KLİNİK ÇALIŞMA / CILINICAL RESEARCH

THE EFFECT OF CIRCADIAN RHYTHM ON VECURONIUM INDUCED NEUROMUSCULAR BLOCK

VEKÜRONYUMA BAĞLI NÖROMUSKÜLER BLOKAJ ÜZERİNE SİRKADİYEN RİTMİN ETKİSİ

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SUMMARY

Objective: *This study aimed to analyze the effect of the circadian rhythm on the neuromuscular block duration induced by a standard dose of vecuronium bromide.*

Methods: *After ethical committee approval, we enrolled 104 ASA class I-II patients who were to have a surgical operation with an expected duration not less than 60 minutes into the study. Anesthesia induction was provided with 2-2.5 mg kg^{-1} propofol, 0.1 mg kg^{-1} vecuronium bromide, and the maintenance of anesthesia with sevoflurane + 50% N_2O + 50% O_2 in 1-2% concentration. According to the application time of the vecuronium, the patients were divided into four groups: Group I (n=26) who had anesthesia in the forenoon (06:00- 12:00 a.m.) (in the morning), Group II (n=26) who had anesthesia in the afternoon (12:00-18:00 p.m.) (in the afternoon), Group III (n=26) who had anesthesia in the evening (18:00- 24:00) and Group IV (n=26) who had anesthesia at night (24:00- 06:00). The neuromuscular block time was measured using 'single twitch' (ST) mode of TOF- Watch apparatus.*

Results: *A total of 104 patients, 50 women and 54 men, aged between18 - 65 years who had elective and/or emergency surgery were evaluated statistically in this study. One patient in the morning group and three patients in the evening group were excluded (four patients in total) because surgery ended before reaching ST 25%. A significant difference was not observed among four groups in terms of ST first lag time, ST maximum lag time, first response time to ST, ST 10% and 25% recovery times related to the neuromuscular conduction.*

Conclusion: *We concluded that the standard induction dose of vecuronium bromide applied in the different hours of the day did not affect the neuromuscular block duration.*

KEY WORDS: *Anesthesia; Sevoflurane; Vecuronium Bromide; Chronobiology*

ÖZET

Amaç: *Bu çalışma standart doz vecuronyum bromidle sağlanan nöromüsküler blok süresine sirkadiyen ritmin etkisini değerlendirmeyi amaçladı.*

Materyal-Metod: *Etik komite onamı alındıktan sonra ASA I-II sınıfı, cerrahi operasyon geçirecek ve operasyon süresi 60 dakikadan kısa beklenmeyen 104 hastayı çalışmaya seçtik. Anestezi indüksiyonu 2-2,5 mg kg^{-1} propofol, 0,1 mg kg^{-1} vekuronyum bromür ile, anestezi idamesi ise %1-2 konsantrasyonda sevofluran + %50 N_2O + % 0 O_2 ile sağlandı. Hastalar vekürönyumun uygulama zamanı açısından; öğleden önce (saat 06:00-12:00) 26 kişi Grup I (sabah), öğleden sonra (saat 12:00-18.00) 26 kişi Grup II (öğlen), akşam (saat 18:00-24:00) 26 kişi Grup III ve gece (saat 24:00-06:00) 26 kişi Grup IV olmak üzere 4 gruba ayrıldı. Nöromüsküler blokaj süreleri TOF-Watch aleti kullanılarak tekli uyarı "single twitch" (ST) şekli ile değerlendirildi.*

Bulgular: *Elektif ve/veya acil cerrahi gerektiren 50 si kadın ve 54 ü erkek, yaşları 18-65 arasında toplam 104 hasta istatistiksel değerlendirildi. Sabah grubundan 1 hasta ve gece grubundan 3 hasta (toplam 4 hasta) ST %25 e ulaşmadan cerrahi bittiği için çalışma dışı bırakıldı. Nöromüsküler iletiyle ilgili ST ilk düşme zamanı, ST maximum düşme zamanı, ST'e ilk yanıt süresi, ST %10 ve %25 derlenme süreleri açısından dört grup açısından gruplar arasında anlamlı fark tespit edilmedi.*

Sonuç: *Günün farklı saatlerinde standart indüksiyon dozunda uygulanan vekürönyum bromürün nöromüsküler blok süresini etkilemediği sonucuna vardık.*

ANAHTAR KELİMELER: *Anestezi; Sevofluran; Vekürönyum Bromide; Kronobiyoloji*

INTRODUCTION

All living organisms including human beings perform most of their physiological functions with specific rhythms. The most common biological rhythm is the circadian rhythm in which a single cycle is almost one day long (22-24 hours). Chronopharmacology is a branch of science that studies the time-dependent rhythmic changes in the pharmacokinetic and pharmacodynamic characteristics of drugs (1). Like all other medicines, it is thought that cronopharmacology of the anesthetic substances are important for their clinical use. The data concerning the effect of the circadian rhythm on the neuromuscular block duration induced by neuromuscular blockers is based only on a limited number of studies (2-6).

There are many factors known to affect neuromuscular block. Circadian rhythm is also among the factors which determine the efficiency or toxicity of the medicines used in anesthesia, and the effect of the circadian rhythm on the effects of the anesthetic agents must be taken into consideration not only in the experimental studies but also during their use in daily practice (5).

Today, vecuronium bromide is one of the nondepolarizing muscle relaxants most frequently preferred by the anesthetists because it does not cause cardiovascular side effects and histamine release, provides good intubation conditions, sufficient muscle relaxation for surgery, and is cost - effective (7). On that account, we aimed to analyze the effect of the circadian rhythm on the neuromuscular block duration induced by vecuronium bromide, a nondepolarizing muscle relaxant with a moderate duration of action. In our study, we compared the effects of the standard induction dose of vecuronium bromide, used in different periods of the day, on the neuromuscular block duration.

MATERIAL AND METHOD

This study is a prospective clinical study, performed between May, 2008 and December, 2009 in the general surgery and emergency surgery rooms after obtaining the approval of Ankara Numune Training and Research Hospital Ethics Committee. Before the operations, the patients were informed about the study and their written informed consents were obtained.

One hundred and four ASA I-II patients between 18 and 65 years of age were included in the study. Inclusion criteria were as follows: presence of a proper fasting duration, a need for intubation and muscle relaxation with general anesthesia, absence of factors for difficult intubation, no known liver dysfunction or renal failure, no history of illness or drug use which is known to interfere with neuromuscular transmission, no sensitivity to the anesthetic agents that are intended to be used, a plan for elective and/or emergency surgical procedure, a body mass index (BMI) <30 kg m^2 and a Mallampati score under III.

According to the hour of vecuronium bromide application within the day (according to the hour of the day at which the cases were taken into operating room), the patients were grouped in four main groups as Group I: Morning (between 06:00-12:00 hours) (n:26), Group II: Afternoon (between 12:00-18:00 hours) (n:26), Group III: Evening (between 18:00-24:00 hours) (n:26), and Group IV: Night (between 24:00- 06:00 hours) (n: 26).

Moreover, in order to investigate the possible differences in neuromuscular conduction, the data were re-analyzed after dividing each group into two three-hour subgroups. The subgroups were entitled as follows:

Group Ia: The operations performed between 06:00-09:00 a.m. (n: 10)

Group Ib: The operations performed between 09:00-12:00 a.m. (n: 16)

Group IIa: The operations performed between 12:00-15:00 p.m. (n: 21)

Group IIb: The operations performed between 15:00-18:00 p.m. (n: 5)

Group IIIa: The operations performed between 18:00-21:00 p.m. (n: 14)

Group IIIb: The operations performed between 21:00- 24:00 p.m. (n: 12)

Group IVa: The operations performed between 24:00-03:00 a.m. (n: 17)

Group IVb: The operations performed between 03:00-06:00 a.m. (n: 9)

The demographic data (age, height, weight, BMI, sex, ASA class) were recorded preoperatively after examining major systemic medical history, drug use and the history of allergies. The application hour of anesthesia (study group), the dose of vecuronium, diagnosis for surgery and type of surgical procedure were recorded.

The patients were taken into the operating room and administered 10 ml kg^{-1} crystalloid infusion through a peripheral vein accessed through a 20 G intravenous cannula, and 0.03 mg kg^{-1} intravenous (i.v.) midazolam was given for premedication. Basic non-invasive hemodynamic monitoring [non-invasive blood pressure (BP), pulse rate (HR), electrocardiography (ECG), peripheral oxygen saturation (SpO_2)] was performed to follow up the vital signs, (ADU S/5, Datex-Ohmeda, Finland), and mean arterial pressure (MAP), HR and SpO_2 were recorded and checked during surgery.

For neuromuscular monitoring, TOF-Watch S© (Organon Teknika) device which used acceleromyography method was used with single twitch (ST) stimulation mode. Before anesthesia induction, the device was placed on the right or left wrist. For this, skin was cleansed with alcohol and acceleromyograph probe was placed to the volar aspect of the distal phalanx of the thumb and the movement of the forearm was prevented by fixing it with plaster while other four fingers were in supine position and extension. Pediatric electrodes were placed over the ulnar nerve region at 1 cm intervals, up to 1 cm from the wrist. The negative outlet of TOF-Watch S© monitor (black) was connected to the distal signal electrode and the positive outlet (white) to the proximal signal electrode. The arm was covered to keep its temperature over 32°C.

Four L min^{-1} oxygen was applied for 3 minutes for preoxygenation before the anesthesia induction. In all cases, intravenous anesthesia induction was provided with propofol 2-2.5 mg kg^{-1} and fentanyl 1-2 µg kg^{-1}. After induction, following the loss of eyelash reflex, TOF watch calibration was provided by operating the device and using the Single Twich (ST) startup procedure before a neuromuscular blocking agent was administered. Using ST sign type, the control twitch value was obtained as percent of the muscle response of the case in response to electrical stimulation, and the measured muscle response was accepted as 100%.

Vecuronium bromide (in 0.1 mg kg^{-1} standard induction dose) was given to the patients as a neuromuscular blocker, and chronometer was switched on to follow-up the neuromuscular data. Ventilation was provided with 100% O_2 applied with mask until ST value was <5%. The patients were intubated when "adductor pollicis" muscle response to ST stimulus was lost at a rate of 95%. After endotracheal intubation, all cases were ventilated mechanically to keep ET CO_2 values between 30–35 mmHg. To maintain hemodynamic stability and depth of anesthesia, according to the clinical response, narcotic analgesic was administered or the inhalation agent concentration was regulated when necessary. Anesthesia maintenance was provided with sevoflurane [1-2 % minimum alveolar concentration - (MAC)] and 50% N_2O + 50% O_2. To analyze the neuromuscular block duration, the parameters below were recorded by an anesthetist who was uninformed about the study.

Induction time data: Control ST percentage, ST initial decrease percentage, Lag time [the period from vecuronium bromide injection to the beginning of ST (min)], onset time of reaction [the period from vecuronium bromide injection to 95% depression of ST (min)].

Recovery time data: Deep block time (min) (the period between the time that ST sign is zero to the beginning of a new ST sign), 10% recovery time (the period from vecuronim bromide injection to 10% (of the control twitch value of ST) spontaneous compile time of muscle reaction), 25% recovery (clinical effect) time (the period from vecuronium bromide injection to 25% (of the control twitch value of ST) spontaneous recovery of muscle reaction, the first decrease in the unit of time: the initial decrease percentage of ST/ the first decrease time of ST (minute).

Depending on the prolongation of the surgical time, neuromuscular blocker was applied again if the patient needed an additional dose at the end of the 25% recovery (clinical effect) time. Before neuromuscular block was recovered completely (TOF > 70%), the patient was not extubated. At the end of the anesthesia, neuromuscular block was repulsed with atropine 0.02 mg kg^{-1} + neostigmine 0.04 mg kg^{-1} in the patients who needed decurarisation.

Statistical Method: The statistical analyses were performed with SPSS version 13.0.1 software (SPSS Inc., Chicago, IL, USA). Results were evaluated at 95% confidence interval and P values < 0.05 were considered significant. The sample size was calculated as performed in a previous study (5). For quantitative data (ST first lag time, ST 95% block time, ST 10% and ST 25% block times, average blood pressure and heart rate), unilateral variance analysis (ANOVA) was used to determine the presence of significant differences among ensemble averages of the variables. For qualitative data, Chi-square test was used to study whether the distribution of the data to the groups was arbitrary (or whether there was dependence between the groups). Paired t - test was used to investigate any significant difference between the averages of the two variables, and the variables were tested twice.

RESULTS

A total of 104 patients, 50 women and 54 men, aged between 18-65 years who had elective and/or emergency surgery were evaluated statistically in this study One patient in the morning group and three patients in the evening group were excluded (four patients in total) because surgery ended before reaching ST 25%. Any statistically significant difference was not found for age, height, BMI, sex or ASA score distributions of the groups (Table 1) (p> 0.05).

In terms of concomitant diseases, no significant difference was found for hypertension, diabetes mellitus, cardiovascular system disease, respiratory disease,

Table 1. The demographic data according to the groups. Data are expressed as mean ± SD or the number of the patients (n).

	Group I (n:25)	Group II (n:26)	Group III (n:23)	Group IV (n:26)
Age (year)	44.1±13.2	38.6±15.1	40.8±16.4	38.5±16.6
Height (cm)	166.1±9.3	167.7±9.1	168.8±8.0	171.2±7.5
Weight (kg)	72.4±15.2	71.3±14.0	71.9±10.1	75.5±11.8
BMI (kg/m^2)	26.0±3.8	25.4±5.1	25.2±3.4	25.7±3.9
Sex (F/M)	15/10	16/10	9/14	8/18
ASA (I/II)	8/17	7/19	10/13	7/19

Table 2. The ST rates and induction times according to main groups. Data are expressed as mean±SD.

	Group I (n:25)	Group II (n:26)	Group III (n:23)	Group IV (n:26)	*p*
Control ST %	100.80±12.15	101.46±8.11	103.87±14.26	104.92±12.57	0.681
ST first decrease %	82.96±11.72	83.31±11.08	87.87±10.03	84.12±13.44	0.882
Lag time (min.)	0.90±0.42	0.8532±0.40	0.85±0.35	0.82±0.39	0.185
First decrease in period of time	112.52±57.00	118.31±49.81	123.30±58.87	126.75±61.19	0.830
Onset time (min.)	3.18±1.18	2.92±0.95	2.94±0.50	3.04±0.74	0.450

Table 3. The ST rates and induction times according to the subgroups. Data are expressed as mean±SD.

		Control ST %	ST first decrease %	Lag time (min.)	First decrease in unit of time	Onset time (min.)
Group Ia (n: 9)	06:00- 09:00	105.78±14.34	86.44±11.11	0.78±0.28	133.25±80.00	3.50±1.55
Group Ib (n: 16)	10:00- 12:00	98.88±10.31	82.63±09.56	0.94±0.51	116.25±65.42	2.97±0.98
Group IIa(n: 21)	12:00- 15:00	101.43±8.80	82.57±11.99	0.83±0.43	121.38±50.83	2.91±1.04
Group IIb (n: 5)	15:00- 18:00	101.60±4.93	86.40±5.81	0.92±0.30	105.36±48.25	2.95±0.52
Group IIIa (n: 14)	18:00- 21:00	106.71±16.90	88.64±11.31	0.86±0.33	118.89±54.76	2.87±0.56
Group IIIb (n: 9)	21:00- 24:00	99.44±7.65	86.67±8.13	0.83±0.40	130.16±67.60	3.06±0.40
Group IVa (n: 17)	24:00- 03:00	106.76±10.87	87.18±6.55	0.87±0.39	120.54±55.15	3.24±0.64
Group IVb (n: 9)	03:00- 06:00	101.44±15.40	78.33±20.52	0,72±0,38	138.48±73.34	2,67±0,81
p		0.441	0.403	0.951	0.975	0.569

smoking or impaired thyroid function among the groups (p> 0.05).

Neuromuscular conduction data: The parameters of induction time were compared among 4 main groups; any significant difference was not found for control ST rate, ST first lag rate, ST first lag time, the first lag rate in the unit of time and ST maximum onset time (Table 2) (p> 0.05). The longest lag time was observed in the morning group with 2 minutes; the shortest lag time was evident in evening group with 0.25 minutes; the longest onset time was seen in morning group with 6 minutes and the shortest onset time was observed in afternoon group with 1.03 minutes.

The induction time parameters were compared among the sub-groups, any significant difference was not found for control ST rate, ST first lag rate, ST first lag time, maximum block rate or ST maximum onset time (Table 3) (p> 0.05). Analysis of the parameters concerning recovery times among 4 main groups did not yield any significant difference for ST first response time, 10% recovery time or 25% recovery (clinical effect) time (Table 4) (p> 0.05). The longest first response (acute block) to ST was observed in the night group with 64 minutes, the shortest first response (acute block) to ST was observed in the morning group with 10 minutes, the longest 10% recovery time was seen in the night group with 81 minutes, the shortest 10% recovery time was evident in the morning group with 11 minutes, the longest 25% recovery (clinical effect) time was observed in the evening group with 98 minutes and the shortest 25% recovery time was observed in the afternoon group with 18 minutes. Twenty five percent recovery time averages were as follows: 52.85±16 minutes in Group I, 48.23±18.27 minutes in Group II, 54.09±18.03 minutes in Group III and 55.54±19.09 minutes in Group IV (Table 4) (p> 0.05).

Table 4. The ST rates and recovery times according to the main groups. Data are expressed as mean±SD.

	Group I (n:25)	Group II (n:26)	Group III (n:23)	Group IV (n:26)	*p*
First response time to ST (min.)	34.96±9.75	34.38±11.21	33.48±10.09	37.85±13.10	0.543
10% recovery time (min.)	41.76±12.35	40.15±14.26	44.48±13.62	45.23±16.94	0.565
25% recovery time (min.)	52.84±16.00	48.23±18.27	54.09±18.03	55.54±19.09	0.495

Table 5. The ST rates and recovery times according to subgroups. Data are expressed as mean±SD.

		First response time to ST (min.)	10% recovery time (min.)	25% recovery time (min.)
Group Ia (n: 9)	06:00- 09:00	34.56±14.70	43.22±21.43	54.56±26.12
Group Ib (n: 16)	10:00- 12:00	36.25±7.05	43.38±8.14	55.31±12.64
Group IIa (n: 21)	12:00- 15:00	34.24±11.61	40.10±15.22	48.76±19.57
Group IIb (n: 5)	15:00- 18:00	35.00±10.53	40.40±10.59	46.00±12.78
Group IIIa (n: 14)	18:00- 21:00	32.07±8.55	41.93±13.40	50.64±17.38
Group IIIb (n: 9)	21:00- 24:00	35.67±12.34	48.44±13.74	59.44±18.70
Group IVa (n: 17)	24:00- 03:00	38.76±13.95	46.53±18.29	57.24±19.81
Group IVb (n: 9)	03:00- 06:00	36.11±11.90	42.78±14.75	52.33±18.34
p		0.877	0.871	0.744

The parameters concerning the recovery time were compared among the subgroups, there was no significant difference for ST first response time, 10% recovery time or 25% recovery (clinical effect) time (Table 5) (p> 0.05).

We analyzed mean heart rate before induction, we found 11.99 pulse min^{-1} difference in favor of the evening group when we compared the morning and the evening groups. Similarly, we found 14.07 pulse min^{-1} difference in favor of the evening group when we compared the afternoon and the evening groups. The comparison of mean arterial pressure (MAP) after intubation (ET+5 mins.) among the groups yielded 12.56 mmHg difference in favor of the morning group when compared to the evening group. We found that mean OAB values at 10th minute (ET+10 mins.) was 8.38 mmHg higher in the afternoon group compared to the night group, and 8.89 mmHg higher in the evening group compared to the night group. Other hemodynamic data were not different among diurnal groups studied. (Table 6, 7) (p> 0.05).

DISCUSSION

The data about the significance of the chronopharmacology on the clinical applications of anesthetic materials is based on limited number of studies. These experimental and clinical studies that analyzed the application time - activity relation showed that the duration of action of the neuromuscular blockers had a circadian change (2-5). These studies employed different methods and technologies (6-9). In our study we found that different application times during the day did not significantly affected the duration of action of vecuronium bromide

Table 6. Mean arterial pressures of the groups. Data are expressed as mean±SD.

MAP	Group I (n:25)	Group II (n:26)	Group III (n:23)	Group IV (n:26)	*p*
BI	98.8±13.1	97.5±15.2	93.9±12.7	94.3±12.0	0.497
AI	87.3±16.5	89.4±17.2	81.39±16.4	82.3±16.5	0.264
ET+5	96.6±16.8†	90.7±19.5	89.0±19.3	84.0±21.3	0.148
ET+10	85.8±12.6	87.8±16.9§	88.3±15.1■	79.4±14.5	0.133
ET+20	91.9±17.4	87.7±16.2	87.4±18.8	81.2±12.6	0.140
ET+30	89.8±16.7	88.5±14.4	90.5±16.4	87.2±15.3	0.886
ET+45	93.2±16.1	90.0±17.8	89.1±15.8	86.8±14.7	0.568
ET+60	89.8±16.1	91.6±14.2	90.3±17.5	87.9±15.4	0.538

†p< 0.05 in accordance with group IV, § p< 0.05 05 in accordance with group IV, ■ p< 0.0505 in accordance with group IV.

MAP; Mean arterial pressure, BI: Before induction, AI: After induction, ET+5.dk: 5minute after endotracheal intubation, ET+10: 10 minutes after endotracheal intubation, ET+20: 20 minutes after endotracheal intubation, ET+30: 30 minutes after endotracheal intubation, ET+45:45 minutes after endotracheal intubation, ET+60: 60 minutes after endotracheal intubation.

Table 7. The heart rates of the groups. Data are expressed as mean±SD.

HR	Group I (n:25)	Group II (n:26)	Group III (n:23)	Group IV (n:26)	*p*
BI	85.9±15.2†	83.8±14.9§	97.9±14.3	91.8±20.7	0.018*
AI	82.0±14.8	82.8±15.4	86.8±17.6	86.8±17.4	0.607
ET+5	87.4±13.0	87.9±10.5	90.8±19.4	87.7±15.4	0.851
ET+10	81.2±9.0	84.6±14.9	83.7±23.6	83.3±15.3	0.897
ET+20	81.2±13.2	82.1±13.7	85.4±16.5	80.8±16.7	0.716
ET+30	78.5±9.8	77.5±13.3	83.7±14.7	80.5±14.3	0.394
ET+45	76.7±9.7	77.7±14.5	82.7±17.8	82.0±15.5	0.368
ET+60	74.2±8.1	76.0±12.8	79.9±15.0	76.7±15.1	0.506

*p<0.05 recognized as statistically significant.

†p< 0.05 in accordance with group III, § p< 0.05 in accordance with group III.

HR: Heart rate, BI: Before induction, AI: After induction, ET+5.dk: 5 minute after endotracheal intubation, ET+10.dk: 10 minute after endotracheal intubation, ET+20.dk: 20 minute after endotracheal intubation, ET+30.dk: 30 minute after endotracheal intubation, ET+45.dk: 45 minute after endotracheal intubation, ET+60. dk: 60 minute after endotracheal intubation .

among four main groups when it was applied at the standard induction dose (0.1 mg kg^{-1}). With regard to the neuromuscular conduction; any significant difference was not found for the lag time, onset time, acute response time, ST 10% or 25% recovery (clinical effect) time among morning, afternoon, evening and night periods. These data were analyzed again by dividing each group into three-hour subgroups to reveal the differences related to the neuromuscular conduction, and any significant difference was not found among the neuromuscular block times of the subgroups.

Hiroshi et al. (10) reported the time of the clinical effect (25% recovery time) as 44.5±2.7 minutes where vecuronium bromide 0.1 mg kg^{-1} was used as the intubation dose. This value was the most compatible one with 25% recovery time (48±18 minutes) of the afternoon group in our study. There was no concordance when other time periods were concerned. The reason for this may be because of that the patients were given anesthesia at noon in the study of Hiroshi et al. (10). Rimaniol et al. (11) found 25% recovery time as 38±7 minutes with the same dose of vecuronium bromide. Slavov et al. (12) found this time as 50±18 minutes for patients > 65 years of age and as 36±8 minutes for the control group (ages between 18-50 years) with a dose of 0.1 mg kg-1. Although ST stimulation method was used in all these studies, their results show wide variations. This is why we think that the effect time of neuromuscular blockers may show wide, unpredictable particular variations.

The effect of circadian rhythm on actions of rocuronium was investigated by Cheeseman et al. (5) who reported that duration of action of rocuronium was the longest in the morning hours and the shortest in the afternoon. In contrast to the previous studies which investigated the effect of circadian rhythm on the action of neuromuscular blocker agents, the application time did not affect the neuromuscular block time induced by vecuronium in our study when applied in standard induction dose (0.1 mg kg^{-1}) (2-5). Any statistical significant difference was not found when the neuromuscular block time was compared among morning, afternoon, evening and night applications. We found the ST 25% clinical effect time as 52.84±16 minutes in the morning group, 48.23±18.27 minutes in the afternoon group, 54.09±18.03 minutes in the evening group and 55.54±19.09 minutes in the night group in our study. The data were re-analyzed by dividing each group into three-hour subgroups, and the shortest clinical effect was found as 46.00±12.78 minutes in 15:00-18:00, and the longest clinical effect as 54.56±26.12 minutes in 06:00 to 09:00 groups. However, the longest 25% clinical effect time was in 21:00 - 24:00 group with 59.44±18.70 minutes. Although the differences among these times were not found significant statistically, we suppose that the difference between the afternoon group and the other groups may be clinically significant. These times are similar to clinical effect times reported by Cheeseman et al. (5), however the differences among our groups did not reach statistical significance and the possible reason for this may be attributed to the different nerve stimulation methods used in these two studies.

Cheeseman et al. (5) found significant differences in clinical effect time of rocuronium applied in different times of the day. Although the duration of neuromuscular block induced by vecuronium bromide is expected to be similar to rocuronium since these two agents have similar pharmacokinetic features, we did not find statistically significant results. This difference may be due to

differences of the patient groups and nerve stimulation methods (ST stimulation) rather than the pharmacokinetic mechanisms.

Various hypotheses have been put forward to explain how application time affects neuromuscular block time. These hypotheses argue that the circadian time could affect the drug metabolism, liver blood flow, kidney/liver elimination of the drug, the diurnal changes (the affinity toward receptor expression and receptors) in the number and activities of the target nicotinic receptors, and the cholinesterase activity (1,5-8).

Levi et al. showed that liver blood flow was at its maximum level between 02:00 and 08:00 hours while it was at its minimum level at 14:00 during the day (13). High blood flow observed in liver at night may result in shorter clinical effect times of some drugs, such as vecuronium bromide. However, in our study we could not show any changes in the duration of action of vecuronium bromide in parallel with the liver blood flow fluctuations in the day.

It has been shown that the melatonin, the primary hormone secreted according to circadian time, affects presynaptic nicotinic acetylcholine receptors (14-15), and this effect may be related to changes of neuromuscular block time according to application time of the agent. Carneiro et al. (16) showed that the contraction blocker effect of hexamethonium was more pronounced at 09:00 hours when compared to 03:00 hours in rats, and concluded that a functional pineal gland caused a diurnal variation under the effect of acetylcholine by melatonin synthesis.

The main hormone secreted in a circadian rhythm is melatonin, and the data show that melatonin exerts its effects more during sleep. Melatonin and cardiovascular circadian rhythm are closely related. A study which studied heart rate variations in human reported that heart rate and blood pressure decrease as well as plasma noradrenalin and dopamine levels depending upon an increase in cardiac vagal tone in supine position after oral melatonin administration. This effect results from suppression of the sympathetic tone by melatonin (17). However, this effect disappeared when the person stood up. Melatonin decreased the blood pressure and heart rate of healthy individuals when given before sleep at night (18). We found a minimal change among the groups for HR and MAP, and it may be related to minimal effects of vecuronium bromide on cardiovascular system and autonomic nervous system.

One of the limitations of our study may be our small sample size. Although our sample size is greater when compared to that of Cheeseman et al. (5), we think that it can still be small because of the particular variations in the responses of neuromuscular blockers. Moreover, we cannot control many other factors that could affect the agent's action (genetic factors, environmental factors, fasting state, social environment, state of mind, anxiety etc.) and those may have been an obstacle for us to present the diurnal differences in the duration of neuromuscular block. Another limitation of our study was our inability to assess the 25-75% clinical recovery times, since we had to use anticholinesterases and there was no standardization because plasma levels of plasma vecuronium bromide levels were not measured and the cases were given anesthesia at different times of the day.

The strong part of our study is that it provided the data of the patients who had emergency surgery between 02:00 and 08:00 hours. We investigated the effect of the altered hormone levels on vecuronium during night. To our knowledge, no studies up to date have investigated this subject in this time period. In response to surgery, catecholamines cause an increase in plasma concentration of cortisol as well as some other hormones. It has been pointed out that being sick, staying at a hospital and surgical procedures, especially emergency abdominal surgery, are sources of stress and cause anxiety as well as increased cortisol release (19). It is not known in those patients how increased cortisol release in response to anxiety and surgical stress affects the circadian rhythm of endogenic cortisol release. It is believed that stress response in connection with anxiety influences circadian rhythm and this response influences the neuromuscular relaxing metabolism. We suppose that further and more advanced investigations are needed on this issue.

In conclusion, we found that the neuromuscular block time induced by vecuronium bromide does not show a statistically significant circadian difference. However, we think that effect onset and clinical effect may be affected by many individual and environmental factors that cannot be standardized, and there may be many other factors which can affect neuromuscular block time.

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REFERENCES

1. Chassard D, Bruquerolle B. Chronobiology and anesthesia. Anesthesiology 2004;100(2):413-27.
2. Bruguerolle B, Mesdjian E, Jadot G, et al. Variations in the activity of various curarizing substances as a function of the time of administration. Ann Anesthesiol Fr 1975;16(5):349-53.
3. Bruquerolle B, Valli M, Jadot G, et al. Chronopharmacology of pancuronium in rats anesthetized by CT 1341 (Alfatesine). C R Seances Soc Biol Fil 1978;172(3):498-504.
4. Descorps-Declere A, Bonnafous M, Reinberg A, Begon C. Sex related differences in diurnal and seasonal changes in effectiveness of pancuronium bromide in man. Chronobiologia 1983;10:121–2.
5. Cheeseman JF, Merry AF, Pawley MD, et al. The effect of time of day on the duration of neuromuscular blockade elicited by rocuronium. Anaesthesia 2007;62(11):1114–20.
6. Balkancı ZD, Sevgili AM. Biyolojik ritimler ve anestezi. Anestezi Dergisi 2005;13(4):223–36.
7. Viby-Mogensen J. Neuromuscular Monitoring. In: Miller RD, ed. Miller's Anesthesia. 6th Edition, Philadelphia: Churchill Livingstone, 2005;1551-69.
8. Chassard D, Duflo F, et al. Chronobiology and anesthesia. Curr Opin Anaesthesiology 2007;20(3):186-90.
9. Chassard D, Allaouchiche B, Boselli E. Timing is everything: the pendulum swings on. Anesthesiology 2005;103(3):454-6.
10. Takahashi H, Nishikawa T. Oral clonidine does not alter vecuronium neuromuscular blockade in anaesthetized patients. Can J Anaesth 1995;42(6);511-5.
11. Rimaniol JM, Dhonneur G, Sperry L, Duvaldestin P. A comparison of the neuromuscular blocking effects of atracurium, mivacurium, and vecuronium on the adductor pollicis and the orbicularis oculi muscle in humans. Anesth Analg 1996;83(4):808-13.
12. Slavov V, Khalil M, Merle JC, Ruggier R, Duvaldestin P. Comparison of duration of neuromuscular blocking effect ofatracurium and vecuronium in young and elderly patients. Br J Anaesth 1995;74(6):709-11.
13. Levi F, Metzger G, Massari C, Milano G. Oxaliplatin: pharmacokinetics and chronopharmacological aspects. Clin Pharmacokinet 2000;38(1):1-21.
14. Markus RP, Zago WM, Carneiro RC. Melatonin modulation of presynaptic nicotinic acetylcholine receptors in the rat vas deferens. J Pharmacol Exp Ther 1996;279(1):18–22.
15. Markus RP, Santos JM, Zago W, Reno LA. Melatonin nocturnal surge modulates nicotinic receptors and nicotineinduced (3H) glutamate release in rat cerebellum slices. J Pharmacol Exp Ther 2003;305(2):525–30.
16. Carneiro RC, Markus RP. Presynaptic nicotinic receptors involved in release of noradrenaline and ATP from the prostatic portion of the rat vas deferens. J Pharmacol Exp Ther 1990;255(1):95–100.
17. Nishiyama K, Yasue H, Moriyama Y, et al. Acute effects of melatonin administration on cardiovascular autonomic regulation in healthy men. Am Heart J 2001;141(5):E9.
18. Lusardi P, Preti P, Savino S, Piazza E, Zoppi E, Fogari R. Effect of bedtime melatonin ingestion on blood pressure of normotensive subjects. Blood Press Monit 1997;2(2):99-103.
19. Selimuzzaman SM, Begum N, Islam N, Begum S. Effects of Surgical Stress on Serum Cortisol Level: A Comparative Study between Elective and Emergency Surgery. J Bangladesh Soc Physiol 2007;2:28-33.