Reversal Effects of Sugammadex in Diabetic Patients Having Neuromuscular Block with Rocuronium

Rokuronyumla Nöromusküler Blok Sağlanan Diyabetik Hastalarda Sugammadeks'in Nöromusküler Derlenme Üzerine Etkileri

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ABSTRACT Objective: In our study we aimed to compare the time of antagonism and effect of sugammadex which is used for antagonism of rocuronium on diabetic and nondiabetic patients. Sugammadex is a new generation antagonist of neuromuscular blockade which effects by encapsulating rocuronium molecules in the neuromuscular junction through acting like a synthetic receptor of rocuronium. **Material and Methods:** Included patients were divided into two groups: diabetic (n=21) and non-diabetic (n=20). After loss of eyelid reflex and automatically identification of supramaximal stimulating current by the neuromuscular monitoring system, rocuronium 0.6 mg/kg IV was administered. Train-of-four (TOF) stimulation with the supramaximal current was applied and by recording of second TOF value the patient was intubated. TOF stimulation was performed and recorded every 20 seconds. Intraoperatively by return of T2, rocuronium 0.15 mg/kg IV was administered. T2i time was recorded as intubation time whereas T2d time was recorded as clinical effect time. At the end of the operation sugammadex 2 mg/kg IV was administered. When TOF ratio reached 0.9, patients were extubated and the time interval was recorded. **Results:** There was no differences between two groups of intubation time (p=0.696). The clinical effect time were 2549.6±913.2 [2360 (1144-4718)] seconds in diabetics and 2208.9±475.0 [2252 (1310-3015)] seconds in non-diabetics (p=0.145). Extubation time (time from sugammadex administration to TOF ratio reaching 0.9) was 434.6±857.1 [205 (67-4120)] seconds in diabetics and 250.4±108.4 [247 (106-462)] seconds in non-diabetics (p= 0.948). Recovery time (time from extubation to reaching an Aldrete's score of 0,9) was 295,19±239,21 [228 (20-945)] seconds in diabetics and 228,20±115,22 [238.5 (54-446)] seconds in non-diabetics (p=0.611). There were no statistical significant difference between the two groups in intubation time, clinical effect time, extubation time and recovery time. **Conclusion:** Contrary to expected delay of clinical effect and recovery times with conventional reversal agents in diabetic patients resulting from diabetic complications has not occurred with sugammadex. In conclusion, sugammadex seems to be like a good alternative for diabetic patients because of its role in reversing the effects of neuromuscular blocking agents as well as alleviating problems in recovery period.

Key Words: Diabetes mellitus; neuromuscular blockade; sugammadex

ÖZET Amaç: Bu çalışmada, rokuronyumun antagonizması için kullanılan sugammadeksin antagonizma ve etki sürelerinin diyabetik ve diyabetik olmayan hastalarda karşılaştırılması amaçlanmıştır. Sugammadeks, etkisini nöromusküler kavşaktaki rokuronyum moleküllerini enkapsüle ederek gösteren, rokuronyum için sentetik bir reseptör gibi davranan yeni nesil nöromusküler blok antagonistidir. **Gereç ve Yöntemler:** Hastalar diyabetik (n=21) ve diyabetik olmayan (n=20) olmak üzere iki gruba ayrıldı. Kirpik refleksi kaybından sonra supramaksimal uyarı nöromusküler monitörizasyon sistemi tarafından otomatik olarak belirlendi ve rokuronyum 0,6 mg/kg intravenöz olarak uygulandı. Supramaksimal uyarı ile "train-of-four (TOF)" stimülasyonu yapıldı ve TOF2 değeri elde edilince hasta entübe edildi. Yirmi saniyede bir TOF stimülasyonu yapılarak, değerler kaydedildi. İntraoperatif dönemde T2 geri dönüşü görüldüğünde 0,15 mg/kg rokuronyum intravenöz olarak eklendi. T2i zamanı, entübasyon süresi olarak, T2d zamanı ise klinik etki süresi olarak kaydedildi. Operasyon sonunda sugammadeks 2 mg/kg intravenöz uygulandı. TOF oranı 0,9'a ulaştığında hastalar ekstübe edilerek, süre kaydedildi. **Bulgular:** Entübasyon süreleri açısından iki grup arasında fark bulunmadı (p=0,696). Klinik etki süreleri diyabetik hasta grubunda 2549,6±913,2 [2360 (1144-4718)] saniye, diyabetik olmayan grupta 2208,9±475,0 [2252 (1310-3015)] saniye olarak bulundu (p=0,145). Ekstübasyon süresi (sugammadeks yapılmasından TOF oranının 0,9'a ulaşmasına kadar geçen süre) diyabetik grupta 434,6±857,1 [205 (67-4120)] saniye, diyabetik olmayan grupta ise 250,4±108,4 [247 (106-462)] saniye olarak bulundu (p=0,948). Derlenme süresi (ekstübasyondan sonra Aldrete derlenme skoru 0,9'a ulaşma süresi) diyabetik grupta 295,19±239,21 [228 (20-945)] saniye, diyabetik olmayan grupta ise 228,20±115,22 [238,5 (54-446)] saniye olarak bulundu (p=0,611). Gruplar arasında entübasyon süresi, klinik etki süresi , ekstübasyon süresi ve derlenme süresi açısından istatistiksel olarak anlamlı bir fark gözlenmedi. **Sonuç:** Geleneksel nöromusküler geri döndürücü ajanlar kullanıldığında diyabetik hastalarda diyabet komplikasyonları nedeni ile beklenen klinik etki ve derlenme sürelerindeki uzama, sugammadeks ile gözlenmemiştir. Sonuçta sugammadeks, nöromusküler bloker ajanın etkilerinin ortadan kaldırılmasındaki rolü ve diyabetik komplikasyonlara bağlı görülebilecek derlenme sorunlarını azaltması yönünden diyabetik hastalar için güvenli bir alternatif olarak görünmektedir.

Anahtar Kelimeler: Diabetes mellitus; nöromusküler blokaj; sugammadeks

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Diabetes mellitus (DM) is a chronic metabolic disease resulting from impaired insulin synthesis or impaired tissue response to insulin secretion. The incidence of DM has rapidly increased over the past 20-30 years and it is predicted to be duplicated in the next few decades. Furthermore its significance is higher in patients requiring surgery.[1] Also the possibility of operative complications increases in diabetic patients undergoing elective surgery.[2] Diabetic complications existing preoperatively can cause an increase of perioperative morbidity in these patients.[1]

Neuropathy affecting motor nerve fibers and terminal nerve plate is one of the considerable complications of DM, which should be taken into consideration during anesthetic management. Partial degeneration or segmental demyelination of the nerve fiber and loss of motor units cause neuropathy in diabetic patients.[3-5] Neuromuscular blocking agents used during induction and maintenance of anesthesia affect neuromuscular junctions, therefore the efficacy profile of these agents is an important subject for further investigation in diabetic patients.

Multisystem diseases like DM can unclear the level of the neuromuscular blockade and its reversal by changing the pharmacokinetic profiles of neuromuscular blocking agents. At this point, the importance of neuromuscular monitoring is noticeable for identifying the level of neuromuscular blockade intraoperatively and for determination of duration and onset time of the reversal of the neuromuscular blockade.[6,7]

One mechanism of neuromuscular blockade reversal is to conduct a chemical bond between the neuromuscular blocking agent and another molecule. Sugammadex- a new generation antagonist of neuromuscular blockade with its gamma-cyclodextrin-structure represents strong affinity to steroidal neuromuscular blocking agents and inactivates them through a chemical bond. Sugammadex acts like a synthetic receptor to rocuronium which is a steroidal neuromuscular blocking agent. Sugammadex encapsulates rocuronium in its lipophilic cavity and inhibits the interaction between rocuronium and acetylcholine receptors.[2]

In our literature search we found no study about reversal of neuromuscular blockade in diabetic patients designed with sugammadex. On the other hand neuromuscular blockade and its reversal in diabetic patients is a common research base mostly designed with anticholinesterases. In two of aforementioned studies Saitoh and colleagues concluded that the recovery parameters obtained through neuromuscular monitorisation were delayed in diabetic patients receiving anticholinesterase and concurrently parameters of return of neuromuscular function in diabetics were significantly longer than in the control groups.[8,9] We planned our study in light of the prior with the hypothesis, that times to reversal and recovery from neuromuscular blockade which is reversed with sugammadex will not differ significantly in diabetic and nondiabetic patients due to its unique mechanism of action.

MATERIAL AND METHODS

Our study is sustained by the Commission of Scientific Researches of Duzce University with the Project number 2013.4.2.147. The protocol of this study was approved by our Institutional Ethics Committee at date 03/29/2012 and with the project number 2012/25. This work was done in the Department of Anesthesiology, Duzce University School of Medicine between January 2013 and September 2013. Written informed consent was obtained from each patient. Twenty-one adult patients, ASA physical status II, who had had type 2 DM for more than ten years, and twenty adult patients, ASA I to II without DM were studied. Exclusion criteria were, neuromuscular diseases (myasthenia gravis, myotonic dystrophia, motor neuron disease), diabetic nephropathy, hepatic, renal or cardiac failure, fluid-electrolyte imbalance, usage of drugs known to interfere with the action of neuromuscular blocking drugs.

In the premedication room an intravenous line with a 18 G cannula was placed in the antecubital vein. Premedication consisting of midazolam 0.03 mg/kg IV was given before induction of anesthesia. All patients received infusion of NaCl 0.9 % with an infusion rate of 10 ml/kg/h. After arriving in the operating room, patients were monitored with the anesthesia machine Datex Ohmeda S/5 Avance. ECG (DII derivation), peripheral oxygen saturation (SPO_2), non-invasive blood pressures [systolic (SBP), diastolic (DBP), mean (MBP)], respiratory rate, end-tidal carbon dioxide concentration ($ETCO_2$), and inspiratory sevoflurane concentrations were recorded every 5 minutes before and after anesthesia induction and in the peroperative period. Two stimulating electrodes were placed over the ulnar nerve at the wrist. Two recording electrodes were attached over the adductor pollicis muscle. Surface skin temperature over the adductor pollicis muscle was monitored in every patient throughout the anesthetic management. Anesthesia was induced with propofol 2 mg/kg and fentanyl l μg/kg. A specific electromyographic neuromuscular monitoring system was employed after loss of eyelid reflex (Datex-Ohmeda Inc., Helsinki, Finland). This system automatically identified supramaximal stimulating currents. After recording supramaximal stimulating current, rocuronium 0.6 mg/kg IV was administered to facilitate tracheal intubation. Train-of-four (TOF) stimulation with the supramaximal current was applied every 10 seconds with a frequency of 2 Hz and by recording of second TOF value (TOF2) endotracheal intubation was performed. After fixing the position of the endotracheal tube the operation was allowed to start. Anesthesia was maintained with 50% O_2 + 50% air and sevoflurane of 1 MAC. Mechanical ventilator parameters were modified to achieve $ETCO_2$ values of 35-40 mmHg. TOF stimulation was performed and recorded every 20 seconds. In the intraoperative period by return of TOF2 rocuronium 0.15 mg/kg IV was administered (maintanence dose).

T2i time (time to achieve TOF2 after the first administration of rocuronium) was recorded as intubation time, T2d time (time from rocuronium administration to return of TOF2) was recorded as clinical effect time, T0 time (time to achieve no TOF response after the first administration of rocuronium) was recorded maximal blockade onset time and T1d time was recorded as time from rocuronium administration to return of TOF1. Sugammadex 2 mg/kg IV was administered after double switch response was observed all the patients at the end of the operation. When TOF rate reached 0.9, patients were extubated. Tsug (time from the last rocuronium administration to the administration of sugammadex) was recorded as time to administration of sugammadex and Tex (time from sugammadex administration to the return of a TOF ratio of 0.9) was recorded as the extubation time. After arriving at the recovery room and maintaining postoperative analgesia, all patients were assessed on Aldrete's Recovery Score and Tder (time from extubation to achieving an Aldrete's recovery score of 9) was recorded as recovery time. Patients who achieve an Aldrete's recovery score of 9 were discharged.

STATISTICAL ANALYSIS

In light of literature search and clinical information, it was considered that the changes of 2 min ± 2 minutes were of importance for time to achieve a TOF ratio of 0.9. When taken the power of the test as 80% and the possibility of making a type I error as 5%, it is considered that 20 patients per diabetic and non-diabetic group are sufficient. Since time of achieving a TOF ratio of 0.9 was determined as a major criterion, the minimum sample size was determined according to this time as well. All results were expressed as number, mean±Standard Deviation or median (minimum-maximum). In comparison of the mean values of the numeric variables in diabetic and non-diabetic groups, Independent t test was used if data is normally distributed and Mann-Whitney U test was used if data is not normally distributed. Relation between categorical variables was analyzed by Fisher' exact test. $p<0.05$ was considered statisti-

cally significant. Statistical analyses were performed using a statistical package (PASW (ver. 18) (Predictive Analytics Software) running on a personal computer.

RESULTS

In terms of the age, body weight, body mass index (BMI) and fasting blood glucose level (FBG) variables statistically significant difference was observed between the groups. The mean values of age (p=0.013), body weight (p=0.048), BMI (p=0.005) and FBG (p=0.001) in the diabetic group were significantly higher when compared with the nondiabetic group (Table 1). ASA scores (p=0.107), anesthesia and surgery times did not differ significantly between the diabetic and nondiabetic groups (p=0.896 for anesthesia time, p=0.969 for surgery time) (Table 1).

Peroperative non-invasive diastolic blood pressure (DBP), heart rate and end-tidal carbon dioxide concentration ($ETCO_2$) values did not differ significantly between the groups when peroperative peripheral oxygen saturation (SPO_2) and non-invasive blood pressures [systolic (SBP), mean (MBP)] values differ significantly between the groups (Table 2).

TOF responses (p=0.696 for T2i, p=0.175 for T0, p=0.502 for T1d, p=0.145 for T2d) (Table 3), total rocuronium doses used throughout the operation (p=0.163) (Table 1), times from last rocuronium administration to the administration of sugammadex (p=0.917 for Tsug) (Table 3), times from administration of sugammadex to TOF ratio reaching 0,9 (extubation times, p=0.948 for Tex) and times from extubation to achieving an Aldrete's recovery score of 9 (recovery times, p=0.611 for Tder) did not differ significantly between the diabetic and nondiabetic groups (Table 3).

The presence of DM did not affect extubation and recovery times from rocuronium induced neuromuscular blockade when it was reversed with sugammadex 2 mg/kg.

TABLE 1: Comparison of patient characteristics between groups.

	Diabetic (n=21)	Nondiabetic (n=20)	p value
ASA I/II (n)	0/21	3/17	0.107
	Mean±SD	**Mean±SD**	
Age (years)	55.23±8.5	45.85±14.1	**0.013**
Body weight (kg)	80.20±13.7	72.1±11.6	**0.048**
BMI (kg/m^2)	29.9±5.6	25.6±3.3	**0.005**
	Median (Min-Max)	**Median (Min-Max)**	
FBG (mg/dl)	156 (87-265)	95.5 (81-153)	**0.001**
Anesthesia time (min)	90 (38-270)	81 (52-290)	0.896
Surgery time (min)	75 (26-230)	70 (40-250)	0.969
Total rocuronium (mg)	60 (50-100)	60 (40-120)	0.163

ASA: American Society of Anesthesiologist's score;
BMI: Body mass index;
FBG: Fasting blood glucose.

TABLE 2: Comparison of peroperative SPO_2, SBP, DBP, MBP, heart rate and $ETCO_2$ values between groups.

	Diabetic (n=21)	Nondiabetic (n=20)	
	Median (Min-Max)	**Median (Min-Max)**	**p value**
Per-SPO_2	97 (92-100)	98 (94-100)	0.026
N-SBP	160 (131-210)	133 (98-159)	<0.001
N-DBP	88 (64-120)	83 (61-96)	0.097
N-MBP	118 (91-147)	102.5 (80-125)	0.001
Heart Rate	81 (60-113)	75.5 (56-96)	0.179
$ETCO_2$	32 (21-41)	29.5 (19-39)	0.080

Per-SPO_2: Peroperative peripheral oxygen saturation;
N-SBP: Non-invasive systolic blood pressure;
N-DBP: Non-invasive diastolic blood pressure;
N-MBP: Non-invasive mean blood pressure;
$ETCO_2$: End-tidal carbon dioxide concentration.

DISCUSSION

This study indicates that onset of neuromuscular blockade; times of sugammadex induced reversal from neuromuscular blockade and times to recovery do not differ in diabetic patients when compared with non-diabetic patients.

Demographic data including age, body weight and BMI in the diabetic group were significantly higher when compared with the non-diabetic group. We reason out this case due to the fact that

TABLE 3: Comparison of TOF responses, extubation times and times from last rocuronium administration to sugammadex administration and to achieving an Aldrete's recovery score of 9 between groups.

	Diabetic (n=21) Median (Min-Max)	Nondiabetic (n=20) Median (Min-Max)	p value
T2i (s)	151 (80-484)	152.5 (85-266)	0.696
T0 (s)	260 (115-1749)	211.5 (85-455)	0.175
T1d (s)	1920 (510-366.7)	1654.5 (941-4478)	0.502
T2d (s)	2360 (1144-4718)	2252 (1310-3015)	0.145
Tex (s)	205 (67-4120)	247 (106-462)	0.948
Tsug (s)	1886 (460-7140)	1718 (915-4645)	0.917
Tder (s)	228 (20-945)	238.5 (54-446)	0.611

T2i: time to achieve TOF2 after the first administration of rocuronium (intubation time);
T0: time to achieve no TOF response after the first administration of rocuronium (maximal blockade onset time);
T1d: time from rocuronium administration to return of TOF1.;
T2d: time from rocuronium administration to return of TOF2 (clinical effect time);
Tex: time from sugammadex administration to the return of a TOF ratio of 0.9 (extubation time);
Tsug: time from last rocuronium administration to the administration of sugammadex;
Tder: time from extubation to achieving an Aldrete's recovery score of 9 (recovery time).

DM type II appears mostly by obese patients over 45 years. Even so the reason for observing significantly higher FBG levels in the diabetic group when compared with the non-diabetic group stems from our patient selections, which were diagnosed with DM type II for over 10 years. The longer the duration of DM is, the more long-term diabetic complications occur.[10-12]

Studies about onset and reversal of neuromuscular blockade including patients with DM indicate similarity with nondiabetic patients.[13] In a study of Saitoh and colleagues observing neuromuscular monitoring after vecuronium administration in patients with DM, supramaximal stimulating currents were significantly higher in diabetic patients when compared with nondiabetic patients, but the onset times of neuromuscular blockade was similar between the groups.[13] Also in our study the onset times of rocuronium induced-neuromuscular blockade did not differ significantly between diabetic and nondiabetic patients. In the same study of Saitoh and colleagues reversal of neuromuscular blockade with neostigmine is compared between diabetic and nondiabetic groups and it is reported that times to return of T1 and T4 were longer in diabetic patients.[13] In other studies of the same author, the TOF ratio was lower at 3 min, 6 min, 9 min, 12 min and 15 min after administration of the reversal agent neostigmine in the diabetic group than in the control group, however the differences did not reach statistical significance.[8] The recovery of T1/control and TOF ratio were delayed in diabetic patients receiving anticholinesterase.[9] Times to return of T2, T3, T4 and a TOF ratio of 0.9 were significant longer in diabetic patients.[9] In our literature search we found no study about reversal of neuromuscular blockade in diabetic patients designed with sugammadex. In our study comparing sugammadex-induced reversal of neuromuscular blockade between diabetic and nondiabetic patients, times for reversal of neuromuscular blockade did not differ between diabetic and nondiabetic patients.

Degeneration, demyelination of the nerve fibre and loss of axons cause a decrease in acetylcholine secretion in diabetic patients, therefore a delay in recovery of neuromuscular blockade with an anticholinesterase can occur.[4,5,8] This fact can explain the delayed return of the neuromuscular function in aforementioned studies of Saitoh and colleagues. However, sugammadex effects by incapsulation of rocuronium molecules without any impact on the neuromuscular junction, thus we think that is the reason of why no difference occurred in terms of reversal times from neuromuscular blockade between diabetic and nondiabetic patients.

Neuromuscular blocking agents and their inadequate reversal can cause postoperative residual curarisation. The incidence of postoperative residual curarisation can be attenuated by effective neuromuscular monitoring and adequate reversal of neuromuscular blockade.[7,14] But in patients with serious pathologies in peripheral nerve system, postoperative residual curarisation should not be avoided despite neuromuscular monitoring. Dia-

betic neuropathy with its large spectrum takes place in these diseases.

In a study of Armendáriz-Buil and colleagues about patients with DM type II it is reported that diabetic patients, even in the absence of complications, have an increased risk of residual neuromuscular blockade after rocuronium administration compared with those without diabetes. Appropriate dose and vigilant monitoring of the neuromuscular blocker are recommended.[15] In another study of Yesil and colleagues it is demonstrated that phrenic nerves are affected like peripheric nerves in prediabetic and diabetic patients and reminding phrenic neuropathy in newly onset respiratory failure in diabetic and prediabetic patients without any prior existing cardiovascular or respiratory complaints is suggested.[16] That fact gives the impression that in diabetic patients without any prior existing complaints should evolve respiratory failure intra- or postoperatively due to undiagnosed phrenic neuropathy. There are studies sustaining that neuromuscular monitoring and pharmacologic reversal of neuromuscular blockade should be routine.[7] In our literature search we contributed with studies about sugammadex being effective on preventing postoperative residual curarisation.[17] Also in our study, times to achieving an Aldrete's recovery score of 9 did not differ significantly between diabetic and nondiabetic patients.

The negative point of our study is that we designed no neostigmine-induced reversal groups in diabetic and nondiabetic patients in addition to our two sugammadex-induced reversal groups. If we had compared sugammadex groups and neostigmine groups we should prefer the argument of our study more confidentially. The time interval of our study was limited with one year because it was sustained by Duzce University as a scientific research project, so in this limited time interval we could only accomplish our two existent groups. We plan to design another study including two further neostigmine groups.

CONCLUSION

Our study indicates that times of sugammadex induced reversal from neuromuscular blockade and times to recovery are similar in diabetic and nondiabetic patients. When studies in literature about increased reversal and recovery times from neuromuscular blockade with neostigmine in diabetic patients are taken into consideration, we suggest that sugammadex is a promising alternative but further comparison studies about economic assessment are needed. Additionally, we think that our study and future studies on comparison of anticholinesterases and sugammadex in diabetic patients can enlighten recovery difficulties caused by postoperative residual curarisation.

REFERENCES

1. Robertshaw HJ, Hall GM. Diabetes mellitus: anaesthetic management. Anaesthesia 2006; 61(12):1187-90.
2. Glinka L, Onichimowski D, Sieniuta P, Korecki A. [Sugammadex--two years in clinical practice]. Anestezjol Intens Ter 2010;42(3): 155-9.
3. Lawrence DG, Locke S. Motor nerve conduction velocity in diabetes. Arch Neurol 1961;5: 483-9.
4. Abu-Shakra SR, Cornblath DR, Avila OL, Chaudhry V, Freimer M, Glass JD, et al. Conduction block in diabetic neuropathy. Muscle Nerve 1991;14(9):858-62.
5. Lamontagne A, Buchthal F. Electrophysiological studies in diabetic neuropathy. J Neurol Neurosurg Psychiatry 1970;33(4):442-52.
6. Giquel J, Rodriguez- Blanco YF, Matadial C, Candiotti K. Diabetes mellitus in anaesthesia. The British Journal of Diabetes and Vascular Disease 2012;12(2):60-4.
7. Miller RD, Ward TA. Monitoring and pharmacologic reversal of a nondepolarizing neuromuscular blockade should be routine. Anesth Analg 2010;111(1):3-5.
8. Saitoh Y, Hattori H, Sanbe N, Nakajima H, Akatu M, Murakawa M. Reversal of vecuronium with neostigmine in patients with diabetes mellitus. Anaesthesia 2004;59(8):750-4.
9. Saitoh Y, Hattori H, Sanbe N, Nakajima H, Akatu M, Murakawa M. Delayed recovery of vecuronium neuromuscular block in diabetic patients during sevoflurane anesthesia. Can J Anaesth 2005;52(5):467-73.
10. Clark CM Jr, Lee DA. Prevention and treatment of the complications of diabetes mellitus. N Engl J Med 1995;332(18):1210-7.
11. Dyck PJ, Davies JL, Clark VM, Litchy WJ, Dyck PJ, Klein CJ, et al. Modeling chronic glycemic exposure variables as correlates and predictors of microvascular complications of diabetes. Diabetes Care 2006;29(10): 2282-8.

12. Valensi P, Pariès J, Attali JR; French Group for Research and Study of Diabetic Neuropathy. Cardiac autonomic neuropathy in diabetic patients: influence of diabetes duration, obesity, and microangiopathic complications--the French multicenter study. Metabolism 2003;52(7):815-20.
13. Saitoh Y, Kaneda K, Hattori H, Nakajima H, Murakawa M. Monitoring of neuromuscular block after administration of vecuronium in patients with diabetes mellitus. Br J Anaesth 2003;90(4):480-6.
14. Stewart PA, Phillips S, de Boer HD. Residual neuromuscular blockade in myotonic dystrophy: lessons unlearned and sugammadex. Anaesth Intensive Care 2011;39(4):756-7; author reply 757.
15. Armendáriz-Buil I, Lobato-Solores F, Aguilera-Celorrio L, Morros-Díaz E, Fraile-Jiménez E, Vera-Bella J. Residual neuromuscular block in type II diabetes mellitus after rocuronium: a prospective observational study. Eur J Anaesthesiol 2014;31 (8):411-6.
16. Yesil Y, Ugur-Altun B, Turgut N, Ozturk ZA, Kuyumcu ME, Yesil NK, et al. Phrenic neuropathy in diabetic and prediabetic patients without neuromuscular complaint. Acta Diabetol 2013;50(5):673-7.
17. Abrishami A, Ho J, Wong J, Yin L, Chung F. Cochrane corner: sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. Anesth Anal 2010;110(4):1239.