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Reversal effect of sugammadex in isoflurane, sevoflurane, and desflurane induced anesthesia: a randomized-controlled clinical study

İsofloran, sevofluran ve desfluran ile sağlanan anestezide sugamadeksin geri döndürücü etkisi: randomize kontrollü klinik çalışma

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Abstract

Aim. In the present study, we aimed to compare the effects of isoflurane, sevoflurane and desflurane on the effect of sugammadex in reversing neuromuscular block. **Methods.** Ninty patients who were planned to undergo elective lower abdominal surgery under general anesthesia were included and were randomly assigned to 6 groups of 15. After intubation, group I1 and I2 patients received isoflurane, group S1 and S2 patients received sevoflurane and Group D1 and D2 patients received desflurane volatile anesthetic at 1.25 MAC. TOF values were recorded at the 10th, 20th, 30th, 60th and 90th minutes of the operation by an anesthetist blind to the groups. Group I1, S1 and D1 patients were given 2 mg kg-1 sugammadex and group I2, S2 and D2 patients were given neostigmine after the second response to TOF following the latest rocuronium dose was observed again. In each patient, the time elapsed between sugammadex administrations and 10%, 25% and 90% TOF ratio was recorded. **Results.** There was no difference among the groups in terms of the time elapsing to reach 10% TOF values while the times elapsing to reach 25% and 90% TOF were found to be the shortest in sevoflurane group and the longest in isoflurane group. **Conclusion.** We think that inhalation anesthetics used in general anesthetic practice, have different effects on the reversal action of sugammadex in neuromuscular blockade and that reversal effect of sugammadex is faster in patients receiving sevoflurane.

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Keywords: Sugammadex, train of four, isoflurane, desflurane, sevoflurane, rocuronium

Özet

Amaç. Bu çalışmada sugamadeksin nöromusküler blokör etkisini geri döndürücü etkisine isofluran, sevofluran ve desfluranın etkilerini kıyaslamayı amaçladık. **Yöntem.** Genel anestezi altında elektif alt batın operasyonu planlanan 90 hasta çalışmaya alındı ve rasgele 15 er kişilik 6 gruba ayrıldı. Entübasyondan sonra, grup I1 ve I2 hastalar izofluran, grup S1 ve S2 hastalarda sevofluran ve grup D1 ve D2 hastalarda desfluran volatil anestetik olarak 1.25 MAC den aldı. TOF değerleri gruplardan habersiz bir anestezist tarafından operasyonda 10, 20, 30, 60. ve 90. dakikalarda kaydedildi. I1, S1 ve D1 grubu hastalara son rokuronyum dozunun ardından TOF a alınan ikinci yanıtın tekrar gözelnmesi sonrası 2 mg kg-1 sugamadeks ve I2, S2 ve D2 grubu hastalarada yine aynı şekilde neostigmine verildi. Her hastaya, sugamadeks uygulanması ile % 10,% 25 ve% 90 TOF oranı arasındaki süre kaydedildi. **Bulgular.** Gruplar arasında TOF un %10 a ulaşmasına kadar geçen sure açısından fark bulunamazken TOF un % 90 a ulaşma süresi sevofluran grubunda kısa ve izofluran grubunda en uzun olduğu bulunmuştur. **Sonuç.** Genel anestezi pratiğinde kullanılan inhalasyon anesteziklerinin sugamamdeksin nöromusküler blokaj geri döndürücü etkinliğini farklı oranlarda etkilediğini ve sevofluran anestezisinde sugamadeksin geri döndürücü etkisinin en hızlı olduğunu düşünmekteyiz.

Anahtar Sözcükler: sugamadeks, dörtlü cevap, isofluran, desfluran, sevofluran, roküronyum

Introduction

Reversal of neuromuscular blocker drugs accelerates recovery and prevents residual curarisation [1]. Cholinesterase inhibitors are commonly used to reverse the action of neuromuscular blocker drugs. These drugs are nonselective and have many side effects such as bradycardia, hypersalivation, residual curarisation. These unwanted effects pushed the authors to find out new alternatives to cholinesterase inhibitors [2, 3]. Sugammadex is a novel selective relaxant binding drug which is a satisfactory alternative drug to cholinesterase inhibitors. It reverses steroidal nondepolarizing neuromuscular blocker drugs, mostly rocuronium [4, 5].

It is a known fact that inhalation anesthesia produces some neuromuscular relaxation even though not as high as the one with neuromuscular blocker drugs [6, 7]. Various studies have been undertaken thinking that volatile anesthetics may be influencing the relaxation effect of neuromuscular blocker drugs when used together and it has been found that several volatile anesthetics affect neuromuscular blocker drugs and that there is no significant difference among these effects [7, 8]. In the light of this information, it may be postulated that volatile anesthetics may have an effect in reversing the action of neuromuscular blocker agents too. Although there are studies showing how volatile anesthetics affect the reverse action of neostigmine, our literature review revealed no studies showing or comparing the effects of isoflurane, sevoflurane and desflurane on the reverse action of sugammadex.

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In the present study, our aim was to compare the effects of isoflurane, sevoflurane and desflurane on the effect of sugammadex in reversing neuromuscular block. Besides we studied neostigmine to compare it with sugammadex. We hypothesized that volatile anesthetics may have an effect on the action of sugammadex and that there is no difference among them.

Materials and Methods

Ninty patients (aged between 18-60) in ASA I-II risk group and who were planned to undergo elective lower abdominal surgery under general anesthesia were included in the present randomized clinical study after getting approval from the institutional ethical committee and written consents from the patients. Those having major organ dysfunction, atrioventricular block, obesity (those having a body mass index over 30%), myasthenia gravis, using hypnotic analgesia, opioid analgesia or magnesium sulphate, having a calcium channel blocker treatment, having a pregnancy and using anticoagulants, using oral contraceptives, having a history of using toremifene and flucloxacilin and having no consent to participate in the study were excluded.

During postoperative examination, patients were grouped into 6 groups. Each group, consisting of 15 patients, was randomly assigned by sealed enveloped method. After admission to the operating room, electrocardiography, heart rate, average arterial blood pressure and peripheral oxygen saturation (SpO2) were monitorized. The level of neuromuscular block was measured by an acceleromyography (TOF-Watch©-SX Monitor, Organon Teknika, Duplin, Ireland). Pre-induction demographic data and baseline heart rate, average arterial blood pressure and peripheral oxygen saturation values of the patients were recorded. All the records were kept by an anesthetist blind to the patient groups.

In all the groups, the doses used for the induction of anesthesia were 6 mg kg-1, 1 mcg kg-1 and 0.6 mg kg-1 for thiopental sodium, fentanyl and rocuronium, respectively. Baseline train of four (TOF) value of each patient was measured and recorded before administration of muscle relaxant. After administration of muscle relaxant, the patients were intubated using adequate endotracheal tube once the TOF count was zero. After confirming the localization of the tube, group I1 and I2 patients received isoflurane, group S1 and S2 patients received sevoflurane and Group D1 and D2 patients received desflurane volatile anesthetic at 1.25 MAC. In all the groups, TOF was monitored throughout the operation and additional rocuronium bolus of 0.15 mg kg-1 was administered when TOF value was %25. TOF values were recorded at the 10th, 20th, 30th, 60th and 90th minutes of the operation by an anesthetist blind to the groups and present at the operating room only during the recording procedure.

Group I1, D1 and S1 patients were given 2 mg kg-1 sugammadex and group I2, D2, and S2 patients were given neostigmine after the second response to TOF following the latest rocuronium dose was observed again. In each patient, the time elapsed between sugammadex administrations and 10%, 25% and 90% TOF ratio was recorded.and those having a TOF value of 0.90 were extubated. The initial response measured by TOF values during the operation, how many minutes it took to reach TOF 10% and TOF 25% after induction and total rocuronium consumption were recorded.

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The data were analyzed with SPSS v.14 (SPSS Inc, Chicago, IL, USA). Kruskal-Wallis test, Mann Whitney U test and chi-square tests were used to evaluate the data as appropriate. Statistical significance was taken as 0.05.

Results

When the patients were evaluated in terms of demographic features, no difference was found among the groups (Table 1, Table 2).

Table 1. Demographic data of study groups used sugammadex.

	Group I1 (n=15)	Group D1 (n=15)	Group S1 (n=15)
Age (y)	42.9±11.0	37.5±11.7	42.6±8.1
Height (cm)	165.4±7.1	164.0±7.2	150.8±8.7
Weight (kg)	77.8±11.5	76.4±13.5	72.7±15.52
Operation time (min)	104.6±49.3	72.4±38.3	83.1±29.7
All data are expressed as mean ± SD. There was no statistical significance among the study groups with regard to age, height, weight, and operation time (p>0.05).			

Table 2. Demographic data of study groups used neostigmine.

	Group I2 (n=15)	Group D2 (n=15)	Group S2 (n=15)
Age (y)	42.0±9.4	36.1±12.5	37.2±10.3
Height (cm)	164.0±2.4	171.6±2.6	168.8±2.2
Weight (kg)	73.8±2.2	79.9±2.5	77.6±2.8
Operation time (min)	103.2±49.3	97.1±38.3	119.6±29.7
All data are expressed as mean ± SD. There was no statistical significance among the study groups with regard to age, height, weight, and operation time (p>0.05).			

When the patients in all 6 groups were compared in terms of heart rate, mean arterial blood pressure and peripheral oxygen saturation (SpO2), there was no significant difference among the groups.

In terms of total rocuronium consumption, no difference was found among the groups. There was no difference among the groups, when the patients were compared in terms of intra-operative TOF values (Table 3).

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Table 3. Intraoperative TOF data of study groups used sugammadex.

	Group I1 (n=15)	Group D1 (n=15)	Group S1 (n=15)
10 min	0.06±0.25	0.26±0.59	0.00±0.00
20 min	0.00±0.00	0.20±0.56	0.00±0.00
30 min	0.06±0.25	0.25±0.45	0.00±0.00
60 min	0.20±0.77	0.85±0.89	1.22±3.66
90 min	0.00±0.00	0,00±0.00	0.00±0.00
All data are expressed as mean ± SD. There was no statistical significance among the study groups with regard to age, height, weight, and operation time (p>0.05).			

Reversal effects of sugammadex was clearly found shorter than neostigmine between groups (p<0.05).

When the patients in all the groups were compared in terms of the time to reach 10%, 25% and 90% TOF after sugammadex administration, there was no difference among the groups in terms of the time elapsing to reach 10% TOF values while the times elapsing to reach 25% and 90% TOF were found to be the shortest in sevoflurane group and the longest in isoflurane group (p<0.05) (Table 4).

Table 4. Time to reach TOF 10%, 25%, 90% in study groups used sugammadex.

	Group I1 (n=15)	Group D1 (n=15)	Group S1 (n=15)
Time to TOF 10% (min)	0.86±0.39	0.84±1.24	0.60±0.42
Time to TOF 25% (min)	1.26±0.59	1.04±1.53	0.86±0.51[a]
Time to TOF 90% (min)	3.06±1.43	2.65±3.66	1.93±0,96[b]
All data are expressed as mean ± SD. [a, b]P<0.05 vs. Groups I1 and D1.			

Discussion

In the present study, the effects of isoflurane, sevuflurane and desflurane on the reversal effect of sugammadex administered at the end of anesthesia were investigated. 2 mg kg-1 sugammadex is an effective and safe dose accepted in many studies and thus the same dose was used in our study too [9]. Studies carried out have shown that the time elapsing to reach TOF 0.9 shortens, namely the reverse action is accelerated as the dose of sugammadex increases [9]. Similarly, in our study, total cumulative dose of rocuronium was recorded for each patient and no difference was found among the groups in terms of rocuronium doses.

Before mentioning the effects of volatile anesthetics on the antagonization of neuromuscular blockers, it would be of benefit to mention about the studies showing what type of effects either inhalation anesthetics or intravenous anesthetics have on neuromuscular blockers. In a study on the effects of isoflurane and desflurane on the neuromuscular blocker effects of rocuronium, Wulf et al. [6] found more pronounced TOF T1 depression with desflurane or sevoflurane but did not find any difference in the duration of the block or recovery from block.

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In a study published in 1998, Lowry et al. [10] investigated the effects of sevoflurane, isoflurane and propofol on rocuronium and stated that sevuflurane potentialized the effect of rocuronium and recommended monitorization of TOF in sevoflurane anesthesia. In a study conducted on dogs, Kastrup et al. [11] showed that sevoflurane produced more potentiation of atracurium compared to propofol. Kumar et al. [7] found in a study conducted in 1996 that potency of rocuronium during anesthesia with desflurane and isoflurance was not different but the time for TOF ratios to reach 0.7 was longer- but not significantly different- with desflurane when compared to isoflurane. As shown in these and similar studies, volatile anesthetics potentiated neuromuscular blocker drugs.

In the literature, there are many studies showing the effects of volatile anesthetics on the revers effect of neostigmine which is an old and commonly used neuromuscular blocker antagonist. Sutcliffe et al. [12] evaluated antagonism using neostigmine and glycopyrrolate in isoflurane and sevoflurane induced anesthesia and found no difference in antagonism profile in terms of volatile anesthetics. Reid et al. [13] examined the influence of sevoflurane and isoflurane during reversal with neostigmine and found a delay in recovery from block. As seen in these studies, volatile anesthetics delay antagonism of neuromuscular block with neostigmine.

Together with the introduction of sugammadex into clinical practice, various studies comparing efficacy of sugammadex and neostigmine and finding a superior efficiency with sugammadex started to take place in the literature. In a study on 50 patients, Illman et al. [14] compared efficacy of neostigmine and sugammadex through TOF and found that reversal of neuromuscular block with sugammadex was safer and faster than reversal with neostigmine. Khuenl-Brady et al. conducted a multicenter, prospective and randomized trial at 13 centers and found that the reversal time was seven times faster with sugammadex compared to neostigmine [15]. Recovery to a TOF ratio of 0.9 is a gold standard. Thus, just like in our study, time to achieve a TOF ratio of 0.9 was employed in such studies too.

In a study conducted by Flockton et al. [16] on 85 patients in 2008, neostigmine and sugammadex were used for cisatracurium-induced neuromuscular block and the time from the start of administration of reversal agent to recovery of the TOF ratio to 0.9 was found to be 4.7 times faster with sugammadex than with neostigmine. In their study, Sugammadex and neostigmine were stated to be safe and well tolerated too. Lemmens et al. [17] compared neostigmine and sugammadex in reversal of profound vecuronium-induced neuromuscular block in patients under sevoflurane anesthesia and found that recovery from profound blocks was significantly faster with sugammadex compared to neostigmine.

The question of how different anesthetics affect the reversal action of sugammadex has been occupying researchers. Vanacker et al. [2] stated that although sugammadex was equally effective under propofol and sevoflurane anesthesia, safety profile of sugammadex was more favourable under propofol. In a study conducted on 52 patients between 2006-2007, Rex et al. [18] induced blockage by 0.6 mg kg-1 rocuronium followed by continuous infusion of rocuronium, administered a single dose of 4 mg kg-1 sugammadex to both groups and found that sugammadex was well tolerated in both groups and there was no significant difference in terms of recovery of the TOF ratio to 0.9.

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Pühringer et al. [19] stated that sugammadex could provide rapid and safe reversal of rocuronium induced neuromuscular block. In another study where time to recovery of TOF ratio to 0.9 was evaluated in randomly selected 176 patients receiving a high-dose of muscle relaxant during propofol anesthesia and then receiving 2, 4, 8, 12 or 16 mg kg-1 sugammadex or placebo at the 3rd and 15th minute, Pühringer et al. found that sugammadex was well tolerated by the patients and led to better results compared to placebo. They faced no problems other than QT prolongation in one patient and abnormal arterial blood pressure lasting 15 minutes in another one.

In conclusion, inhalation anesthetics isoflurane, sevoflurane and desflurane used in general anesthetic practice may have different effects on the reversal action of sugammadex in neuromuscular blockade and reversal effect of sugammadex can be faster in patients receiving sevoflurane.

Conflict of Interest

The authors declare that no conflicts of interest.

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