

## Effect of body temperature on residual neuromuscular blockade of intermediate-acting neuromuscular blocking agents

Vücut sıcaklığının orta-etkili kas gevşeticilerde rezidüel nöromusküler blokaja etkisi

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### Abstract

**Aim:** Aim of this study was to compare the rates of residual neuromuscular block in patients at different postoperative body temperatures. We also investigated incidence of early postoperative residual neuromuscular block with intermediate acting neuromuscular blocking agents and the factors affecting early postoperative residual neuromuscular block with intermediate acting neuromuscular blocking agents.

**Material and Methods:** Two hundred and sixty-eight patients who underwent surgery under general anesthesia were enrolled in this study. Patients were monitored with an acceleromyograph from the moment of admission to post anesthesia care unit. In addition to Train of Four (TOF) measurements, patients' clinical findings (tongue depressor test, hand squeezing, existence of diplopia, ability to swallow, ability to lift head and legs for 5 seconds) were monitored and recorded. Patients body temperatures are measured with a tympanic thermometer and residual neuromuscular block at different body temperatures were compared.

**Results:** The incidence of residual neuromuscular block was 48.9%. Univariate analysis of the data showed that surgical duration, maintenance dose administration, administration of reversal agent and body temperature were significantly relevant with residual neuromuscular block. There weren't any statistically significant difference between TOF values of patients with body temperatures lower or higher than 35°C who were administered either one of the 3 neuromuscular blocking agents utilized in this study.

**Conclusion:** We conclude that choice of intermediate acting neuromuscular blocking agent has no influence on residual neuromuscular block in patients with both intraoperative and postoperative mild hypothermia.

**Keywords:** Residual neuromuscular blockade, body temperature, acceleromyography.

### Öz

**Amaç:** Erişkin hastalarda postoperatif ölçülen farklı vücut sıcaklıklarında orta etkili kas gevşeticilerin rezidüel nöromusküler blok oranlarının karşılaştırılmasıdır. Ayrıca orta etki süreli kas gevşeticilerine bağlı erken postoperatif rezidüel nöromusküler blok insidansını ve buna etki eden faktörleri araştırmaktır.

**Gereç ve Yöntem:** Çalışmaya genel anestezi altında opere olan 268 hasta dahil edildi. Hastalar derlenme ünitesine giriş anlarından itibaren akseleromyografi tekniği ile değerlendirilmiştir. Yapılan "train of four" (TOF) ölçümlerine ek klinik bulgular kaydedilmiştir. Ayrıca hastanın demografik verilerinin yanısıra cerrahi tipi, süresi, ek doz uygulanıp uygulanmadığı, deküarizasyon yapılıp yapılmadığı, uygulanan inhalasyon anesteziği ve diğer anestezi ajanlar kaydedilmiştir. Hastaların vücut ısıları timpanik ısıölçer ile ölçülerek, farklı vücut sıcaklığında orta etkili kas gevşeticilerin rezidüel nöromusküler blok oranları karşılaştırılmıştır.

**Bulgular:** Çalışmamızda rezidüel nöromusküler blok oranı % 48.9 olarak saptandı. Tek-değişkenli analizlerde cerrahi süresi, kas gevşetici tekrarı, deküarizasyon ve vücut ısı ile rezidüel nöromusküler blok arasında anlamlı fark saptandı. Çok-değişkenli analizde ise cerrahi süresi, deküarizasyon ve vücut ısı ile rezidüel nöromusküler blok arasında anlamlı fark saptanırken, kas gevşetici tekrarı ile rezidüel nöromusküler blok arasında anlamlı fark saptanmadı. Hastalar 35 derecenin altında ve üstünde iki grupta değerlendirilerek çalışmamız dahilinde kullanılmış olan üç nöromusküler bloker arasında ortalama TOF değerleri açısından istatistiksel anlamlı fark saptanmadı.

**Sonuç:** Kullanılan nöromüsküler bloker ajanın intraoperatif ve postoperatif ılımlı hipotermisi olan hastalarda rezidüel nöromüsküler blok üzerine etkisi olmadığı sonucuna varıldı.

**Anahtar Sözcükler:** Rezidüel nöromüsküler blokaj, vücut sıcaklığı, akseleeromyografi.

## Introduction

Postoperative residual neuromuscular block is a major problem in post-anesthesia care units caused by neuromuscular blocking agents which are used to produce intraoperative relaxation and appropriate conditions for tracheal intubation (1,2). Postoperative residual neuromuscular block, which was a problem caused by the use of long-acting neuromuscular blocking agents in the past, is still observed frequently with the use of intermediate-acting neuromuscular blocking agents (3). Postoperative residual neuromuscular block, which is defined as a ratio of train-of-four (TOF) lower than 0.9, is related with postoperative mortality and morbidity and especially with respiratory complications (4). Although recovery of neuromuscular function is evaluated with clinical findings in daily practice, it is widely accepted that an objective and quantitative assessment of recovery could and should only be made by monitoring neuromuscular transmission.

Postoperative residual neuromuscular block continues to be a major problem in postoperative care despite preventive measures such as clinical assessment, TOF, use of reversal agents, preferring short and intermediate-acting neuromuscular blocking agents instead of longer-acting ones.

In this study, we investigated the rate of postoperative residual neuromuscular block following the use of intermediate-acting neuromuscular blocking agents and factors affecting the rate of postoperative residual neuromuscular block.

## Materials and Methods

This study was conducted in accordance with the principles of Helsinki Declaration with the permission of local ethics committee and with written and informed consent from volunteers. Patients between the ages of 20-60, and in American Society of Anesthesiologists (ASA) physical status score I-II, who were scheduled to receive general anesthesia with intermediate-acting neuromuscular blocking agents, were enrolled in this prospective observational study. Without being informed about the study anesthetists performed general anesthesia within their routine practice. 268 patients are arranged into three groups according to randomly used neuromuscular blocking agents which are atracurium (A), vecuronium (V) and rocuronium (R).

Two hundred and sixty-eight patients without a history of neuromuscular disease, malignant hyperthermia, phosphodiesterase enzyme deficiency, type I or type II diabetes mellitus, pulmonary disease, psychiatric disease, hepatic or renal disorders, hypothyroidism or hyperthyroidism were operated under general anesthesia between April 2011-December 2012 were enrolled in this study.

Patients' hemodynamic parameters including electrocardiography (ECG) on standard DII derivation, heart rate per minute (HR), non-invasive systolic arterial blood pressure (SBP), diastolic arterial blood pressure (DBP), mean arterial blood pressure (MAP) and peripheral oxygen saturation (SpO<sub>2</sub>) were monitored in post-anesthesia care unit and measurements of 1st, 5th, 10th and 30th minute were recorded. Area for TOF (acceleromyograph-TOF-Watch-SX Monitor, Organon Teknika, Dublin, Ireland) electrodes to be placed in the wrist was cleaned with alcohol. Distal electrode (Neotrode ® Neonatal ECG Electrode, USA) was placed on the possible path of ulnar nerve, 1cm proximal to the wrist on the volar face. Proximal electrode was placed 2-3 cm proximal to the distal electrode. Acceleration transducer was placed on thumb with a finger adapter. Acceleromyographic measurements of the stimuli (40 mA current, 2 Hz frequency 0.2 milliseconds stimulus interval) applied to adductor pollicis muscle were recorded at 1st, 5th, 10th, 30th minutes alongside the hemodynamic measurements.

Patients' dermal and tympanic body temperature measurements were recorded at the same time with TOF and hemodynamic measurements. Clinical findings such as tongue depressor test, hand squeezing, existence of diplopia, ability to swallow, ability to lift head and legs for 5 seconds were assessed and recorded. Type of surgical intervention (head-neck surgery, laparoscopic abdominal surgery, open abdominal surgery, extremity surgery and other surgeries), duration of the surgery, whether an additional neuromuscular blocking agent is administered, whether a reversal agent is administered, volatile and non-volatile anesthetics administered were recorded.

During post-anesthesia care unit stay patients whose peripheral oxygen saturation dropped under 93% were administered 2-3 L/min oxygen.

Data was analyzed using computer program SPSS ver.18 (Statistical Package for Social Sciences for Windows, Ver. 18.0 New York, USA). Data was expressed as mean,  $\pm$  standard deviation and percentages (%). Shapiro-Wilk Test was used in addition to graphical methods as normality tests, to determine if the data is well-modeled by a normal distribution. Student's-T test and Mann Whitney-U test were used to analyze numerical data. Assessment of residual neuromuscular block risk factor rates and rate of clinical findings according to type of neuromuscular blocking agent was made either with chi-squared test or Fischer's exact test as it fits. Parameters that were found to be relevant for prolonged residual neuromuscular block in univariate analysis were assessed with multivariate analysis using logistic regression model. Pearson product-moment correlation coefficient was used to analyze linear correlation between numerical data.

## Results

Patients' demographics are presented in (Table-1). Eighty-three patients underwent head-neck surgery, 73 patients underwent laparoscopic abdominal surgery, 34 patients underwent open abdominal surgery, 16 patients underwent extremity surgery and 63 patients underwent other surgical interventions (perianal surgeries, breast surgery, plastic surgery) under general anesthesia.

One hundred and seven patients (39.9%) were administered a repeat dose neuromuscular blocking agent and 187 patients (69.8%) were administered a reversal agent.

**Table-1.** Demographic Characteristics of the Patients\*.

Gender F/M (n)	155/113
Age (mean $\pm$ SD) (years)	43.9 $\pm$ 11
BMI (mean $\pm$ SD)	26.8 $\pm$ 4.8
ASA 1/ASA 2 (n)	197/71
Surgery Duration (mean $\pm$ SD) (min)	102 $\pm$ 48

\* SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiologists Physical Status Score

When patients are evaluated in terms of residual neuromuscular block, we determined that mean TOF values were low in early term and increased proportionally with postoperative time passed. Number of patients with TOF values lower than 90 at 1st, 5th, 10th and 30th minutes were 131(48.9%), 99 (36.9%), 43 (16%) and 9(3.4%) respectively.

Risk factors' relevance with early term residual neuromuscular block was investigated with univariate analysis. Among those investigated mean age and body mass index, gender, type of surgery, type of induction anesthetic administered, type of volatile anesthetic

administered and type of neuromuscular blocking agent administered was not significantly relevant with a change in risk of early term residual neuromuscular block, whereas surgical duration, mean body temperature, additional neuromuscular blocking agent dose and administering reversal agents were significantly relevant with changes in risk of residual neuromuscular block (Table-2).

**Table-2.** Evaluation of Cases for Risk Factors\*.

	No Residual Block	Residual Block	p
Age	43.6 $\pm$ 10.9	44.2 $\pm$ 11.1	0.704
BMI*	26.9 $\pm$ 4.8	26.7 $\pm$ 4.7	0.679
Surgery Duration	91 $\pm$ 37	118 $\pm$ 55	<b>&lt;0.001</b>
Body Temperature	35.5 $\pm$ 0.7	35.2 $\pm$ 0.7	<b>&lt;0.001</b>
Gender (female/male)	75/62	80/51	0.295
Type of Surgery (h/l/a/e/o)	42/36/13/11/35	41/37/21/5/27	0.281
Neuromuscular Blocking Agent (v/a/r)	80/31/26	64/37/30	0.292
Induction Anesthetic (thiopenthal/propofol)	119/18	122/9	0.081
Inhalation Anesthetic (sevoflurane/desflurane)	56/81	64/67	0.189
Repeating Dose of Neuromuscular Blocking Agent (no/yes)	94/43	67/64	<b>0.004</b>
Reversal (no/yes)	29/108	52/79	<b>&lt;0.001</b>

\* BMI: Body mass index, h: head and neck surgery, l: laparoscopic surgery, a: open abdominal surgery, e: extremity surgery, o: other surgery, v: vecuronium, a: atracurium, r: rocuronium

Parameters that are shown to be significantly relevant risk factors for residual neuromuscular block with univariate analysis are also investigated with multivariate analysis with logistic regression model. Results are shown in Table-3.

**Table-3.** Multivariate Analysis of the Risk Factors for Residual Neuromuscular Blockade.

	Beta	Wald	P	Odds Ratio	Odds Ratio 95% CI	
					Lower Limit	Upper Limit
Surgery Duration	0.722	10.4	<b>0.001</b>	2.059	1.330	3.190
Repeat Dose	-0.06	0.03	0.858	0.941	0.484	1.830
Reversal	-0.91	9.89	<b>0.002</b>	0.401	0.227	0.709
Body Temperature	-0.28	5.52	<b>0.019</b>	0.753	0.595	0.954

Evaluation of risk factors showed every one hour increase of surgical duration increases risk of early term residual neuromuscular block by two folds (Odds ratio 2; 95% CI 1.3-3.1; P<0.01), administering reversal agents decreases risk of early term residual neuromuscular block by two and a half folds (Odds ratio 2.5; 95% CI 1.4-4.5; P<0.01), every 1°C drop in dermal body temperature increases risk by one and a half folds (Odds Ratio 1.5; 95% CI 1.1-1.6; P=0.019). Although additional neuromuscular blocking agent dose was found to increase residual neuromuscular block in univariate analysis, we failed to demonstrate this relevance in multivariate analysis (P>0.05).

Assessment of clinical findings of patients with TOF values lower than 90% are stated in Table-4.

**Table-4.** TOF Values According to Clinical Findings\*.

	TOF≥90%	TOF<90%	p
1 <sup>st</sup> min Diplopia	13 (9.5%)	68 (51.9%)	<0.001
1 <sup>st</sup> min Swallowing	137 (100%)	122 (93.1%)	0.002
1 <sup>st</sup> min Head Lift	128 (93.4%)	69 (52.7%)	<0.001
1 <sup>st</sup> min Leg Lift	125 (91.2%)	72 (55%)	<0.001
1 <sup>st</sup> min Hand Squeeze	128 (93.4%)	85 (64.9%)	<0.001
1 <sup>st</sup> min Tongue Depressor Test	134 (97.8%)	112 (85.5%)	<0.001

\* TOF: Train of four.

There were no statistically significant difference in mean TOF values between different type of neuromuscular blocking agent groups for patients with a body temperature over or under 35°C (p= 0.205; p=0.330).

## Discussion

Postoperative residual neuromuscular block has been a major problem for anesthetists. While existence of postoperative residual neuromuscular block was searched only with clinical findings such as muscle weakness in the past, it is currently known that clinical findings cannot always successfully rule out residual paralysis and that quantitative monitoring is necessary to this end (4,5). Studies evaluating neuromuscular transmission in general anesthesia applications with objective monitoring methods such as acceleromyography or mechanomyography has found that postoperative residual neuromuscular block incidence related with non-depolarizing neuromuscular blocking agents is considerably high (3). Residual neuromuscular block rate of 48.9% independent from agent type found in our study suggests that it might be a crucial mistake to ignore this risk in general clinic practice and puts forward the importance of neuromuscular monitoring. A study by Tsai et al. (2) where 308 patients are evaluated in in post-anesthesia care unit suggests that neuromuscular

monitoring for neuromuscular block with intermediate acting neuromuscular blocking agents is a cheap, non-invasive, evidence based technique which is an invaluable tool to be used in operating rooms before extubation. High rates of postoperative residual neuromuscular block in our clinic could be explained by absence of routine use of TOF monitoring, a high patient load and with the fact that TOF monitoring is not used until transfer to in post-anesthesia care unit in 268 patients. Previous studies stated necessity of neuromuscular acceleromyographic monitoring as a part of routine monitoring in operating room (6,7).

Some receptors in neuromuscular junction may still be bound with neuromuscular blocking agent if the end of effect is decided based upon clinical assessment. A wrong judgement of recovery based on clinical assessment and early transfer to recovery room may lead to respiratory failure due to weakness in respiratory muscles induced by an insufficient reversal of neuromuscular block. It is suggested that postoperative hypoxia is closely related with residual neuromuscular block (8), patients could raise their heads for 3 seconds, open their eyes, stick their tongues out even when their TOF values are 60% nevertheless their vital capacity remains low (9). Surveys show that clinicians rely on clinical assessment for detection of residual neuromuscular block (10). Eikerman et al. (11) stated that patients could raise their heads for 5 seconds even with a TOF value of 0.5. Recently, a cohort study by Murphy et al. (12) where 149 patients are monitored in post-anesthesia care unit with acceleromyography technique suggested that the group with lower initial TOF values had significantly higher incidence and severity of symptoms and findings related to muscle weakness. Similarly in our study diplopia rate at the 1st minute in the group with a TOF values were significantly lower than 0.9 and rate of positive clinical findings (swallowing, head raising, leg raising, hand squeezing, tongue depression test) were also significantly lower.

While some studies comparing residual neuromuscular block rate of different intermediate acting neuromuscular blocking agents (13,14) found no difference, Khan et al. (15) found that risk of residual neuromuscular block was higher after rocuronium block rather than vecuronium. While no significant difference was observed in rate of postoperative residual neuromuscular block with several different neuromuscular blocking agents in temperatures both more and less than 35°C, a statistically significant increase in rate of PORB was noted in correlation with body temperature drops. This suggests that preserving body temperature in optimal values plays a more effective role in preventing postoperative residual neuromuscular block than choice of the neuromuscular blocking agent.

Risk of early term residual neuromuscular block increases by two fold with every 1 hour increase in surgery duration, it is increased by one and a half fold with every 1°C drop in body temperature and it is decreased by two and a half fold with administering reversal agent. As a consequence it is very important to preserve optimal body temperature in cold operating room environment during a prolonged surgery. Although it is found that repeat doses of neuromuscular blocking agent increased the risk of residual neuromuscular block in univariate analysis, this finding was not backed in multivariate analysis of the data ( $P>0,05$ ). This probably is related with a stable cumulative plasma concentration due to administration of repeat dose nearly when the effect of the initial dose of neuromuscular blocking agent.

Duration of anesthesia is one of the important factors that affects residual neuromuscular block incidence yet there are controversies about this effect in several studies. In studies where only one dose of intermediate acting neuromuscular blocker used for tracheal intubation and surgery duration is relatively shorter (16), anesthesia duration is determined as a risk factor for residual neuromuscular block, whereas anesthesia duration is not determined to be a risk factor in other studies (17) where surgery and anesthesia durations are relatively longer ( $P>0,05$ ). It is stated that when anesthesia duration is longer and frequency of maintenance doses of neuromuscular blocking agent is increased, the risk of residual neuromuscular block increases in a dose dependent fashion (17). In our study

we probably found anesthesia duration as a risk factor due to hypothermia as a consequence of cold operating rooms rather than repeating maintenance doses of neuromuscular blocking. The fact that no difference is determined between several neuromuscular blocking agents in risk of postoperative residual neuromuscular block shows that in cold operating rooms where warming is not possible choice of neuromuscular blocking agents wouldn't affect the rate of postoperative residual neuromuscular block.

Restriction of our study was that it was conducted on patients with ASA physical status scores of I and II, also the procedures that patients underwent didn't carry a serious risk of hypothermia. We didn't evaluate postoperative residual neuromuscular block incidence for several neuromuscular blocking agents in cases where there is need for serious hypothermia such as cardiovascular surgery.

### Conclusion

Routine implementation of acceleromyography both intraoperative and postoperative period, protecting patients from hypothermia especially during prolonged procedures and acting promptly treating hypothermia when existent are some of the factors that could help prevent prolonged residual neuromuscular block.

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