Coadministration of intravenous calcium along with neostigmine for rapid neuromuscular blockade recovery: A systematic review and meta-analysis

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Abstract

Postoperative residual curarization (PORC) and the impact of the coadministration of intravenous calcium along with an acetylcholinesterase inhibitor on it are not well addressed. Extensive electronic database screening was done until October 7, 2022 after enlisting the protocol of this systematic review in PROSPERO (CRD42021274879). Randomized controlled trials (RCTs) evaluating the impact of intravenous calcium and neostigmine coadministration on neuromuscular recovery were included in this meta-analysis. Our search retrieved four RCTs with a total of 266 patients. The application of calcium shortened the neuromuscular recovery time (SMD = −2.13, 95% confidence interval [CI]: −2.66 to −1.59, I^2 = 66%) and reduced the risk of PORC at 5 min (odds ratio [OR] = 0.21, 95% CI: 0.10–0.46, I^2 = 0%), with an improved train-of-four (TOF) ratio at 5 min (mean difference [MD] = 9.28, 95% CI: 4–14.57, I^2 = 66%). However, neither significant reduction in PORC at 10 min (OR = 0.41, 95% CI: 0.15–1.09, I^2 = 0%) nor a better TOF ratio was associated with coadministration of calcium (MD = 0.40, 95% CI: −1.3–2.11). Coadministration of calcium along with neostigmine during the early period of neuromuscular blockade reversal can be used to enhance neuromuscular recovery.

Keywords: Calcium, postoperative residual curarization, train of four

Introduction

In recent times, though the application of non-depolarizing neuromuscular blocking agents (NDMAs) is an indispensable part of general anesthesia, the residual neuromuscular blockade (RNMB) or postoperative residual curarization (PORC) due to inadequate or delayed recovery from it is not only pertinent, but also often overlooked.[1]

Despite stringent neuromuscular monitoring and widespread use of neostigmine, an anticholinesterase antagonist for reversal of neuromuscular blockade, the incidence of RNMB on arrival at the post-anesthesia care unit ranges from 30% to 52%.[2,3] The presence of RNMB impairs the pharyngeal function, thereby leading to airway obstruction and hypoxemia, increasing overall morbidity and mortality.[4-7]

Adequate reversal of neuromuscular blockade for tracheal extubation can be identified by an adductor pollicis train-of-four (TOF) ratio of at least 0.90 or 1.0. Although the PORC is multifactorial and exceeds the realm of the present study, electrolyte imbalance plays a crucial part.[8]

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A recent preclinical study found calcium reverses around 52% of gentamycin-induced tetanic fade and is even more effective than neostigmine in mouse phrenic nerve-hemidiaphragm preparation. The authors suggested an elevated calcium concentration at the nerve terminal could explain the increase in acetylcholine release and its concentration in the synaptic cleft.[9] Several other preclinical studies also acknowledged the impact of elevated ionized calcium on responsiveness to NDMAs.[10,11]

The role of calcium ion and voltage-gated calcium channels in the presynaptic motor nerve endings in releasing acetylcholine (Ach) at the neuromuscular junction is widely acknowledged. It not only evokes the release of Ach from the motor end plates, but also diminishes the degree of Ach-induced depolarization.[12,13] Several studies indicate that an elevated ionized calcium concentration can reduce the sensitivity to NDMAs.[11,14,15]

However, the impact of the coadministration of calcium and neostigmine immediately before the depolarizing phase on early recovery from neuromuscular blockade is not well established. Thus, this systematic review aims to summarize whether the coadministration of intravenous calcium along with neostigmine enhances the rate of recovery from neuromuscular blockade according to the "preferred reporting items for systematic review and meta-analysis" (PRISMA) statement.[16]

Material and Methods

The protocol of this systematic review was enlisted in PROSPERO (CRD42021274879) before the collection of information.

Eligible articles for this study were searched in all the principal electronic databases (PubMed, MEDLINE, Embase, Ovid, Cochrane Library database), Google Scholar (https://scholar.google.com), preprint platforms MedRxiv (https://www.medrxiv.org), SSRN (https://www.ssrn.com), and clinical trial database (https://ClinicalTrials.gov) from January 1, 2000 to October 7, 2022 by two independent researchers (SS and AD) with the following terminologies: "calcium" OR "calcium chloride" OR "calcium gluconate" AND "neuromuscular blockade recovery" OR "neostigmine" OR "TOF" OR "train-of-four."

Only the randomized controlled trials (RCTs) published in English with the following PICO criteria were incorporated:

- Patients: Patients undergoing elective surgery under general anesthesia with neuromuscular monitoring
- Intervention: Coadministration of intravenous calcium chloride or calcium gluconate along with neostigmine
- Comparator/Control: Patients did not receive intravenous calcium
- Outcome (s):

Primary: neuromuscular recovery time (TOF ratio to ≥.0.9).

Secondary: incidence of the RNMB (RNMB was defined as a TOF ratio <.0.9) and TOF ratio at 5 and 10 min after neostigmine administration.

Preclinical studies, comparative cohort studies, case series, cross-sectional studies, case–control studies, and articles without the full retrievable text in English were excluded.

Initially, AD and SS screened every abstract individually to remove duplications. Then, they retrieved the full text of available literature according to the eligibility criteria. Disagreements were settled with the opinion of PK. A preconceived data extraction sheet was used to extract the following data: author, year, center, number of patients, neuromuscular recovery time from neostigmine administration, and the incidence of the RNMB after neostigmine administration at 5 and 10 min.

The risk of bias in individual studies was examined by two independent authors (SS and PK) according to the "RoB 2.0" tool, comprising five domains: "randomization process," "deviations from intended interventions," "missing outcome data," "measurement of the outcome," and "selection of the reported result," Each domain was graded as "low," "moderate," "serious," and "critical."[17] Any difference of opinion was resolved by consulting with the third researcher (AD).

The evidence quality was estimated using the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) tool.[18-20]

SS and AD conducted the statistical analysis with "Review Manager version 5.4." We estimated the relative risk (RR) with 95% confidence intervals (CIs) for dichotomous data and mean differences (MDs) with 95% CI for continuous data, as per the "Cochrane Handbook for Systematic Reviews of Interventions."[21] Statistical heterogeneity was evaluated with the I^2 statistic, with >50% pointing out substantial heterogeneity. The risk of publication bias was estimated with the funnel plot.

Results

A total of four RCTs[22-25] out of 71 publications [Figure 1] were included in the final analysis, of which none had a significant degree of bias [Figure 2]. In three studies,

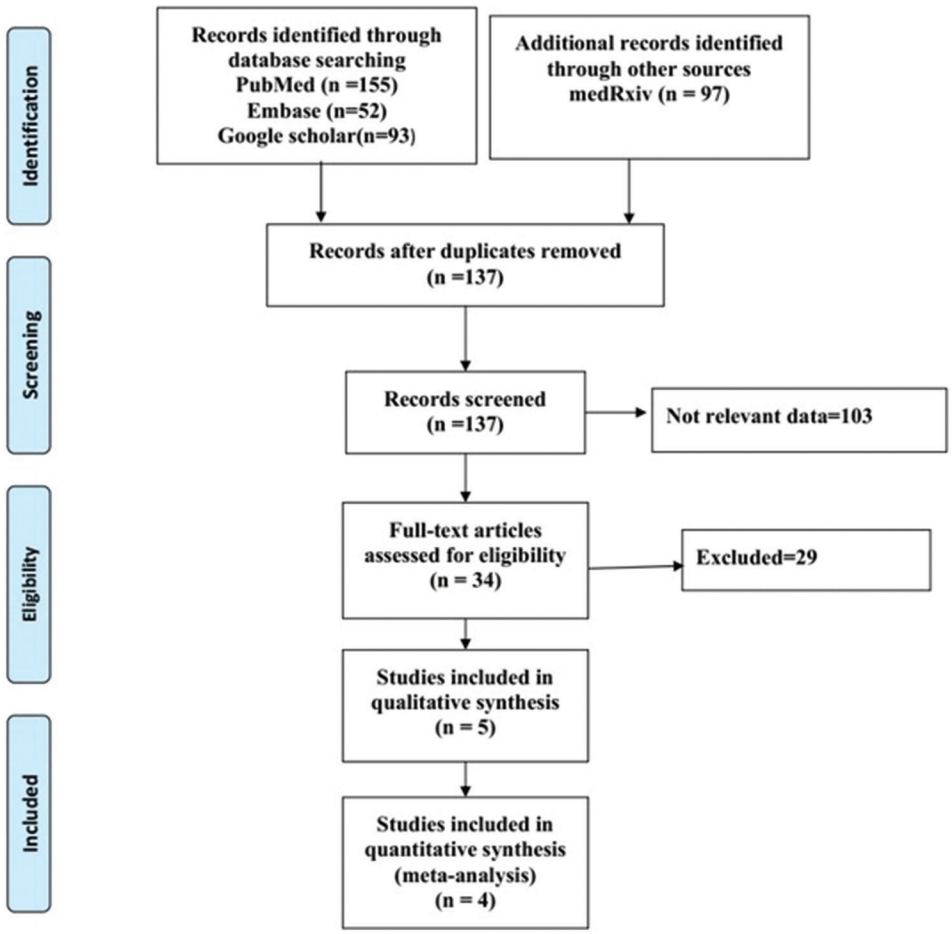

Figure 1: PRISMA-2009 flow diagram. PRISMA = preferred reporting items for systematic review and meta-analysis

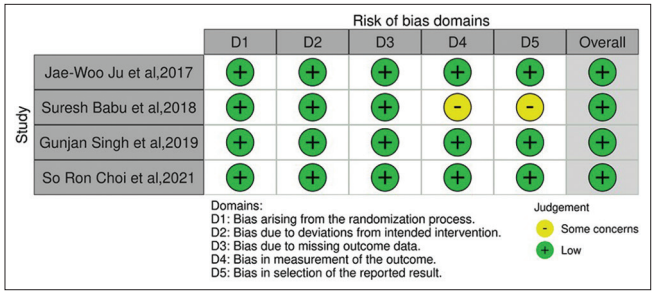

Figure 2: RoB 2 assessment for the included RCTs. RCTs = randomized controlled trials

calcium was used concurrently[22,24,25] and in a single study, it was applied immediately after the application of neostigmine[23] [Table 1].

Meta-analyses

Neuromuscular recovery time

Four articles with 266 patients were evaluated for the duration of recovering from RNMB. Coadministration of calcium decreases the recovery time for a complete reversal of RNMB significantly (Standardized mean difference [SMD] = −2.13, 95% CI: −2.66 to −1.59, I^2 = 66%) [Figure 3a].

RNMB at 5 min

Three studies with a total of 206 patients were evaluated for the incidence of RNMB at 5 min after administration of neostigmine. Intravenous calcium reduces the risk of residual blockade significantly at 5 min (odds ratio [OR] = 0.21, 95% CI: 0.10–0.46, I^2 = 0%) [Figure 3b].

TOF ratio at 5 min

A significantly better TOF ratio was found with calcium coadministration (MD = 9.28, 95% CI: 4–14.57, I^2 = 66%, n = 206) [Figure 3c].

RNMB at 10 min

No significant reduction in RNMB was found at 10 min after administration of neostigmine with coadministration of calcium, irrespective of dosages, in three studies with a total of 206 patients (OR = 0.41, 95% CI: 0.15–1.09, I^2 = 0%) [Figure 3d].

However, another study found a lesser risk of PORC at 10 min only with the administration of calcium at 10 mg/kg (one out of 26) in comparison to calcium

Table 1: Characteristics of included studies

Authorref	Design	Country	Sample size	Non-depolarizing neuromuscular blocker used	Intervention	Time point of intervention	Primary outcome
Ju *et al.*[22]	RCT, SC	South Korea	53	Intubation: rocuronium (0.8 mg/kg) Maintenance: rocuronium (0.15 mg/kg)	3% Calcium chloride (5 mg/kg) was given along with neostigmine (25 μg/kg) and atropine (15 μg/kg)	When the TOF count reached 4	The neuromuscular recovery time was 25% shorter than that of the control group without calcium chloride
Babu *et al.*[23]	RCT, SC	India	60	Non-depolarizing muscle relaxant used (drug not specified)	10 ml of 10% calcium gluconate immediately after neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg)	When the TOF count reached 4	Coadministration of calcium along with neostigmine decreased neuromuscular recovery time
Singh *et al.*[24]	RCT, SC	India	75	Intubation: atracurium (0.5 mg/kg) Maintenance: atracurium (0.1 mg/kg)	10% calcium gluconate in the dose of 5 mg/kg with neostigmine (70 μg/kg) and glycopyrrolate (20 μg/kg)	When the TOF count reached 4	Calcium administration with neostigmine enhanced neuromuscular recovery from non-depolarizing muscle relaxant. The time for reversal from administration to extubation as well as to end of anesthesia was also significantly reduced
Choi *et al.*[25]	RCT, SC	South Korea	78	Intubation: rocuronium (0.8 mg/kg) Maintenance: vecuronium (0.02 mg/kg)	5 or 10 mg/kg of calcium gluconate with neostigmine (0.04 mg/kg) and both 0.2 mg of glycopyrrolate and 0.4 mg of atropine per 1 mg of neostigmine	When the TOF count reached 4 and the TOF ratio was between 0.2 and 0.7	The neuromuscular recovery time was 5.3 min in the control group, 3.9 min in the calcium 5 group, and 4.1 min in the calcium 10 group (P=0.004)

RCT=randomized controlled trial, SC=single center, TOF=train of four

administered at 5 mg/kg (four out of 26) and the control group (four out of 26).[25]

TOF ratio at 10 min

No significant difference was found in patients who received calcium compared to those who did not (MD = 0.40, 95% CI: −1.3–2.11) [Figure 3e].

Significant heterogeneity was found among studies assessing the recovery period for a complete reversal of RNMB and TOF ratio at 5 min.

Quality of evidence

We found a low quality of evidence on the utility of the coadministration of calcium in rapid recovery from RNMB [Table 2].

Publication bias

The funnel plot indicated no qualitative publication bias [Figure 4].

Discussion

We found low-quality evidence that coadministration of calcium and neostigmine leads to a shorter neuromuscular recovery time, improved TOF ratio, and lesser incidence of PORC at 5 min.

Similarly, another recent study also found administration of 5 mg/kg of calcium chloride after neostigmine improves the neuromuscular recovery by increasing the TOF ratio at 5 and 10 min and reducing the PORC.[26]

A significant improvement in a depressed TOF ratio due to clindamycin overdose was reported with intravenous calcium chloride (1.5 mg/kg) and neostigmine (2 mg).[27]

A decline in the duration of action of NDMAs was noted among patients with hyperparathyroidism due to hypercalcemia.[15,16,28] On the other hand, with the application of a calcium channel blocker (verapamil or amlodipine), the presynaptic Ach release was found to be deferred.[12,29] Similarly, nicardipine was found to facilitate the ease of intubation by fastening the onset of action of rocuronium.[30]

All these findings indicate an anti-neuromuscular blockade potential of calcium, as it not only increases the Ach release presynaptically, but also transmutes the affinity of receptors postsynaptically.

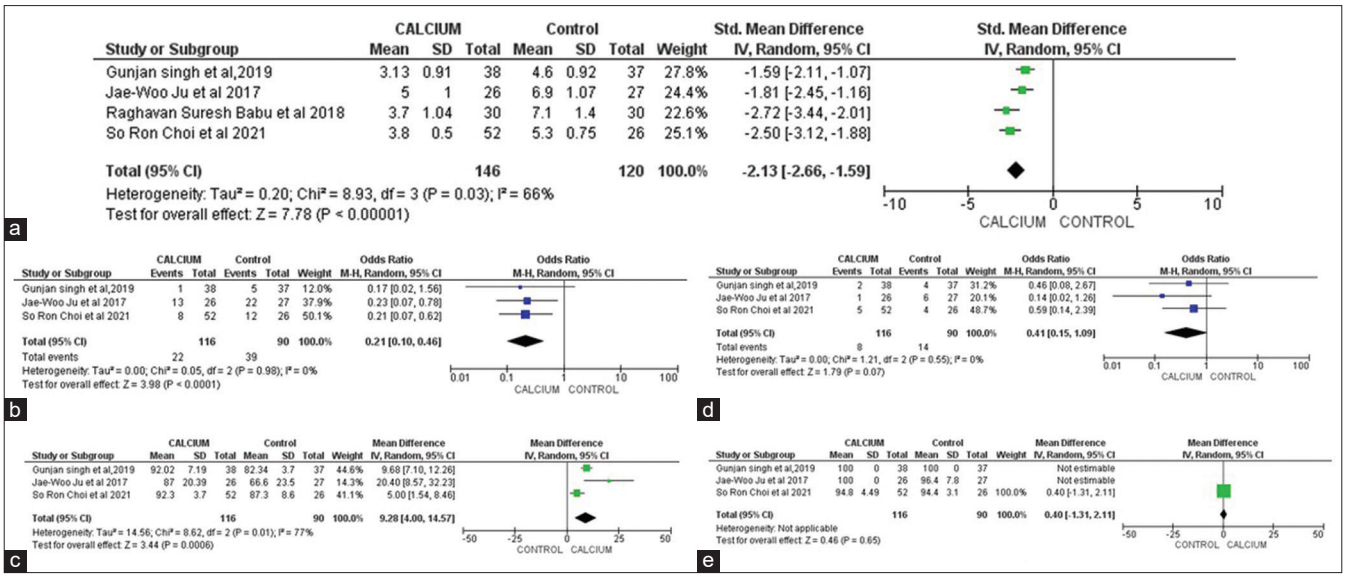

Figure 3: The impact of coadministration of calcium with neostigmine on neuromuscular recovery time (a), residual neuromuscular blockade at 5 min (b), TOF ratio at 5 min (c), residual neuromuscular blockade at 10 min (d), and TOF ratio at 10 min (e). TOF = train of four

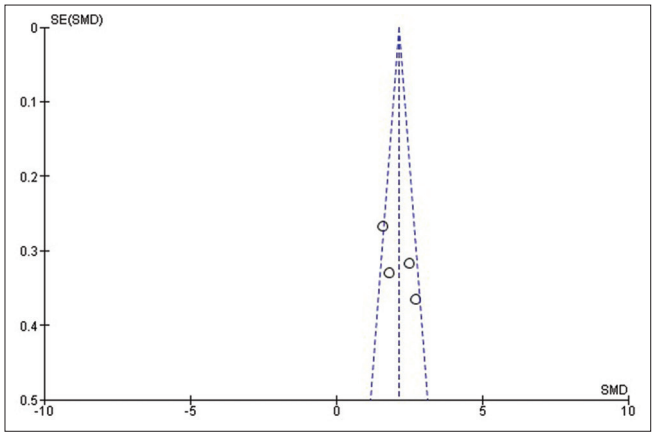

Figure 4: Funnel plot of the included studies for assessment of publication bias

Although the coadministered calcium with a classic reversal agent accelerates recovery, the dose–response relationship of muscle relaxants with calcium concentration is unclear and is yet to be recommended.

There is a positive correlation between total calcium and ionized calcium. However, ionized calcium plays a crucial role at the neuromuscular junction.[31]

While administration of 5 mg/kg of calcium chloride increased the serum calcium level by 0.7 mg/dl, 10 mg/kg of calcium gluconate increased it by 1.4 mg/dl.[32] Thus, it can be safely coadministered in normocalcemic patients, as symptomatic hypercalcemia usually occurs with serum calcium ≥15 mg/dl, and the normal serum calcium concentration is 8.5 to 10.5 mg/dl.

Choi *et al.*[25] reported an initial transient hyperdynamic change of ≤20%, which subsides within 10 min. They reasoned it with a possible synergistic effect of acetylcholinesterase inhibitors and calcium through the rapid exchange of calcium in contractile cell membranes of the myocardium along with the effect of anticholinergic agents.[20]

Another study also reported early hemodynamic alterations within 20 s and normalization of cardiac index in around 1 min.[33]

Strengths and limitations

The current study is one of the extensive systematic reviews of the utility of calcium in neuromuscular recovery in the early period of neuromuscular blockade, highlighting an important, yet overlooked topic.

However, the findings are heterogeneous and of low-quality evidence. Variation in the selection of NDMR across the studies and application of calcium along with or immediately after the application of neostigmine with a TOF count of 4 but with different TOF ratios may be the probable explanation. The formulation and dosage of calcium are also yet to be standardized, and the level of magnesium, a physiological antagonist of calcium that may affect neuromuscular recovery. Subgroup analyses could not be done due to the scarcity of data.

Conclusion

Calcium can be coadministered along with neostigmine during the early neuromuscular blockade period to enhance neuromuscular recovery. However, further studies on calcium concentration and the dose–response relationship with muscle relaxants and acetylcholinesterase inhibitors are required.

Table 2: GRADE evidence profile of the impact of co-administration of calcium with neostigmine

Out come	No. of participants			Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quality of evidence (grade)	Relative effect
	Total no.	Intervention	Control							
Neuromuscular recovery time	266	146	120	No	No	Yes	No	None	Low ⊕⊕⊖⊖	SMD = −2.13 (95% CI: −2.66 to −1.59)
Residual neuromuscular blockade at 5 min	206	90	116	No	No	Yes	No	None	Low ⊕⊕⊖⊖	OR=0.21 (95% CI: 0.1–0.46)
TOF ratio at 5 min	206	90	116	No	No	Yes	No	None	Low ⊕⊕⊖⊖	MD=9.28 (95% CI: 4–14.57)
Residual neuromuscular blockade at 10 min	206	90	116	No	No	Yes	Yes	None	Very low ⊕⊖⊖⊖	OR=0.41 (95% CI: 0.15–1.09)
TOF ratio at 10 min	206	90	116	No	No	Yes	Yes	None	Very low ⊕⊖⊖⊖	MD=0.40 (95% CI: −1.3–2.11)

CI=confidence interval, GRADE=Grading of Recommendations Assessment, Development, and Evaluation, MD=mean difference, OR=odds ratio, TOF=train of four

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Conflicts of interest

There are no conflicts of interest.

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