

## Reversal of Neuromuscular Blockade Based on Train of Four Response: a Prospective Randomized Controlled Trial

Spurti Kalburg<sup>1</sup>, Handattu Mahabaleswara Krishna<sup>1\*</sup>, Ajith kumar Pillai<sup>1</sup>

<sup>1</sup>Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, India

**Background and aims:** Use of neostigmine to reverse the non-depolarizing neuromuscular block is a standard practice. Reversal with neostigmine based on body weight is still commonly followed. However, neostigmine may affect adversely if used empirically in the absence of residual blockade. This study compares the empirical technique of reversal based on body weight with reversal using neostigmine dose adjusted to train-of-four (TOF) response. **Methods:** This prospective, double-blinded, randomized controlled trial included 126 patients undergoing surgery under general anaesthesia, lasting for >1 hour. They were randomized into group control receiving weight-based reversal (0.05 mg/kg neostigmine) and group study receiving dose determined by TOF response. Signs of residual paralysis after extubation were observed. TOF ratios/count, reversal to extubation time, dose and side-effects of reversal agent were also noted. **Results:** Patient characteristics were comparable in both groups. Number of patients with signs of residual weakness was less in group study (26/63), but comparable to group control (40/63,  $p=0.094$ ). Number of patients with  $\text{TOF} \geq 0.9$  at reversal and extubation was significantly high in group study (40/63) than group control (22/63), and number of patients with TOF count <4 were significantly high in group control than group study (17/63 vs 8/63). Overall TOF ratio at reversal and extubation, reversal-extubation time, time taken to reach TOF 0.9 and side-effects were comparable. **Conclusion:** Reversal of neuromuscular block with neostigmine dose based on TOF ratio is comparable to weight-based reversal with respect to postoperative residual weakness, reversal-extubation time and side effects of reversal agent.

**Keywords:** Neostigmine, Postoperative residual paralysis, Reversal, Train-of-four ratio, Vecuronium

### Introduction

Postoperative residual neuromuscular blockade is a known, potentially preventable complication after general anaesthesia.<sup>1</sup> It is still a common practice to reverse the non-depolarizing neuromuscular blockade using neostigmine based on body weight of the patient without using the quantitative neuromuscular monitor (0.03-0.075 mg/kg; 0.05 mg/kg being the most commonly used empirical dose).<sup>2</sup> This dose is often chosen even when intraoperative neuromuscular monitoring is done. Though the positive effects of intraoperative neuromuscular monitoring on postoperative outcomes have been demonstrated, still it may not be used due to non-availability of

the equipment or reluctance on part of the anaesthesiologist.<sup>3</sup>

When acetyl cholinesterase enzyme is inhibited maximally by neostigmine, any further increase in dose will not provide an additional effect. Unfortunately, complete inhibition of acetyl cholinesterase enzyme occurs within a narrow therapeutic dose range. Therefore, neostigmine provides only partial recovery. If neostigmine is given during profound block (Train of four count 1 or 2), the time taken for complete recovery of the patient is almost equal to spontaneous recovery time. Hence reversal at this deep neuromuscular block may lead to paradoxical muscle weakness. In contrast to this if neostigmine is administered after complete spontaneous recovery, collapsibility of airway is increased and activation of genioglossus is impaired in response to negative pharyngeal pressure. Hence antagonizing with anticholinesterase is not advised if established neuromuscular block is not present.<sup>4,5</sup> Neostigmine can produce several systemic side effects.<sup>6</sup> Hence, dosing neostigmine based on the extent of neuromuscular blockade may be the appropriate practice.

This study aimed to find out whether dosing neostigmine based on Train of four (TOF) ratio is

\*Correspondence: Handattu Mahabaleswara Krishna

E mail: [hmkrishna20032002@yahoo.com](mailto:hmkrishna20032002@yahoo.com)

 <https://orcid.org/0000.0002-6106-4556>

Received: 22/02/2021

Accepted: 31/05/2022

DOI: <http://doi.org/10.4038/slja.v30i2.8790>



beneficial or not compared to the routinely practiced empirical dosing based on body weight following clinical judgement for reversal. The primary objective was to compare the incidence of residual muscle weakness in the postoperative period in the two groups. The secondary objectives were to compare (a) TOF ratio while giving reversal agent (b) TOF ratio at extubation (c) Time taken for extubation after giving reversal agent (d) Time taken to achieve TOF ratio 0.9 after giving reversal agent and (e) Side effects of neostigmine.

### Methods

This prospective, double-blinded randomized controlled trial was conducted after obtaining approval from Institutional ethics committee and registration at Clinical Trial Registry (CTRI/2018/05/014182). Inclusion criteria were age 20-60 years, either gender, American Society of Anesthesiologists Physical Status (ASA) 1 or 2, body mass index (BMI) <30 Kg/m<sup>2</sup>, surgeries requiring general anaesthesia with intubation, and lasting > 1 hour. Exclusion criteria were neurological impairment, neuromuscular disorders, pregnant women, use of drugs interfering with neuromuscular transmission, renal insufficiency (serum creatinine > 1.8 mg/dL), hepatic disorders (liver function tests > 50% of normal values), surgical positions that prevent access to neuromuscular monitoring.

Preoperative assessment was done and written informed consent was taken. Standard guidelines for fasting and premedication were advised. On the day of surgery, randomization was done using computer generated random number table. Group allocation was concealed using sequentially numbered opaque sealed envelopes. All the patients and the study investigator were blinded to the group allocation. The two groups were Group control and Group study. Standard monitoring was used. Intravenous (IV) access was secured. After preoxygenation, anaesthesia was induced with IV fentanyl (2 mcg/kg) and IV propofol (2-2.5 mg/kg) titrated to loss of verbal response. Manual ventilation was confirmed, non-depolarizing muscle relaxant IV vecuronium (0.1 mg/kg) was administered and ventilated with 2% isoflurane in 100% oxygen. After three minutes, tracheal intubation was done. Anaesthesia and analgesia were maintained according to the discretion of the concerned anaesthesiologist. Intermittent boluses of 0.02 mg/kg of IV vecuronium was administered every 20 minutes or as considered required by the

concerned anaesthesiologist. Quantitative neuromuscular monitoring device- TOF guard was attached to all the patients and used to measure TOF ratio (residual paralysis). The standard site chosen was the ulnar nerve and the adductor pollicis muscle. The negative electrode was placed distally at the proximal wrist crease and the positive electrode 2 cm proximal to this. Nerve was stimulated using supramaximal current which had been determined for the patient after induction of anaesthesia but before neuromuscular blockade.

There were 2 observers in the study. Observer 1 performed the preoperative evaluation, enrolled the participants, obtained consent and was blinded to the patient's allocated group while observing the outcome measures. Observer 2 randomized the patients and provided reversal agent dose as per the group allocation.

In group control, at the end of the surgery, all inhalational anaesthetic agents were tapered. Once the patient had some spontaneous respiratory efforts, TOF ratio was noted by observer 1 and conveyed to observer 2. Irrespective of the TOF ratio, reversal drug, i.e. combination of IV neostigmine (0.05 mg/kg) and glycopyrrolate (0.01 mg/kg) was given based on the actual weight of the patient by observer 2.

In group study, the same was followed except that the dose of reversal given by observer 2 was based on the recommendations given in Table 1.<sup>7</sup>

**Table 1.** Neostigmine dose based on TOF response

TOF Response	Neostigmine dose
TOF count 0 or 1	Delay until count is 2 or 3
TOF count 2 or 3	70 mcg/Kg
TOF count 4 (ratio<0.4)	40-50 mcg/Kg
TOF count 4 with fade (ratio 0.4-0.9)	20 mcg/Kg
TOF count 4 without fade (ratio>=0.9)	Avoid anticholinesterase

Extubation was done as per the discretion of the consultant anaesthesiologist based on his or her clinical judgement. The outcome measures mentioned before were observed and recorded by observer 1. The amount of residual muscle weakness in the immediate postoperative period was assessed under the following headings

- Inability to sustain head lift > 5sec
- Inability to sustain limb lift > 5 sec
- Inability to sustain hand grip > 5 sec
- Inability to speak
- Inability to swallow
- Inability to smile (inability to show all teeth)
- Tidal volume < 5mL/Kg

The following side effects of reversal agent were actively looked for - nausea/ vomiting, bradycardia (heart rate > 20% drop from the baseline value), bronchospasm, airway obstruction (stridor), hypoxaemia/ desaturation (SpO<sub>2</sub> <90%). Sample size was calculated using the formula  $n = 2[Z_{1-\alpha/2} + Z_{1-\beta}]^2 \sigma^2 \div d^2$  where,  $\alpha$  = level of significance,  $\beta$  = power of study,  $Z_{1-\alpha/2} = 1.96$  for  $\alpha$  at 5% level of significance,  $Z_{1-\beta} = 0.84$  for 80% power of study,  $d/\sigma =$  effect size (0.5 is anticipated value). Sample size was estimated taking time taken to reach TOF ratio 0.9 after giving reversal agent as the outcome measure, a difference in effect size of 50% between the groups was considered to be

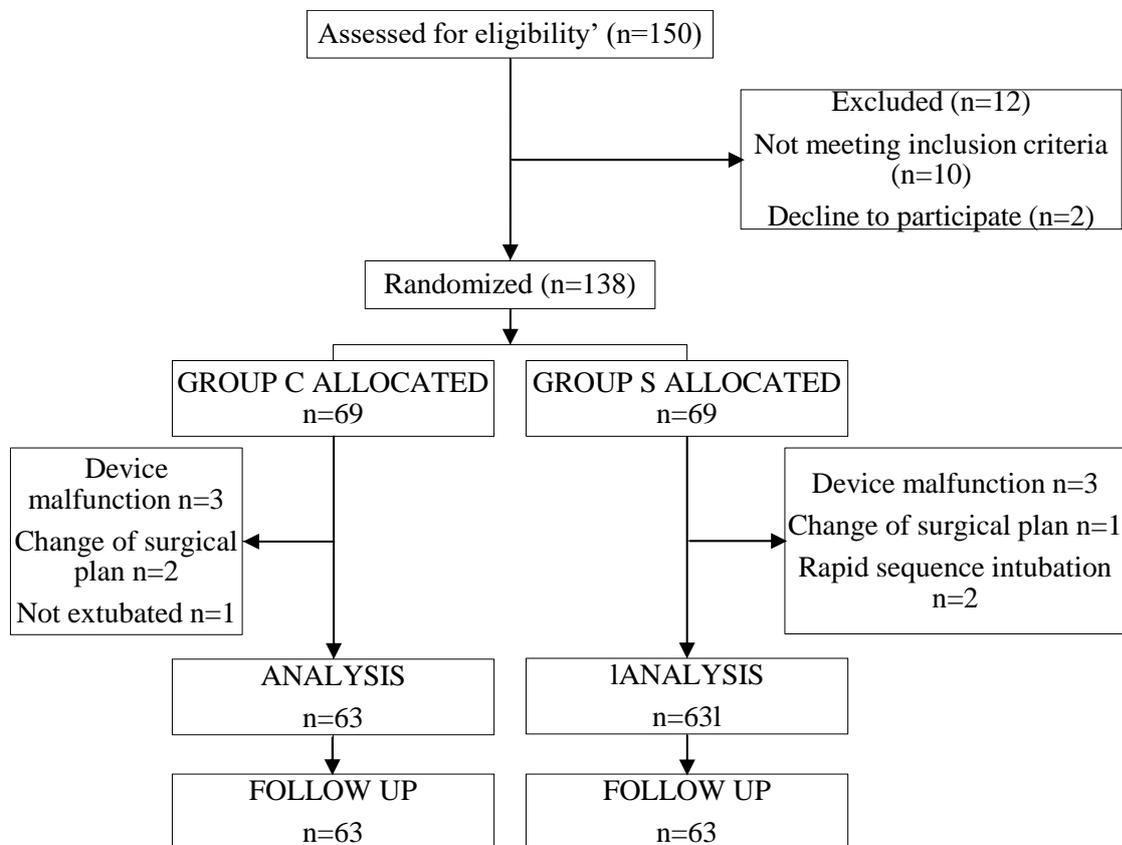
significant. Upon calculation, sample size of 63 patients was required in each group.

Data were analyzed using *SPSS version 16* for Windows. Numerical data were analyzed using Independent t-test or Mann Whitney U test and categorical data were analyzed using the Chi-square test.  $P < 0.05$  was considered significant.

### Results

Consort flow chart for the study is given in Figure 1. The patient characteristics are given in Table 2. The mean (standard deviation) duration of surgery was 113.49 (37.88) min in group control and 128.25 (37.34) min in group study ( $P=0.029$ ). But this difference in the duration of surgery (about 15 min) is unlikely to have influenced the results. Table 3 shows number of patients with signs of residual paralysis. Many patients in both the groups were unable to smile (show teeth) as a test for residual paralysis. Ability to smile may not be reliable to determine residual weakness due to difficulty in its assessment.

**Figure 1.** CONSORT flow diagram



**Table 2.** Patient characteristics

	Group control	Group study
Age (years)	39.76 (10.79)	42.23 (11.91)
Height (cm)	156.28 (5.46)	153.04 (6.67)
Weight (Kg)	57.51 (6.53)	56.55 (5.99)
Body Mass Index (Kg/m <sup>2</sup> )	23.50 (2.09)	24.10 (2.0)
Gender (Male/Female)	25/38	24/39

Mean (standard deviation) for age, height, weight, body mass index and absolute numbers for gender

**Table 3.** Signs of residual paralysis

	Group control (No of patients)	Group study (No of patients)	P value*
Inability to sustain head lift > 5 seconds	14	7	0.094
Inability to sustain limb lift > 5 seconds	4	1	0.171
Inability to sustain hand grip > 5 seconds	4	1	0.171
Inability to smile	16	17	0.839
Inability to swallow	0	0	-
Inability to speak	2	0	0.154
Tidal volume <5mL/kg	0	0	-
Number of patients with no signs of residual paralysis	44	46	0.693

\* Chi Square test

Table 4 shows TOF ratios at the time of giving reversal agent. The numbers of patients with TOF ratio  $\geq 0.9$  was significantly different in both the groups. This could be the reason for relatively less number of patients with signs of residual paralysis in group study as 10 patients had already reached TOF ratio  $\geq 0.9$  at reversal when compared to 3 patients in group control. Similarly, the difference in number of patients with no TOF ratio (TOF count was less than 4, hence ratio cannot be obtained) was statistically significant between the groups. This suggests more number of patients in group control were at

deep level of neuromuscular blockade at the time of reversal, thus accounting for more number of patients with residual paralysis. In all other TOF ratios the numbers of patients in both the groups were comparable.

Table 5 shows TOF ratios at the time of extubation. The number of patients who had complete reversal as evidenced by TOF ratio  $> 0.9$  at the time of extubation was greater in group study compared to group control ( $p=0.04$ ). Residual neuromuscular block is defined as presence of signs of residual weakness with TOF ratio  $< 0.9$  after extubation.

**Table 4:** TOF ratios at reversal

TOF ratio	Group control (n=63)	Group study (n=63)	P value*
$\geq 0.9$	3	10	0.04
0.8-0.89	7	4	0.34
0.7-0.79	3	6	0.29
0.6-0.69	6	5	0.75
0.5-0.59	8	5	0.37
0.4-0.49	5	4	0.72
0.3-0.39	3	10	0.04
$\leq 0.29$	11	11	-
No ratio	17	8	0.04

Data are absolute number of patients having the specified TOF ratio. \*Chi square test

**Table 5.** TOF ratio at extubation

TOF ratio	Group control (n=63)	Group study (n=63)	P value*
≥0.9	19	30	0.04
0.8-0.89	24	18	0.25
0.7-0.79	13	8	0.23
0.6-0.69	5	2	0.24
0.5-0.59	2	3	0.64
≤0.49	0	2	-

Data are absolute number of patients having the specified TOF ratio. \*Chi square test

The time taken for extubation after giving the reversal drug was 3.5 (2-5) min in group control and 4 (3-5) min in group study [data are median (interquartile range), compared with Mann Whitney U test, P=0.682]. Time taken to reach TOF ratio >0.9 was comparable between the two groups [5 (3-8) min in group control and 6 (3-8) min in group study, Mann Whitney U test, P=0.608].

### Discussion

In this study, empirical administration of neostigmine dose based on body weight (0.05 mg/Kg) was compared with dose based on the amount of residual paralysis at the end of surgery, with respect to residual weakness of muscles in the postoperative unit. It was found that there was no difference in the clinical incidence of postoperative residual weakness with these two regimens.

The dose of neostigmine adjusted to the amount of residual neuromuscular blockade was as per the recommendations reviewed by Kopman and Eikermann.<sup>7</sup> We found that 34.92% patients required less (20mcg/kg) dose of reversal and 15.8% did not receive any reversal agent. Total 8/63 patients (12.69%) required more than usual dose (70mcg/kg) due to reduced TOF count at the time of reversal and nearly half of the patients in study group required less than usual dose. This shows that 50% of the patients would get exposed to the potential harmful effects of unwarranted neostigmine dose if they belonged to control group.

Frank Herbstreit and colleagues had demonstrated, in awake volunteers, that neostigmine administered in the absence of neuromuscular block causes upper airway collapsibility and impairs respiratory function. This suggests the undesirability of reversal with neostigmine in the absence of neuromuscular block.<sup>4</sup> Contrasting with this was the study which demonstrated no decrease in TOF ratio after

administration of moderate dose of neostigmine after spontaneous recovery to TOF 0.9.<sup>8</sup> This ruled out significant paradoxical muscle weakness attributable to neostigmine. Similar to this, our study also could not detect the unwanted side effects of neostigmine, including significant residual muscle weakness, if given even after recovery from neuromuscular blockade.

Among the patients who had few signs of residual paralysis in both groups, there was an overlap in the count. That is, same patient had one or more signs of weakness. It is evident that percentage of patients with signs of residual weakness was less in group study when compared to group control, though statistically not significant.

Wardhana and colleagues compared optimized reversal using neostigmine, with and without TOF monitoring to know the incidence of residual muscle weakness.<sup>9</sup> The incidence was found to be high (16.7%) in non-monitored group when compared to 2.8% in monitored group (P=0.107). The incidence of residual neuromuscular blockade in our study correlates with theirs.

Assessing ability to smile in the immediate postoperative period was found to be difficult due to multiple reasons. In this study we found that about 16/63 patients in group control (25.3%) and 17/63 patients in group study (26.9%) were unable to smile. This could be attributed to pain or emotional background. Even if we exclude the number of patients with inability to smile, the total number of patients with no signs of residual weakness in the immediate postoperative period would still remain comparable.

Postoperative residual paralysis depends on the amount of paralysis at the time of antagonizing the block. Studies have demonstrated that giving reversal at a deeper level of block have higher incidence of postoperative residual weakness. In the present study, TOF counts/ratios at the time of reversing the block were comparable in both the groups. However, 3 patients in group control and 10 patients in group study had a TOF ratio ≥ 0.9

just before giving the reversal agent ( $P=0.04$ ). Similarly, overall TOF ratios at the time of extubation, which would have influenced residual muscle weakness, did not differ much between two groups. Again, the number of patients with TOF ratio  $\geq 0.9$  at the time of extubation was significantly greater in study group compared to control group. Relatively greater number of patients were at a deep level of neuromuscular blockade at the time of reversal in group control. This could be the reason for relatively less percentage of patients with residual weakness in group study than group control.

By clinical criteria (presence of signs of residual neuromuscular blockade) the incidence of residual neuromuscular blockade was comparable between the two groups. But if we consider presence of residual paralysis as evidenced by objective monitoring with TOF  $< 0.9$ , then the two groups differed significantly with higher incidence of residual neuromuscular blockade in control group.

This study did not standardize the criteria and time for extubation. It was as per the discretion of the concerned anaesthetist in charge (blinded to group allocation). We found that the reversal to extubation time did not differ between the groups nor did time taken to reach TOF ratio  $\geq 0.9$ . These findings are in contrast to the study done by Wardhana and colleagues.<sup>9</sup>

Several harmful effects of administering neostigmine have been described.<sup>6</sup> None of the patients in present study had episodes of hypoxaemia, desaturation, airway obstruction, nausea, vomiting during the transfer or in the postoperative unit.

There are certain limitations in this study. Firstly, there were some confounding factors responsible for postoperative generalized weakness or inability to perform those tests, such as high minimum alveolar concentration (MAC) of anaesthetic agent at extubation, intraoperative use of opioids for analgesia which were not standardized. Secondly, the total dose of relaxants used, time gap between last relaxant and reversal were not monitored (though the time interval between two doses of vecuronium was at least 20 min).

Thus we conclude that reversal of neuromuscular blockade based on TOF ratio, is comparable to empirical weight based reversal with respect to incidence of postoperative residual muscle weakness as observed by clinical signs, time taken for extubation after giving reversal agent, time taken to reach TOF ratio 0.9 after giving

reversal agent and side effects of reversal agents. The number of patients with TOF ratio  $< 0.9$  is higher with empirical weight based reversal compared to reversal based on TOF ratio suggesting the presence of subclinical residual neuromuscular blockade.

Conflict of interest – None declared

## References

1. Brull SJ, Kopman AF. Current status of neuromuscular reversal and monitoring: challenges and opportunities. *Anesthesiology* 2017; **126**: 173-90.
2. Naguib M, Kopman AF, Ensor JE. Neuromuscular monitoring and postoperative residual curarisation: a meta-analysis. *Br J Anaesth* 2007; **98**: 302-16.
3. Murphy GS, Szokol JW, Avram MJ et al. Intraoperative acceleromyography monitoring reduces symptoms of muscle weakness and improves quality of recovery in the early postoperative period. *Anesthesiology* 2011; **115**: 946-54.
4. Herbstreit F, Zigran D, Ochterbeck C, Peters J, Eikermann M. Neostigmine/glycopyrrolate administered after recovery from neuromuscular block increases upper airway collapsibility by decreasing genioglossus muscle activity in response to negative pharyngeal pressure. *Anesthesiology* 2010; **113**: 1280-8.
5. Kent NB, Liang SS, Phillips S et al. Therapeutic doses of neostigmine, depolarising neuromuscular blockade and muscle weakness in awake volunteers: a double-blind, placebo- controlled, randomised volunteer study. *Anaesthesia* 2018; **73**: 1079-89.
6. Srivastava A, Hunter JM. Reversal of neuromuscular block. *Brit J Anaesth* 2009; **103**: 115-29.
7. Kopman AF, Eikermann M. Antagonism of non-depolarising neuromuscular block: current practice. *Anaesthesia* 2009; **64**: 22-30.
8. Murphy GS, Szokol JW, Avram MJ et al. Neostigmine administration after spontaneous recovery to a train-of-four ratio of 0.9 to 1.0: a randomized controlled trial of the effect on neuromuscular and clinical recovery. *Anesthesiology* 2018; **128**: 27-37.
9. Wardhana A, Kurniawaty J, Uyun Y. Optimised reversal without train-of-four monitoring versus reversal using quantitative train-of-four monitoring: An equivalence study. *Indian J Anaesth* 2019; **63**: 361-67.