e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15 (5); 1057-1065

Original Research Article

Assessment of Postoperative Residual Neuromuscular Blockade with Vecuronium as a Muscle Relaxant using Peak Expiratory Flow and Train of Four Ratios: A Prospective Observational Study

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Received: 25-03-2023 / Revised: 25-04-2023 / Accepted: 15-05-2023

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Conflict of interest: Nil

Abstract

This study was conducted to assess and compare the incidence of post-operative residual neuromuscular blockade in patients who were administered intermediate acting (30-45 min) neuromuscular blocking agents (vecuronium) for maintenance of neuromuscular blockade in the intra-operative period with those in patients who were not administered neuromuscular blocking agents for maintenance of neuromuscular blockade during general anesthesia, with regard to the time required to extubate the patients after reversal of neuromuscular blockade, the Peak Expiratory Flow (PEF) and TOF after extubation and percentage of preoperative PEF at 60 minutes after extubation.

Methods: This was a hospital based prospective observational study conducted among 60 patients who underwent elective orthopedic surgery, otorhinolaryngologic surgery, urological surgery and plastic surgery at BGS Global Hospital, Bangalore, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Results: Among the intraoperative variables statistically significant difference was observed in the total dose of vecuronium and total dose of fentanyl used among the two groups. Total dose of Fentanyl used was found to be statistically significant. A comparison of R-TOF interval among two groups was found to be statistically significant. Statistically significant difference was observed in PEF values performed 60 min after extubation, expressed as percentage of preoperative PEF values. Statistically significant difference was observed among the two groups in sedation score after extubation. Sedation score was more in group B compared to group A till 15 minutes after extubation.

Conclusion: Neuromuscular blocking drugs should be avoided for maintenance of neuromuscular blockade wherever possible, i.e., surgeries that do not require muscular relaxation such as certain peripheral limb surgeries, surgery on the skin (plastic surgery) etc.

Keywords: Neuromuscular Blockade, Vecuronium, Muscle Relaxant, Peak Expiratory Flow, Train of Four Ratios.

Introduction

General anesthesia consists of four components: sleep or unconsciousness, blockade of autonomic reflexes, motor blockade and analgesia. [1] Neuromuscular blocking drugs (NMBD) act on acetyl choline receptors situated at the neuromuscular junction (NMJ). They produce muscle relaxation, which is required during endotracheal intubation and during specific surgical procedures. Vecuronium is a non-depolarizing, intermediate acting neuromuscular blocking agent. Restoration of complete skeletal muscle strength post-operatively is essential to ensure that patients are able to sustain adequate ventilation, adequate cough and to maintain a patent airway. [2] Postoperative respiratory impairment after anesthesia and surgery is due to various causes, which include patient factors like obesity, surgical factors like site of incision, tight dressing, gastric dilatation, postoperative pain and effects of residual anesthetic agents and neuromuscular blocking drugs (NMBDs). [3] The muscle response to peripheral nerve stimulation (usually of the ulnar nerve) adequately measures reversal of non-depolarizing neuromuscular blockade. In fact, peripheral nerve stimulators are often used in preference to (and in the absence of) tests of ventilation. A train of four (TOF) ratio of 0.9 indicates adequate recovery of neuromuscular blockade (NMB). [4] The diaphragm recovers from the effects of non-depolarizing NMBDs more rapidly than does the adductor pollicis. [5] Residual neuromuscular blockade (RNMB) is an important complication after use of non- depolarizing muscle relaxants. More than 25 yrs ago, it was documented that RNMB was frequent in patients given long-acting neuromuscular blocking agents. [6] Later studies have confirmed this finding even with intermediate acting neuromuscular blocking agents. [7-10] In fact, 16-42% of patients receiving intermediate acting muscle relaxants in the operating room (OR) and who were extubated using clinical criteria have TOF ratios < 0.7-0.8 in the PACU. [7,10,11] These findings suggest that anaesthesia care providers are unable to reliably detect residual neuromuscular block in the operating theatre using standard clinical criteria. Respiratory and pharyngeal muscle function can be adversely affected even with minimal neuromuscular blockade. Studies in awake volunteers and surgical patients have demonstrated that TOF ratios of 0.7 – 0.9 are associated with impaired airway protective reflexes, [12] upper airway obstruction, [13] decreased hypoxic ventilatory response, [14] and post-operative hypoxemia. [15] On the basis of these findings, several investigators have recommended that full recovery of neuromuscular function (TOF $\geq$ 0.9) should be present at the time of tracheal extubation. [10,13,16] Because clinical tests are insensitive in detecting TOF ratios between 0.5-1.0, quantitative neuromuscular monitoring is required to exclude the presence of residual paresis.

Aims and Objectives

To assess the incidence of post-operative residual neuromuscular blockade in patients who are administered intermediate acting (30-45 min) neuromuscular blocking agents (vecuronium) for maintenance of neuromuscular blockade in the intraoperative period versus those who are not administered neuromuscular blocking agents for maintenance of neuromuscular blockade during general anesthesia.

To compare the time required to extubate the patients after reversal of neuromuscular blockade.

To compare the Peak Expiratory Flow (PEF) and TOF after extubation and percentage of preoperative PEF at 60 minutes after extubation.

Methods

This was a hospital based prospective observational study conducted among 60 patients who underwent elective orthopedic surgery, otorhinolaryngologic surgery, urological surgery, plastic surgery at BGS Global Hospital, Bangalore, after obtaining clearance from the institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Age above 18 years
- ASA 1 and 2
- Elective orthopedic surgery
- Otorhinolaryngologic surgery
- Urological surgery
- Plastic surgery
- Duration >90min

Exclusion Criteria

Patients with cardiorespiratory abnormalities (New York Heart Association heart failure grades 3 and 4, active bronchial asthma, chronic obstructive pulmonary disease, and restrictive lung disease).

Renal insufficiency (serum creatinine more than 1.6mg/dl), liver dysfunction – liver enzymes-serum glutamate oxaloacetate transaminase/serum glutamate pyruvate transaminase values elevated by more than 50% of normal.

Underlying neuromuscular diseases.

The use of drugs known to interfere with neuromuscular transmission.

History of smoking.

Thoracic and upper abdominal surgeries.

Unwillingness to perform pulmonary function test (PFT) and

Severe obesity (body mass index greater than 35)

Statistical Methods

The demographic data such as age and weight were analyzed using Student t-test (two tailed, independent). Gender, ASA grading were analyzed by Chi-square test. P value of less than 0.05 was considered statistically significant.

Results

The gender distribution (male:female) in Group A and Group B was 20:10 and 11:19 respectively. Statistically significant difference was observed between the two groups in gender distribution (P value was 0.02 by chi-square test). Female patients were significantly more in number in group B compared to that of group A.

Table 1: Comparison of Total Dose of Fentanyl (mcg) used in Two Groups

	Group	**N**	**Mean**	**SD**	**P-Value**
Total Dose of Vecuronium (mg)	A	30	8.900	1.4288	<0.0001
	B	30	6.217	0.5522	
Comparison of Total Dose of Vecuronium used in both Groups					
	Group	N	Mean	SD	P-Value
R-E Interval(min)	A	30	7.40	1.940	0.408
	B	30	7.83	2.086	
Comparison of R-E Interval among Two Groups					
	Group	N	Mean	SD	P-Value
Total Dose of Fentanyl (mcg)	A	30	224.33	31.149	<0.0001
	B	30	304.50	50.264	

Total dose of vecuronium administered was higher in group A compared to group B which was statistically significant (p value<0.0001).

There was no statistically significant difference observed in the time taken from the time of administration of reversal agent to the time of extubation in either of the two groups (p value=0.408). Total dose of Fentanyl used was higher in group B than group A and it was statistically significant.

Table 2: Comparison of Time required for TOF 0.9

	Group	**N**	**Mean**	**SD**	**P-Value**
R-TOF (min)	A	30	24.17	6.412	<0.0001
	B	30	0.00	0.000	
Comparison of R-TOF Interval among Two Groups					
	Group	N	Mean	SD	P-Value
E-PEF Interval (min)	A	29	12.28	4.333	<0.0001
	B	30	17.50	4.689	
Comparison of E-PEF Interval among Two Groups					
	Group	N	Mean	SD	P-Value
TOF 0.9(min)	A	30	16.83	5.490	<0.0001
	B	30	0.00	0.000	

Statistically significant difference was observed among the two groups in interval from administration of reversal agent to the time of attaining TOF ratio of 0.9. Thenterval was longer in group A compared to group B. Statistically significant difference was observed among the two groups in the interval from time of extubation to performing first PEF. The interval was longer in group B (17.50±4.689 min) compared to group A (12.28±4.333 min).

The time taken for patients to be able to perform the first PEF after extubation was longer in group B and it was statistically significant. Statistically significant difference was observed among the two groups in the time required to attain a TOF ratio of 0.9 after extubation. The interval was longer in group A (16.83±5.490 min) compared to group B (0 min), i.e., patients in group B had a TOF ratio of 0.9 at the time of extubation.

Table 3: Comparison of PEF Values Attained at 60 Minutes Expressed as Percentage of Preoperative PEF

	No. of Subjects	**Mean TOF**	**P-Value**
Group A	30	0.76	<0.001
Group B	30	0.9	
TOF Ratio Comparison at Extubation			
	No. of Patients	Mean % PEF	P-Value
Group A	30	81.45	<0.0001
Group B	30	94.5	

Statistically significant difference was observed among the two groups in the mean TOF ratio immediately after extubation. Mean TOF was higher in group B (0.76) than group A (0.9) with a p-value <0.001. Statistically and clinically significant difference was found among two groups in PEF values at 60 min after extubation expressed as percentage of preoperative PEF values. In group A it was 81.45% and in group B it was 94.5%, which was statistically significant (p-value <0.0001).

Table 4: PEF Values Measured Preoperatively and Every 5 Minutes after Extubation till 60 Minutes

	Group	N	Mean	SD	P-Value
PRE PEF	A	30	465.03	49.763	0.111
	B	30	444.77	47.076	
PEF (10 min)	A	18	178.50	22.022	0.298
	B	3	194.00	31.575	
PEF 15(min)	A	29	212.34	27.419	0.136
	B	17	198.29	34.653	
PEF 20(min)	A	29	246.66	31.221	0.121
	B	25	231.00	41.613	
PEF 25(min)	A	29	264.90	35.932	0.798
	B	30	262.03	48.583	
PEF30(min)	A	30	286.83	36.704	0.240
	B	30	299.97	48.233	
PEF 35(min)	A	30	298.40	37.098	0.004
	B	30	329.20	43.064	
PEF 40(min)	A	30	315.80	37.930	0.000
	B	30	362.00	42.414	
PEF 45(min)	A	30	329.10	38.067	0.000
	B	30	381.47	43.041	
PEF 50(min)	A	30	346.57	38.852	0.000
	B	30	397.87	45.636	
PEF 55(min)	A	30	362.67	40.087	0.000
	B	30	413.63	48.048	
PEF 60(min)	A	30	381.30	40.197	0.000
	B	30	431.60	48.343	

Table 5: Comparison of Sedation Scores every 5 Minutes after Extubation

	Group	N	Mean	SD	P-Value
E-TOF0.9(min)	A	30	17.67	5.529	<0.0001
	B	30	0.00	0.000	
Comparison of E-TOF 0.9 Time Interval					
	Group	N	Mean	SD	P-Value
TOF at 1st PEF	A	30	0.845	0.04424	<0.0001
	B	30	0.9	0.00000	
Comparison of TOF Ratio at First PEF					
	Group	N	Mean	SD	P-Value
Sedation at 0 min	A	30	3.07	0.450	<0.0001
	B	30	3.73	0.640	
Sedation at 5 min	A	30	2.60	0.498	0.006
	B	30	3.07	0.740	
Sedation at 10 min	A	30	2.17	0.379	0.002
	B	30	2.57	0.568	
Sedation at 15 min	A	30	2.00	0.000	0.006
	B	30	2.23	0.430	
Sedation at 20 min	A	30	2.00	0.000	0.161
	B	30	2.07	0.254	

Patients were able to perform PEF only after 10 minutes from extubation in both the groups. PEF was performed every 5 minutes thereafter.
The number of patients who performed PEF at 10, 15 and 20 minutes was higher in Group A than in Group B.

Statistically significant difference in PEF values was found between the two groups from 35 minutes onwards. PEF values were significantly lower in group A compared to group B from 35 minutes onwards after extubation.

Statistically significant difference was observed among two groups in the time interval from extubation to attaining a TOF ratio of 0.9. The interval was longer in group A (17.67±5.529 min) compared to group B (0.0±0 min) with a p-value of <0.0001.

Statistically significant difference was found between the two groups. Thw TOF ratio at the time of performing the first PEF was higher in group B (0.9±0.00) than group A (0.845±0.0442) with a p-value <0.0001.

Statistically significant difference was observed among two groups in sedation score after extubation. Sedation was higher in group B compared to group A till 15 minutes after extubation.

Patients in group A took 8.5 min to attain a sedation score of 2 while those in group B took 13 min to attain a sedation score of 2.

Discussion

Residual neuromuscular blockade (RNMB) is commonly observed in the post anesthesia care unit (PACU) after the use of non-depolarizing neuromuscular blocking drugs (NMBDs) during anesthesia and surgery. Despite the use of intermediate-acting NMBDs and antagonism of neuromuscular blockade at the conclusion of the procedure, RNMB is still a clinical problem in the PACU indicating the need for objective neuromuscular monitoring to be performed per operatively to ensure patient safety. [17]

Residual neuromuscular block is perhaps most accurately defined as the presence of signs or symptoms of muscle weakness in the postoperative period after the intraoperative administration of a NMBD. Patients with adequate neuromuscular recovery should have the ability to breathe normally, maintain a patent upper airway, preserve protective airway reflexes, swallow, cough, and talk. These physiologic end points are achieved in most patients at a TOF ratio of 0.9. [18]

Eikermann et al. [13] observed that impaired inspiratory flow and upper airway obstruction occurred frequently at a TOF ratio of 0.83. The hypoxic ventilatory response was reduced by approximately 30% in awake volunteers with TOF ratios of 0.7 [14] and an association between mild residual neuromuscular block and postoperative hypoxemia has been described. [15] These findings suggest that the removal of an endotracheal tube in the presence of minimal levels of residual block can potentially contribute to adverse pulmonary outcomes.

Studies suggest that TOF ratios measured with quantitative monitoring must recover to values >0.9 to ensure optimal patient safety. [19] Studies on volunteers have demonstrated that pharyngeal dysfunction and an increased risk for aspiration occur at TOF ratios < 0.9. Impaired inspiratory flow and partial upper airway obstruction have been observed frequently at TOF ratios of 0.8. [13] Furthermore, subtle levels of neuromuscular blockade may produce distressing symptoms in awake patients, which are not seen at TOF ratios >0.9. [20]

These studies suggest that the new ―gold standard‖ for the minimal acceptable level for neuromuscular recovery is a TOF ratio of 0.9. [21]

In our study, all patients who were not given vecuronium for maintenance of neuromuscular blockade (Group B) had a TOF ratio of 0.9 at extubation, (based on clinical criteria) whereas the other group of patients who had received vecuronium for maintenance of neuromuscular blockade (Group A) had a mean TOF ratio of only 0.76 at extubation. These patients in Group A took 16.8± 5.5 minutes to attain a TOF ratio of 0.9 which is clinically and statistically significant. These patients were at risk of upper respiratory obstruction and aspiration at this time period.

The use of intraoperative neuromuscular monitoring is known to reduce the incidence of RNMB in the PACU. [22] However, some studies have also reported residual neuromuscular blockade despite the use of TOF monitoring. [23,24] Therefore we used PEF measurement in this study to verify the degree of residual neuromuscular blockade. In healthy subjects, PEF is determined by the volume of the lungs, the elastic properties of the lung; by the power and co-ordination of the expiratory muscles and the gender of the subjects. [25] We used a cut-off of 15% reduction of PEF from the preoperative value as clinically significant. [2]

By the end of one hour (60 min) after extubation, patients who did not receive vecuronium for maintenance of anesthesia (Group B) had achieved 94.5% of preoperative PEF values as against 81.45% in the patients who had received vecuronium (Group A) for maintenance of neuromuscular blockade (NMB). This is both clinically and statistically significant. It is worth noting that these patients in Group A had achieved a TOF ratio of 0.9 (adequate recovery of NMB) at 17 ± 5.5 min itself after extubation. Despite achieving an adequate TOF of >0.9 at 60 min after extubation, these patients lagged behind in achieving an adequate PEF.

Patients in Group B had better PEF values as compared to patients in Group A, only from 35 minutes onwards after extubation and we could not demonstrate a statistically significant increase in PEF in this group without vecuronium (Group B). This may be because these patients required a higher dose of opioids and were more sedated in the first 20 minutes after extubation as suggested by the sedation score >2 and also because of the significant increase in the number of female patients in this group. (PEF values are higher in males than in females). [25]

The PEF results of our study are less likely to have been influenced by other causes such as pain, as we have excluded patients undergoing abdominal and thoracic surgery.

Conclusion

Our study showed that all patients (100%) who were given vecuronium for maintenance of neuromuscular blockade (NMB) during intraoperative period and who were extubated based on clinical criteria had a significant residual NMB in the postoperative period as shown by TOF <0.9. These patients recovered their neuromuscular function i.e. TOF of 0.9 at 17.7± 5.5min after extubation. Despite this, at 60 min following extubation they had only 81.45% of their pre-operative PEF. This shows that patients who received vecuronium for maintenance of NMB during intraoperative period are at significant risk of respiratory compromise in this period. Clinical criteria for extubation do not correlate with TOF recovery. Ability to perform adequate PEF, do not match with adequate TOF recovery. Patients who were not given vecuronium for maintenance of neuromuscular blockade, required higher dose of fentanyl. Despite the sedation, these patients had adequate recovery of TOF and they were able to perform adequate PEF. Therefore, we suggest that neuromuscular blocking drugs should be

avoided for maintenance of neuromuscular blockade wherever possible, i.e., surgeries that do not require muscular relaxation such as certain peripheral limb surgeries, surgery on the skin (plastic surgery) etc.

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