal at $T_1 < 5\%$ (4 studies)

Naguib,[28] Devcic[15] and Kao[26] studied 1 mg/kg edrophonium for reversal, but starting point and endpoint varied (Table 3). In Naguib[28] edrophonium was administered at PTC 1, while Devcic[15] used first detection of T_1 (T_1 1%-8%), and Kao[26] administered edrophonium when mivacurium infusion was stopped (T_1 2%-3%). As endpoints TOF 0.75 and TOF 0.7 was used in Naguib[28] and in Devcic[15] respectively, while Kao[26] used TOF 0.7 as well as TOF 0.9. Time saved using edrophonium compared to spontaneous recovery was 1.1 (−3.9; +1.7) min [−8%],[28] 7.8 (−8.6; −7.0) min [−49%],[15] and 4.7 (−9.2; −0.3) min [−34%] or 5.7 (−12.2; +0.9) min [−31%] depending on endpoint.[26] Only the results from Devcic[15] and the first of Kao[26] were statistically significant.

Ripart[27] administered edrophonium around T_1 1%-5%. Two doses met our inclusion criteria (0.5 and 1.0 mg/kg). The time to TOF 0.7 was reported. Both doses resulted in a significant accelerated recovery of 9.2 (−13.0; −5.4) min [−50%] and 7.6 (−11.1; −4.1) min [−42%], respectively.

3.3.2 | Reversal at $T_1 \geq 5\%$ (7 studies)

Bartunek[30] administered edrophonium for reversal at two different levels of NMB (T_1 5% and T_1 25%). The reversal to TOF 0.7 was accelerated with 8.2 (−10.6; −5.8) min [−52%] and 5.4 (−7.2; −3.6) min [−51%], respectively as compared to the spontaneous group.

TABLE 3 Reversal with edrophonium: characteristics, results and quality assessment

References	Population n (dropouts)	Maintenance of anaesthesia and type of NM-monitoring	Groups (n)	Mivacurium mg/kg	EDRO mg/kg	Start of reversal	Endpoint TOF	Duration of spontaneous reversal mean ±SD min	Duration of reversal with EDRO mean ±SD min	Difference EDRO-SP mean ΔT(CI) min %	Comments	Quality of study
Naguib[28]	Both sexes, 16-52 y 20 (0)	70% N_2O and 0.5%-1% isoflurane in O_2 NM: MMG AP	SP (10) EDRO (10)	Bolus 0.15	- 1.0	After first detection of muscle contractions in response to PTC	0.75	13.3 ± 2.7	12.2 ± 3.2	−1.1 (−3.9; +1.7) −8%	Unclear method of randomizing in group SP/2	1−
Devcic[15]	Both sexes, adults 20 (0)	60% N_2O in O_2 + propofol infusion and bolus fentanyl EMG n. ulnaris (muscle not specified)	SP (10) EDRO (10)	Bolus 0.2 followed by infusion to maintain T_1 = 1%-5%	- 1.0	At first detection of T_1 (T_1 = 1%-8%)	0.7	15.8 ± 0.9	8 ± 0.9	−7.8 (−8.6; −7.0) −49%	Actual administration time	1++
Kao[26]	Adult 20 (NK)	70% N_2O in O_2 + sufentanil and isoflurane (up to 1%) if required EMG AP	SP (NK) EDRO (NK)	Bolus of 0.15 followed by infusion maintained at T_1 = 2%-3%	- 1.0	When infusion was stopped (T_1 = 2%-3%)	0.9 0.7	17.9 ± 6.4 13.8 ± 4.4	12.2 ± 6.7 9.1 ± 4.5	−5.7 (−12.2; +0.9) −31% −4.7 (−9.2; −0.3) −34%	Not mentioned if male is included. High SD Actual administration time	1+
Ripart[27]	Both sexes, adult 45 (0)	60% N_2O in O_2 + propofol infusion and bolus alfentanil EMG AP	SP (15) EDRO0.5 (15) EDRO1 (15)	Bolus of 0.15. When T_1 response was seen infusion was started and adjusted to maintain T_1 = 5%	- 0.5 1.0	When infusion was stopped (T_1 = 2%-3%)	0.7	18.3 ± 5.4	9.1 ± 4.8 10.7 ± 3.9	−9.2 (−13.0; −5.4) −50% −7.6 (−11.1; −4.1) −42%	Large majority of females in all groups, but similarly between groups. In French	1+
Bartunek[30]	Both sexes, adult 29 (0)	N_2O in O_2 (2:1) + fentanyl and thiopental as needed MMG AP	SP (10) EDROT$_1$ = 5(10) EDROT$_1$ = 25 (9)	Bolus 0.2	- 1.0	T_1 = 5% T_1 = 25%	0.7	15.9 ± 2.9 10.7 ± 2.2	7.7 ± 2.2 5.3 ± 1.5	−8.2 (−10.6; −5.8) −52% −5.4 (−7.2; −3.6) −51%	Uneven sex distribution. Mean BCHE activity similar. In germen. Listed as non-significant in the article	1+
Miller[34]	Both sexes, adult 57 (7)	70% N_2O in O_2 + propofol infusion +alfentanil as needed EMG At the first dorsal interosseous muscle	SP (25) EDRO 3 (25)	Bolus of 0.15. Followed by infusion adjusted to maintain T_1 = 5%-10%	- 0.5	Immediately after infusion stop (T_1 = 5%-10%)	0.7	13.5 ± 3.1	9.2 ± 3.3	−4.3 (−6.1; −2.5) −32%		1++

(Continues)

TABLE 3 (Continued)

References	Population n (dropouts)	Maintenance of anaesthesia and type of NM-monitoring	Groups (n)	Mivacurium mg/kg	EDRO mg/kg	Start of reversal	Endpoint TOF	Duration of spontaneous reversal mean ±SD min	Duration of reversal with EDRO mean ±SD min	Difference EDRO-SP mean ΔT(CI) min %	Comments	Quality of study
Marcotte[29]	Both sexes, adult 45 (0)	70% N_2O and 0.5%-1.5% enflurane end-tidal concentration in O_2 + alfentanil as needed EMG AP	SP (15) EDRO0.5 (15) EDRO1.0 (15)	Bolus of 0.15. Followed by infusion adjusted to maintain T_1 = 5%	- 0.5 1.0	Immediately after infusion stop (T_1 = 7%-8%)	0.7	19.7 ± 4.7	11.1 ± 3.5 11.4 ± 3.0	−8.6 (−11.7; −5.5) −44% −8.3 (−11.2; −5.4) −42%	Large majority of females in all groups, but similarly between groups	1+
Suzuki[13]	Male, adult 26 (5)	70% N_2O in O_2 + propofol infusion +fentanyl + midazolam as needed Pressure measuring at the cuff, when stimulating the laryngeal adductor	SP (10) EDRO (11)	Bolus of 0.25	- 0.5	T_1 = 10%	0.9 0.7	32.9 25.0	29.3 22.5	−3.6 −11% −2.5 −10%	Read from a graph	1+
Naguib[35]	Both sexes, adult 20 (NK)	70% N_2O and 0.5% isoflurane in O_2 (Isoflurane was administered for 30 min before control T_1 was recorded MMG AP	SP (10) EDRO (10)	Bolus of 0.15. Additional 0.1 mg/kg were given when T_1 = 10% if continued NMB was required	- 1.0	T_1 = 10%	0.75	16.8 ± 3.3	8.9 ± 3.6	−7.9 (−11.1; −4.7) −47%	2 pt. in the EDRO group had T_1>25% when EDRO was given - unclear if they are included in the result	1+
Maddineni[39]	Both sexes, adult 20 (0)	67% N_2O and 0.75%-1.0% halothane in O_2 + thiopentone and fentanyl as needed MMG AP	SP (10) EDRO (10)	Bolus 0.2 At T_1 = 10%, infusion was started and adjusted to maintained at T_1 = 10%	- 0.75	When infusion was stopped (around T_1 = 10%, the exact is seen in the article)	0.7	13.5 ± 2.3	6.8 ± 1.4	−6.7 (−8.5; −4.9) −50%		1+
Bevan[32]	Both sexes, children Age 2-12 12(NK)	N_2O in O_2 + propofol infusion +fentanyl as needed EMG AP	SP (6) EDRO1000 (6)	Bolus 0.2, if necessary extra doses of 25% of initial dose were given. When T_1 = 5%-10% infusion was started and maintained at T_1 = 5%-10%	- 1.0	T_1 = 10%	0.7	7.94	3.82	−4.12 −52%	Secondary outcome. Read from graph. Same SP for NEO and EDRO group, but different reading	1−

AMG, acceleromyography; AP, adductor pollicis muscle; EMG, electromyography; MMG, mechanomyography; NEO, neostigmine; NK, not known; NM, neuromuscular monitoring; NMB, neuromuscular block; PTC, post tetanic count; SP, spontaneous; TOF, train-of-four.

In Miller[34] 0.5 mg/kg edrophonium was administered at T_1 5%-10%. Time to TOF 0.7 was accelerated with 4.3 (−6.1; −2.5) min [−32%] compared to the placebo group.

Marcotte[29] used methods similar to Miller[34] in regard of mivacurium, edrophonium and endpoint, but with the differences that the mivacurium infusion was titrated to T_1 5% and an additionally dosage of 1.0 mg/kg edrophonium was used. The exact T_1 at reversal was reported (T_1 7%-8%). The time saved when using edrophonium compared to spontaneous reversal was 8.6 (−11.7; −5.5) minutes [−44%] and 8.3 (−11.2; −5.4) min [−42%], in the 0.5 and 1.0 mg/kg group, respectively.

In Suzuki[13] edrophonium was administered or spontaneous recovery was allowed when T_1 had recovered to 10%. Time to TOF 0.7 and TOF 0.9 was measured. The edrophonium group was 2.5 [−10%] and 3.6 min [−11%] faster in reaching these endpoints compared to spontaneous recovery.

Naguib[35] administered edrophonium at T_1 10%. Time to TOF 0.75 was measured. The edrophonium group accelerated the recovery with 7.9 (−11.1; −4.7) min [−47%] compared to the spontaneous group.

Maddineni[39] administered edrophonium around T_1 10%. Edrophonium accelerated recovery to TOF 0.7 with 6.7 (−8.5; −4.9) minutes [−50%] compared to the spontaneous group.

In Bevan[32] edrophonium was administered at T_1 10%. The recovery was accelerated with 4.12 minutes [−52%], compared to spontaneous recovery.

All results regarding reversal at moderate NMB, except from Suzuki[13] and Bevan,[32] were statistically significant (Table 3).

3.4 | Summary statement

There is low quality of evidence (Table 2) that edrophonium administered at moderate and deeper mivacurium-induced NMB accelerates the reversal compared to spontaneous recovery in adults.

4 | DISCUSSION

This review found that neostigmine and edrophonium administered when some spontaneous recovery had occurred accelerated the recovery of mivacurium-induced NMB.

Low quality of evidence was found that *neostigmine* administered when $T_1 \geq 5\%$ accelerated the reversal time with up to 6.5 minutes. Four out of six studies showed an effect of at least 5 minutes. The effect was not clarified at deeper mivacurium-induced NMB in adults.

Low quality of evidence was found that *edrophonium* administered at moderate and deeper mivacurium-induced NMB accelerated the reversal time in adults with around 9 minutes. Six out of ten studies found an effect of at least 6 minutes. If administered at $T_1 \geq 5\%$, four out of seven studies found an effect of at least 6 minutes.

We would argue that a clinical relevant difference should be of at least 5 minutes. In this perspective, the times for reversal found in this systematic review may be of little clinical importance. However, administration of reversal agents should be based on the individual patient and type of surgery. For example, in a fast track schedule with minor surgical procedures differences of 6-9 minutes may play an important role in turn over time between cases.

The strength of our study lies in the conduction of a protocol that follows the PRISMA-P criteria in advance of conducting the study,[23] as well as the systematic approach in the methodology. A broad search strategy, including three databases was used. The outcomes and the quality assessment of included studies were extracted and assessed independently by two authors. Our broad inclusion criteria are however also a limitation as this resulted in a large variation between the different studies regarding anaesthesia method used, as well as administration of the cholinesterase inhibitor at different levels of NMB and in different doses. This heterogeneity probably explains a major part of the variability in effect found throughout the studies. For example, seven studies used inhalation agents[26,28,29,33,35,38,39] which is known to decrease mivacurium requirements.[40-42] Also the time for administration varied from first detection of muscle contraction in response to PTC up to T_1 = 25%. The doses of cholinesterase inhibitor also varied. Neostigmine doses ranged from 0.02 to 0.07 mg/kg and edrophonium from 0.5 to 1 mg/kg. Only four of the studies used TOF 0.9 or more as endpoint. The majority of the results are based on time to reach TOF 0.7-0.75. Most of the studies were of older date, where TOF 0.9 was not recognized as the level to preclude residual NMB.[43] The three included studies which used TOF 0.9 also reported TOF 0.7. No tendency as to whether the effect became more or less pronounced could be seen when looking at TOF 0.9 instead of TOF 0.7. Another limitation is that level of NMB was not pre-specified and there is a potential risk of bias since our definitions of deeper and moderate NMB may have provided the most favourable findings. From a clinical perspective, further limitation is that the beneficial effect is not seen in relation to adverse effects of cholinesterase inhibitors combined with anticholinergics.

When comparing the two reversal agents, edrophonium seemed to be the most effective, especially when administered at $T_1 < 5\%$. At moderate NMB ($T_1 \geq 5\%$), the effect seemed more similar. The use of edrophonium accelerated the reversal with a maximum of 9.2 minutes in contrast to 6.5 minutes when using neostigmine. Based on the study by Trévien[33] one can argue that the maximum time saved when using neostigmine should be 8.5 min instead, even though not being significant. No SD was available to this time in Trévien[33] why the largest SE listed in the study was used to calculate the CI. In the studies investigating both edrophonium and neostigmine, only small differences in accelerated reversal time were seen between the two drugs. In Bartunek[30] edrophonium was 2.3 minutes faster compared to neostigmine when administered at T_1 5%, while only 0.2 minutes difference was seen when administered at T_1 25%. In Maddineni[39] the difference was 0.2 minutes as well, while a difference of 1.6 minutes was seen in Bevan.[32] Looking at the percentage saved, the difference is minimal. The maximum percentage saved for neostigmine and edrophonium was almost identical (52%). Overall, the effect when administered at $T_1 \geq 5\%$ was very similar.

Beemer[10] described reversal of NMB as a function of direct antagonism produced by the cholinesterase inhibitor and spontaneous recovery, with the latter being most important at deep NMB. Neostigmine, but not edrophonium, inhibits BChE. This could be the reason that edrophonium seemed to be more effective than neostigmine at deeper NMB. Applying this theory to our results, it is possible that the direct antagonism of neostigmine overcomes the negative effect of inhibiting BChE around T_1 5%. Devcic[15] described a large variability in their results achieved when using neostigmine, with some subjects having accelerated reversal while others had a reversal time similar to that of spontaneous recovery. This variability was not seen to the same extend in the edrophonium or spontaneous groups. This variability might be explained by a variance in administration time of neostigmine around this point (T_1 1%-8%).

Regardless of type of non-depolarizing muscle relaxant, reversal is recommended in the absence of full spontaneous recovery (TOF > 0.9).[12,44] If reversal of mivacurium-induced NMB is required, it is important to consider level of NMB along with the dose of the cholinesterase inhibitor. Also, the adverse effects of a reversal agent should be considered. These include dry mouth, cardiac arrhythmias as well as potential muscle weakness if administered when full recovery has occurred.[20-22]

In conclusion, low quality of evidence was found that neostigmine and edrophonium administered when $T_1 \geq 5\%$ accelerates the recovery time of mivacurium-induced NMB in adults with approximately 5-6.5 and 6-9.0 minutes, respectively. At deeper NMB ($T < 5\%$) edrophonium accelerated the recovery, while the effect was not clarified for neostigmine in adults.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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