ORIGINAL RESEARCH

Study of Intraoperative requirement of Inj. Atracurium (NMBA) with and without the use of neuromuscular monitoring in patients undergoing Laparoscopic Cholecystectomy

[1]Dr. Sachin Asaram Devgude, [2]Dr. Santosh Ratan Kalushe, [3]Dr. Vivek Ravindra Gadhari, [4]Dr. Dipti Kotwani

[1]Assistant Professor, Department of Anaesthesia, Parbhani Medical College, Parbhani, India
[2,3]Assistant Professor, Department of Anaesthesia, BKL Walawalkar Rural Medical College, At post Sawarda Taluka -Chiplun, District- Ratnagiri, India
[4]Associate Professor, Department of Anaesthesia, L.T.M.M.C. Sion, Mumbai, India

Corresponding author
Dr. Dipti Kotwani
Associate Professor, Department of Anaesthesia, L.T.M.M.C. Sion, Mumbai, India
Email: drdeeptiagrawal@gmail.com

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ABSTRACT

Background: Neuromuscular blocking agents (NMBA) are routinely administered during anaesthesia to facilitate endotracheal intubation and to provide good muscle relaxation for optimal surgical conditions. In most clinical settings, intubating time after administration of NMBA is determined by clinical feel of the patient (ease of ventilation, jaw and upper airway tone) or timeof onset of action of the NMBA. Literature recommendsneuromuscular block should be monitored for all patients who receive NMBAs during anaesthesia, to guide appropriate NMBA dosing and appropriate timing for administration of reversal agents. **Methodology**-The above study was conducted on 70 patients undergoing elective laparoscopic cholecystectomy in operation theaters at Tertiary care hospital from November 2019 to September 2021. Patients were monitored and data was collected, analyzed and entered in the form of tables. **Results**- Frequency of mean Atracurium doses needed in the neuromuscular monitoring group was significantly much less than the clinical monitoring group ($P < 0.001$). Mean interval for top-up dose of Atracurium was 26.87±6.68 minutes in the neuromuscular monitoring which was highly significant ($p<0.001$). The mean time from the last dose of Atracurium to the start of antagonism of the neuromuscular block agent in the neuromuscular monitoring group was highly significant ($P<0.001$). **Conclusion**- Quantitative neuromuscular monitoring (NMT) should be performed for all patients who receive NMBAs during general anaesthesia.

Keywords- NMBA, Laparoscopic Cholecystectomy, neuromuscular, intubation, anaesthesia.

INTRODUCTION

Neuromuscular blocking agents (NMBA) are routinely administered during anaesthesia to facilitate endotracheal intubation and to provide good muscle relaxation for optimal surgical conditions. The degree of muscle relaxation required depends on the surgical procedure, the patient, the depth of anaesthesia and the skill of the surgeon. The optimal depth of neuromuscular (NM) blockade duringgeneral anaesthesia should be a balance between immobility during the operative procedure and complete recovery at the end of the operation. In most clinical settings, intubating time after administration of NMBA is determined by clinical feel of the patient (ease of ventilation, jaw and upper airway tone) or timeof onset of action of the NMBA. Intraoperative dosages of NMBA are based on predetermined fixed time after administration of the last dose of NMBA, changes displayed on capnography, the ventilatory graphs or on request of operating surgeon. This may often lead to over-dosage of the NMBA thereby delaying administration of reversal agent i.e. cholinesterase inhibitors (Neostigmine), delaying extubation and shifting from the operating room with increased risk of residual paralysis in the recovery room. Literature recommends neuromuscular block should be

monitored for all patients who receive NMBAs during anaesthesia, to guide appropriate NMBA dosing and appropriate timing for administration of reversal agents.[1] Perioperative neuromuscular monitoring has multiple benefits – during induction of anaesthesia it indicates optimal time for laryngoscopy and intubation, intra-operatively it guides the need of NMBA and at the end of surgery it signals readiness for pharmacological antagonism.[1] Neuromuscular monitoring can be done by Qualitative or Quantitative assessment. Qualitative (subjective) assessment is done using peripheral nerve stimulator (PNS) device which provides nerve stimulation without measuring the evoked muscular response. The estimated strength of muscle contractions in response to train-of- four (TOF) stimulation are by visual or tactile means hence prone for errors. The anesthesiologist is the monitor, who makes a subjective evaluation of the strengthof the muscle response.[1]

Quantitative monitoring is an objective real-time measurement of the evoked muscle response to nerve stimulation. It measures, analysis and displays Train-of-Four Ratio(TOFR -calculated by dividing the amplitudeof the fourth response (T4) by the amplitude of the first response (T1)) in real time. With the wide variability ofpatient response to NMBA, quantitative monitoring can be used to guide the intraoperative use of NMBA, to ensure effective antagonism and to prevent residual neuromuscular weakness and its complications.[1] There is transition in the clinical practice currently to prefer intermediate duration NMBA rather than the longer durationNMBA. Studies have shown evidence of inadequate spontaneous recovery even two hours after administration of a single dose of atracurium, vecuronium or rocuronium.(intermediate acting NMBA).[2] So, it may be essential to perform neuromuscular monitoring for all stages of anesthesia even when intermediate duration NMBAs are used.[3] In a study by Baillard *et al.*,[4] the determinants of postoperative residual neuromuscular blockade in patients receiving intermediate acting muscle relaxants were higher dose of muscle relaxants, neuro-muscular function was less likely monitored during surgery and shorter duration of surgery. Studies reveal that Qualitative assessment using nerve stimulators is performed in less than 40% of patients and objective monitoring is only used for 17% of patients.[3]

Hence, the above study was conducted to study Intraoperative requirement of Inj. Atracurium (NMBA) with and without the use of neuromuscular monitoring in patients undergoing Laparoscopic Cholecystectomy.

MATERIALS AND METHODS

Study place-The study was conducted at General Surgery Operation Theatre in Tertiary care hospital from November 2019 to September 2021.

Study design- Prospective observational study.

Inclusion criteria-Patients undergoing elective laparoscopic cholecystectomy in age group of 18 to 65 years, ASA grade 1 or 2 and those willing to give consent for participation.

Exclusion criteria-Patients with known allergy to the drugs used, with anticipated difficult intubation - Malampatti class 3 or 4, Gastro-esophageal reflux disease, having history of Cardiovascular, hepatic, renal, neuromuscular disorders, pregnant ladies, laparoscopic surgery converted to open cholecystectomy and those unwilling to participate.

Sample size- 70 patients (35 patients were included in each group i.e. Group A and Group B)

Data analysis-Data was collected, analyzed and entered using Microsoft SPSS.24.0 version. Further the data was entered in the form of tables, charts and graphs.

Ethical consideration- Approval from the institutional ethics committee was taken before beginning the study.

In Group A patients, Neuro-muscular monitoring was performed whereas in Group B, patients who needed Clinical assessment for administration of muscle relaxant were included.

In Group A, baseline TOF ratio percentage was noted. After standardisation of supra-maximal stimulus intravenous Inj. Atracurium 0.75 mg/kg IV was administered. TOF stimulation (2 Hz current lasting 0.2 ms) was performed every 30 seconds till the complete loss of responses to TOF stimulation (i.e TOF count =0). Time taken to achieve TOF=0 was noted. This was followed by laryngoscopy and endotracheal intubation.

In group B, after confirmation of ventilation Inj. Atracurium 0.75 mg/kg IV was administered. The timing of laryngoscopy was based on ease of ventilation, jaw and upper airway tone. On clinical signs of adequate relaxation i. e. jaw relaxation or 4 minutesfollowing Inj. Atracurium administration, laryngoscopy and intubation was performed by an experienced anaesthesiologist. The time from administration of Inj. Atracurium to the time of tracheal intubation and cuff inflation was noted. The quality of relaxation for intubation was noted as excellent, good or poor as per the intubating condition scoring system proposed by **Viby-Mogensen *et al.*** Time interval between the Inj. Atracurium doses (top ups) and total dose of Inj. Atracurium required for the procedure was noted in both the groups. At the end of surgery, the residual neuromuscular blockade was reversed by administering Inj. Neostigmine 0.06 mg/kg and Inj. Glycopyrrolate 8 mcg/kgIV. Trachea was extubated and the timeto extubate (i.e time from beginning of reversal till extubation) was noted in both groups.

RESULT

Table 1: Comparisons of Mean Heart Rate

Heart rate (Per min)	Group A (n=35)		Group B (n=35)		P-value
	Mean	SD	Mean	SD	
Baseline	87.09	8.40	87.40	9.61	0.885^{NS}
After premedication	81.14	6.60	81.69	7.75	0.753^{NS}
Following propofol	74.31	4.00	73.11	4.29	0.231^{NS}
Prior to intubation	72.49	3.40	75.29	5.04	0.008^{**}
At intubation	86.20	5.55	93.91	6.76	0.001^{***}
5 min after intubation	74.31	4.00	72.77	3.97	0.110^{NS}
15 min after intubation	73.49	2.65	72.34	3.02	0.097^{NS}
30 min after intubation	73.49	2.65	73.51	4.68	0.975^{NS}
45 min after intubation	73.49	3.40	74.03	5.51	0.163^{NS}
60 min after intubation	73.49	2.65	89.17	3.91	0.001^{***}
75 min after intubation	72.40	4.69	85.34	4.81	0.001^{***}
90 min after intubation	84.83	2.41	77.46	5.03	0.001^{***}
Prior to extubation	101.66	4.16	101.11	6.74	0.686^{NS}
5 min after extubation	72.49	3.40	76.54	4.43	0.001^{***}
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					

Table 2: Frequency of Atracurium Dosage in two groups

Time (min)	Group A (n=35)		Group B (n=35)		P-value
	Atracurium Dosage (mg)		Atracurium Dosage (mg)		
	Mean	SD	Mean	SD	
5 min	0.00	0.00	0.00	0.00	0.999^{NS}
10 min	0.00	0.00	0.00	0.00	0.999^{NS}
15 min	0.00	0.00	0.00	0.00	0.999^{NS}
20 min	0.00	0.00	1.14	2.13	0.002^{**}
25 min	0.14	0.84	3.71	2.22	0.001^{***}
30 min	0.29	1.18	0.43	1.42	0.648^{NS}
35 min	2.29	2.53	0.43	1.42	0.001^{***}
40 min	1.43	2.29	0.71	1.77	0.150^{NS}
45 min	0.00	0.00	3.86	2.13	0.001^{***}
50 min	0.29	1.18	0.86	1.91	0.137^{NS}
55 min	0.43	1.42	0.00	0.00	0.079^{NS}
60 min	0.00	0.00	4.00	2.03	0.001^{***}
65 min	1.71	2.41	0.86	1.91	0.104^{NS}
70 min	2.57	2.53	0.00	0.00	0.001^{***}
75 min	0.00	0.00	4.29	1.77	0.001^{***}
80 min	0.00	0.00	0.43	1.42	0.079^{NS}
85 min	0.00	0.00	0.00	0.00	0.999^{NS}
90 min	0.00	0.00	0.00	0.00	0.999^{NS}
Prior to extubation	0.00	0.00	0.00	0.00	0.999^{NS}
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					

Table 3: Mean interval for topup dose of Atracurium.

	Group A (n=35)		Group B (n=35)		P- value
	Mean	SD	Mean	SD	
Interval (Min)	26.87	6.68	19.01	1.81	0.001***
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					

Table 4: Comparison of Total dose of Atracurium

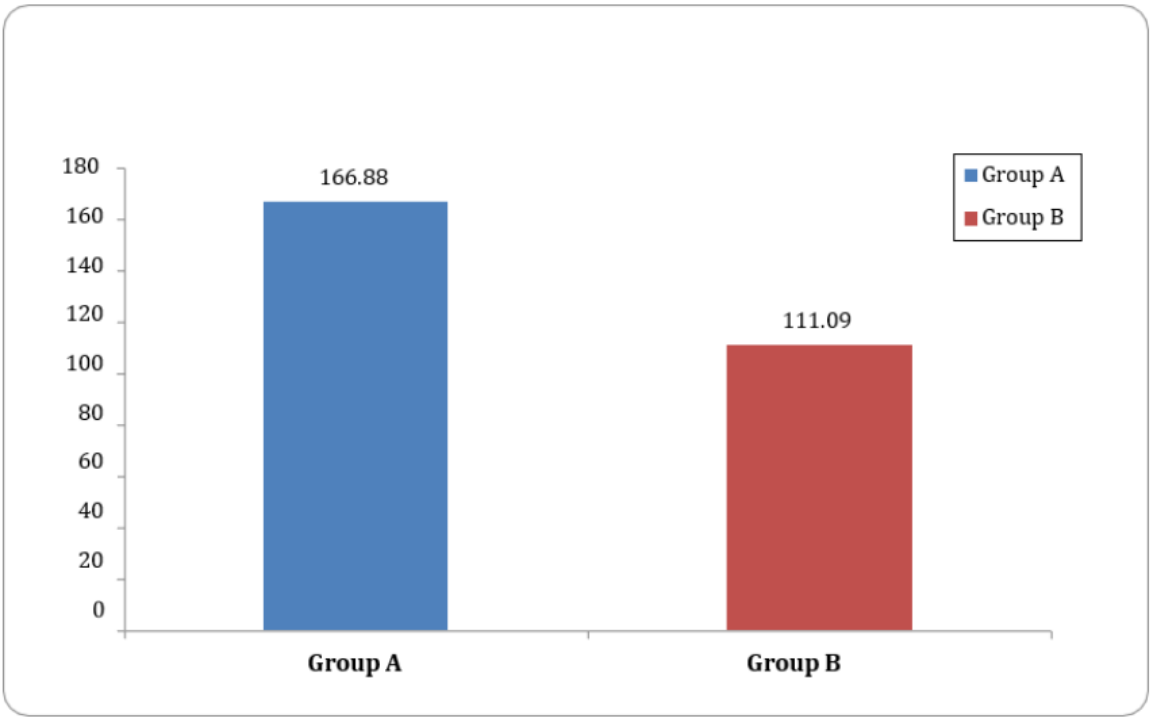
Total dose of Atracurium	Group A (n=35)		Group B (n=35)		P-value
	Mean	SD	Mean	SD	
Total dose of Atracurium (mg)	9.14	1.91	20.71	1.77	0.001***
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					

Table 5: Time from last dose of Atracurium to start of reversal agent.

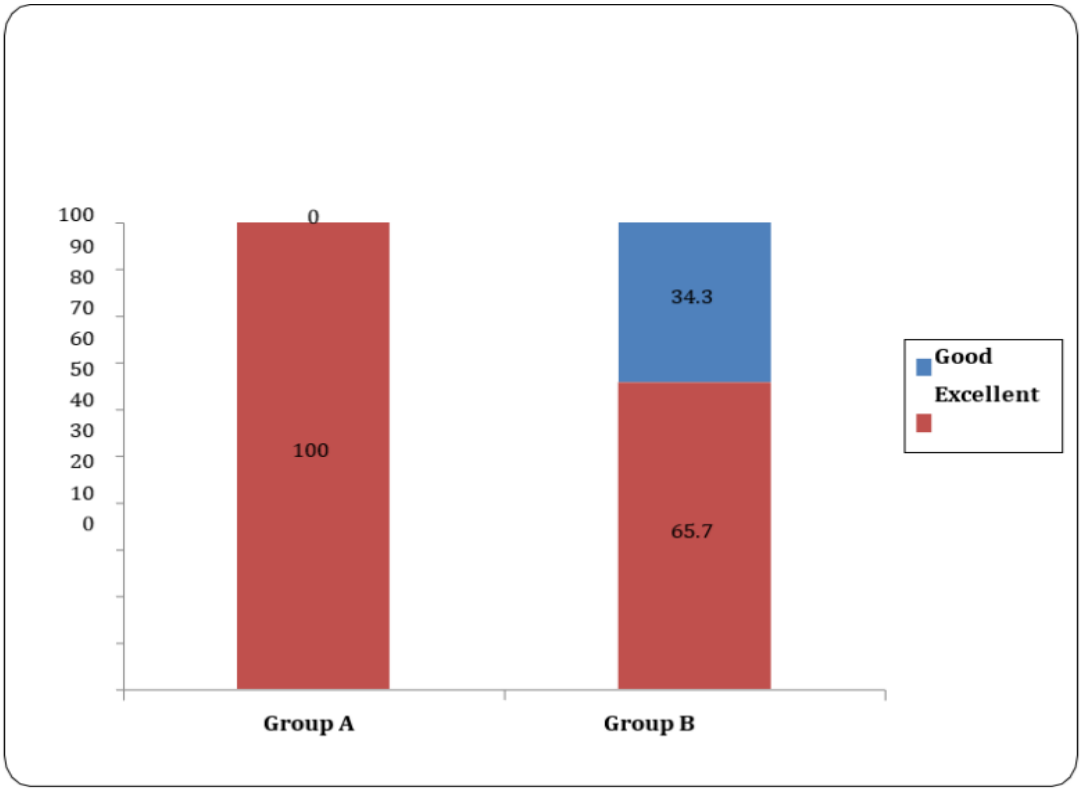
	Group A (n=35)		Group B (n=35)		P-value
	Mean	SD	Mean	SD	
Time (mins)	31.49	2.27	44.49	2.37	0.001***
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					

Table 6: Time from reversal of neuromuscular blockade till the extubation

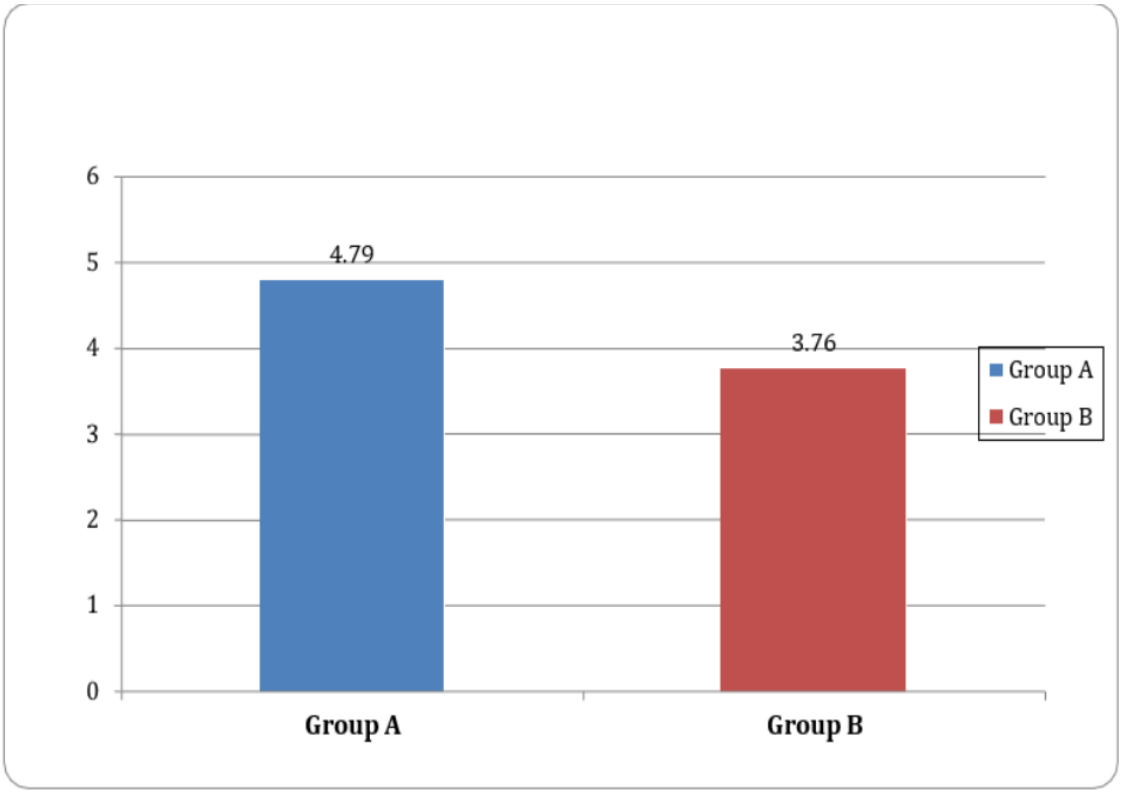
	Group A (n=35)		Group B (n=35)		P- value
	Mean	SD	Mean	SD	
Time (mins)	4.57	0.81	6.63	0.84	0.001***
Independent t- test *Statistically significant if P<0.05, **Statistically highly significant if P<0.001					



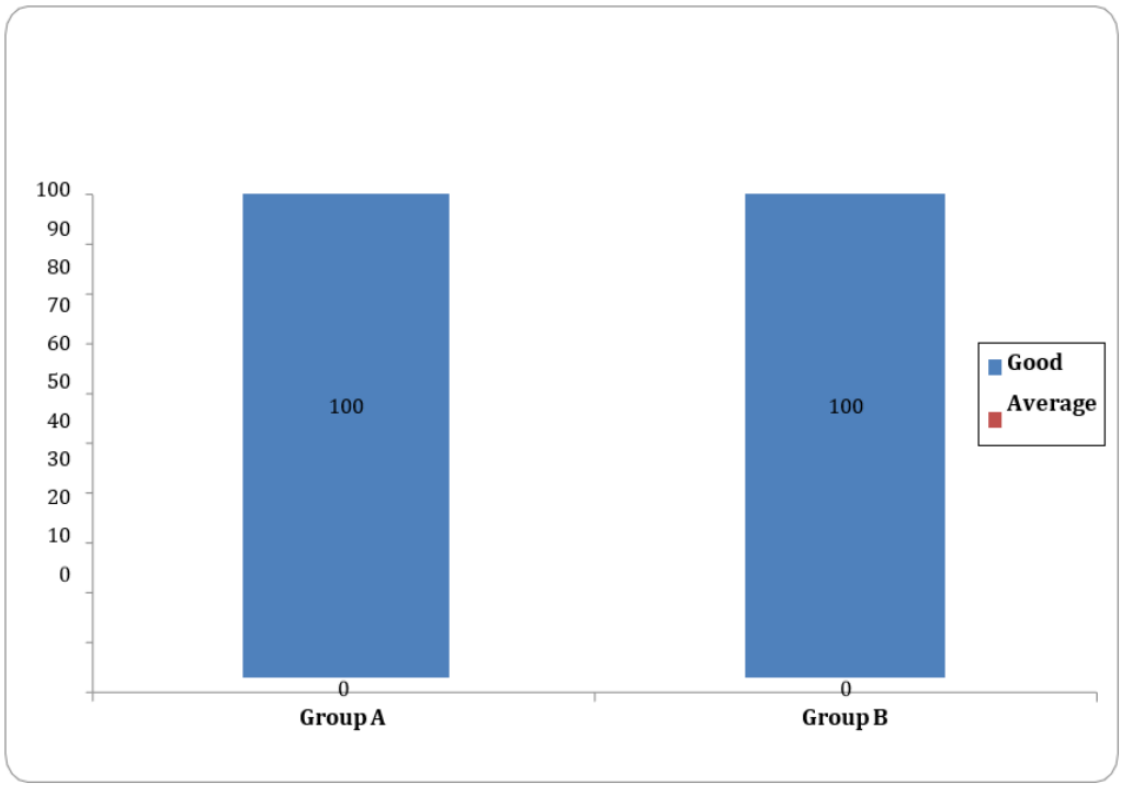
Graph 1: Mean total fentanyl



Graph 2: Quality of relaxation for intubation



Graph 3: Mean time to Intubate after Atracurium Bolus



Graph 4: Quality of operative condition

DISCUSSION

In the above study, it was found that the mean heart rate between the neuromuscular monitoring and clinical monitoring group was found to be statistically not significant (P>0.05) at baseline, after pre-medication, 5min, 15min, 30min, 45 min after intubation and prior to extubation. However, the Mean heart rate just prior to intubation and at intubation, was observed to be significantly higher in the clinical monitoring group compared to neuromuscular monitoring group (P<0.05). The findings were similar to study done by Rudranil Nandi *et al.*[5] where patients who were intubated by clinical judgment showed higher mean values of HR during and after intubation in comparison to the patients who were intubated under guidance of neuromuscular monitoring ($P < 0.05$). Similar findings were observed in studies done by Witkowska M *et al.*[6] Nidhi Malipatil, K.Harshavardhan.[7]

Laryngoscopy and endotracheal intubation can cause profound changes in haemodynamic and intracranial pressure, probably as a result of intense sympathetic nervous system stimulation. These cardiovascular effects can be reduced using various pharmacological drugs.[8-9] However,the effect of these pharmacological drugs may last long after the laryngoscopy and tracheal intubation stimulation ceases, resulting in subsequent haemodynamic variations. In above study, laryngoscopy and intubation in patients with neuromuscular monitoring was done when we achieved TOF count of zero compared to the patients of clinical assessment group where intubation was performed much earlier. More time interval available between neuromuscula blockade administration and tracheal intubation not only improves intubation conditions but also minimises cardiovascular responses as observed by Witkowska M *et al.*[6]

Mean heart rate at 60 minutes, 75 and 90 minutes after intubation and 5 minutes after extubation was significantly higher in clinical assessment group compared to patients of group with neuromuscular monitor (P<0.05). This observation in above study may be related to the difference in the dosages of Inj. Fentanyl given peri-operatively. Inj. Fentanyl received in the patients of clinical assessment group was much lesser as compared to the neuromuscular monitoring group. In above study, the clinical assessment group was observed to have higher SBP compared to NM monitoring group. This may be due to difference in the doses of Inj. Fentanyl given. As the TOF count recorded was < 2 in the neuromuscular monitoring group, intra-operative rise in HR and SBP must be due to inadequate analgesia rather than need of muscle relaxant. So, Inj. Fentanyl was administered additionally to these patients. On the contrary, in the clinical assessment group, it could be dueto inadequate analgesia or sign of inadequate muscle relaxant.

The mean interval for top-updose of Atracurium was 26.87±6.68 minutes in neuromuscular monitoring compared to the clinical monitoring group which was 19.01±1.81 minutes which was observed to be highly significant (p<0.001) in above study. The logical explanation for this finding is linked to the TOF guided dose of Atracurium administered in the neuromuscularmonitoring group. Muscle relaxant was

administered only if the TOF count > 2 in this group of patients. On the contrary, inthe clinical monitoring group Inj. Atracurium was given by the attending anaesthesiologist based on spontaneous respiratory attempts, changes in airway pressure monitor and capnography, haemodynamic changes, surgeon perceiving inadequate relaxation or poor visibility. Since the NMBA was administered frequently, the mean total doseof Atracurium (mg) was observed to be statistically significantly higher in clinical monitoring group (20.71 ± 1.77) compared to neuromuscular monitoring group (9.14 ± 1.91) (P<0.001). Similar findings were observed in a study by Baillard *et al.*[10] where the intermediate-acting neuromuscular blocking agent dose (Vecuronium) differed significantly between the patients with or without neuromuscular monitoring (1.24±0.58 vs 1.48 ±0.95, ED 95/ hr ,P=0.005). The distribution of quality of relaxation for intubation is significantly higher in Group A compared to Group B (P-value<0.05). The mean time interval from Intubating dose of Atracurium to Intubate in Group A and Group B was 287.51sec (4.76min) ± 36.08 and 225.74sec (3.76min) ± 5.47 respectively. The mean time interval from Intubating dose of Atracurium to Intubate was statistically highly significantly in Group A compared to Group B(P<0.001). Intubation score was observed to be excellent in all 35 patients (100%) in the neuromuscular monitored group compared to the clinical assessment group where it was 65.7% (n=23) (p<0.001).

The possible observation for delay in intubation in the NM monitored group was due to our protocol for intubation at TOF count=0 in this group of patients. But time needed to achieve TOF=0 was higher (4.76min) in this group of patients thereby increasing time required to intubate in comparison with the clinical assessment group(3.76min). This mean time interval from Intubating dose of Atracurium to Intubate was found to be statistically highly significantly (P<0.001). Similar findings were found in the study by Nidhi Malipatil, K. Harshavardhan,[7] Rudranil Nandi *et al.*,[6] Witkowska M *et al.*[5] that time to intubate and quality of relaxation for intubation were significantly higher in group with neuromuscular monitor ascompared to clinical assessment group ($P < 0.05$).

In above study, we observed that the mean time from last dose of Atracurium to start of antagonism of the neuromuscular block agent in the monitoring group was 31.49±2.27 minutes compared to 44.49±2.37 minutes in the clinical assessment group. This was found to be statistically highly significant (P<0.001). Also, we observed that the mean time from administration of antagonism of the neuromuscular block agent (reversal agent) till the extubation in NM monitoring group was 4.57±0.81 min and Clinical assessment group was 6.63±0.84 min. This was found to be statistically highly significant (P<0.001). Antagonism of low degrees of atracurium-induced neuromuscular blockade (TOF count=4, TOF ratio > 0.4) was studied by Fuchs-Buder *et al.*[11] and they found successful block's reversal within 10 minutes with as little as 20 μg/kg neostigmine. Kim *et al.*[12] established that the average time of23 minutes (range 8–57) was required to reverse moderate block with rocuronium.

Murphy *et al.*[13] conducted a study of TOF ratio quantified using AMG, immediately before tracheal extubation. It was concluded that residual paralysis was present in most patients at thetime of extubation. Despite a protocol designed for monitoring and reversal, and despite the use of an intermediate-acting NMBA, there was some degree of residual paralysis at the end of surgery, while the patient was still in the operating room. Hence, they recommended neuromuscular monitoring to ensure that recovery is complete and that respiratory and pharyngeal function is normal.[14]

In above study, reversal of NM blockade was done when the TOF count= 4 in the NM monitoring group. Thilen *et al.*[15] recommended that with the quantitative NM monitoring, neostigmine can be administered at a lower TOF count of 1 or 2. While it would be expected that reversal to a TOF ratio of 0.9 often takes 20 min or even longer, the quantitative monitor eliminates the problem of the zone of blind paralysis (i.e. TOF ratio 0.4–0.9) and the patient can be accurately monitored throughout. In some cases, reversal will occur more quickly, and when this is confirmed with the quantitative monitor, extubation can be safely performed without delay. Murphy *et al.*[13] conducted a study of TOF ratio quantified using AMG, immediately before tracheal extubation. It was concluded that residual paralysis was present in most patients at the time of extubation. Similar findings were found in studies done by Baillard *et al.*[10] that incomplete recovery from muscle relaxant was found in the clinical assessment group than neuromuscular monitoring group with use of the intermediate-acting muscle relaxant.

In above study, neuromuscular monitoring in addition to its benefits during the intraoperative period, we used it to indicate appropriate time for laryngoscopy and intubation following the intubating dose of Inj. Atracurium. In the study conducted, we observed that the mean time interval from Intubating dose of Atracurium to Intubate in NM monitoring group was 287.51sec (4.76min) ± 36.08 compared to the clinical assessment group where it was 225.74sec(3.76min) ± 5.47 respectively. This mean time interval from Intubating dose of Atracurium toIntubate was found to be statistically highly significantly in NM monitoring group compared toclinical assessment group (P<0.001) Intubation score was observed to be excellent in all 35 patients (100%) in the neuromuscular monitored group compared clinical assessment group where it was 65.7% (n= 23) (p<0.001).Similar findings were found in the study by Nidhi Malipatil, K. Harshavardhan,[7] Rudranil Nandi

et al.,[5] Witkowska M *et al.*[6]

The quality of operative condition based on Surgeon's rating scale did not differ significantly between two study groups. (P>0.05). Quantitative monitoring has proved to be not only efficacious but also effective.[13,16] Currently, the most widely available monitor is the TOF- Watch® which is based on acceleromyography. Calibration of this monitor is easily performed in less than 30 s and improves its accuracy. It is performed after induction of general anesthesia but before administration of NMBDs. Measurements often show some variability and it is therefore customary to perform several measurements until two consecutive measurements are within 10 % and then to average these. The monitor works best when applied to a freely moving thumb, and devices have been developed to protect the thumb from external disturbances during surgery. If a freely moving thumb is not available intra-operatively, the monitor can be used at alternate sites but should be moved to the ulnar nerve/adductor pollicis when this site becomes available at the end of the case. As mentioned, reversal can be administered at lowerTOF counts with the quantitative PNS monitors as the TOF ratio can be assessed continuouslyto ensure a TOF ratio equal to or greater than 0.9 prior to extubation. Studies have documented that when all operating rooms inan anaesthesia department were equipped with these monitors, the incidence of residual paralysis declined continuously from 62 % to just 3%.[4] This improvement was accomplished while the only reversal agent available was neostigmine.[15]

CONCLUSION

Quantitative neuromuscular monitoring (NMT) should be performed for all patients who receive NMBAs during general anaesthesia to guide the dosage & frequency of NMBAs, optimal timing and conditions for intubation, administration of reversal agents and extubation.This may help anaesthesiologist for accurate titration, a more rational use of the NMBA and thus may reduce theincidence of postoperative residual neuromuscular block.

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