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Postoperative Residual Neuromuscular Blockade (rNMB) Following Low-Dose (<2×ED_{95}) Atracurium in Patients Receiving Laryngeal Mask Airway - An Audit Study

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Abstract

Background: Low dose neuromuscular blockers, typically <2×ED_{95} or <0.46 mg/kg, have been shown to improve conditions of Laryngeal Mask Airway (LMA) placement and ease of ventilation during general anesthesia (GA), but its effects on the prevalence of residual neuromuscular blockage (rNMB) is poorly defined. A previous study in a large tertiary institution showed that 19% of patients undergoing GA with LMA received neuromuscular blockers. This study aims to audit the practice and establish the prevalence of rNMB.

Methods: A cross-sectional, observational study was designed. Patients were included if they received a low dose of atracurium (<2×ED_{95}). Quantitative neuromuscular monitoring with electromyography was performed on emergence upon removal of LMA (Train of Four ratio <0.9).

Results: Two hundred patients were sampled randomly, 109 met the inclusion criteria. The overall prevalence of rNMB was 22.0% (average dose of atracurium (0.275 (± 0.093) mg/kg)). It was three times higher in patients who were not reversed (8.3% *vs.* 25.9%). The lack of use of reversal agents (OR 6.623, CI 0.030-0.771, p<0.05) and a shorter duration from the atracurium dose to emergence (OR 1.029, CI 0.956-0.988, p<0.05) were found to be associated with an increased risk of rNMB.

Conclusion: Administering low-dose (<2×ED_{95}) atracurium in patients receiving laryngeal mask airway still results in significant prevalence of residual neuromuscular blockade post-operatively. It is critical to monitor and reverse patients where appropriate.

Keywords: Postoperative complications; Residual muscular blockade; Monitoring; Neuromuscular function

Abbreviations: rNMB: Residual Neuromuscular Blockade; LMA: Laryngeal Mask Airway; GA: General Anesthesia; ToF: Train of Four; PACU: Post Anesthseia Care Unit; EMG: Electromyography; MMG: Mechanomyography.

Background

Post-operative residual neuromuscular blockade (rNMB) is defined as the incomplete recovery of muscle function following intra-operative administration of neuromuscular blockers, evidenced by a train-of-four (ToF) ratio of <0.9 [1], and is associated with various pulmonary and general postoperative complications [2,3], as well as increased risk of 30 day readmission [4]. The prevalence of rNMB varies from 5% to 88% [5-7], and is exacerbated by inappropriate omission of pharmacological reversal [8].

Koh et al. demonstrated the role of low dose atracurium (0.05 mg/kg or 0.1 mg/kg) in improving conditions for LMA insertion [9]. A recent study evaluating risk factors for difficult ventilation with LMA in a major tertiary care hospital in South-East Asia also showed that 19% of the patients who had LMA also received neuromuscular blockers [10]. Despite this high prevalence, few studies have evaluated the effects of low dose neuromuscular blockers, and the prevalence of postoperative residual paralysis in such situations is not known [11-14]. In the Koh et al. study cohort, there were rapid spontaneous respiration returned after giving low dose atracurium, and patients were able to achieve good tidal volumes spontaneously.

This may result in the anesthesiologists' clinical decision not to reverse patients who were given the low dose atracurium.

This study aims to audit the practice of the major tertiary hospital by establishing the prevalence of rNMB in patients undergoing general anesthesia with LMA following a low dose of atracurium (<2xED_{95}, or <0.46 mg/kg). Our secondary aim looks at the use of neostigmine in preventing rNMB and if there is a dose-dependent relationship, as well as post-operative complications associated with rNMB.

Methodology

This is a cross-sectional observational audit study conducted from February 2016 to April 2016 in a single tertiary medical center (National University Hospital, Singapore). The study was registered at ClinicalTrials.gov (NCT 02673853). All documentations regarding study design, objectives and conduct of the audit was approved by the National Health Group-Domain Specific Review Board (NHG-DSRB).

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Waiver of informed consent was obtained, as the audit was purely observational using anonymous patient data.

Inclusion criteria for the audit were patients who underwent general anesthesia with LMA as the sole airway device throughout the operative period, and were given a single dose of atracurium that is lesser than 2×ED_{95} (<0.46 mg/kg). Those who received an additive atracurium dose larger than 2×ED_{95} throughout the entire length of surgery, or did not receive any atracurium, were excluded from the audit. None of the patients included in our study had quantitative peripheral nerve stimulator used to assess for Train of Four before being assessed by the assessors for this study.

The primary outcome was to determine the prevalence of rNMB on emergence in our cohort of patients receiving a low dose of atracurium, and identification of risk factors associated with rNMB.

The presence of rNMB was assessed via Train of Four (ToF) stimulation of the adductor policis with the NeuroMuscular-Transmission Module (GE Datex-Ohmeda) using the ElectroSensor™ electromyography(EMG), which has equal accuracy compared to mechanomyography (MMG) [15]. A threshold of <0.9 was defined as rNMB, in accordance with current definitions. ToF ratio readings were taken on emergence (taken as time of removal of LMA) in post anesthesia care unit (PACU). Two readings were taken and their results were averaged if they were within 0.10 of each other. If not, additional readings were taken until two readings were within 0.10 of each other, and these two were averaged and used. Readings were spaced out at least 10 seconds from each other to minimize the effects of repeated stimulation on the neuromuscular junction.

The dose and timing of atracurium administration, as well as the use of reversal agents, were retrieved from the intra-operative notes. Potential confounders including anesthetic drug choice, use of inhalational agents, presence of hypothermia, drug-drug interactions were recorded.

Secondary outcomes included usefulness of neostigmine reversal in a dose-dependent relationship and evaluation of postoperative complications in the PACU.

Post-operative data and complications during PACU stay, specifically pulmonary complications such as hypoxia (SpO_2<92%) and laryngospasm, cardiovascular events such as hypotension (<90/60 mmHg) and new onset arrhythmias, immediate postoperative temperature, presence of shivering, and postoperative nausea and vomiting were recorded.

Data analysis was carried out using IBM SPSS Statistics version 23 (ARMONK NY).

Descriptive analysis was carried out to determine overall rNMB prevalence and patient demographics. Univariate analysis using logistic regression was subsequently used with both discrete and continuous variables. Variables with univariate associations were selected with an inclusive cutoff of p<0.10, and were subsequently included in the multivariate analysis using backward stepwise conditional analysis with a critical α of 0.15 to identify independent predictors of rNMB [16]. Linear regression was used to analyze the relationship between variables.

Results

A total of 2122 patients received LMA during the 3-month data collection period between February and April 2016, of which 742 patients received atracurium (35%). A total of 200 patients who received atracurium with LMA were sampled at random during the 3-month period. Thirty-nine of the patients (19.5%) received a dose of atracurium larger than 2XED_{95}, and 52 patients (26%) received atracurium more than once. The remaining 109 (54.5%) patients met the inclusion criteria and were included in the analysis (Figure 1). Their demographics are shown in (Table 1). The overall prevalence of rNMB was 22.0%.

Univariate analysis (Table 2) showed lack of use of reversal agent (p=0.084), and duration from last inhaled anesthetic (min) (p=0.005) as potential risk factors for rNMB as defined by p<0.1. On multivariate analysis, the lack of use of reversal agents (OR 6.623, CI0.030-0.771, p<0.05) and a shorter duration from the last atracurium dose to emergence (OR 1.029, CI 0.956-0.988, p<0.05) were found to be associated with an increased risk of rNMB (Table 3).

Among the 85 patients who were not reversed, 22 patients (25.9%) had rNMB on emergence. Out of the 24 patients who were reversed with neostigmine, 2 patients (8.3%) had rNMB. The demographics and perioperative parameters between the reversed and not reversed cohorts were similar. All the patients had adequate spontaneous tidal volumes (>6 ml/kg) at the end of the surgery.

The closer the last dose of atracurium was to the time of emergence, the higher the prevalence of rNMB. The highest prevalence of rNMB was seen when latest dose was given within 60 minutes to emergence. The prevalence of rNMB at 0-60 min, 61-90 min, 91-120 min and more than 120 min was 35.7%, 32.0%, 22.0%, and 9.5% respectively in patients who were not reversed, and 18.2%, 0%, 0% and 0% respectively in patients who were reversed with neostigmine (Figure 2).

Quantitative neuromuscular monitoring was conducted in all patients, but only 70.0% of patients could be assessed clinically due to postoperative drowsiness. For prediction of ToF ratio <0.9, using both the head lift and hand grip maneuvers as clinical tests only identified 28.6% of patients with rNMB in patients whom clinical tests could be performed.

There were 13 patients (11.9%) with pulmonary events noted in the post anesthesia care unit stay, the majority of which were transient hypoxia (85%) (SpO_2 <92% on room air) (Table 4). Out of those with rNMB, 4 patients (16.7%) suffered from pulmonary events.

Patients with pulmonary complications had a higher ASA class, increased median of BMI and increased age. The presence of rNMB did not result in a significant difference in terms of the incidence of post-operative pulmonary events, cardiovascular events, shivering, average postoperative temperature, or nausea and vomiting.

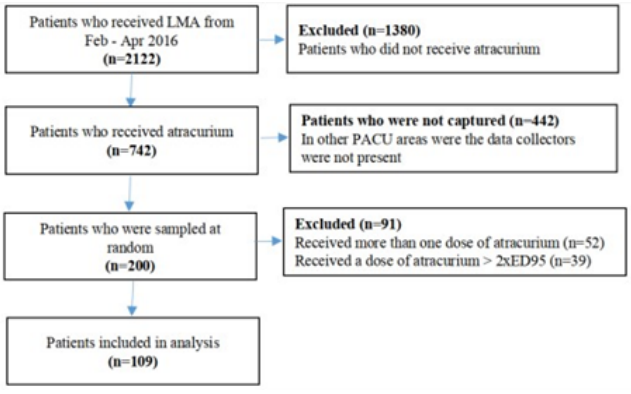

Figure 1: Flow chart of patient identification.

	Total
Number	109
Gender (M:F)	57(52.3%):52 (47.7%)
Age	50.8 (± 17.8)
BMI	26.4 (± 4.8)
ASA status I II III IV	 29 (26.6%) 59 (54.1%) 20 (18.3%) 1 (0.9%)
Asthma Obstructive sleep apnea	4 (3.6%) 2 (1.8%)
Operative procedures Breast Orthopedics Obstetrics & Gynaecology Eye Urology Arterial General surgery Dental ENT	 13 (11.9%) 32 (29.4%) 9 (8.3%) 11 (10.1%) 8 (7.3%) 8 (7.3%) 20 (18.3%) 6 (5.5%) 2 (1.8%)
Duration of procedure (min)	90 (± 38)
Dose of atracurium given (mg/kg)	0.275 (± 0.093)
Number of patients given: Propofol Fentanyl Morphine Midazolam	 109 (100%) 107 (98.1%) 72 (66.1%) 62 (56.9%)
Inhaled anesthetics: Sevoflurane Desflurane TIVA	 81 (74.3%) 25 (22.9%) 3 (2.7%)
Neostigmine Full dose (30-50ug/kg) Half dose (10-30ug/kg)	 16 (14.7%) 8 (7.4%)
Postoperative parameters: Temperature	 36.1 ± 0.32
Data are number of patients (% of total) for discrete or median (25th to 75th percentile) for continuous data or mean ± SD for continuous.	
ToF = train-of-four; ASA = American society of Anesthesiologists; URTI = recent URTI within past 2 weeks.	

Table 1: Patient demographics.

Discussion

Thirty-five percent of patients given LMA also received atracurium in the 3-month data collection period, out of which 80.5% were given low doses (54.5% given atracurium once, and 26% received subsequent top up low doses). The practice of using low dose neuromuscular blockers (<2xED_{95}) in the major tertiary hospital remains significant.

The prevalence of residual neuromuscular blockade was 22.0% in our cohort of patients who received low dose atracurium (<2xED_{95}). Other studies on full intubating dose (>2xED_{95}) of atracurium with ETT showed prevalence ranging from 32-64.6% [17-19].

Prevalence of rNMB was three times higher in the cohort that was not reversed than in the cohort that was reversed (25.9 % versus 8.3%).

The lower reported prevalence of rNMB in this study population could be attributed to the lower dose of atracurium given. The median latest dose of atracurium used in this study is 0.275 mg/kg (1.2xED_{95}), which is significantly lesser than full intubating dose described in other studies. However, it is important to note that the use of "sub-intubating" low dose atracurium in our cohort was still associated with an unacceptable rate of rNMB, more than one in four patients.

Despite the use of atracurium, a sizable proportion of patients (85 out of 109, 78.0%) were not reversed. The RECITE trial also shows a startling rNMB prevalence of 64.6% even among patients who were reversed with neostigmine [18]. None of the patients in our study population were assessed via peripheral nerve stimulator to accurately assess the ToF at the end of the surgery to guide usage of neostigmine. A common reason was attributed to patients already resuming spontaneous respiration with good tidal volume without reversal agents (>6 ml/kg), and the lack of easy access to the equipment in the department.

Where a neuromuscular monitoring device is not available, the use of reversal agents can significantly lower prevalence of rNMB, even when patient was only given a low dose of neuromuscular blocking agent at the start of the surgery (OR 6.623, p<0.05).

Factors	Patients without rNMB (n=85)	Patients with rNMB (n=24)	Univariate analysis			
			p-value	Odds ratio	95% C.I. (Lower)	95% C.I. (Higher)
Sex (M:F)	46 (54.1%) : 39 (45.9%)	11 (45.8%): 13 (54.2%)	0.474	1.394	0.562	3.460
Age	52 (34 to 66)	53 (43 to 69)	0.214	1.017	0.990	1.044
BMI	25.3 (23.1 to 29.0)	25.5 (22.8 to 29.9)	0.842	1.009	0.920	1.108
ASA I II III IV	 23 (27.1%) 45 (52.9%) 17 (20.0%) 0 (0.0%)	 6 (25.0%) 14 (58.3%) 3 (12.5%) 1 (4.2%)	0.857	1.062	0.554	2.035
Dose of atracurium (0.1 mg/kg)	0.27 (0.20 to 0.35)	0.28 (0.21 to 0.35)	0.468	6.150	0.045	832.720
Duration from latest dose of atracurium to emergence (min)	95.0 (70.0 to 125.0)	65.0 (45.0 to 85.0)	0.005	1.021	0.965	0.994
Lack of use of reversal agents	63 (74.1%)	22 (91.7%)	0.084	3.846	0.057	1.198
Use of Reduced Dose of neostigmine (10-30 ug/kg)	15 (17.6%)	1 (4.2%)	0.102	0.467	0.116	39.469
Fentanyl (ug)	100 ± 33.7	100 ± 27.1	0.373	0.993	0.979	1.008
Morphine (mg)	3 ± 3.18	3 ± 2.70	0.929	1.007	0.868	1.167
Duration from last inhaled anesthetic (min)	15 (10 to 25)	16.5 (10 to 20)	0.398	0.985	0.951	1.020
Temperature on PACU arrival (°C)	36.1 (36.0 to 36.4)	36.2 (36.0 to 36.3)	0.939	1.057	0.260	4.302
Data are number of patients (% of total) for discrete or median (25th to 75th percentile) or mean ± SD for continuous.						
BMI = Body Mass Index; ASA = American Society of Anesthesiologists; MAC = Minimum alveolar concentration.						

Table 2: Risk factors of residual neuromuscular blockade.

Parameters	p-value	Odds ratio	95% C.I. (Lower)	95% C.I. (Higher)
Duration from latest dose of atracurium to emergence (min)	0.001	1.029	0.956	0.988
Lack of use of reversal agents	0.023	6.623	0.030	0.771

Table 3: Multivariate analysis of risk factors of neuromuscular blockade.

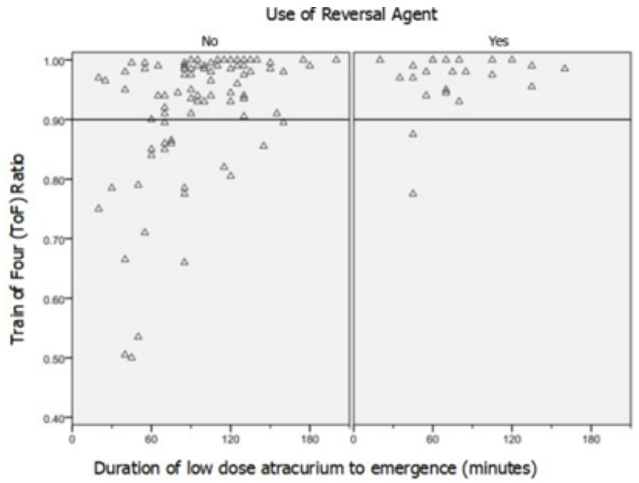

Figure 2: Train of Four (ToF) ratio against the duration of low dose atracurium to emergence. Each symbol represent a single patient, the line at 90% shows the threshold for definition of residual neuromuscular blockade (ToF <0.9).

	Patients without rNMB (n=85)	Patients with rNMB (n=24)	p-value
Total number	85	24	
Pulmonary events Hypoxia	9 (10.6%) 9 (10.6%)	4 (16.7%) 2 (8.4%)	0.421 0.963
Cardiovascular events	4 (4.7%)	0 (0%)	0.999
Shivering	6 (7.1%)	3 (12.5%)	0.399
Post-operative nausea and vomiting	3 (3.5%)	3 (12.5%)	0.111
Data are number of patients (% of total) for discrete or median (25^{th} to 75^{th} percentile) for continuous.			

Table 4: Postoperative complications in patients who are reversed and not reversed.

The use of 10-30 ug/kg neostigmine (reduced-dose) compared to 30-50 ug/kg neostigmine (full-dose) was not associated with a significant difference in prevalence of rNMB (OR 2.14, p=0.608). Presumably, this could be due to the shallower block achieved with the lower dose of atracurium used in the study. The use of low dose neostigmine to antagonize shallow neuromuscular blockade has been shown to be effective in reversing shallow neuromuscular blockage [20]. Smaller dose of neostigmine can thus be given when low dose of neuromuscular blockers are used, which may avoid potential neostigmine- induced side effects such as longer time to PACU discharge and longer postoperative hospital stay [21].

Many clinicians also rely on the duration from the latest atracurium dose to decide if reversal is warranted, and are less likely to reverse patients if the duration is greater than 60 minutes [22]. The typical duration of action of atracurium is 20-35 minutes, with a time to recovery of approximately 60-70 minutes [23]. However, the study data suggests such reliance may be inaccurate, as duration from the dose of atracurium to emergence is a significant risk factor for rNMB in our cohort (OR 1.029, p<0.05).

A high prevalence of rNMB was seen in patients in whom a dose of atracurium was given within 60 minutes to end of surgery, with 18.2% of patients having rNMB even with neostigmine given. Presumably, this is due to administration of reversal agents before sufficient recovery of neuromuscular blockage. Neostigmine itself also has direct effects on endplate receptor channel complex, which are unrelated to acetylcholinerase inhibition and may potentiate neuromuscular blockade [24]. Reversal agents should only be given when more than 2-3 twitches are seen on qualitative or quantitative neuromuscular monitoring, in line with current guidelines [25].

In addition, when the latest dose of atracurium given was more than 120 minutes before the end of surgery, one in ten patients who were not reversed experienced residual muscular blockade. This is well beyond the reported duration of action of atracurium.

Conversely, the use of reversal in our study was found to be uniformly associated with lower prevalence of rNMB across all time groups. The potential for neuromuscular blockers to have a prolonged duration of action has been increasingly reported in recent studies, and Debaene et al. found that time interval greater than 120 min between the administration of muscle relaxant and the arrival in PACU did not guarantee the lack of rNMB [17]. This is presumably due to interindividual variability in NMB sensitivity. It is hence hard to predict which patients will have rNMB purely based on time estimates. Our findings support the recent guidelines by Association of Anaesthetist of Great Britain and Ireland (AAGBI) that all patients who had received neuromuscular blocks should be monitored with quantitative peripheral nerve stimulator to guide the decision for reversal [26].

There were 11.9% of the patients had pulmonary complications including hypoxia (SpO_2<93%) and laryngospasm. Due to the limited number of patients with adverse outcomes, and our patient population demographics (majoriy ASA I and II patients, 54.1% and 26.6%), there were no significant differences between patients with rNMB and without rNMB (p=0.421). Patients who have higher ASA status, increasing age and BMI had worse pulmonary outcomes. These factors are independently associated with pulmonary complications [26,27].

Conclusion

Our audit showed that the use of LMA with a low dose atracurium (<2xED_{95}) is common practice. Prevalence of rNMB is significant at 22.0%. Patients who had a shorter duration from the atracurium dose to end of surgery and were not reversed had higher risks of rNMB. Reversal of neuromuscular blockers can reduce rNMB by two-thirds. Ongoing efforts are necessary to educate anesthetists about rNMB even with low dose, and patients should be monitored with quantitative neuromuscular monitoring devices and reversed where appropriate. However when low dose atracurium is given, reduced dose neostigmine may be sufficient.

Trial Registry Number

Funding institution: National University Hospital (NUH), Singapore.

Clinical Trial number: NCT02673853

Registry URL: https://clinicaltrials.gov/ct2/show/NCT02673853

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Author's Contributions

Ke YH and Koh WJ wrote the main manuscript, carried out data collection and prepared figures and tables, carried out data analysis. Ayuningtyas R obtained the ethics approval and participated in initial brain storming of the project

Chew ST and Ti LK reviewed manuscripts and oversaw the mentoring of the project

Ethics Approval

All documentations regarding study design, objectives and conduct of the audit was approved by the National Health Group-Domain Specific Review Board (NHG-DSRB), and waived requirements of informed consent.

Competing Interest

The authors declare that they have no competing interests.

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Consent for Publication

Not applicable

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