



## ORIGINAL RESEARCH PAPER

## Anaesthesiology

### CALCIUM GLUCONATE CO-ADMINISTERED WITH NEOSTIGMINE FASTEN NEUROMUSCULAR BLOCKADE RECOVERY IN PEDIATRIC PATIENTS: A DOUBLE- BLIND RANDOMIZED CONTROLLED PILOT STUDY

**KEY WORDS:** Train of four, Coadministration, Acceleromyography, Tubocurarine

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#### ABSTRACT

**Background :** Reversal agents given after completion of surgery have variations in neuromuscular recovery time. Few studies are published regarding the role of using calcium with reversal agents for faster recovery in adults only but not in pediatric group.

**Aim :** Compare the duration of neuromuscular recovery after giving reversal drug with or without calcium gluconate in pediatric patients.

Primary outcome was assessment of neuromuscular recovery time. Secondary outcome, train of four was measured at the end of surgery at 3, 5 and 10 minutes after giving reversal

**Results:** Neuromuscular recovery time, Train of four ratio (TOFr) 5 min after neostigmine administration was significantly decreased in calcium group. Residual neuromuscular blockade 3 min after giving reversal was significantly higher in control group.

**Conclusion:** In the calcium group, time for reversal administration to extubation as well as to end of anaesthesia was significantly shorter than in the control group.

## INTRODUCTION

Reversal of residual neuromuscular block by neostigmine is an established practice in modern anaesthesiology. Neostigmine reversibly inhibits acetylcholinesterase at the neuromuscular junction and thereby increases available acetylcholine at the muscle end-plate. Neostigmine has a peak action at 9 minutes and duration is about 20- 30 minutes only. Incomplete reversal of neuromuscular blocking agent at the end of surgery is associated with both postoperative morbidity and mortality as it may be associated with severe hypoxemia or upper airway obstruction. Several patient related clinical factors such as acid-base or electrolyte abnormalities and hypothermia cause a delayed recovery from neuromuscular blockade. Calcium evokes the release of acetylcholine from the muscle cell but also decrease the degree of acetylcholine induced depolarization at the motor end plate. A recent small randomized controlled trial in adult patients reported that intravenous calcium gluconate administered with neostigmine hasten recovery of neuromuscular blockade and decreases incidence of post operative recurarization (PORC). However, response to muscle relaxants in the pediatric practice is fundamentally different than that in adults mainly due to high cardiac output, increased sensitivity of receptors to the muscle relaxants and high volume of distribution. This leads to faster onset and also faster reversal of blockade in comparison to the adults. However, no study has evaluated clinical effects of calcium coadministered with neostigmine on recovery profile neuromuscular blocking agent.

## Method

After approval of the institute ethics committee and registration in the National Clinical Trial Registry of India ([www.ctri.nic.in](http://www.ctri.nic.in)); registration no: CTRI/2018/03/012386 dated 07 March 2018) this prospective double blind randomized controlled trial was conducted in a tertiary care teaching hospital in India.

After obtaining written informed consent from the parents, n=76 patients of American Society of Anesthesiologists physical status I-II aged between 5-15 years, for elective infra-umbilical surgeries involving endotracheal intubation under general anaesthesia were recruited in this study. Assent was also taken for all the children of more than seven years age.

The exclusion criteria involved suspected difficult airway, history of bronchial asthma, neuromuscular disease, hepatic or renal disease, clinically suspected hypercalcemia, severe or significant congenital heart disease, bleeding diathesis, allergies to glycopyrrolate or neostigmine, parental refusal and weight of less than 10 kg.

All patients were evaluated by anaesthesia team on the day before surgery as per institute protocol. All the patients had an intravenous cannula in situ and general anaesthesia was induced with propofol 2mg/kg and fentanyl 1mcg/kg. After induction of general anaesthesia, continuous neuromuscular monitoring using acceleromyography at the adductor pollicis muscle was used to determine train of four ratio (TOF). The acceleration transducer was placed on the volar side of the distal phalanx of the thumb. Electrodes were then placed over the ulnar nerve on the volar side of the wrist. After the calibration and standardization, intravenous atracurium at a dose of 0.5 mg/kg was administered and TOF was monitored every 20s. Trachea was intubated with an appropriate sized endotracheal tube when a TOF count (TOFc) of 0 was achieved. During the course of surgery whenever the TOFc was at least 2, 0.1 mg/kg of atracurium was given. Patients were kept warm using hot air blanket to maintain core temperature of more than 36°C. At the end of surgery, it was observed to keep the TOFc-4 to return on its own. As TOFc of 4 achieved, all the patients received 70µg/kg of neostigmine and 20µg/kg of glycopyrrolate. In group CG, 10% calcium gluconate in the dose of 5mg/kg was

given with neostigmine and glycopyrrolate and same volume of normal saline was administered to the patients in the group C. Patients were extubated after meeting the extubation criteria and moved to the postanaesthesia care unit (PACU).

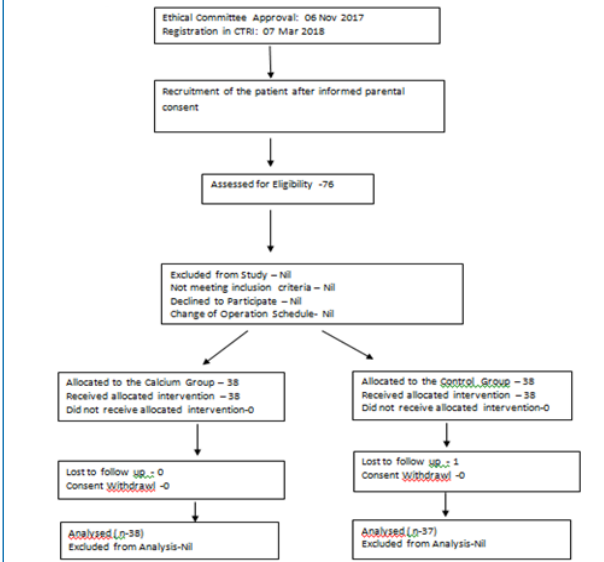


Fig 1 Consort Flowchart

Randomization sequence was generated from a computerized program, and randomization sequences were kept inside a sealed opaque serially numbered envelope, only opened just before administering study drug. Both the study drugs were prepared by an anaesthesiologist who were not a part of this study in identical syringes and handed over to the attending anaesthesiologist just before administration. Postoperative outcome data were collected by an anaesthesiologist who was blinded to the group allocation of the patients.

The primary outcome of this study was the neuromuscular recovery time [time from neostigmine administration to the TOF ratio (TOFr) of 0.9]. Secondary outcomes were TOFr at 3, 5, 10 and 20 min after neostigmine administration and the incidence of PORC at each time point. PORC was defined as a TOFr less than 0.9 with quantitative neuromuscular monitoring. As far as PACU is concerned the clinical symptoms indicating PORC was assessed by the nurse blinded to the study. She provided details about general weakness, visual symptoms and difficulty swallowing.

Table 2: Comparison between Calcium (CG) and the Control (C) group.

	Calcium Group (n= 38)( CG)	Control Group (n= 37)(C)	P Value
<b>Neuromuscular Recovery Time (min)</b>	3.09 (1.33-5.25)	4.61 (2.83-6.75)	<0.001
<b>Time from neostigmine administration to Extubation(min)</b>	7.10 (4.17-10.25)	8.82(6.75-12.17)	<0.001
<b>TOFr(Train of Four Ratio) after neostigmine administration(%)</b>			
5 min	92.02	82.34	<0.001
10 min	100	100	1
20 min	100	100	1
<b>Residual Neuromuscular Blockade after Neostigmine Administration (number of patirnts)</b>			
3 min	18	37	<0.001
5 min	1	5	0.108
10 min	2	4	0.430
20 min	0	0	0

DISCUSSION

With best of our knowledge, this is only randomized trial that evaluated role of ionized calcium on neuromuscular recovery after non- depolarizing muscle relaxant in pediatric patients. Most important finding of this study is that calcium decreases time to achieve TOFr 0.9 after neostigmine administration which leads to a shorter time to extubation. Mean TOFr at 5 minutes after neostigmine administration and incidence of PORC was also significantly lower.

Analysis was conducted using IBM SPSS STATISTICS (version 22.0). 75 patients including 38 in the Calcium group and 37 in the Neostigmine group were included in the study as one of the patients in the neostigmine group was excluded from the study . The distribution of variables was tested with the Shapiro-Wilk test/ Kolmogorov-Smirnov tests of normality. Group comparisons of values of skewed data were made with the Mann Whitney test for 2 groups. Independent t-test was applied for comparison of 2 groups when data was normally distributed.Group comparisons were made with the Chi-Square test. P value < 0.05 was considered significant.

RESULTS

Baseline demographic parameters were comparable in both the groups and none of the patients had an esophageal temperature of less than 36 degree C.

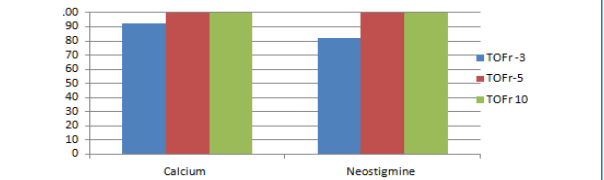


Fig 2 Train of Four Ratio comparison between the two groups

In the group CG, neuromuscular recovery time was significantly shorter than group C [median (IQR) 3.09 (1.33-5.25)] minutes versus 4.61 (2.83-6.75); p<0.01, Mann Whitney U test]. Time to extubation from neostigmine administration was significantly shorter in group CG compared to group C [median (IQR) 7.10 (4.17-10.25)] minutes versus 8.82(6.75-12.17) minutes; p<0.001, Mann- Whitney U test. Mean TOFr at 5 minutes after neostigmine administration and incidence of residual neuromuscular blockade was higher in group C than group CG.

Table 1: Demographic and baseline characteristics of the patients [Data represented as median (IQR)]

	Group CG (n=38)	Group C (n=37)	P value
<b>Age(yrs)</b>	8.44(5-14)	8.59(5-14)	0.810
<b>Weight(kgs)</b>	29.28(20-40)	32.02(20-55)	0.157
<b>Gender</b>	Male 25 Female 13	Male 09 Female 28	0.347
<b>Duration of Surgery (hr)</b>	1.99(0.75-3.33)	1.71(0.80-3.25)	.081
<b>Duration of Anaesthesia(hr)</b>	2.60(1.17-4.17)	2.14(1-3.67)	.009

Calcium is known to decrease the degree of depolarization produced by acetyl choline, accentuate desensitization, and alter the affinity of receptors postsynaptically. Presynaptically, calcium increases the acetyl choline release. Despite knowing the above facts it is too difficult to estimate precisely about the overall effect of change in calcium concentration on the dose response relationship of muscle relaxants.<sup>1,2</sup> Calcium channel blockers like verapamil and amlodipine have been proved to alter the

neuromuscular transmission in healthy volunteers<sub>3</sub>. Nicardipine was also found to improve intubation conditions and decreased onset of action of rocuronium<sub>4</sub>. In comparison to calcium, magnesium was also found to reduce the onset time of rocuronium and also attenuated non depolarizing neuromuscular recovery after neostigmine administration<sub>5,6</sub>. There are case reports that indicate decreased duration of action of muscle relaxants in patients with hypercalcemia<sub>7</sub>.

Spontaneous recovery from the effects of neuromuscular blockers (NMB) is possible and depends upon the elimination of the drug by any of the mechanisms between metabolism, spontaneous degradation or excretion via kidneys. Addition of inhalational anaesthetic agents intensifies the effects of NMB. In addition to all the above factors, interindividual variation also exists. Due to these multiple mechanisms working simultaneously, anticipation of spontaneous recovery becomes unreliable. Pediatric patients can have upto 25% standard deviation of an average response for all neuromuscular parameters including time to full recovery<sub>8</sub>. This unpredictability prevents efficient scheduling of short surgical cases that require use of muscle relaxants. More importantly, the risk of residual curarisation is high and complications are clinically important<sub>9</sub>. These high incidences of residual NMB can be associated with post operative upper airway obstruction requiring intervention and severe hypoxemia<sub>10</sub>. It is therefore important to ensure that the duration of recovery is short and highly predictable.

This can be done with the help of clinical evaluations that depends on signs of residual muscle weakness, qualitative neuromuscular monitoring using nerve muscle stimulator or quantitative neuromuscular monitoring like single twitch response, double burst suppression or train of four.

Relying on clinical signs for estimation of recovery from the NMB is not a very efficient method as a considerable level of NMB is still present at the time of extubation. It was estimated from the studies that if using clinical criteria for extubation the TOF ratio of 0.5 and 0.67 was present in children and adults respectively when atracurium and rocuronium was used<sub>11,12</sub>.

In clinical practice, time and again we have included hypocalcaemia as one of the differential diagnosis in cases of delayed recovery and given calcium. Despite this, the role of calcium in NMB is underrated and not reported.

Our study has some limitations. First, we did not measure the blood calcium and magnesium concentration of the children prior to taking them up for the study presuming them to be in normal range. Second, the calcium gluconate was administered at the reappearance of TOFc-4, so the efficacy was measured only for the shallow block and not for the deep blocks. Finally, all the patients were administered the fixed dose of calcium gluconate irrespective of age of the patient, amount of relaxant given, or the duration of surgery. Further work can be done on dose response relationship.

## CONCLUSION

In conclusion, calcium gluconate given with neostigmine for neuromuscular blockade reversal in patients posted for general surgery under inhalational agent has decreased the neuromuscular recovery in terms of train of four at 3 minutes. Being a pilot study involving 75 patients, it will be prudent to do the study on large scale.