doi: 10.53446/actamednicomedia.1371998

Acta Medica Nicomedia

Cilt: 7 Sayı: 2 Haziran 2024 / Vol: 7 Issue: 2 June 2024
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

EFFECTS OF REVERSAL AGENTS ON AWAKENING TIME AND BISPECTRAL INDEX AFTER SEVOFLURANE ANESTHESIA: SUGAMMADEX VERSUS NEOSTIGMINE

SEVOFLURAN ANESTEZİSİ ALTINDA REVERSE AJANLARININ BİSPEKTRAL İNDEKS VE UYANMA ZAMANINA ETKİLERİ: SUGAMMADEKSE KARŞI NEOSTİGMİN

Yasemin Masatlıoğlu[1*], Pelin Çorman Dinçer[2], Alper Kararmaz[1], Didem Dal[3], İsmail Cinel[4]

[1] Marmara University Pendik Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Türkiye. [2] Memorial Hospital, Department of Anesthesiology and Reanimation, Istanbul, Türkiye. [3] Liv Hospital, Department of Anesthesiology, İstanbul, Türkiye. [4] Acıbadem Atasehir Hospital, Department of Anesthesiology and Reanimation, Istanbul, Türkiye.

ABSTRACT

Objective: Sugammadex has widely changed clinical approach to the reversal of neuromuscular agents, owing to its particular mechanism of action. Studies on the effects of sugammadex on bispectral indeks (BİS) and clinical arousal are limited. Thus, we aimed to compare the effects of sugammadex and neostigmine on the BIS and awakening time after sevoflurane anesthesia.

Methods: A hundred patients scheduled to receive sevoflurane anesthesia under neuromuscular blockade were divided into two groups based on the reversal agent: Group S (sugammadex) and Group N (neostigmine). Anesthesia was maintained with sevoflurane, at BIS values 40-60. At the end of surgery, 2 mg/kg sugammadex (group S) or 0.03 mg/kg neostigmine (group N) was administered. Postoperative BIS and train-of-four (TOF) values, time-to-extubation, response to painful stimulus, eye opening, spontaneous movements and response to verbal commands were recorded. Additionally, the fraction of inspired sevoflurane (FiSEV) and end-tidal expired sevoflurane concentration (EtSEV) were recorded in 40 patients and analyzed in two subgroups (group S' and group N').

Results: Time to extubation, response to painful stimulus, eye opening after extubation, response to verbal commands, and spontaneous movements were significantly shorter ($p < 0.001$) in Group S than in Group N. Postoperative BIS values were significantly higher in Group S than in Group N (p <0.05). EtSEV decreased faster in group S' than in Group N' ($p < 0.05$).

Conclusion: Reversal of neuromuscular blockade with sugammadex was associated with a faster increase in BIS values and shorter awakening time compared with neostigmine.

Keywords: Bispectral index, neostigmine, postoperative recovery, sevoflurane, sugammadex.

ÖZ

Amaç: Sugammadeks özel etki mekanizması sayesinde nöromusküler ajanların etkilerinin revers edilmesine yönelik yaklaşımı büyük ölçüde değiştirmiştir. Sugammadeksin bispektral indeks (BIS) ve klinik uyarılma üzerindeki etkilerine ilişkin çalışmalar sınırlıdır. Bu nedenle sugammadeks ve neostigminin sevofluran anestezisi sonrası BIS ve uyanma süresi üzerine etkilerini karşılaştırmayı amaçladık.

Yöntem: Sevofluran anestezisi altında operasyon planlanan nöromusküler blokaj yapılacak 100 hasta revers ajanına göre 2 gruba ayrıldı: Grup S (sugammadeks) ve Grup N (neostigmin). Anestezi idamesi BIS değerleri 40-60 arasında olmak üzere sevofluran ile yapıldı. Cerrahi işlem bitiminde, 2 mg/kg sugammadeks (grup S) veya 0.03 mg/kg neostigmin (grup N) uygulandı. Postoperatif BIS ve train-of-four (TOF) değerleri, ekstübasyon, ağrılı uyarana yanıt, göz açma, spontan hareket ve sözel uyarılara cevap süreleri kaydedildi. Ek olarak, 2 alt grup (grup S' ve grup N') olarak 40 hastada inspire edilen sevofluran fraksiyonu (FiSEV) ve end-tidal sevofluran konsantrasyonu kaydedildi.

Bulgular: Ekstübasyon süresi, ağrılı uyarana yanıt, ekstübasyon sonrası göz açma, sözlü uyarılara cevap ve spontan hareket süresi Grup S'de Grup N'deki hastalardan belirgin daha kısaydı ($p < 0.001$). Postoperatif BIS değerleri Grup S'de anlamlı olarak Grup N'den yüksekti ($p < 0.05$). EtSEV Grup S' 'de Grup N' 'den daha hızlı azaldı ($p < 0.05$).

Sonuç: Neostigmin ile karşılaştırıldığında sugammadeks ile nöromusküler revers, BIS değerlerinin daha hızlı artışı ve daha kısa uyanma zamanı ile ilişkilidir.

Anahtar Kelimeler: Bispektral indeks, neostigmin, postoperatif derlenme, sevofluran, sugammadeks.

***Corresponding author/İletişim kurulacak yazar:** Yasemin Masatlıoğlu; Marmara University Pendik Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Türkiye.
Phone/Telefon: +90 (532) 5805096 **e-mail/e-posta:** yaseminmasatlioglu@gmail.com
Submitted/Başvuru: 09.09.2023 • **Accepted/Kabul:** 04.06.2024 • **Published Online/Online Yayın:** 30.06.2024

Introduction

The number of ambulatory surgeries increasing worldwide, and the need for rapid recovery from the anaesthetic agents, especially neuromuscular blocking agents, is gaining more importance. Thus, the discovery of sugammadex, a selective reversal agent for amino steroid neuromuscular blocking agents, having a high affinity for rocuronium bromide, is an important clinical development.[1] Its mechanism of action is completely different from that of other reversal agents, such as neostigmine.

Awareness and consciousness during general anaesthesia and recovery period can be detected via bispectral index (BIS) monitoring.[2-5] Neuromuscular blocking agents do not cause amnesia or unconsciousness; hence, their reversal would not result in arousal of the patient. However, Dahaba et al. demonstrated that the administrations of sugammadex and neostigmine increases the BIS values during propofol/remifentanil recovery, in the presence of some electromyographic (EMG) activity.[6] Their study highlighted the need for further evaluation of the effects of these agents on the awakening time and recovery characteristics after general anaesthesia. Based on the fact that sugammadex provides clinical benefits, such as fast and safe reversal with a low incidence of residual block, we hypothesized that it may aid in the rapid increase in BIS values by the accelerating the wash-out of the inhalational anaesthetics.

We aimed to compare the effects of sugammadex and neostigmine on BIS and awakening time after sevoflurane anaesthesia. The primary outcome of the study was the increase in BIS values and decrease in awakening time after sugammadex administration. The secondary outcome was the identification of a possible relationship between BIS values and the end inspiratory and end expiratory sevoflurane concentrations.

Methods

This prospective randomized controlled study was approved by the local ethics committee (B104İSM4340029/1009/89; 13/11/2012. Marmara University School of Medicine Ethical Committee). All patients provided written informed consent. A total of 100 consecutive patients with ASA classification I-II, aged 18-65 years, who were planned to undergo minor or moderate surgery lasting 1-3 hours, with neuromuscular blockade under sevoflurane anesthesia were enrolled in the study. Figure 1 demonstrated the CONSORT flow-diagram. The inclusion criteria were as follows: patients with no clinically manifestation of infections; no history alcohol or drug abuse, no contraindication to administration of atropine sulphate, neostigmine and sugammadex, and patients who underwent moderate (such as extremity surgeries other than tumor resections) and minor (such as varicose vein surgery, varicocelectomy, ureteroscopy) surgeries. The excluding criteria were no written informed consent, history of respiratory or cardiac arrest, cerebral hemorrhage, cerebral infarct or ischemic events during the procedure, allergy to drugs used in the study (atropine sulphate, neostigmine or sugammadex) and operative time >3 hours. All data were collected from a single center, Anesthesiology and Reanimation Department of the Marmara university.

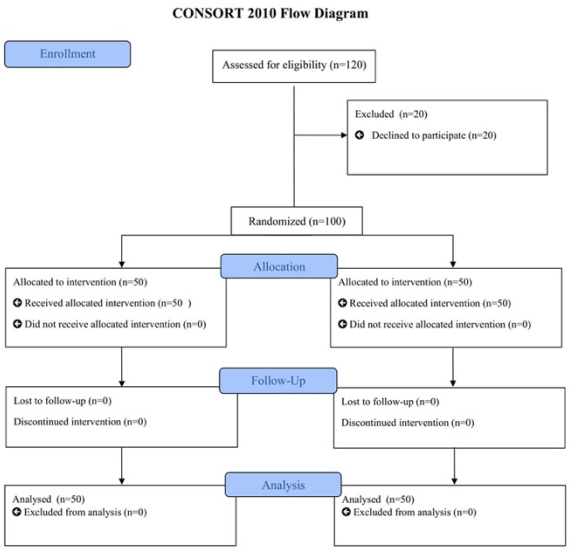

Figure 1. CONSORT flow-diagram.

Patients were randomized into two groups (n = 50) according to the administered reversal agent: sugammadex (Group S) and neostigmine (Group N). Sequentially numbered, sealed, opaque envelopes were used for randomization. All patients were premedicated with midazolam 3 mg intramuscularly, 45 minutes before the operation. Anesthesia was induced with intravenous thiopental sodium (5 mg/kg). After recording the basal train-of-four ratio (TOF%), rocuronium bromide (0.6 mg/kg) was intravenously administered for muscle relaxation. When TOF was zero, the patients were intubated orotracheally. Heart rate (HR), noninvasive mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), BIS (Bispectral Index Monitor Covidien, Dublin, Ireland) and TOF (TOF-Watch Organon, Ireland) values in all groups were recorded with 10-minutes intervals. Sevoflurane concentration was adjusted to maintain BIS values at 40-60. Patients were ventilated with a mixture of oxygen (40%) and nitrous oxide (60%). No additional neuromuscular blocking agent was administered within the last 45 minutes of the surgery.

At the end of surgery, sugammadex (2 mg/kg) or neostigmine (0.03 mg/kg) were administered intravenously in Group S and N, respectively. Sevoflurane vaporizer was switched off, the mixture of oxygen and nitrous oxide was discontinued, and patients were ventilated with oxygen (100%) manually. The injection time of the reversal agents was accepted as “time zero”. TOF and BIS values in all groups and the fraction of inspired sevoflurane concentration (FiSEV) and postoperative end tidal sevoflurane (EtSEV)

concentration in subgroups were recorded with 1-minute intervals during the subsequent 10 minutes. When TOF reached to 0.90, the patients were extubated. Time to extubation, first response to painful stimulus, eye opening, spontaneous movement and response to verbal stimulus were recorded.

In Group N, if the HR reduced by ≥5 beats after the administration of neostigmine, atropine sulfate 0.5 mg was administered intravenously. All patients were observed for potential adverse effects, including bradycardia, bronchospasm, desaturation, and allergic reactions.

During the study implementing, at first 60 patients rapid clinical awakening and fast increase in TOF and BIS values were pointedly observed. The results of the interim statistical analysis on these patients demonstrated that sugammadex provided faster clinical awakening time and faster increase in BIS values than neostigmine. We updated the study design and postoperative EtSEV and FiSEV values, as well as the difference between EtSEV and FiSEV were recorded for the remaining 40 patients were recorded with 1-minute intervals during the subsequent 10 minutes. These 40 patients were evaluated in two subgroups (n = 20) according to the administered reversal agent again: sugammadex (group S') and neostigmine (group N').

Statistical Analysis

Student's t-test was used to compare statistical significance between two sample means. Chi-square (χ^2) test was used to compare categorical variables. Repeated measures analysis of variance was used to compare timely changes in parameters in groups and between groups. Statistical significant was set at $p < 0.05$.

The sample size was calculated based on data from a similar study[1] where the BIS value increased significantly, compared to baseline values, after injection of the reversal agent. The difference in increase in the BIS values with the other agent (7.1 ± 7.5 versus 2.2 ± 3.4) was considered significant. Accordingly, the minimum sample size required was calculated as 74 (n = 37 in each group), at an alpha of 0.05 with 80% power. To account for a high possible drop-out rate, a total of 100 patients were included in the study.

Results

There was no statistically significant difference in the demographic data between Group S and N ($p < 0.05$). The operative and anesthesia time and the total amount of rocuronium bromide administered was similar in both groups (Table 1).

Table 1. Demographic data of groups.

	Group N n=50	Group S n=50	p
Age (years)	41,46 ± 11,20	38,90 ± 12,15	0,28
Gender			
Male	25 (%50)	25 (%50)	1
Female	25 (%50)	25 (%50)	1
Weight (kg)	76,88 ± 13,52	73,24 ± 13,26	0,18
Surgery time (min)	69,90 ± 33,19	72,20 ± 36,24	0,74
Anesthesia time (min)	89,20 ± 35,73	95,10 ± 40,06	0,44
Total rocuronium dose (mg)	52,14 ± 14,08	51,70 ± 14,41	0,88
Extubation time (sec)	191,28 ± 109,69	76,12 ± 54,64	<0,001*
First response to painful stimulus (sec)	355,98 ± 147,80	211,22 ± 90,61	<0,001*
Eye opening after extubation (sec)	654,42 ± 192,98	414,12 ± 152,38	<0,001*
Response to verbal stimulus (sec)	969,86 ± 294,85	608,44 ± 158,22	<0,001*
Spontaneous movement (sec)	691,74 ± 268,97	348,02 ± 128,96	<0,001*

p<0,001, Min: Minutes. Sec: Seconds

The postoperative TOF values recorded for 10 minutes were statistically higher in Group S than they were in Group N at all time points, except at 0, 8 and 9 min. Postoperative TOF values in Group S were 90% higher than those of Group N at 1 min and 4 min (Table 2).

Intraoperative MAP, HR, SpO2, BIS and TOF values were not statistically different between Group S and N at any measurement time point ($p<0.05$). The baseline and postoperative 0-minute BIS values were similar in both groups, whereas the subsequent values were higher in Group S than they in Group N ($p < 0.05$) (Figure 2).

In 90- and 20-s postoperative EtSEV was significantly lower in Group S' than it was in Group N'. There was no significance difference at other time points (Figure 3). EtSEV was completely cleared at 180 s and 240 s in the Groups S' and N', respectively (Figure 4).

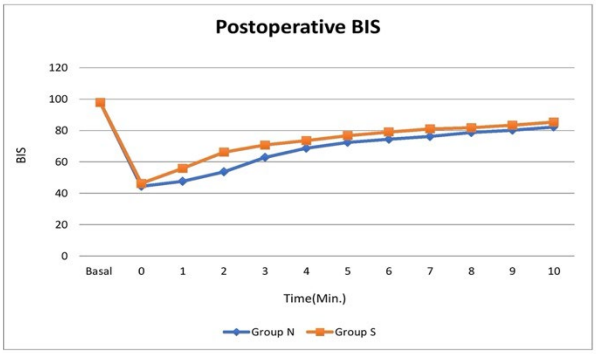

Figure 2. Postoperative BIS values. Min: Minutes

Table 2. Comparison of median postoperative TOF measurements.

	Group N (n=50)	*Group S (n=50)*	*p*
Basal TOF	113.30 ±18.27	115.06 ±18.26	0.63
Postoperative			
0. Minute	54.46 ±30.81	62,20 ±23,77	0.16
1. Minute	65.12 ±28.87	94.48 ±18.88	<0.001*
2. Minute	78.00 ±24.45	106.50 ±17.16	<0.001*
3. Minute	88.68 ±24.35	117.82 ±18.04	<0.001*
4. Minute	99.08 ±21.98	121.98 ±19.76	<0.001*
5. Minute	106.84 ±21.18	120.66 ±17.78	0.001*
6. Minute	106.78 ±16.21	119.40 ±15.77	<0.001*
7. Minute	108.38 ±16.45	121.86 ±17.21	<0.001*
8. Minute	113.34 ±19.29	120.18 ±17.74	0.07
9. Minute	114.44 ±19.40	119.48 ±15.51	0.16
10. Minute	115.63 ±19.89	121.72 ±14.10	0.08

(*: p<0,001)

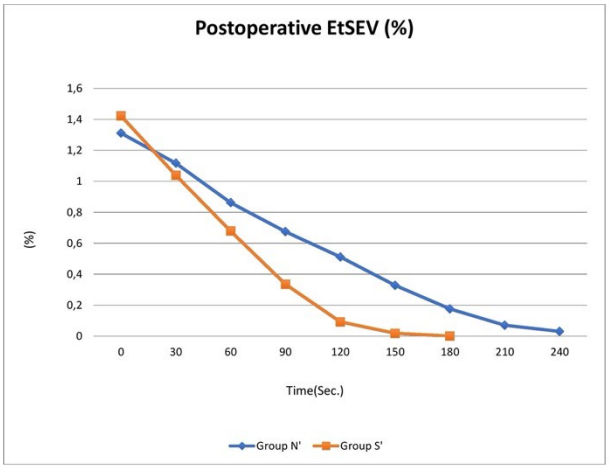

Figure 3. Postoperative EtSEV concentration (%). Sec: Seconds. EtSEV: End-tidal Sevoflurane.

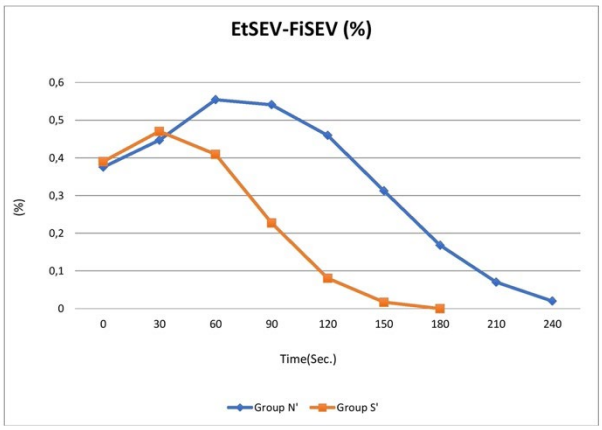

Figure 4. Postoperative EtSEV minus FiSEV concentration (%). Sec: Second. EtSEV: End-tidal sevoflurane. FiSEV: Fraction of inspiratory sevoflurane.

In Group S, extubation, first response to painful stimulus, eye opening, spontaneous movement, and response to verbal stimulus times were significantly lower than in Group N ($p < 0.001$).

All patients' HR reduced by ≥5 beats after the administration of neostigmine in Group N, were received atropine sulfate 0.5 mg intravenously. All patients in Group N received. In Group S, no adverse effect was observed.

At the end of the surgery, patients were ventilated manually and were observed for vital signs. All patients had begun to respirate spontaneously and no patients had desaturated.

Discussion

The present study showed that the reversal of neuromuscular blockade with sugammadex results in enhanced clinical awakening. This was confirmed by the quicker increase in BIS values in Group S than in Group N. These effects may be associated with the quick and powerful return of respiratory efforts, resulting in faster elimination of the inhalational agents. The BIS monitor has two components: electroencephalography and EMG. EMG measures the activity of the frontalis muscle and interferes with BIS signal, thereby influencing the BIS calculation. For example, an increase in muscle tone will cause an increase in EMG activity and BIS value. Neuromuscular blocking agents do not provide amnesia and analgesia[7]; however, some clinical trials have demonstrated that these agents could decrease BIS. [6-8] Therefore, we hypothesized that administration of any reversal agent could increase the BIS values to some degree. Anticholinesterase agents, such as physostigmine and neostigmine, reportedly induce clinical arousal via different mechanisms.[9] Physostigmine can cross the blood-brain barrier and induce some degree of arousal via a central cholinergic transmission.[10] In contrast, neostigmine cannot cross the blood-brain barrier; it stimulates the brain arousal centers via the afferentation theory.[10] In this theory, afferent signals arising from the muscle stretch receptors play an important role.[10] This theory is also applicable to sugammadex; its particular mechanism of action makes reversing muscle block quicker than by neostigmine. Dahaba et al.[6] reported that in patients with high EMG activity, both sugammadex and neostigmine were associated with a significant rise in BIS values, under propofol-remifentanil anaesthesia. Because the administration of propofol-remifentanil infusions was not discontinued at the time of reversal, they concluded that the rise in BIS values was related to increased EMG

activity and not to the arousal itself. [6,11] They suggested to take into consideration EMG activity reappearance after administration of the reversal agents.[6] Studies on the effects of sugammadex on BIS and clinical arousal are limited. Furthermore, they focused on the effects of reversal agents on BIS under intravenous, rather than inhalational, anaesthesia. Therefore, we compared the effects of sugammadex and neostigmine on the BIS values and awakening time after sevoflurane anaesthesia.

Rapid clinical awakening and fast increases in TOF and BIS values were subjectively observed in the first 60 patients during the study period. The interim statistical analysis results demonstrated that sugammadex provided faster clinical awakening and increase in BIS values than neostigmine did. For the remaining 40 patients, the postoperative EtSEV and FiSEV values and the difference between them were also recorded and analysed. The results confirmed the rapid recovery of muscle activity due to accelerated anaesthetic gas elimination. After sugammadex administration, the EtSEV in Group S' reached zero faster than it did in Group N' (240 vs. 180 s), implying a quicker wash-out of sevoflurane in group S'. The quick wash-out theory was also supported by the lower postoperative FiSEV values in Group S' than in Group N' (90 s vs. 120 s) after the discontinuation of the anaesthetic gas. Effective ventilation is an important factor in the reversal of the effects of volatile anaesthetic agents. This phenomenon may be explained by the faster return of muscle activity with sugammadex due to its particular mechanism of action. Anaesthetic agent elimination in Group S' may have been facilitated by the effective ventilation, resulting in the difference between the two groups. In our study, sevoflurane was discontinued at the end of the surgery to allow for the comparison of the net effects of sugammadex and neostigmine on BIS.

Sugammadex provides faster neuromuscular recovery than neostigmine.[12] However, in one study, sugammadex and neostigmine effectively and comparably reversed a rocuronium-induced shallow block in 2 min at a TOF of 0.5. In our study, although there was no significant difference in the immediate postoperative TOF values between the study groups, the time to reach a TOF of 0.9 was faster with sugammadex than with neostigmine (1 min vs. 4 min). This may be attributed to the administration of clinically recommended doses, which were higher doses than that used in the study by Schaller et al.[13] (2 mg/kg vs. 0.22 mg/kg). Time-to first-response to painful stimulus, eye opening, and reaction to verbal stimulus were significantly shorter in patients administered sugammadex than in those administered neostigmine, demonstrating better clinical recovery characteristics with sugammadex. Moreover, administration of neostigmine after the total recovery from neuromuscular block decreases the upper airway expanding volume and activity of the diaphragm and genioglossus muscle due to negative pharyngeal pressure, causing impaired respiration.[14-15] This was not the case in our study; the time-to-TOF≥0.9 was 4 min in group N, implying that muscle activity was not completely recover, and thereby avoiding the negative effect of neostigmine.

This study had some limitations. One limitation was that the respiratory parameters, such as tidal volume, respiratory rate, and inspiratory to expiratory ratio, were not recorded after the administration of reversal agents. Furthermore, the EMG component was not taken into consideration in the evaluation of BIS values. Therefore, we could not demonstrate both the effects of increased sevoflurane wash-out and the reflection of muscle stimulation on BIS. Fast recovery time leads to early discharge from the OR, decreased complication rates, and increased patient satisfaction.[16-17] Another limitation of the study was that we did not record the times spent in the recovery room because of various logistic issues of our center prevented the recording of time spent in the PACU.

The study also had its strengths. Increased elimination of the anesthetic gas from the respiratory system as a result of increased respiratory effort, the quick wash-out theory, was the proposed theory in the study. Sugammadex administration resulted in rapid clinical awakening and increase in BIS. Furthermore, the anesthesia used was opioid-free, excluding the possibility of opioid-related respiratory depression. Therefore, the effects of both sugammadex and neostigmine on awakening were more clearly studied. For example, in the study by Dahaba et al., remifentanil infusion was continued for 10 min after the administration of the reversal agents, which may have interfered with the ventilation and awakening process.[6] Eliminating the possibility of opioid-related respiratory depression, may affect the time spent in recovery room and PACU, and also the length of the hospital stay. This may help discharging the patient safely from PACU to ward. Apart from this, rapid awakening and stronger respiration may provide safer recovery especially in patients predicted muscle weakness. As mentioned in a recently published systematic review "Recent evidence indicates that sugammadex plays a role in accelerating postoperative recovery, specifically with regard to pulmonary functions".[18] Further investigations are needed to determine the aforementioned issues.

In conclusion, sugammadex provides faster neuromuscular recovery than neostigmine and indirectly increases BIS values through eliminating inhalational anesthetic agent. Anesthesia providers can prefer sugammadex to neostigmine for faster and safe postoperative recovery. Further investigations may determine the cost effectivity of sugammadex in faster postoperative recovery.

Compliance with Ethical Standards

Marmara University School of Medicine Ethical Committee approved this study (B104İSM4340029/1009/89; 13/11/2012). Informed consent was obtained from all participants.

Conflict of Interest
The author declares no conflicts of interest.

Author Contribution
All the authors equally contributed to this work.

Financial Disclosure
None

References

1. Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. Anesth Analg. 2007;104(3):575-581. doi: 10.1213/01.ane.0000244594.63318.fc
2. Rosow C, Manberg PJ. Bispectral index monitoring. Anesthesiol Clin North Am. 2001;19(4):947-xi. doi:10.1016/s0889-8537(01)80018-3.
3. Kaskinoro, K. (2013). The Effects of Anesthetic Induced Loss of Consciousness on Quantitative Electroen Cephalogram, and Bispectral and Spectral Entropy Indices. Studies on Healthy Male. Publications of the University of Turku (D 1075). Retrieved from: https://urn.fi/URN:ISBN:978-951-29-5425-4.
4. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet. 2004;363(9423):1757-1763. doi:10.1016/S0140-6736(04)16300-9.
5. Avidan MS, Zhang L, Burnside BA, et al. Anesthesia awareness and the bispectral index. N Engl J Med. 2008;358(11):1097-1108. doi:10.1056/NEJMoa0707361
6. Dahaba AA, Bornemann H, Hopfgartner E, et al. Effect of sugammadex or neostigmine neuromuscular block reversal on bispectral index monitoring of propofol/remifentanil anaesthesia. Br J Anaesth. 2012;108(4):602-606. doi:10.1093/bja/aer495
7. Flood P. The importance of myorelaxants in anesthesia. Curr Opin Pharmacol. 2005;5(3):322-327. doi: 10.1016/j.coph.2004.12.009
8. Ledowski T, Hillyard S, O'Dea B, Archer R, Vilas-Boas F, Kyle B. Introduction of sugammadex as standard reversal agent: Impact on the incidence of residual neuromuscular blockade and postoperative patient outcome. Indian J Anaesth. 2013;57(1):46-51. doi:10.4103/0019-5049.108562
9. Vasella FC, Frascarolo P, Spahn DR, Magnusson L. Antagonism of neuromuscular blockade but not muscle relaxation affects depth of anaesthesia. Br J Anaesth. 2005;94(6):742-747. doi:10.1093/bja/aei120.
10. Lanier WL, Iaizzo PA, Milde JH, Sharbrough FW. The cerebral and systemic effects of movement in response to a noxious stimulus in lightly anesthetized dogs. Possible modulation of cerebral function by muscle afferents. Anesthesiology. 1994;80(2):392-401. doi:10.1097/00000542-199402000-00019.
11. Aho AJ, Kamata K, Yli-Hankala A, Lyytikäinen LP, Kulkas A, Jäntti V. Elevated BIS and Entropy values after sugammadex or neostigmine: an electroencephalographic or electromyographic phenomenon? Acta Anaesthesiol Scand. 2012;56(4):465-473. doi:10.1111/j.1399-6576.2011.02647. x.
12. Illman HL, Laurila P, Antila H, Meretoja OA, Alahuhta S, Olkkola KT. The duration of residual neuromuscular block after administration of neostigmine or sugammadex at two visible twitches during train-of-four monitoring. Anesth Analg. 2011;112(1):63-68. doi:10.1213/ANE.0b013e3181fdf889.
13. Schaller SJ, Fink H, Ulm K, Blobner M. Sugammadex and neostigmine dose-finding study for reversal of shallow residual neuromuscular block. Anesthesiology. 2010;113(5):1054-1060. doi:10.1097/ALN.0b013e3181f4182a
14. Murphy G., Boer H. D. D., Lars I. E., Miller R. D. Reversal (Antagonism) of Neuromuscular Blockade. In: Gropper M. A. (Ed.). Miller's Anesthesia. 9th ed. Philadelphia, PA: Elsevier; 2020:849.
15. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. Anesthesiology. 1997;86(4):836-847. doi:10.1097/00000542-199704000-00014.
16. Bilen-Rosas G, Karanikolas M, Evers A, Avidan M. Impact of anesthesia management characteristics on severe morbidity and mortality: are we convinced? Anesthesiology. 2006;104(1):204-206. doi:10.1097/00000542-200601000-00033.
17. Gu X, Gao R, Li P, et al. Sugammadex enhances recovery after abdominal surgery in cancer patients: a real-world, observational study. Ann Palliat Med. 2021;10(12):12566-12574. doi:10.21037/apm-21-3398.
18. Liu, HM., Yu, H., Zuo, YD. et al. Postoperative pulmonary complications after sugammadex reversal of neuromuscular blockade: a systematic review and meta-analysis with trial sequential analysis. BMC Anesthesiol 23, 130 (2023). https://doi.org/10.1186/s12871-023-02094-0.