

THE INCIDENCE OF RESIDUAL NEUROMUSCULAR BLOCKADE ASSOCIATED WITH SINGLE DOSE OF INTERMEDIATE-ACTING NEUROMUSCULAR BLOCKING DRUGS

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Abstract

Background: The goal of this study is to investigate the incidence and risk factors of residual paralysis associated with single-dose intermediate-acting muscle relaxants (atracurium, vecuronium, rocuronium) during early postoperative period.

Methods: Adult patients (ASA I and II) who received a single dose of vecuronium, atracurium or rocuronium during general anesthesia for elective surgical procedure were included in the study. Train-of-four (TOF) ratios under 0.9 were recorded as “postoperative residual neuromuscular block (PRNB)”. Age, weight, gender, reversal, anesthesia duration, time for transfer to the recovery room after extubation were studied regarding with PRNB.

Results: 84 patients were included in this study. 29 patients were received vecuronium, 28 patients were received atracurium and 27 patients were received rocuronium. Neostigmine was used for reversal in 49 patients (58.3%) at the end of the surgery. PRNB incidence (TOF<0.9) was 13.1%. Based on the regression analysis, the only risk factor affecting PRNB was found as gender. PRNB risk was increased in women (OR: 7.250, 95%, CI: 1.019-51.593).

Conclusion: In patients who have general anesthesia longer than one hour, “gender” may affect residual paralysis incidence associated with single-dose intermediate-acting muscle relaxants use.

Key words: neuromuscular blockade, residual paralysis, neuromuscular monitoring, atracurium, vecuronium, rocuronium.

Introduction

Neuromuscular blocking drugs (NMBDs) are widely used to facilitate endotracheal intubation during anesthesia induction and provide muscle relaxation during surgery. Postoperative residual neuromuscular block (PRNB), postoperative residual paralysis or residual curarization are defined as; “the presence of postoperative muscle weakness signs or symptoms after the administration of an intraoperative non-depolarizing NMBDs”¹. While, in practice, the sufficiency of recovery in neuromuscular functions and reversal treatment (acetylcholinesterase inhibitor) are evaluated based on clinical signs, neuromuscular transmission monitoring is considered not only possible

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but also a requirement for objective and quantitative assessments². Acceleromyography is frequently used in PRNB research as a useful and objective monitoring method³. In the past years, the threshold value for train-of-four (TOF) ratio was 0.7, and values less than this threshold were considered as PRNB. Because of studies showed that upper airway protective reflexes are not completely recovered and aspiration risk is high at this level; 0.9 was accepted as the threshold value for TOF ratio⁴⁻⁷.

According to clinical findings, objective data obtained through neuromuscular monitoring showed that intermediate-acting NMBDs associated PRNB incidence was quite high^{1,8}. Naguip et al⁸ report the incidence to be 41%.

In this study, we investigated the incidence and affecting factors of PRNB associated with single-dose intermediate-acting non-depolarizing NMBDs, (vecuronium, atracurium, rocuronium) in patients during the early postoperative period.

Patients and Methods

Patients

This prospective and observational study was conducted after obtaining informed consent forms from the patients after getting permission of the local ethics committee. The American Society of Anesthesiologists (ASA) I and II adult patients who underwent elective surgical operation under general anesthesia were included in this study. And they received single-dose intermediate-acting NMBDs (vecuronium, atracurium or rocuronium) in order to facilitate endotracheal intubation.

Patients who had renal, hepatic, neuromuscular and metabolic diseases, craniotomy, cardiac, thoracic, major vascular surgeries, emergency surgeries, anesthesia duration longer than 120 minutes, surgical procedures requiring excessive amount of blood and liquid replacement, body mass index (BMI) over 30%, pregnant and who did not want to participate in the study, were excluded from the study.

Study Design

The decisions about the anesthetic agents,

muscle relaxants, reversal with neostigmine after the completion of the surgery, extubation and transfer to the recovery room were made by the anesthesiologist.

Patients were brought into the recovery room by the anesthesiologist after the operation and, they were quickly checked whether they meet the criteria to be included in this study or not by using the anesthesia recording chart. The patients received neuromuscular transmission monitoring using acceleromyography (TOF-Watch SX Monitor®, Organon Ltd, Dublin, Ireland), in addition to routine hemodynamic monitoring. The ulnar nerve was stimulated with TOF stimulation (4 pulses 0.2 ms in duration, at a frequency of 2 Hz). A supra-maximal stimulation of 50 mA was applied. Three consecutive TOF stimulations were applied and recorded at 15-second intervals. The evoked responses at the thumb were calculated and two thresholds of the TOF ratio (0.9) were used to assess the presence of a PRNB.

Based on anesthesia charts of patients, age, weight, gender, intravenous and inhalation agents used in anesthesia induction and maintenance, anesthesia duration, duration between extubation and transfer to the recovery room and whether they had reversal with neostigmine or not were recorded.

During the follow-up in the recovery room patients, whose peripheral oxygen saturation decreased below 93%, were applied 2-3 lt/min oxygen using a face mask. Patients who were clinically thought to have residual effects of muscle relaxants received a second dose of reversal medications (0.5 mg atrophine with 0.03 mg/kg neostigmine). These interventions were recorded.

Statistical analysis

SPSS 10.0 (Statistical Package for Social Sciences-SPSS Inc. Chicago, IL) program was used in the statistical analysis of data. Kolmogorov-Smirnov test showed that; age, weight, anesthesia duration, duration between extubation and transfer to recovery room had normal distribution. Since the age variable showed normal distribution, descriptive statistics are summarized as mean±standard deviation, and for comparison based on groups, with independent t-test was used. Due to other variables not showing normal distribution, descriptive statistics are shown

as median (25th-75th percentiles) and Mann-Whitney U test was used for comparisons according to groups. In order to investigate risk factors that may affect residual curarization, Stepwise Logistic Regression analysis was conducted. Chi-square test was used for comparing frequencies. Any p value of <0.05 was considered statistically significant.

Results

84 patients were included in this study. The distribution of patients according to their demographic characteristics and operation types is shown in Table 1. Propofol (2-3 mg/kg), fentanyl (1-2 µg/kg) and lidocaine (1 mg/kg) were used for anesthesia induction in all patients. In order to facilitate endotracheal intubation, vecuronium (0.1 mg/kg) was administered to 29 patients, 28 patients received atracurium (0.6 mg/kg), and 27 patients received rocuronium (0.5 mg/kg). For the maintenance of anesthesia, isoflurane was administered to 52 patients and sevoflurane was administered to 32 patients. After the operation, 0.03 mg/kg neostigmine and 0.5 mg of atrophine was administered to 49 patients, reversal application rate was 58.3%. Reversal was not applied to 35 patients

(41.7%). Median anesthesia duration was 80 minutes. Patients were taken to the recovery room from the operating room in 9 minutes (5-10 minutes, 25th-75th percentiles) as median time (Table 1).

Table 1
Demographic characteristics of patients

| | |
|--|----------------|
| Gender (Female / Male) (n) | 37 / 47 |
| Age (mean ± standard deviation) (year) | 40.0 ± 15.2 |
| Weight [median (25th-75th percentiles)] (kg) | 70 (60.2-77.5) |
| ASA I / II (n) | 70 / 12 |
| Anesthesia duration [median (25th-75th percentiles)] (minute) | 80 (60-100) |
| Extubation–Time to recovery room [median (25th-75th percentiles)] (minute) | 9 (5-10) |
| Surgery types | |
| Ear-Nose | 17 |
| Orthopedics | 14 |
| Plastic | 21 |
| Laparoscopy | 32 |

Among 84 patients in 11 patients (13.1%), TOF ratio measured at the recovery room arrival was less than 0.9. Gender, reversal use, and type of NMBDs distribution are summarized in Table 2. Postoperative

Table 2
Comparison of patients who did and did not have postoperative residual neuromuscular block

| | TOF ≥ 0.9 (n=73) | TOF < 0.9 (n=11) | P |
|--|------------------|------------------|-------|
| Reversal drug (n) | present | 40 | 0.090 |
| | absent | 33 | |
| NMBDs (n) | atracurium | 25 | 0.715 |
| | rocuronium | 24 | |
| | vecuronium | 24 | |
| Gender (n) | female | 29 | 0.040 |
| | male | 44 | |
| Age (year) (mean ± SD) | 39.7 ± 15.6 | 41.6 ± 12.7 | 0.701 |
| Weight (kg) [median (25th-75th percentiles)] | 70 (60-77) | 67 (62-83) | 0.947 |
| Extubation- recovery room duration (minute) [median (25th-75th percentiles)] | 10 (5-10) | 5 (5-10) | 0.043 |
| Anesthesia duration (minute) [median (25th-75th percentiles)] | 80 (60-100) | 90 (45-100) | 0.858 |

TOF, Train of Four

NMBDs, Neuromuscular blocking drugs

SD, standart deviation

residual neuromuscular blockade frequency was found to be higher in female patients compared to males ($P=0.040$) (Table 2). When age, weight, and anesthesia duration were compared, no difference was determined between the patients with and without PRNB (Table 2). Time duration from extubation to the recovery room was found to be shorter in those who had PRNB compared to those who did not (median time 5 minutes and 10 minutes, respectively) ($P= 0.043$).

Based on the logistic regression analysis, gender was determined to affect PRNB. Female gender is a factor which increased PRNB (Odds ratio 7.250, 95% CI: 1.019-51.593). Other risk factors were not found to have a significant effect on PRNB (Table 3).

In the recovery room, peripheral oxygen saturation of 10 patients decreased below 93%, and additional dose of reverse was administered to two of them.

Discussion

In this study, among patients who had endotracheal intubation using atracurium, vecuronium or rocuronium and did not receive additional dose of intraoperative neuromuscular blocker, 13.1% of them were determined to have continuing PRNB (TOF ratio <0.9) when they arrived to the recovery room. In women, PRNB incidence was higher compared to men, and female gender was determined to be a factor in increasing PRNB (Odd's Ratio 7.250; 95% Confidence levels of OR: 1,019-51,593). Age, weight, reversal

with neostigmine, anesthesia duration, intermediate-acting NMBDs used and time duration from operating room to recovery room were not determined to have any effect on PRNB.

Studies show that "effect potential and duration of neuromuscular nondepolarizing blocking agents vary based on gender; women are more sensitive than men and these drugs have longer effects in women⁹⁻¹⁶. Semple et al¹¹ reported that women are more sensitive to vecuronium than men and in order to achieve the same level of neuromuscular block, they require 22% less drugs. Xue et al¹² showed that during TOF monitoring following vecuronium administration, average T1 depression was 43% greater, dose-response curve of vecuronium shifted to the left and it has prolonged efficacy in women, compared to men. In another study¹³, the same authors reported that compared to women, plasma vecuronium concentration was found to be low in men due to a higher vecuronium distribution volume.

In two studies conducted by Adamus et al¹⁴ and Xu et al¹⁵ it was published that, women were more sensitive to rocuronium, onset time of rocuronium was shorter and had prolonged effective period. Based on this research, both authors stated that the dose of rocuronium routinely used in women could be reduced^{14,15}.

In another study, atracurium clearance was reported to be greater in men than women and elimination half-life to be shorter, however, distribution volume was not affected by gender¹⁶. On the other

Table 3
Logistic regression analysis for postoperative residual neuromuscular blockade

| | Odd's Ratio (OR) (%95 Confidence levels of OR) | Beta | P |
|------------------------------------|---|--------|-------|
| Age | 1.016 (0.958-.076) | 0.015 | 0.602 |
| Gender (#female/male) | 7.250 (1.019-51.593) | 1.981 | 0.048 |
| Anesthesia duration | 0.977 (0.942-1.014) | -0.023 | 0.215 |
| Reverse (#absent/present) | 0.144 (0.019-1.082) | -1.938 | 0.060 |
| Weight | 1.066 (0.985-1.153) | 0.064 | 0.111 |
| Extubation- recovery room duration | 0.816 (0.625-1.065) | -0.204 | 0.134 |
| Neuromuscular blocker | 1.303 (0.191-8.904) | 0.265 | 0.577 |

Baseline

hand, Xue et al¹⁸ show that atracurium action duration and dose response curve vary between genders, the effective dose was greater and action duration was approximately 25% shorter in men compared to women¹⁷.

Studies showing the effect of gender on PRNB are few. Alkhazrajy et al¹⁸ evaluated residual muscle; in the group that received muscle relaxants, muscle weakness levels were shown to be different between genders at one hour after the operation. The hand shaking power of women who received vecuronium or rocuronium was determined to be significantly lower than men (32% and 34% in women, 14% and 19% in men, respectively)¹⁸. Based on these findings, female patients who received muscle relaxants during general anesthesia were reported to possibly have a greater predisposition for PRNB and postoperative pulmonary complications associated with it¹⁹. The variability of sensitivity and action duration of neuromuscular blockers, between men and women, is thought to be associated with physiological difference in body structures. It has been reported that, women having a greater amount of fat tissue, and less muscle mass may lead to a decrease of distribution volume and an increase of plasma concentrations of muscle relaxant drug^{12,13,15}. Due to lower levels of total protein and albumin in the plasma of women, drugs that attach to albumin at a 30% rate such as vecuronium, may increase in the plasma¹²⁻¹⁴. In addition, due to gender related differences in liver microsomal enzyme activity, drugs that are metabolized in the liver were published to be broken down faster in men¹⁵. Also, in this study, PRNB incidence was determined to be higher in women, compared to men, possibly associated with prolonged action duration of neuromuscular blockers.

Studies that quantitatively evaluate neuromuscular transmission using objective monitoring methods such as acceleromyography and mechanomyography have shown the PRNB incidence associated with nondepolarizing neuromuscular blockers to be quite high. In these studies, PRNB incidence vary between 2% and 64%, many factors associated with perioperative approach may influence the results¹. In their study where vecuronium, atracurium and rocuronium were used for only intubation, intraoperative neuromuscular monitoring was not performed and none of the patients

was administered a reversal drug, Debane et al²⁰ determined NMB incidence to be 45%. In the same study, they reported continued residual block (TOF < 0.9) in 37% of patients whose operation duration surpassed two hours²⁰. However, Baillard et al²¹ who performed neuromuscular monitoring on 60% of patients and used reversal drug in 42% of them, published vecuronium and atracurium associated PRNB incidence to be 3.5%. On the other hand, Murphy et al⁴ used reversal drug and neuromuscular monitoring on all patients and determined postoperative PRNB to be at a rate of 30%. After this, in their study investigating PRNB incidence, its causes and possible risk factors, the same researchers¹ evaluated in detail possible reasons for such discrepancy between results. They reported the following important differences between the studies: 1. Clinical characteristics of patients, 2. Operations performed and their duration, 3. Type of neuromuscular blockers used, 4. Cumulative dose used for maintenance, 5. Reversal drug (acetylcholinesterase inhibitor) use and time of its administration, 6. The method chosen for intraoperative neuromuscular transmission monitoring¹. In our study, PRNB incidence was 13.1%, which is low compared to similar studies. We believe that the participation of healthy, adult patients (ASA I,II) in the study, the lack of additional nondepolarizing neuromuscular blocker use, anesthesia duration of 60-100 minutes (27-75 percentiles) and reversal with neostigmine in 58.3% of patients, were effective in the low PRNB incidence determined in our study.

There are studies which report that there is no difference in PRNB incidence among intermediate-acting NMBDs^{24,25}. In one of these studies, where Hayes et al²² studied 150 patients who had vecuronium, atracurium and rocuronium administered, they determined the PRNB (TOF < 0.8) to be 64%, 52%, 39%, respectively, when they arrived at the recovery room, and no difference between the three muscle relaxants was reported. They suggested the high incidence was associated with the high number of elderly patients²². However, studies that determined a statically significant difference are also present²⁵. In a study which looked at 107 female ASA-II patients who had elective breast surgery, Khan et al²⁵ found that rocuronium (37%) had a greater residual curarization (TOF < 0.7) incidence compared with

vecuronium (17%). In our study, however, a difference in postoperative PRNB incidences was not determined between atracurium, vecuronium and rocuronium.

Although there are studies reporting the use of acetylcholine esterase inhibitor in order to eliminate the residual effects of nondepolarizing NMBDs does not change PRNB incidence²³, reversal drug use have been shown to reduce PRNB risk by numerous studies^{26,27}. Based on these results, many authors stressed the necessity of the use of reversal drugs to decrease PRNB risk, furthermore, they suggested that in patients who had nondepolarizing NMBDs administered, reversal drugs should be used routinely, if neuromuscular function cannot be monitored quantitatively²⁶⁻²⁹. Despite the implementation of reversal with acetylcholinesterase inhibitor drugs, if TOF ratio is still below 0.9, it is reported that this might also be associated with insufficient reversal medication³⁰.

Another reason for the insufficient recovery of muscle power during early postoperative period, despite the use of reversal drugs, may be associated with the maximum effect of neostigmine that has not begun yet. In patients who were administered rocuronium, Murphy et al³¹ discovered that on average, eight minutes after reversal with neostigmine, 88% of patients had TOF ratios less than 0.9, after 19 minutes, they found this ratio to go below 32% and recommended rocuronium antagonism to be administered 20 minutes before extubation³¹.

In our study, we could not find the effect of reversal drug use on PRNB. The median anesthesia duration in the study was 80 minutes (27-75 percentiles: 60-100 minutes); we did not have intraoperative neuromuscular monitoring, however, in some of the patients, the effect of neuromuscular drugs may have terminated during this time. Furthermore, recording of TOF ratio before neostigmine shows its maximum effect may have affected our result. Because, the time it took to be moved to the recovery room after extubation was shorter in patients who were determined to have PRNB, compared to those who did not ($P=0.043$) (median values: 5 and 10 minutes, respectively).

It has been published that effects of NMBDs were prolonged in the elderly, PRNB incidence increased up to 65%, in older patients, muscle relaxant distribution and spontaneous recovery associated with change in eliminations decelerated and antidote use accelerated recovery²². However, Baillard et al²¹ reported that the age factor did not have an effect on PRNB. In our study, an effect of “age” on PRNB was not found. We believe that low number of older patients and the lack of serious systemic diseases among patients included in the study, may be influential in the result obtained.

While the length of anesthesia duration is one of the most important factors affecting PRNB, results from studies on this subject are variable. In studies where a single-dose intermediate-acting muscle relaxant is used for intubation, “anesthesia duration” is a factor that increases PRNB risk³², however, in studies with moderately long anesthesia duration, this risk was not determined²⁰. In studies with long anesthesia duration, it has been stressed that if the frequency of muscle relaxant use has increased during maintenance, PRNB risk associated with increased dose escalates³².

In summary, PRNB may be missed with subjective or qualitative assessments, even in the absence of clinical symptoms and findings, TOF ratio may be between 0.4 and 0.9¹. Even if sufficient ventilation can be provided for patients with normal tidal volume, airway and coughing reflexes may be insufficient, due to pharyngeal dysfunction; aspiration risk may increase, hypoxia, and chemoreceptor sensitivity may decrease^{6,7}. The effects of single-dose intermediate-acting NMBDs administered to healthy, adult patients; may continue even after one hour and with 58.3% patients who had reversal. In patients who do not have a serious systemic disease, “age” and “weight” may not have an effect on PRNB, however, compared to males, in female patients, PRNB may be seen more frequently, possibly associated with longer action duration of atracurium, vecuronium or rocuronium. Based on the results from our study, we believe that the fact that PRNB associated with intermediate-acting muscle relaxants may have longer duration in female patients compared to males, should be taken into consideration.

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