Original Article

Reversal agents: do we need to administer with neuromuscular monitoring – an observational study

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ABSTRACT

Background and Aims: In clinical practice, in the majority of patients, recovery from the effect of muscle relaxants is assessed using subjective methods such as head lift, eye-opening, or by sustained hand grip after giving anticholinesterases (neostigmine) at the end of surgery. We planned a prospective observational cohort study to test the hypothesis that objective neuromuscular monitoring can help us in avoiding the use of anticholinesterases for reversal. **Methods:** The patients posted for surgery of <2 h duration were included in the study. The cohort of patients was formed on the basis of those who were exposed to objective neuromuscular monitoring of recovery (train-of-four [TOF] ratio of 0.9 or more; exposed group) and the patients who were not exposed to objective neuromuscular monitoring (non-exposed group) acting as a control. Using objective neuromuscular monitoring, the time required for recovery from muscle relaxation when neostigmine was not given for reversal was noted and it was then compared with that of the control group. **Results:** A total of 190 patients were enrolled over a period of 3 years. With the use of TOF ratio of 0.9 for extubation, patients safely recovered from neuromuscular blockade, without using neostigmine, with no difference in the mean recovery time (14.48 ± 1.138 min) as compared to the control group (12.14 ± 1.067 min, $P = 0.139$). There was no incidence of reintubation in post-operative period. **Conclusion:** With objective neuromuscular monitoring, we can ensure complete recovery from the neuromuscular blockade while avoiding the use of anticholinesterases.

Key words: Objective neuromuscular monitoring, recovery duration, reversal agents

INTRODUCTION

A wide range of surgeries are done under general anaesthesia, and the maintenance of muscle relaxation is important in facilitating surgical procedures. It is challenging for anaesthesiologists to change their practice of subjective assessment of recovery from neuromuscular blockade.[1,2] In most of the centres, the subjective assessment of recovery from the effect of a neuromuscular blocking agent (NMBA) is done by observing eye-opening, tongue protrusion, head lift and sustained hand grip for more than 5 s. Although objective neuromuscular monitoring has been available since decades, its routine use still remains negligible. Thus, patients may suffer from potentially serious morbidity due to the residual effect of muscle relaxants. Recent evidence showed that about 20% of European Anaesthetists and about 10% of American or Australian anaesthesiologists never used neuromuscular monitoring devices during surgery as they believed that their patients rarely experienced clinically significant outcomes due to the residual neuromuscular blockade.[3,4] The literature is replete with data documenting the inadequacy of clinical criteria and less reliable subjective assessment

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of neuromuscular recovery after administration of reversal agents.[5] The return of diaphragmatic activity, which is documented by the return of spontaneous respiration, does not always ensures the return of activity of upper airway muscles, i.e., genioglossus, geniohyoid and masseter muscle which protects the upper airway from aspiration.[6,7] Numerous studies have described that incomplete neuromuscular recovery is associated with a variety of adverse outcomes in the early post-operative period, which involves upper airway obstruction leading to hypoxia, post-operative muscle weakness and an unpleasant feeling of breathlessness after regaining consciousness during reversal.[8,9] On the other hand, while neostigmine acts as an antagonist for NMBA, when administered incorrectly, it may either be ineffective or have undesirable paradoxical effects.[10-13]

We hypothesised that the use of objective neuromuscular monitoring (train-of-four [TOF]) may help guide the frequency of repeating the NMBAs during surgery, and avoiding the anticholinesterases at the time of recovery from Anaesthesia. In a prospective cohort study, we observed the use of objective neuromuscular monitoring in assessing adequate muscle relaxation for intubation, for the maintenance of intra-operative relaxation and recovery from NMBA without using neostigmine.

METHODS

We planned a prospective, cohort study in our Institute over a period of 3 years (March 2014 to February 2017). After approval of the Institute Ethics Committee (AIIMS/IEC/2014/0000044 dated: September 15, 2014) and written informed consent, patients posted for abdominal surgeries of <2 h duration under general anaesthesia were enrolled into the study. The inclusion criteria were: patients of the American Society of Anaesthesiologists (ASA) physical status I, of either sex, aged between 18 and 45 years and having no history of any neuromuscular disorders. The exclusion criteria were: history of diabetes, myasthenia gravis, hepatorenal impairment or surgery at the site where electrodes were to be applied and emergency surgeries. All the patients were reviewed during pre-operative visit, 1 day before surgery by the attending anaesthesiologist. Blood investigations were advised in PAC clinic (pre-anaesthesia check-up) according to the National Institute for Health and Care Excellence guidelines.[14] Patients were kept fasting for 8 h to solids and for 2 h to clear liquids before scheduled time of surgery.[15]

The cohort of patients who were exposed to quantitative neuromuscular monitoring intraoperatively and at the time of extubation, were included in the exposed group, whereas in the non-exposed group, the cohort of patients were not exposed to quantitative neuromuscular monitoring intraoperatively and at the time of extubation. The groups were allocated based on the surgery list of that day; every alternate patient was monitored using NMT monitoring, thus included in exposed group while other alternates on same day were included in non-exposed group.

Anaesthetic management was standardised in all the patients. Before transporting the patient to the operating room (OR), pre-medication with injection midazolam was given. Monitors were applied in the OR for baseline readings of vital parameters like electrocardiography (ECG), peripheral oxygen saturation monitor (SpO_2), non-invasive blood pressure (BP), bispectral index (BIS) electrodes (BIS™ monitoring system, Covidien, Mansfield, MA, USA) and core temperature through nasopharyngeal probe. In the exposed groupd, a NM monitor using the principle of acceleromyography (Drager Infinity Trident NMT Smartpod®) was used. The adductor pollicis muscle was chosen for neuromuscular monitoring. After the skin was cleansed with chlorhexidine, two surface electrodes (distal black and proximal red in colour), separated by a distance of not more than 6 cm, were placed over course of ulnar nerve at the wrist. The peripheral temperature of the hand was kept more than 32°C for reducing the skin impedance, to avoid inaccurate TOF readings due to peripheral hypothermia. The acceleration transducer was attached to the distal phalanx of the thumb through a hand adapter that also applied a constant preload and allowed a reproducible baseline thumb position. After pre-oxygenation with 100% oxygen (O_2) for 3 min, anaesthesia was induced with injection Fentanyl 2 μg/kg intravenous (IV) and injection Propofol 2 mg/kg IV until the loss of consciousness (absence of eyelash reflex) and the loss of response to verbal commands. For calibration, TOF stimulation (four pulses of 0.2-ms duration at a frequency of 2 Hz) was monitored in patients in after induction and before injection of muscle relaxant, and the current intensity selected was between 30 and 50 mA. During nerve stimulation, the monitored extremity was observed to ensure free movement of the thumb. After assurance of adequate mask ventilation, injection Rocuronium 0.5 mg/kg IV was given as NMBA for facilitation of tracheal intubation. Direct laryngoscopy and endotracheal

intubation was performed after the TOF count of zero (0) was observed on the monitor screen in all patients. Volume controlled ventilation was used with tidal volume 6–8 ml/kg and RR was adjusted to keep end-tidal CO_2 between 30 and 36 mm Hg. Anaesthesia was maintained with sevoflurane (1%–4% in oxygen-air mixture), minimum alveolar concentration adjusted to keep BIS between 40 and 60, supplemented with additional boluses of fentanyl 1 μg/kg and injection Rocuronium was repeated (25% of the intubating dose) on reappearance of second count on TOF (TOF 2). As the surgical closure was done, patients were kept sedated using sevoflurane with BIS value between 60 and 80, until the recovery of TOF ratio to 0.9 and were extubated without the use of reversal agents (neostigmine) when the TOF ratio exceeded 0.9, the primary outcome, i.e. the time elapsed from the end of surgery to time of extubation (without using neostigmine) was noted in every patient. In non-exposed group, no NM monitor was applied, and neuromuscular blockade was reversed using neostigmine (50 μg/kg) and the trachea extubated when patient followed verbal command for eye-opening, and had tongue protrusion, head lift and sustained hand grip for more than 5 s. The patients of both the groups were then shifted to post-anaesthesia care unit (PACU) where continuous monitoring of O_2 saturation, heart rate, respiratory rate, respiratory pattern, ECG and blood pressure was done, at every 5 min interval for initial 30 min, then after every 15 min for next 2 h. The primary outcome of the study was the time required for complete recovery from neuromuscular blockade in both the groups. This was assessed by TOF ratio of 0.9 at the end of surgery without giving neostigmine in the exposed group and by clinical criteria like eye-opening, tongue protrusion, head lift and sustained hand grip after giving neostigmine in the non-exposed group, followed by extubating the patients. The secondary outcomes included episodes of oxygen desaturation, hypoventilation, need for reintubation, as well as episodes of cardiac arrhythmia or post-operative nausea and vomiting in PACU. The patients with Aldrete score of more than 9 were then shifted to ward and the time spent by each patient in PACU was noted. The patients were followed up in wards for the incidence of pneumonia 48 h after surgery and the operating surgeons were requested to inform the investigating team before discharging the patients, the day of discharge from the hospital was also noted for patients in both the groups, in order to compare the duration of hospital stay in both groups.

Statistical analysis

All statistical analyses were performed with the Graph Pad InStat 6.0 programme (Graph Pad Software, San Diego, CA, USA). Time required from end of surgery to extubation at TOF of 0.9 or more was compared in both the groups using unpaired *t*-test with Welch's correction. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 155 patients were included in the study out of which, a cohort of 89 patients were in exposed group and the cohort of 66 patients were in non-exposed group [Figure 1]. In a cohort of the non-exposed group, extubation was done after reversal of neuromuscular blockade by injection neostigmine and subjective assessment of clinical signs of reversal. The demographic profile (age, sex and body mass index) was noted in both the groups [Table 1]; types of surgeries performed were laparoscopic cholecystectomy, appendectomy, hernia, hysterectomy and exploratory laparotomy [Table 2]. Mean time required from the end of surgery to extubation at TOF ratio of 0.9 in exposed group was 14.48 ± 1.138 min and in the non-exposed group, it was 12.14 ± 1.067 min ($P = 0.139$). In 4 patients of exposed group and in 5 patients of the control group, there were episodes of oxygen desaturation in PACU and these patients required low flow supplemental oxygen in PACU but none of the patients was reintubated [Table 3]. The patients with Aldrette score of more than 9 were then shifted

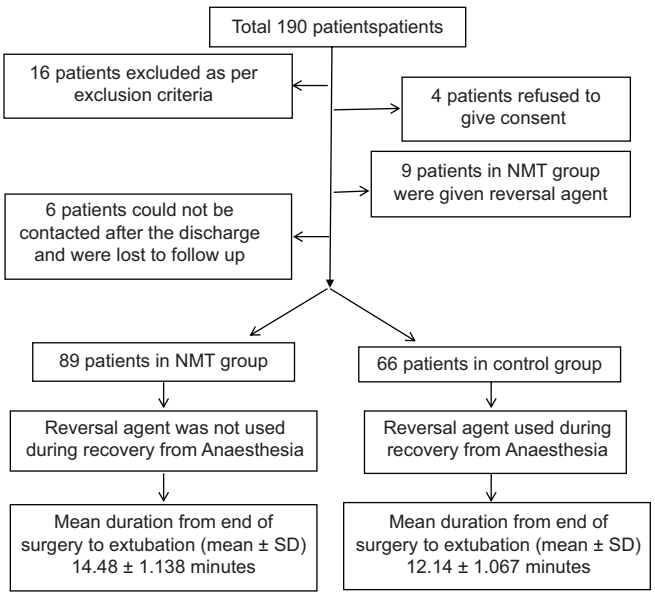

Figure 1: Representation of patients recruited for the study as per STROBES statement

Table 1: Demographic profile (mean±standard deviation)

Demographics	Mean±SD	
	Exposed (NMT group)	Unexposed (Control group)
Age (years)	39±6	37±7
Number of males	45	30
Number of females	55	25
BMI (kg/m^2)		
Males	24±2	22±3
Females	22±3	21±2

SD – Standard deviation; BMI – Body mass index; NMT – Neuromuscular Monitoring Technique

Table 2: Different types of surgeries performed and the time elapsed in min (mean±standard deviation) from end of surgery to extubation at train-of-four ratio of 0.9

Type of surgery	*n*	Time in exposed (NMT group)	Time in unexposed (control group)	*P*
Laparoscopic cholecystectomy	56	16.27±7.63	14.68±4.46	0.24
Laparoscopic appendectomy	20	13.64±4.33	10.36±2.56	0.44
Laparoscopic hernia repair	43	14.66±3.22	13.22±4.33	0.52
Laparoscopic hysterectomy	30	12.56±1.22	11.67±3.44	0.48
Exploratory laparotomy	6	16.46±3.44	12.23±3.44	0.45

NMT – Neuromuscular Monitoring Technique

Table 3: Incidence of post-operative complications

Event	Exposed group (NMT)	Unexposed group (control)
Need for supplementary oxygen in PACU	6	8
Post-operative nausea in PACU	8	7
Post-operative vomiting in PACU	2	4
Reintubation in PACU	0	0
Cardiac arrhythmia in PACU	0	0
Incidence of pneumonia 48 h after surgery	0	2

PACU – Post-anaesthesia care unit; NMT – Neuromuscular Monitoring Technique

to ward and the time spent in PACU in exposed group was 134 ± 12 min and in unexposed group was 129 ± 16 min. The duration of stay in hospital was also comparable in both the groups; most of the patients were discharged on the second post-operative day and were followed up for next 30 days for any delayed respiratory infections, no incidence of any respiratory complication was observed in either group during 30-day follow-up period.

DISCUSSION

In this study, we have observed that by applying the objective neuromuscular monitoring patients could be safely extubated at the end of surgery (after achieving the TOF >0.9) even without using neostigmine. This could protect patients from the potentially harmful side effects of neostigmine, like salivation, bradycardia etc., for which an anticholinergic is routinely given which in turn results in an unpleasant experience of dry mouth in post-operative period. It is a common practice to reverse neuromuscular blockade at the end of surgery by giving neostigmine. Despite this the incidence of residual paralysis varies from 38% to 64% in the immediate post-operative period.[16-19] Recent studies have demonstrated that objective measurement of muscle contraction (TOF ratio >0.9) is the only method to determine the appropriate timing of extubation and prevention of aspiration.[3,16,20] Guidelines from French Society of Anaesthesiology and Intensive Care published in 2000, Czech Society of Anaesthesiology Standards 2010 and most recently the Association of Anaesthetists of Great Britain and Ireland, London, United Kingdom, made it mandatory to attach a peripheral nerve stimulator whenever neuromuscular blocking drugs are given.[21] More recent studies have demonstrated that although neostigmine hastens the recovery by 20–25 min, the return of satisfactory neuromuscular recovery is hardly prompt or complete and patients cannot be safely extubated until they have a sustained hand grip or a TOF ratio of more than 0.9.[17,22,23] Animal studies even demonstrated that neostigmine impairs genioglossus muscle activity, which is a protective upper airway muscle, having an upper airway dilator ability. These studies have reported that when full dose of neostigmine is administered to rats that have completely recovered from the neuromuscular blockade, neostigmine reduced genioglossus muscle activity, along with impaired diaphragmatic functions and breathing.[24] It was thus concluded that if administered incorrectly, neostigmine can either be ineffective or may even have a paradoxical effect and the limitations of neostigmine as an antagonists of residual block is far greater than most clinicians appreciate, which can be demonstrated only by judicious use of neuromuscular monitoring.[25-27]

A large number of other factors such as obesity, comorbidities or mutations in butyrylcholinesterase gene can result in the sustained effect of neuromuscular blockade and the patients with good respiratory reserve can tolerate residual block for some time. As a result, these effects often go unnoticed in the absence of objective monitoring.[16,28] As it is evident that neuromuscular blockers compete with acetylcholine for postsynaptic receptors at the neuromuscular junction, inhibition of acetylcholinesterase enzyme by neostigmine prevents the breakdown of acetylcholine,

leading to increased concentration of acetylcholine at the receptor site, which in turn displaces NMBA from the postsynaptic receptors and reverses their effect. However, once the acetylcholinesterase activity is completely inhibited, further adding neostigmine at this time will not increase the acetylcholine concentration, whereas the circulating NMBA continues to bind with the postsynaptic receptors, leading to the prolonged residual effect of NMBA. In these situations, the use of objective neuromuscular monitoring helps in assessing the depth of block and thus guide us about the timing of neostigmine administration if at all needed. Neostigmine, when used injudiciously without neuromuscular monitoring may even harm the patient during reversal.[29] At times when patients recover spontaneously from NMB, administering neostigmine in such patients will cause acetylcholine surge, leading to a depolarising neuromuscular blockade with no TOF-fade, which may expose the patient to a brief duration of respiratory muscle weakness before PACU arrival. This acetylcholine surge induced by neostigmine has several muscarinic side effects, such as salivation, bronchospasm and even bradycardia, thus predisposing patients for aspiration.[30] These are prevented by adding an anticholinergic agent with it, but the unpleasant side effects of neostigmine can be avoided by the use of objective neuromuscular monitoring and assessing the actual need for anticholinesterases at the time of reversal.[31,32]

The limitations of our study were that the patients enrolled were of ASA physical status I only, and the duration of surgery was <2 h. Thus, the effect of recovery from NMBA under objective neuromuscular monitoring without using neostigmine could not be assessed in patients with comorbidities and in prolonged surgical procedures.

As neuromuscular monitoring is not widely available, neostigmine still remains the main agent for reversing neuromuscular blockade at the end of surgery. We need large scale randomised trials to establish NMT as a standard monitoring tool to avoid the use of neostigmine for reversal of residual neuromuscular blockade.

CONCLUSION

With routine use of objective neuromuscular monitoring, the use of anticholinesterases can be avoided.

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Conflicts of interest

There are no conflicts of interest.

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