

# Dose-reversal effect relationship of three different doses of neostigmine in obese patients: A randomised clinical trial

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## ABSTRACT

**Background and Aims:** Previous studies suggest that administration of vecuronium based on total body weight rather than ideal body weight (IBW) in obesity results in overdosing with prolonged recovery times. We hypothesised that larger doses of neostigmine could result in faster recovery in obese patients administered vecuronium based on total body weight. **Methods:** Forty-five obese American Society of Anesthesiologists' II patients undergoing elective surgery under general anaesthesia were randomised into 3 groups to receive neostigmine 30, 40 and 50 µg/kg. Following induction, patients were paralysed with vecuronium 0.1 mg/kg based on total body weight. Reversal was achieved with neostigmine based on the patient's group, and time to train-of-four (TOF) ratios of 0.5, 0.7 and 0.9 measured. The primary outcome variable was time to achieve TOF ratio >0.9. **Results:** Neostigmine 50 µg/kg achieved faster recovery to TOF 0.7 than neostigmine 30 and 40 µg/kg. There was no significant difference in recovery times to TOF 0.7 in patients receiving either 30 or 40 µg/kg of neostigmine. However, neostigmine 40 µg/kg attained TOF ratio 0.9 faster than 30 µg/kg. We did not note a significant difference between the 40 and 50 µg/kg dose with regard to recovery of TOF to 0.9. **Conclusion:** Facilitated recovery from neuromuscular blockade to TOF of 0.7 was faster with neostigmine 50 µg/kg compared to 40 or 30 µg/kg. Recovery to TOF ratio of 0.9 was not significantly different with 40 or 50 µg/kg doses although such time was faster as compared to 30 µg/kg dose.

**Key words:** Neostigmine, obesity, vecuronium bromide

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Website: [www.ijaweb.org](http://www.ijaweb.org)

DOI: 10.4103/ija.IJA\_297\_17

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## INTRODUCTION

With regard to the use of anticholinesterases for reversing neuromuscular blockade in patients who have received non depolarising muscle relaxants for facilitating surgical procedures, there are two extremes of clinical practice. One group suggests that routine reversal of neuromuscular blockade is not required,<sup>[1]</sup> and the other group recommends routine reversal with a fixed dose of anticholinesterases in all such patients.<sup>[2-4]</sup> There are suggestions that the incidence of residual neuromuscular blockade might be grossly underestimated in the perioperative period.<sup>[5]</sup> While literature is replete with studies on normal patients to establish the appropriate dose of neostigmine to facilitate reversal of neuromuscular blockade, there are limited studies conducted on obese patients.

When vecuronium bromide is given based on total body weight, it is known that the action might be prolonged in obese patients.<sup>[6]</sup> Hence, this study was undertaken to determine whether different doses of neostigmine induced varied recovery patterns, following dosing of the neuromuscular blocker based on the total body weight, in obese patients. The aim of the study was to compare the efficacy of three different doses of

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**How to cite this article:** Parida S, Kausalya V, Mishra SK, Adinarayanan S. Dose-reversal effect relationship of three different doses of neostigmine in obese patients: A randomised clinical trial. *Indian J Anaesth* 2017;61:787-92.

neostigmine on the reversal of neuromuscular block induced with the dose of vecuronium bromide based on the patient's total body weight in obese patients. We hypothesised that the time to facilitated recovery to train-of-four (TOF) ratios of 0.5, 0.7 and 0.9 following neostigmine will be significantly faster in the 50 µg/kg group as compared to the 30 and 40 µg/kg groups.

## METHODS

The study was a randomised, parallel group, multi-arm trial with an allocation ratio of 1:1:1, conducted after obtaining the Institute Ethics Committee approval. Written informed consent was obtained from every patient included in the study. Patients of American Society of Anesthesiologists' physical status II, 20–60 years of age, with body mass index (BMI) between 30 and 40 kg/m<sup>2</sup>, undergoing elective surgery under general anaesthesia were included in the study. Patients with a history of neuromuscular diseases, hepatic or renal disorders, history of drugs known to influence the neuromuscular transmission, pregnancy, history of allergies, and patients for proposed elective post-operative ventilation were excluded from the study. We designed the study protocol based on an approach suggested by Kopman and Eikermann.<sup>[2]</sup> Forty-five patients fulfilling the above criteria were included in the study between December 2012 and December 2014.

The patients were assigned by simple randomisation to one of the three study groups using computer-generated random number table, and a sealed envelope technique was used for concealment of allocation. The random allocation sequence generation, enrollment and allocation of participants to respective groups was carried out by one of the investigators, who played no further part in either administration of the anaesthetic or outcome analysis. Patients were grouped as 1, 2 and 3, according to the dose of neostigmine administered to them, which was one of 30, 40 or 50 µg/kg, respectively. These patients were scheduled to receive neostigmine in the above-mentioned doses at the time of reversal of neuromuscular blockade at the end of surgery. Patients as well as the safety assessor doing the post-operative safety assessments were blinded with respect to which group the patient belonged to.

Once the patients were shifted to the operating room, electrocardiography, noninvasive blood pressure and pulse oximetry were attached, and the baseline parameters recorded. An intravenous (IV) infusion of lactated Ringer's solution was started in an appropriate

forearm vein. Fentanyl 2–4 µg/kg IV was given and the patients were induced with propofol (up to 2.5 mg/kg) IV. Patients received 100% oxygen through an anaesthesia face mask during induction. Once the patients were induced, a neuromuscular monitor was used to stimulate the ulnar nerve at the wrist. We used kinemyograph (neuromuscular transmission module [M-NMT], GE Healthcare, Helsinki, Finland) for this purpose, where the transducer is a piezoelectric crystal that is placed in a band that stretches from the thumb to the index finger. First, the supramaximal stimulus was automatically detected by the monitor using incremental single twitch stimuli. Then, control TOF stimuli were given for 3 min to ensure stable evoked responses. Then, vecuronium bromide 0.1 mg/kg of total body weight IV was given. At TOF count of 0, endotracheal intubation was done. Ventilation was adjusted to maintain end-tidal carbon dioxide (EtCO<sub>2</sub>) between 35 and 40 mm Hg.

During the surgery, maintenance doses of vecuronium bromide 0.01–0.02 mg/kg IV were injected to maintain a TOF count of 0 at all times. Anaesthesia was maintained by 67% nitrous oxide in oxygen, a propofol infusion 4–8 mg/kg/h IV and supplemental fentanyl IV as clinically indicated. Depth of anaesthesia was monitored by Entropy™ (Entropy module, GE Healthcare, Helsinki, Finland) and the propofol infusion manipulated to maintain state entropy values between 40 and 60. Nasopharyngeal temperature was monitored (GE Datex Ohmeda S5, Helsinki Finland), and temperature maintenance done with passive warming and warm IV fluids to target a temperature >36°C. Skin temperature over the thenar muscle was recorded throughout the experiment using a surface probe and kept at >32°C. At the end of surgery, when the T<sub>1</sub> had recovered spontaneously to 25% of control, neostigmine was given according to the groups into which they were randomised, along with atropine at half the dose of neostigmine administered per kg body weight, and patients were allowed to recover to a TOF ratio of 0.9. At emergence from anaesthesia, the awake patient's trachea was extubated based on routine institutional protocols. These included cooperative and alert patient, smooth spontaneous ventilation, sustained head lift and TOF >0.9 at the adductor pollicis, SpO<sub>2</sub> >96% on FIO<sub>2</sub> 1, EtCO<sub>2</sub> <45 mm Hg, stable haemodynamics, core temperature ≥35°C and no evidence of early surgical complications. Heart rate, non-invasive blood pressure and oxygen saturation were monitored after administration of reversal agent and recorded every 5 min until the patient was shifted

to the recovery room. Patients were monitored in the recovery room for 1 h. Every 15 min, the heart rate, blood pressure, respiratory rate and oxygen saturation of the patients were recorded.

The sedation level was assessed in the recovery room as awake and oriented, arousable with minimal stimulation or responsive only to tactile stimulation. Patients were also tested for eye opening for 5 s, sustained head lift for 5 s and sustained arm lift for 5 s. Then, the patients were tested using the Medical Research Council scale<sup>[7]</sup> for generalised muscle weakness: 0 = no movement, 1 = flicker perceptible in the muscle, 2 = movement only if gravity is eliminated, 3 = limb movement against gravity, 4 = movement against gravity and against some resistance, 5 = normal power. A blinded safety assessor performed these post-operative clinical assessments every 15 min upto 1 h post-extubation. The study ended when the patient was discharged from the recovery room to the ward. All patients were monitored for adverse effects by the anaesthesiologist and the safety assessor.

The primary outcome measure studied, similar to the article by Suzuki *et al.*, was the time (min) required for facilitated recovery to TOF ratios of 0.5, 0.7 and 0.9 following administration of neostigmine.<sup>[6]</sup> The secondary outcome measures studied included adverse events such as shivering, bradycardia, hypotension, excessive secretions, bronchospasm, nausea or vomiting. These The other parameters which were studied included cumulative dose (mg) of vecuronium bromide used; lag time (s) from the time of bolus injection of vecuronium bromide to the beginning of depression of T<sub>1</sub>; onset time (s) from the injection of vecuronium bromide to maximum depression of T<sub>1</sub>; TOF ratio (%) at administration of reversal in all three groups; clinical muscle function tests; and evaluation of consciousness. We used the M-NMT which is an integrated piezoelectric motion sensor incorporated in the Datex-Ohmeda GE monitor.

Data are presented as mean  $\pm$  standard deviation or median (range) where appropriate. Statistical analysis was performed using SPSS version 19.0 (IBM Corp., Released 2010, IBM SPSS Statistics for Windows, Version 19.0, Armonk, NY, USA). Kruskal-Wallis test was used to test statistical significance for multiple comparisons. If a significant  $P < 0.05$  was obtained in multiple comparisons, further group comparisons were made using Bonferroni *posthoc* test.

For the sample size calculation, which was based on an anticipated difference in time to recovery to a TOF ratio  $\geq 0.9$  between the three groups, it was assumed that the largest difference between any two means of about 5 min would be significant with a within-group standard deviation of 5 min. Using an analysis of variance testing and a significance level of 5%, it was calculated that a sample size of 15 patients per treatment group would be required to provide a power of 80%. Random sampling was used among the sample population of patients being posted for elective surgery.

## RESULTS

The flow of participants enrolled in this study is shown in Figure 1. A total of 45 patients with BMI between 30 and 40 kg/m<sup>2</sup> were recruited for the study, with the trial ending after completion of the designated number of patients were recruited. The demographic characteristics and duration of surgery were comparable among the three groups [Table 1]. There was no statistically significant difference observed among the groups with respect to the time of onset and maximum effect of the intubating dose of vecuronium bromide or the cumulative dose of vecuronium bromide used [Table 2]. All patients had complete block of T<sub>1</sub> with the administered dose of vecuronium bromide. There was also no significant difference among the groups with respect to the TOF percentage at the time of reversal of the neuromuscular blockade [Table 2]. The times required for reversal to TOF ratios of 0.5, 0.7 and 0.9 were significantly longer

**Table 1: Patient characteristics and surgical durations**

	Group 1	Group 2	Group 3	P
Age (years)	42.6 $\pm$ 6.9	46 $\pm$ 9.3	43.3 $\pm$ 6.5	0.46
Height (m)	1.54 $\pm$ 0.04	1.54 $\pm$ 0.03	1.53 $\pm$ 0.05	0.98
Weight (kg)	76.3 $\pm$ 6.9	75.2 $\pm$ 5.1	74.6 $\pm$ 5.5	0.72
BMI (kg/m <sup>2</sup> )	32.32 $\pm$ 2.6	31.78 $\pm$ 1.1	31.63 $\pm$ 0.84	0.51
Ideal body weight (kg)	46.7 $\pm$ 3.2	47 $\pm$ 3.7	46.5 $\pm$ 4.5	0.93
Duration of surgery (min)	151 $\pm$ 33.8	164 $\pm$ 27.5	162 $\pm$ 35.7	0.51

Data are expressed as mean $\pm$ SD, respectively.  $P < 0.05$  would be considered statistically significant. BMI – Body mass index; SD – Standard deviation

**Table 2: Comparison of onset, duration and cumulative dose of vecuronium-induced neuromuscular block as well as train of four percentage at reversal**

	Group 1	Group 2	Group 3	P
Lag time of vecuronium (s)	60 $\pm$ 15	59 $\pm$ 3.9	59 $\pm$ 3.9	0.94
Onset of vecuronium (s)	220 $\pm$ 22.4	201 $\pm$ 21.8	207 $\pm$ 30.1	0.12
Cumulative dose of vecuronium (mg)	10.2 $\pm$ 1.7	10.17 $\pm$ 1.0	10.4 $\pm$ 1.3	0.88
TOF percentage at reversal	0.07 $\pm$ 0.03	0.08 $\pm$ 0.04	0.09 $\pm$ 0.06	0.42

Data are expressed as mean $\pm$ SD, respectively.  $P < 0.05$  would be considered statistically significant. TOF – Train of four; SD – Standard deviation

in the group receiving 30 µg/kg of neostigmine, as compared to those receiving 40 and 50 µg/kg [Table 3]. Among the groups receiving 40 and 50 µg/kg of neostigmine, the time required for recovery to a TOF ratio of 0.7 was significantly longer in the former group, while there was no statistically significant difference between these two groups with respect to recovery to TOF ratios of 0.5 and 0.9 [Table 3]. During the 1-h follow-up period, all 45 patients were awake and oriented, could perform all clinical muscle function tests, had normal power of Medical Research Council Scale 5, and did not have any adverse effects.

## DISCUSSION

This study demonstrates that neostigmine 50 µg/kg achieves a faster recovery to TOF ratio 0.7 than neostigmine 30 and 40 µg/kg. Furthermore, it shows that neostigmine 40 µg/kg attains a TOF ratio of 0.9 faster than a dose of 30 µg/kg and that such difference between the doses was statistically

significant. While there was no significant difference between the 40 and 50 µg/kg groups with regard to recovery of TOF ratios to 0.9, given the rather small sample size, this equivalence of effects between the 40 and 50 µg/kg groups need to be evaluated in much larger patient populations before one can be assured that the two doses perform identically well in obese patients, especially with respect to recovery to a TOF of 0.9, which is the critical decision-making point in reversal of neuromuscular blockade.

Reversal time following administration of neostigmine is resultant of two distinct pharmacological processes that happen simultaneously: facilitated reversal of neuromuscular blockade by direct antagonistic effects of neostigmine and spontaneous recovery from muscle relaxants (vecuronium bromide in this case) secondary to elimination from plasma.<sup>[8]</sup> Reversal effect of neostigmine starts in 1–2 min and the peak effect occurs in 6–10 min.<sup>[9]</sup> It is considered that the early recovery of TOF ratio to about 0.5–0.7 is secondary to the competitive

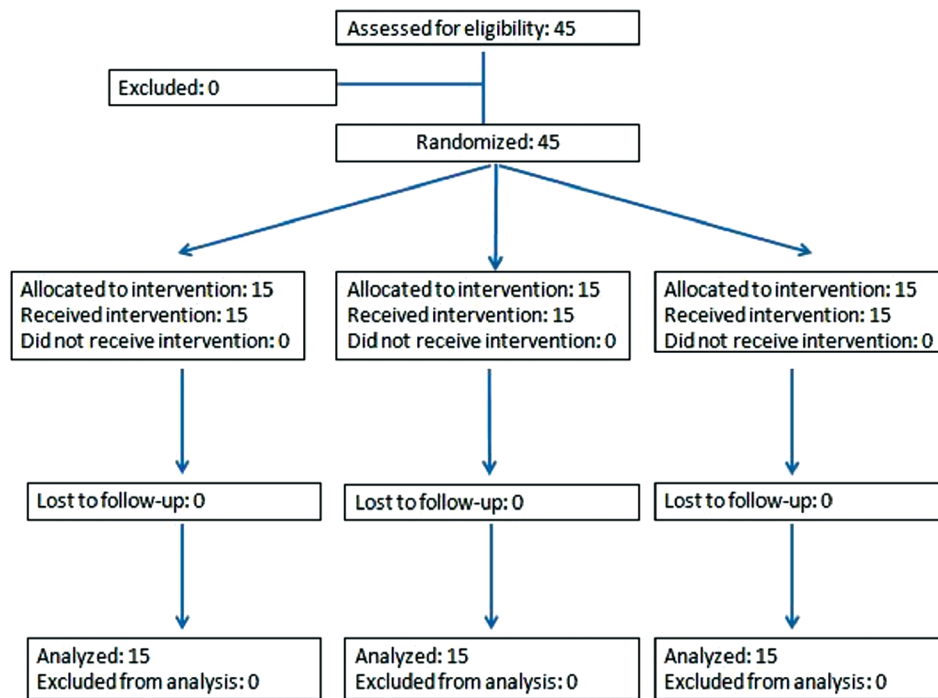


Figure 1: Participant flow for the study

Table 3: Time taken from reversal to the recovery of train of four ratios to 50%, 70% and 90%							
Time in mins	Group 1	Group 2	Group 3	P	Pairwise comparisons		
					Group 1-2	Group 2-3	Group 1-3
TOF 50	8 (4-20)	5 (0.75-10)	4 (2-7)	<0.001*	0.046†	0.39	<0.001*
TOF 70	13 (6.5-30)	11 (1.75-16)	9 (4-11)	0.001*	1.0	0.03†	0.002†
TOF 90	20 (14-34)	16 (2.75-20)	14 (9.5-25)	<0.001*	0.022†	0.53	<0.001*

Data are expressed as median (IQR). Statistical significance was tested using Kruskal–Wallis test. Pairwise comparisons done in case of statistical significance. \*P<0.001; †P<0.05 is considered statistically significant. TOF – Train of four; IQR – Interquartile range

antagonism at the neuromuscular junction because of increased concentration of acetylcholine caused by neostigmine.<sup>[10]</sup> Further recovery to TOF ratio of 0.7–0.9 is secondary to a balance of residual concentrations of neuromuscular blocking agent and residual effects of neostigmine at the neuromuscular junction, that is, this duration is also dependent on the waning vecuronium bromide effect in addition to neostigmine.<sup>[10]</sup> A similar study<sup>[11]</sup> done previously suggests that relative overdosage of vecuronium bromide administered based on the total body weight may be responsible for prolonged duration needed to achieve a TOF ratio of 0.9 in the patients receiving neostigmine 30 µg/kg body weight. Other authors<sup>[12]</sup> have suggested that the muscle relaxants be dosed based on about 20% more than the lean body weight so as to avoid overdosing. There have been attempts<sup>[13]</sup> to use corrected body weight (CBW) for calculating the appropriate dosage in obese patients where  $CBW = IBW + 0.4 (\text{total body weight} - IBW)$ . In our study, we have administered vecuronium bromide based on total body weight.

Earlier studies<sup>[6]</sup> have determined the effect of a single dose of neostigmine in normal weight, overweight and obese patients for reversal of vecuronium bromide-induced neuromuscular block. They found that with neostigmine 40 µg/kg, the recovery of TOF ratio to 0.9 was slower in overweight (mean 14.6 min) and obese patients (mean 25.9 min) when vecuronium bromide was dosed based on the total body weight of the patients. Based on this observation, we attempted to determine if higher doses of neostigmine achieved a faster recovery in the obese patients. Years after the advent of neostigmine, the optimal dose to be administered for the reversal of neuromuscular blockade is yet to be determined.<sup>[14]</sup>

Another interesting fact observed in our study was that some individual patients in group 3 took a longer time (as high as 25 min) for recovery to TOF ratio 0.9 than in group 2 (high range of 20 min) although the TOF ratios at the time of reversal were comparable. This observation is similar to the one made in another study<sup>[15]</sup> while testing cisatracurium-induced neuromuscular blockade with neostigmine 70 µg/kg at recovery of TOF counts to 1, 2, 3 and 4. They observed that some patients in group 1, in which neostigmine was administered at a TOF count of 1, had a faster recovery (as low as 5.9 min) than some in group 4 (11 min), in which the same dose of neostigmine was administered at a TOF count of 4. They attributed this difference to the interindividual variability in the response to cisatracurium. Thus, they

concluded that the duration of action of the relaxant in a given individual is a predictor of reversal time in addition to the TOF count at the time of neostigmine administration.<sup>[16]</sup> We would like to believe that similar interindividual variability also reflects in the results we got, explaining such differences between the groups.

At least three or preferably all four responses to TOF stimuli should have recovered at the time of attempted reversal of neuromuscular blockade.<sup>[17]</sup> None of our patients showed signs of residual neuromuscular blockade or of high doses of neostigmine postoperatively. Of course, these approaches may differ if a reversal agent other than neostigmine, such as edrophonium, is employed since it has been shown that the two agents are not equally effective against vecuronium bromide.<sup>[18]</sup> While close observation of post-operative recovery of neuromuscular function is no doubt important, it must be stressed that objective measurement is the only method to determine appropriate timing of tracheal extubation and ensure normal muscle function and patient safety.<sup>[19]</sup>

This study has several limitations. First, our sample size was small. Second, our study did not evaluate the time to spontaneous recovery from vecuronium bromide block to a TOF ratio of 0.7 or 0.9, without administration of neostigmine. Further, our results gained from this study hold true only for vecuronium bromide and not for other muscle relaxants such as atracurium or rocuronium. Another likely criticism of our study might also be that since reversal was attempted at identical recovery points from neuromuscular blockade (25% recovery of T1), it nullifies the effects of obesity and overdosing with vecuronium bromide on our results, which principally reflect the dose-effect relationships of various doses of neostigmine. However, we would like to point out that the study demonstrates that doses of 30 µg/kg, although within the normally accepted dosage range of neostigmine still result in significant prolongation of reversal to a TOF ratio of 0.9 in obese patients. On the contrary, reversal to 0.9 TOF ratio was not different between the 40 and 50 µg/kg groups, although this finding in obese patients needs to be tested out with studies having larger sample sizes and higher power.

## CONCLUSION

Facilitated recovery from neuromuscular blockade to TOF 0.7 is much faster when neostigmine is

administered at doses of 50 µg/kg compared to doses of 40 or 30 µg/kg, in obese patients who are administered vecuronium bromide according to their total body weight. Total reversal time, defined by a recovery to a TOF ratio of 0.9, is also much faster with the 40 and 50 µg/kg dosages as compared to the 30 µg/kg dose. While in our study both 40 and 50 µg/kg dosages had identical recovery times to TOF ratio of 0.9, a better powered study with a larger sample size may be able to identify which of these two dosages might be appropriate for administration in obese patients.

#### Financial support and sponsorship

Nil.

#### Conflicts of interest

There are no conflicts of interest.

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