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Original Research Article

Clinical assessment of recovery from neuromuscular blockers, is it a safe practise - An observational study

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ABSTRACT

Background: The incidence of residual neuromuscular paralysis (RNMB) with Train of four ratio<0.9 remains as high as 16% in PACU even after administration of reversal when neuromuscular monitoring is not done. Reversal with standard dose of neostigmine and extubation are done based on the clinical signs. We observed the clinical signs of neuromuscular recovery and correlated with neuromuscular monitoring to assess the degree of residual blockade in the post-operative period.

Materials and Methods: 100 Patients posted for surgery under general anaesthesia with endotracheal tube intubation and controlled ventilation were enrolled for the study after obtaining human ethical approval. Standard anaesthesia technique using morphine, propofol, vecuronium, isoflurane with low flow anaesthesia were administered for all patients. TOF was noted at the end of surgical procedure when patient resumed spontaneous respiration, during extubation, and at 15 minutes interval for one hour in the postoperative period. Hemodynamics were observed including respiratory rate.

Results: Overall 32 percent of patients had residual paralysis. 27% at 15 min, 26% at 30min, 6% at 45min and 3% at one hour in the postoperative period showed RNMB. Subgroup analysis showed that at the time administration of reversal 72 patients had (TOFR>0.4) and 28 had (TOFR<.0.4), showed significant difference in improvement in TOFR between 2 subgroups before reversal, immediate extubation and 15 min post extubation (p=0.00,0.001,0.003,) respectively.

Conclusion: Clinical findings of neuromuscular reversal is not foolproof for complete recovery and standard dose neostigmine given during shallow block will accentuate the residual neuromuscular paralysis.

1. Introduction

Neuromuscular blocking agents (NMB) serve the purpose of enhancing intubation, aiding in mechanical ventilation, and inducing immobility during surgical procedures. Additionally, it is crucial to verify that the effects of these drugs have dissipated or been reversed before transitioning the patient to the Post-Anaesthesia Care Unit (PACU). Train-of-four ratio (TOFR)> 0.9 is considered to be complete neuromuscular recovery. Anaesthesiologist most commonly perform the reversal and extubation in response to clinical indicators of recovery from neuromuscular blockade such as sustained head lift >5 secs, raising the legs, tight gripping of the hands, opening the eyes, protruding the tongue, demonstrating satisfactory swallowing, exhibiting effective coughing[1] and standard dose of neostigmine 40-60 μg/kg are used for reversal of neuromuscular blockade. The incidence of residual neuromuscular paralysis has been reported with an overall 16% without neuromuscular monitoring and 3% with neuromuscular monitoring with intermediate acting agents.[2] Adverse effects of residual neuromuscular paralysis include reduction in the upper esophageal sphincter tone, swallowing dysfunction, delayed swallowing reflex, increased risk of aspiration, reduction in

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the upper airway volume, decreased inspiratory air flow and profound symptoms of muscle weakness.[3] Neuromuscular monitoring is not done in routine practise even in developed countries. Survey showed 19.3% in Europe and 9.4% in US did not routinely use a neuromuscular monitor in their practice and most respondents from both Europe and the US did not believe that either conventional nerve stimulators or quantitative TOF monitors should be part of minimal monitoring standards.[4] Recent studies have shown that standard doses of neostigmine given during shallow neuromuscular blockade causes residual muscle paralysis in the post-operative period.[5,6] During reversal of vecuronium induced neuromuscular blockade and extubation based on the clinical signs of recovery we used neuromuscular monitoring to correlate and assess the incidence of residual neuromuscular blockade in the post-operative period.

2. Materials and Methods

The research was registered with the clinical trial registry CTRI/2018/02/0118877. Following approval from the institutional human ethical committee (this observational clinical investigation was done at a tertiary care institute in Pondicherry from March 2017 to June 2018. The study comprised 100 adult patients scheduled for elective surgeries under general anaesthesia (GA). ASA PS I & II patients between age 18 and 60 years, who were posted for surgery under GA with endotracheal tube intubation and controlled ventilation were recruited for the study. Patients with hepatic or renal dysfunction, difficult airway, patients who were under the medications that influence the action of neuromuscular blockade were excluded. After pre-anaesthetic check the patients who had satisfied the inclusion and exclusion criteria were enrolled into the study by continuous sampling. Written informed consent was obtained from these patients. Patients were kept nil per oral for 8 hours, and they were premedicated with tab. ranitidine 150mg and tab. alprazolam 0.25mg the night before and on the morning of surgery. The patients were transferred into the operation room and monitors electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse-oximeter (SPO2) were connected and baseline readings were recorded. Intravenous cannulation was done with 18 G cannula and was started on Ringer Lactate infusion. Surface electrodes were placed over the course of the ulnar nerve, just proximal to the wrist crease and neuromuscular monitor (Organon TOF Watch SX) was connected (Figure 1). Patients were premedicated with inj. morphine (0.1mg/kg) and inj. midazolam 1mg, preoxygenated with 100% oxygen for three minutes and induced with Propofol (2-3mg/kg). At this stage Supramaximal stimulus was calibrated using the preprogrammed TOF-Watch calibration mode. Supramaximal current is the current above which there is no significant increase in electromyographic amplitude. When the TOF-Watch is switched on, it automatically sets the current to 60mA and TOFR was noted. The current was then reduced in decrements of 5 mA till response to single twitch ≤ 95% is reached. Then 10% was added to next higher value and this current was taken as the supramaximal current.

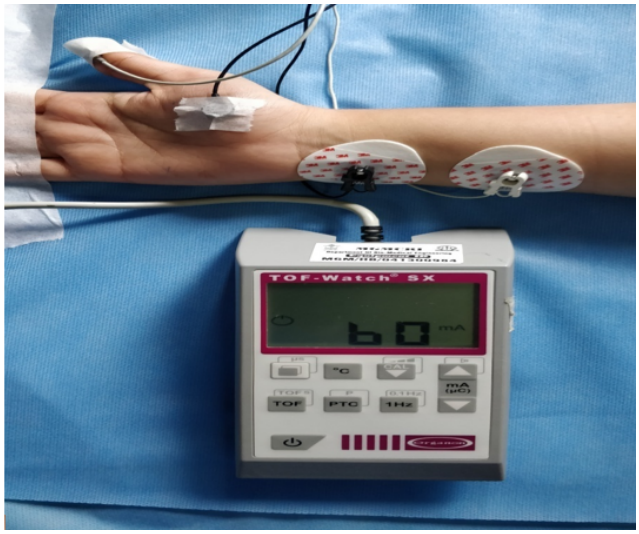

Figure 1: TOF watch with surface electrodes connected to the course of ulnar nerve

After base line recording of the TOF response, vecuronium bromide 0.1mg/kg IV was administered to facilitate tracheal intubation. Mechanical Ventilation was initiated for the patient and Anaesthesia was maintained with 40% oxygen in nitrous oxide (800ml total flow) along with Isoflurane of 1 MAC till the end of the surgery. End tidal concentration of CO2 was maintained between 32 and 36 mmHg and central body temperature was maintained between 35-37 degree Celsius throughout the surgical procedure by using surface warmer and warm fluids.

Isoflurane was stopped 10 minutes before the expected time of end of the surgery. Once the patient starts to breath spontaneously TOF was monitored and respiratory rate and Expiratory Tidal Volume (ETV) was measured and the patient was given 100% oxygen. Following this the patient was given reversal with neostigmine 50mcg/kg and glycopyrrolate 0.01mg/kg. When the patient has had a sustained head lift > 5 seconds they were extubated after thorough oral suctioning and TOFR was monitored. TOF was monitored every 15 minutes for one hour in the PACU. Patients were advised to exhale through the incentive spirometry during the neuromuscular monitor assessment in the PACU and the volume of exhalation were noted. All data were recorded on the data collection proforma and was entered into Microsoft Excel (2010) as a master chart. Privacy and confidentiality were maintained throughout. Data were analysed by SPSS 21(IBM software, Inc., USA).

Sample size calculation was done based on previous studies by Kajal et al[5] who observed 6.6% incidence of residual neuromuscular blockade with 40mcg /kg of

neostigmine. We assumed that when patient is reversed based on clinical signs the TOFR will be less than 0.4 and the incidence of residual neuromuscular paralysis will be 5%, we have calculated the sample size using the formula

$$n = \frac{Z^2_{1-\alpha/2}\,P(1-P)}{d^2}$$

(n= sample size, $Z_{1-\alpha/2}$ (confidence level) = 1.96 (α =0.05), p= (6.6%) 0.66, d= 0.05 (5%),

n>94 (sample size). We did the study on total of 100 patients.)

Demographic data expressed as mean with standard deviation, Gender distribution and ASA physical status expressed as percentage. Incidence of TOFR <0.9 is expressed in terms of percentage. TOFR at the time of starting of reversal, at the time of extubation and 15,30,45 and 60 minutes post extubation expressed in terms of mean and standard deviation. Pearson correlation was used to find the correlation between the exhaled tidal volume with TOFR before reversal of neuromuscular blockade and at the time of extubation. Mean TOF between the two subgroups were compared using unpaired T test.

3. Result

Total 118 patients were screened for eligibility by continuous sampling method. After excluding 12 patients who were not satisfying inclusion criteria, 106 eligible patients entered in the study. There was dropout for 6 patients due to either change in anaesthesia plan or case cancellation. Thus, total of 100 patients completed the study and was included for analysis (Figure 2).

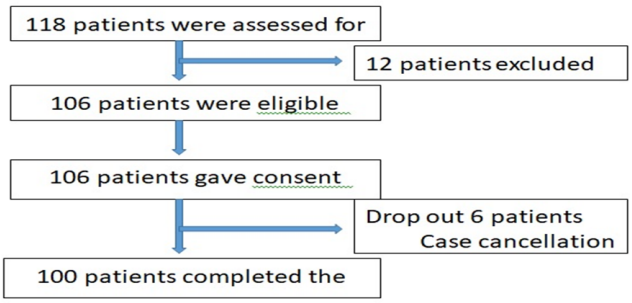

Figure 2: Consort flow chart

There was no difference between the two groups with regards to ASA1, ASA2 and gender distribution. Demographic profile is given in Table 1. Mean duration from last dose of vecuronium and reversal agent was 67.6±18.4 minutes, duration between reversal and extubation was 6.3±2.1minutes. 32 patients had residual paralysis and the incidence of residual paralysis was 27%, 26%, 6% and 3% from 15,30,45 and 60 minutes period respectively (Figure 3). Out of 72 patients who had attained TOFR>0.9, 17 patients (23.6%) had developed residual paralysis at 30 minutes after extubation. Correlation between exhaled tidal volume and TOF before reversal of neuromuscular blockade was (p=0.056, and r=0.19) and immediately after extubation (p=0.690, r=0.040).

Table 1: Demographic data

Parameters	Results
Male/Female	57/43
ASA I/ASAII	55/45
Age (years)	31 35(9.14)
Weight (kg)	57.61(8.63)
Height (cm)	165.86(6.67)
BMI	22.15(5.42)

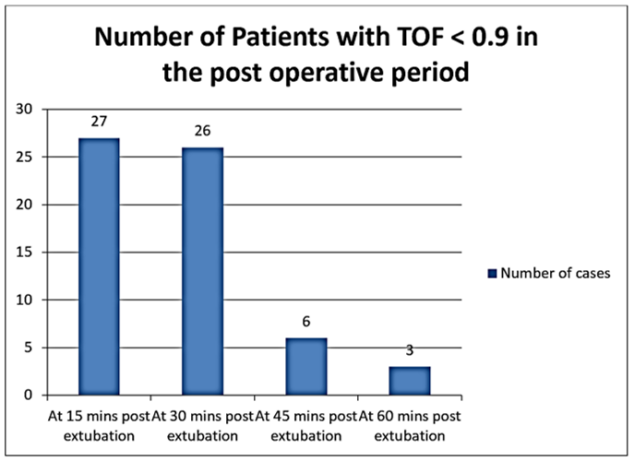

Figure 3: Percentage of patients having TOFR < 0.9

A sub group analysis was done based on the TOFR before starting of reversal, dense blockade group with TOFR <0.4, shallow blockade group with TOFR >0.4 with 28 patients in dense group and 72 patients in shallow group. Among the 28 patients who had dense neuromuscular block showed steady improvement in the TOFR (neuromuscular recovery) in the PACU. Two patients had TOFR of 0 at the time of reversal and their TOFR improved in the PACU. However, two patients in the dense block group had RNMB even after one hour with TOFR <0.9 (Figure 5). Out of 72 patients in the shallow blockade group, 17 (23.6%) patients had developed residual neuromuscular paralysis (TOFR< 0.9) at 15 mins or 30 mins in the PACU (Figure 6). At 30 minutes post extubation significant increase in drop in TOFR was noted (p=0.001) in shallow group compared to the dense group. Haemodynamic parameters were stable in all patients.

4. Discussion

Despite using reversal agents at the end of surgery and clinically apparent about the recovery of neuromuscular function, residual neuromuscular blockade occurs in the PACU.[7–9] RNMB is known to be associated with reduction

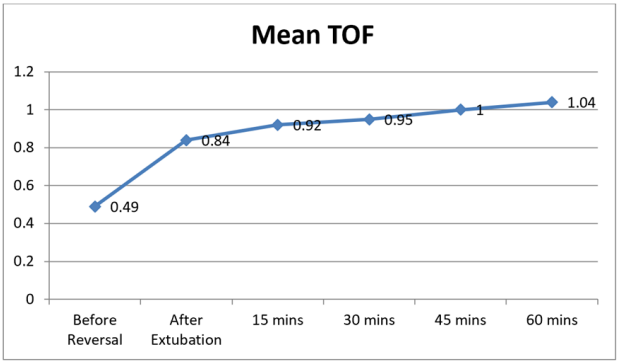

Figure 4: Mean TOFR at various intervals of the study

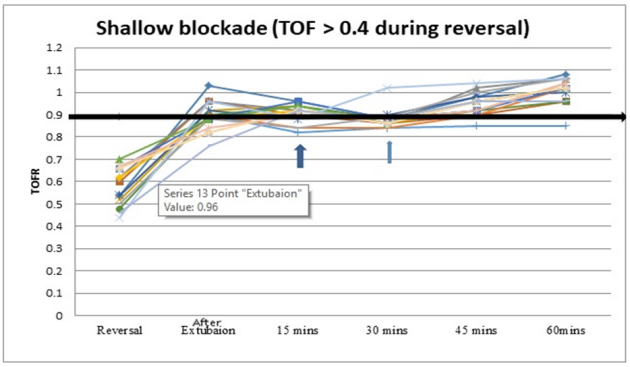

Figure 5: Graph showing the total number patient who developed residual neuromuscular paralysis after obtaining TOF >=0.9 in the postoperative period in the shallow blockade group

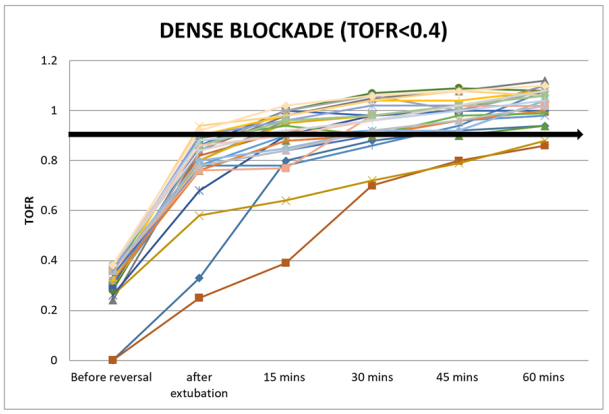

Figure 6: Change in TOFR from the time of giving reversal to 60 minutes post extubation in dense group

in the pulmonary function test in the postoperative period.[10] Clinical signs of recovery from neuromuscular blockade effects are head lifting, leg raising, hand gripping, eye-opening, tongue protrusion, adequate swallowing, and, last but not least, adequate coughing.[11] In our study we used onset of spontaneous breathing as the criteria to start reversal and found the mean TOFR as 0.49 with SD of 0.21 and sustained head lift >5 seconds as clinical criteria for extubation and found mean TOFR as 0.84 with SD 0.12. Studies from the US and Europe reported that clinical signs (such as the ability to sustain a head lift >5-s) were reliable indicators of the adequacy of neuromuscular recovery.[4] Study conducted on volunteers by Kopmann et al. showed that with mean TOFR 0.7, they were able to head lift and the correlation was variable among individuals and however all patients were able to sustain eye opening, hand grasp, and tongue protrusion and able to maintain a 5-second head lift.[12] Since RNMB produce reduction in pulmonary function we correlated exhaled tidal volume with TOFR before administration of reversal and after extubation. But there was no correlation between exhaled tidal volume and TOFR. All our patients demonstrated >500ml exhaled tidal volume irrespective of TOFR in PACU.

Residual neuromuscular paralysis is defined as TOFR< 0.9.[4,5,13] Impaired inspiratory flow and partial upper airway obstruction have been observed frequently at TOF ratios of 0.8.[14] Data derived from volunteer studies have demonstrated that pharyngeal dysfunction and an increased risk for aspiration occur at TOF ratios 0.9.[15,16] Many studies had showed that patients had significant residual neuromuscular blockade ranging from 3% to 83% when extubated based on clinical signs.[2,17,18] Study done by Debane et al. showed poor sensitivity of clinical test and manual assessment of fade to detect residual blockade.[19] In our study after reversal with standard dose of neostigmine(50mcg/kg) and extubation based on clinical signs we observed 32% of patients had residual neuromuscular paralysis (TOFR<0.9) in the PACU.

Neuromuscular monitoring is not routinely done in clinical practise even in developed countries. Surveys of clinical practice in Europe suggest that neuromuscular blockers are often administered without proper monitoring. Surveys in Denmark, Germany, the United Kingdom, and Mexico have suggested that only 43%, 28%, 10%, and 2% of clinicians, respectively, routinely use neuromuscular monitors of any kind.[20–22] However, Survey by Naguib on current management of neuromuscular block in the United States and Europe showed that the incidence of clinically significant postoperative residual neuromuscular weakness to be <1%.[4]

In our study mean duration of extubation from the time of reversal was 6.3 minutes and time interval between last dose of relaxant to reversal was 60 minutes. Since we had used low flow, duration of starting reversal from

last dose of vecuronium was long, contrast to previous studies where duration was less.[5,6] Since it is difficult to appreciate the fade on qualitative monitoring TOFR 0.4 was made as standard value to differentiate into shallow and deep neuromuscular block. In our study the mean TOFR during administration of reversal was 0.49 with SD 0.21. Hence, we made subgroups with patients TOFR <0.4 and >0.4 and 72 and 28 patients had shallow and dense block respectively. In the absence of significant neuromuscular blockade, reversal with neostigmine can potentially cause neuromuscular block by numerous methods. One method is by increasing the acetylcholine in the synaptic cleft that acts at the prejunctional receptors and first node of Ranvier there by inhibiting the transmitter release and secondly the drug itself can cause receptor channel blockade.[23]

In our study patients we used standard dose of neostigmine 50 mcg/kg and found few patients in dense blockade group showed steady improvement in TOFR and took 60 minutes to achieve complete neuromuscular recovery whereas patients in shallow blockade achieved complete neuromuscular recovery earlier but 23% showed drop in TOFR in PACU, and they recovered shortly. Studies with intermediate acting neuromuscular agents had proved that low dose of neostigmine is sufficient to safely reverse shallow neuromuscular blockade[5,23] and standard dose 40mcg/kg neostigmine enhanced the neuromuscular recovery but produced a drop in TOFR in the postoperative period thereby producing RNMB for a brief period in PACU.[5,6]

On analysis between the subgroups, at 15 minutes in the post extubation period we observed residual neuromuscular paralysis in 35.7% in deep block and 23.6% of the patients in shallow block group. At 30 minutes post extubation we observed TOFR<0.9 in 14.2% and 29.1% of the patient in the dense group and shallow group. The patient who had RNMB in the shallow muscular blockade increased from 23.6% to 29.6% from 15 minutes to 30 minutes (Figure 5). In the shallow group out of all the patients who have attained TOFR more ≥ 0.9 after reversal, had developed residual neuromuscular paralysis in the post-operative period which was similar to the studies conducted by Shveta.[5] While this did not happen in the dense blockade group. None of the patients complained of any clinical signs of residual neuromuscular paralysis during their time in PACU.

5. Limitation

In our study limitation was we did not do multifactorial analysis.

6. Conclusion

Clinical signs of neuromuscular recovery do not exclude residual neuromuscular blockade and standard dose of neostigmine can accentuate the residual neuromuscular paralysis in the postoperative period. Hence, we recommend quantitative neuromuscular monitoring in routine practice to prevent RNMB in our clinical practice.

7. Source of Funding

None.

8. Conflict of Interest

None.

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