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The effect of sugammadex on postoperative cognitive function and recovery

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Abstract
Background and objective: Sugammadex is the first selective relaxant binding agent. When compared with neostigmine, following sugammadex administration patients wake earlier and have shorter recovery times. In this study, we hypothesized that fast and clear awakening in patients undergoing general anesthesia has positive effects on cognitive functions in the early period after operation.
Methods: Approved by the local ethical committee, 128 patients were enrolled in this randomized, prospective, controlled, double-blind study. Patients were allocated to either Sugammadex group (Group S) or the Neostigmine group (Group N). The primary outcome of the study was early postoperative cognitive recovery as measured by the Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE). After baseline assessment 12–24 h before the operation. After the operation, when the Modified Aldrete Recovery Score was ≥ 9 the MMSE and 1 h later the MoCA tests were repeated.
Results: Although there was a reduction in MoCA and MMSE scores in both Group S and Group N between preoperative and postoperative scores, there was no statistically significant difference in the slopes ($p > 0.05$). The time to reach TOF 0.9 was 2.19 min in Group S and 6.47 min in Group N ($p < 0.0001$). Recovery time was 8.26 min in Group S and 16.93 min in Group N ($p < 0.0001$).
Conclusion: We showed that the surgical procedure and/or accompanying anesthetic procedure may cause a temporary or permanent regression in cognitive function in the early

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PALAVRAS-CHAVE
Sugamadex;
Neostigmina;
Disfunção cognitiva
no pós-operatório;
MMSE;
MoCA

O efeito de sugamadex sobre a função cognitiva e recuperação no pós-operatório

Resumo

Justificativa e objetivo: Sugamadex é o primeiro agente de ligação relaxante seletivo. Após a administração de sugamadex, os tempos de despertar e de recuperação dos pacientes são menores, em comparação com neostigmina. Neste estudo, a hipótese foi que um despertar mais rápido e claro dos pacientes submetidos à anestesia geral possui efeitos positivos sobre as funções cognitivas no pós-operatório imediato.

Métodos: Após a aprovação do Comitê de Ética local, 128 pacientes foram incluídos neste estudo prospectivo, randômico, controlado e duplo-cego. Os pacientes foram designados para o grupo sugamadex (Grupo S) ou grupo neostigmina (Grupo N). O desfecho primário do estudo foi a recuperação cognitiva no pós-operatório imediato, de acordo com a mensuração da Avaliação de Montreal da Função Cognitiva (MoCA) e com o Mini Exame do Estado Mental (MMSE). Após a avaliação inicial 12–24 h antes da operação. Após a operação, quando o escore de Recuperação de Aldrete modificado era ≥ 9, o teste MMSE e, uma hora depois, o teste MoCA foram repetidos.

Resultados: Embora tenha havido uma redução nos escores de MoCA e MMSE tanto no Grupo S quanto no Grupo N, entre os escores pré- e pós-operatório, não houve diferença estatisticamente significativa nas reduções (p > 0,05). O tempo para atingir TOF 0.9 foi de 2,19 min no Grupo S e de 6,47 min no Grupo N (p < 0,0001). O tempo de recuperação foi de 8,26 min no Grupo S e de 16,93 min no Grupo N (p < 0,0001)

Conclusão: Mostramos que o procedimento cirúrgico e/ou procedimento anestésico de acompanhamento pode causar uma regressão temporária ou permanente da função cognitiva no pós-operatório imediato. No entanto, um desempenho cognitivo melhor não pode ser provado no grupo sugamadex em comparação com o grupo neostigmina.

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Introduction

Patients who undergo major surgery with general anesthesia may experience memory impairment and regression of high-executive functions such as ordering, planning, and organization after the operation.[1] This intellectual and cognitive worsening is known as postoperative cognitive dysfunction (POCD). POCD often creates temporary cognitive impairment but, especially in older patients, it may take the form of permanent decline.[1] To date, controlled studies and animal models have not established diagnostic criteria for POCD, and its etiology is not fully understood.[2–4] However, animal studies have provided strong evidence that exposure to anesthetic agents may cause permanent learning and memory impairment.[5–8]

Sugammadex (Bridion®, Merck Sharp and Dohme (MSD), Oss, The Netherlands) is a rapid and selectively effective aminosteroid agent that has recently entered use. Through rocuronium and vecuronium encapsulation, it causes rapid recovery independent of the time of administration.[9–13] Compared to patients given neostigmine to recover, patients given sugammadex have been observed to recover with a clearer level of consciousness.

In this study, we hypothesized that fast and clear awakening in patients undergoing general anesthesia has positive effects on cognitive functions in the early period after operation. To test this hypothesis, postoperative cognitive functions of patients were evaluated, comparing those given neostigmine or sugammadex for revival after general anesthesia with rocuronium-based neuromuscular block.

Method

This randomized, prospective, controlled, double-blind study was approved by the Bülent Ecevit University Practice and Research Hospital Ethics Committee (2012/07-7). The study included patients with planned operations under general anesthesia (abdominal surgery; upper extremity orthopedic interventions; gynecology; plastic surgery; urology; ear, nose, and throat; and spinal surgery operations lasting at least 60 min) who could read and write Turkish, were between 18 and 60 years of age, and had American Society of Anesthesiologists (ASA) scores of I or II.

Exclusion criteria were congestive heart failure, renal and hepatic failure, adrenal failure, hormonal disorder,

diabetes mellitus (DM), neuropsychiatric disease, chronic alcohol or drug addiction, Glasgow Coma Scale (GCS) <15, history of cardiopulmonary arrest or stroke in the previous 12 months, history of previous operation under general anesthesia, emergency surgery, and postoperative Mini-Mental State Examination[14] (MMSE) score <23 and Montreal Cognitive Assessment[15] (MoCA) score <21.

After receiving informed patient consent, the sugammadex (Group S) and neostigmine (Group N) groups were created using the closed-envelope method. To evaluate cognitive functions, the MMSE and MoCA tests were carried out by the same neurology expert blinded to the patient's group assignment. All patients were visited 12–24 h before the operation. The patients' educational level, accompanying diseases, and demographic information were recorded. Before the operation the patients' memory, attentive executive functions, and motor skills were evaluated with the MMSE and MoCA tests as a control cognitive evaluation (T_0). After the operation, in the PACU, when the Modified Aldrete Recovery Score[16] (MAS) was ≥9 the MMSE and 1 h later the MoCA tests were repeated (T_1). Neither group was given premedication. During the operation mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO_2), bispectral index (BIS), and adductor muscle and nasopharyngeal temperature were monitored and recorded. For neuromuscular transmission monitoring a TOF-WATCH® SX (Organon Teknika B V, Netherlands) device was used. The temperature of the operating room was set to 21–25 °C. The patients were covered, and the skin temperature of the thenar region was monitored to ensure it did not fall below 32 °C. All patients were given intravenous (IV) fentanyl (1 μg/kg) and propofol (2 mg/kg) for anesthesia induction. When BIS values were 40–60, TOF device calibration was completed and three consecutive single twitch control values were recorded. Then, IV 0.5 mg/kg rocuronium was administered and the interval until TOF values reached 0 (TOF_0) was recorded. When TOF_0 was reached the patients were intubated. To maintain anesthesia all patients were given 50:50 O_2/N_2O and 2% sevoflurane titrated to maintain BIS values between 40 and 60. During the operation, when TOF values were 25% (TOF_{25}), a dose of one quarter of the initial dose of rocuronium was administered. At the end of the operation, when TOF_{25} was reached, Group S was given IV 2 mg/kg sugammadex and Group N was given IV 0.03 mg/kg neostigmine + 0.01 mg/kg atropine. Patients were extubated when their TOF values reached 90% (TOF_{90}). The interval between TOF_{25} and TOF_{90} was recorded in seconds (TOF_{25-90}). During the operation, amounts of additional medication and total rocuronium were recorded. After skin suturing was finished, anesthetic gases were stopped in both groups. This time was recorded as the end of anesthesia. The time from when anesthetic gases were stopped until MAS ≥ 9 was recorded as the recovery period. After the operation, patients were transferred to the PACU. All patients were given IV 1 mg/kg tramadol after the skin incision was finished for postoperative pain relief. At 20, 40, 60, and 120 min post-operation, visual analog scores[17] (VAS) were recorded. When VAS > 4 a non-steroidal anti-inflammatory analgesic agent was administered and recorded.

The primary outcome of the study was early postoperative cognitive recovery as measured by the MoCA and MMSE. The secondary outcome was time from the start of the reversal administration to the recovery of a ratio of 0.9 in patients receiving rocuronium as NMBA during general anesthesia for a surgical procedure.

Power analysis

To test the significance of differences between repeated measures in dependent groups the conventional effect size required for the t test is assumed to be medium ($d = 0.50$), so for the study to have 80% power it was calculated that both groups needed a minimum sample size of 128 ($n = 64$).[18]

Statistical analysis

Statistical analyses for this study were completed using the SPSS for Windows 15.0 software package. Descriptive statistics were used (mean, median, standard deviation, minimum and maximum values) to evaluate data. Measurement values are given as means and standard deviations. Categorical variables (number values) are given as numbers and percentages. The chi-square test was used to compare categorical variables. The Levene's test was used to evaluate the homogeneity within groups for parametric conditions. If the results of the homogeneity tests showed that parametric conditions were met, mixed ANOVA was used for comparisons between groups; if parametric conditions were not met, the Wilcoxon signed-rank test was used to compare measurement values before and after, and the Mann–Whitney U test was used for comparisons of independent groups. Significance was accepted at $p < 0.05$.

Results

This study was conducted from September 2012 to July 2013 with 128 patients. Thirty-eight patients were excluded because their MMSE and MoCA target scores were low, and three were excluded because they could not be extubated at the end of the operation. Of the 87 patients included in the study, 48.2% ($n = 42$) were in Group S and 51.8% ($n = 45$) were in Group N.

The demographic characteristics of the patients are presented in Table 1. The total amount of rocuronium consumed was 67.02 ± 15.85 mg in Group S and 62.44 ± 11.65 mg in Group N (Table 1). There was a statistically significant difference in average age between the groups ($p < 0.05$). There were no significant differences between the groups in weight, BMI, duration of operation, duration of anesthesia, and total amount of rocuronium consumed ($p > 0.05$).

The time to reach TOF 0.9 was 2.19 min in Group S and 6.47 min in Group N ($p < 0.0001$). Recovery time was 8.26 min in Group S and 16.93 min in Group N ($p < 0.0001$) (Table 2).

The MMSE T_0 and T_1 scores in Group S were 26.98 ± 1.957 and 26.90 ± 1.936, and in Group N were 27.00 ± 2.286 and 25.82 ± 2.724, respectively. The MoCA T_0 and T_1 scores in Group S were 23.26 ± 1.988 and 23.17 ± 2.294 and in Group N were 23.56 ± 2.482 and 23.04 ± 2.868, respectively. In both tests the T_1 mean was lower than the T_0 mean. Dependent groups were compared with the t-test, and repeated measurement values were compared. To determine the difference between the MMSE and MoCA at T_0 and T_1, the General Linear Model repeated measurement test was used.

Table 1 Distribution of sociodemografic factors and operative details via groups.

	Group S (±SD) (n = 42)	Group N (±SD) (n = 45)	p^a
Mean age, years	32.07 ± 11.50	37.38 ± 11.95	<0.05
Gender (F/M)	12/30	22/23	>0.05
Education years(<9 years/9–12 years/>12 years)	12/18/12	17/18/10	>0.05
Weight, kg	74.83 ± 14.93	75.33 ± 13.92	>0.05
BMI, kg/cm^2	25.25 ± 4.08	26.70 ± 4.63	>0.05
ASA class (I/II)	17/25	18/27	>0.05
Duration of the operation, min	118.86 ± 42.94	115.49 ± 46.51	>0.05
Duration of the anesthesiology, min	125.21 ± 38.91	124.18 ± 48.39	>0.05
Rocuronium, mg	67.02 ± 15.85	62.44 ± 11.65	>0.05
Tramadol, mg	74.83 ± 14.93	75.33 ± 13.92	>0.05

F, Female; M, Male; BMI, body mass index; ASA, American Society of Anesthesiologist score.
[a] Chi-square test ($2 \times n$) and Independent sample t test.

Table 2 Time to recovery of TOF ratio to 0.9 (min) and tıme to recovery of Aldrete ≥ 9 (min).

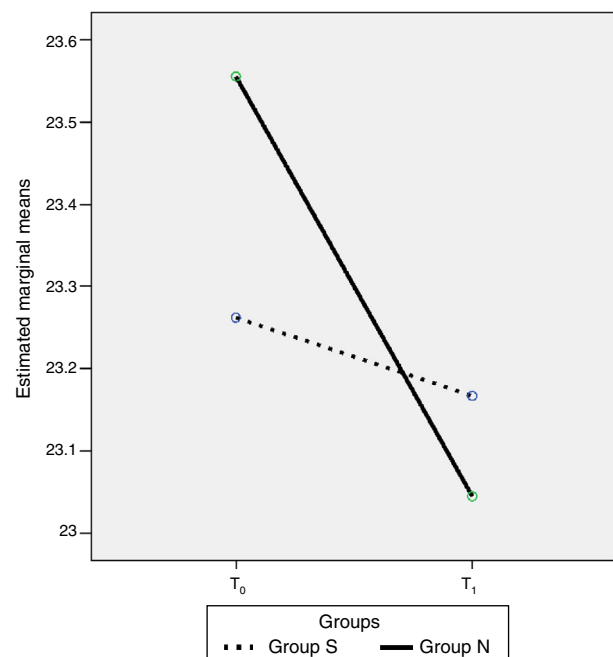|	Group S (±SD)	Group N (±SD)	p^a
Time to recovery of TOF ratio to 0.9	2.19 ± 1.47	6.47 ± 1.92	<0.0001
Time to recovery of Aldrete ≥9	8.26 ± 5.02	16.93 ± 8.00	<0.0001

TOF, train of four.
[a] Independent t test for groups.

The test results are illustrated in Fig. 1, which shows that although the T_0 and T_1 MMSE values in Group S were reduced, the slope of the reduction did not show a statistically significant difference ($p > 0.05$). In Group N, although there was a statistically significant fall in MMSE values from T_0 to T_1 ($p < 0.05$) there was no statistically significant difference between the slope values. Fig. 2 indicates that although there was a reduction in MoCA values in both Groups S and N from T_0 to T_1, there was no statistically significant difference in the slopes ($p > 0.05$) (Table 3; Fig. 3).

Discussion

In this study, the effects of sugammadex on recovery and cognitive functions were compared with those of
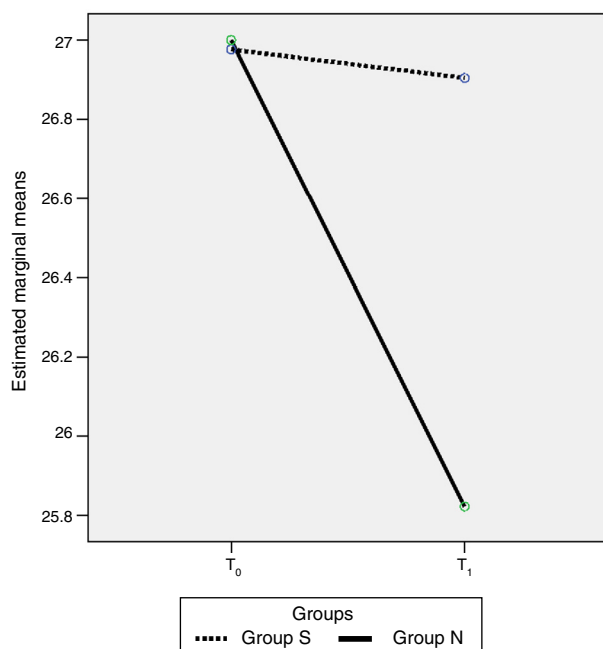
Figure 1 MMSE score slopes of the groups from T_0 to T_1.

Figure 2 MoCA score slopes of the groups from T_0 to T_1.

neostigmine. Although the sugammadex group reached TOF 0.9 earlier than the neostigmine group and had shorter recovery times, no significant improvement in cognitive recovery was identified.

Surgical procedures and accompanying anesthetic procedures may cause temporary or permanent postoperative regression in cognitive functions; this situation is known as POCD.[4] However, whether the surgical procedure or anesthesia administration causes POCD is not fully understood.[2,3,19,20] Many randomized controlled studies have shown that the incidence of POCD increases in patients who are older or undergoing cardiopulmonary bypass and lower extremity orthopedic operations.[20] To determine the effect of sugammadex and neostigmine on cognitive function, this study excluded patients above the age of 60 years and those undergoing cardiac, cranial, and lower extremity operations. Independent risk factors for development of POCD were eliminated. In addition, there was a significant difference in average age between the two groups (Group S: 32.07 $\pm$ 11.50 and Group N: 37.38 $\pm$ 11.95). Johnson et al.[21] found that the incidence of POCD was very low in middle-aged individuals and determined that there was no significant difference in POCD between patients who had undergone an operation in the previous 3 months and healthy volunteers. Therefore, we believe that the difference in age between the two groups did not negatively affect the cognitive test scores.

There is no international consensus on how cognitive function should be evaluated after an operation.[22] To this end, almost 30 tests have been described, but their advantages have not been demonstrated. The MMSE test is frequently used to evaluate cognitive function after anesthesia because it takes a shorter time to administer, and has been found to be more useful by patients and physicians. The MoCA test has become popular recently and is used frequently as it is not dependent on demographic variables such as age and education.[23] Both the MMSE and MoCA tests have high validity and reliability, with Turkish validity and reliability studies having been completed.[23,24] Based on these factors, the MMSE and MoCA tests were used to evaluate cognitive function in this study.

There are some reservations about when and how frequently cognitive evaluation tests should be performed after operations.[2,3,20] Factors that may negatively affect the cognitive evaluation scores are pain after the operation, disrupted sleep, and learning/memorizing of the tests due to their frequent repetition.[1] In this study, to prevent the effects of these factors all patients had a VAS score <4 and MAS score $\geq$9 before postoperative evaluation. In addition, to prevent memorizing and learning of the evaluation tests, the tests were only conducted once after the operation.

It is not known exactly when brain function returns after general anesthesia. Studies have shown that cognitive functions are affected by several factors after surgical procedures with anesthesia.[1-3,19] As rapid and short-term effective anesthetic agents are metabolized less by the body, they may cause less cognitive dysfunction. Matthew et al.,[8] in a study of 921 patients undergoing major noncardiac surgery, administered to one group a standard anesthetic protocol while the other group received a BIS-guided titrated anesthetic protocol. The BIS-guided group was exposed less to anesthetic agents and was determined to have less POCD in the 3 months after surgery. This study used BIS in both groups to reduce exposure to anesthetics and for monitoring.

Sugammadex has entered anesthetic practice in recent years and is used to reverse the neuromuscular block created by rocuronium and vecuronium in a rapid and reliable fashion. When compared with neostigmine, following sugammadex administration patients wake earlier and have shorter recovery times.[11-13] In comparative studies with neostigmine, the time required for TOF to reach 0.9 was considerably shorter for patients given sugammadex.[11,13,25,26] In a randomized, controlled study by Koç et al.,[25] when the TOF ratio of patients with neuromuscular block provided by rocuronium reached 2, sugammadex 2 mg/kg or neostigmine 50 μg/kg + atropine 20 μg/kg were administered for decurarization. The time to reach TOF 0.9 was 2.31 min in the sugammadex group and 9.48 min in the neostigmine group. The same study found that the extubation time was 6.64 min in the sugammadex group and 12.99 min in the neostigmine group. Similarly, Pongrácz et al.[26] compared the time to reach TOF 1.0 in patients given different amounts of sugammadex (0.5, 1, or 2 mg/kg) or 0.005 mg/kg neostigmine. Patients given 2 mg/kg sugammadex reached TOF 1.0 in 1.8 min while those given 0.05 mg/kg neostigmine reached
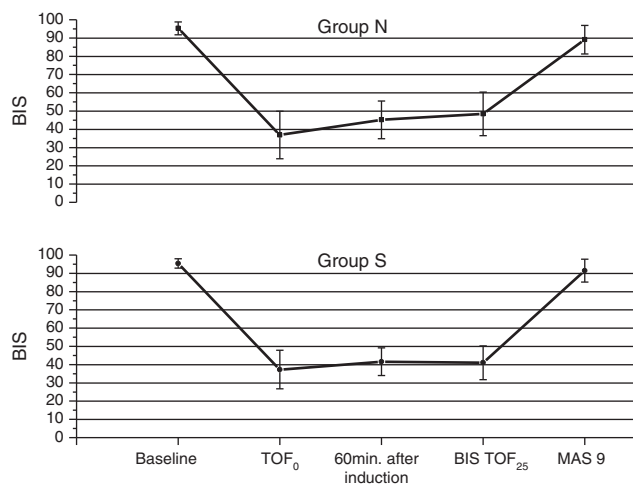
Figure 3 BİS values in group N and group S patients. BİS, Bispectral İndex.

TOF 1.0 in 8.5 min. In our study, the time to reach TOF 0.9 for patients given sugammadex was 2.19 min, and the recovery time was 8.26 min, while for patients given neostigmine these times were 6.47 and 16.93 min. The patients given sugammadex woke and recovered earlier than did those given neostigmine.

Many studies of the effects of fast emergence and recovery from anesthesia on postoperative cognitive function have been conducted. Bronco et al.[27] compared the effects of a rapid-start and recovery inhalation agent, xenon, with another inhalation agent, sevoflurane, in terms of postoperative recovery and cognitive function. Patients in the xenon group had an earlier emergence time and better cognitive recovery. Coburn et al.[28] compared the effects of xenon with desflurane on postoperative cognitive function in elderly patients; the eye-opening and extubation periods were shorter in the xenon group; however, the authors stated that the effects on cognitive function were similar to those of desflurane. Similarly, Rasmussen et al.[29] determined that the effects on cognitive function of the fast-acting inhalation agent xenon and fast-acting intravenous propofol were similar in elderly patients. In our study, to evaluate the cognitive function in both groups, MMSE and MoCA tests were administered at T_0 and T_1. Although there was a numerical reduction in MMSE and MoCA scores at T_1 compared to T_0, there was no statistically significant difference in the reduction slopes. Studies have shown that the surgical procedure and/or accompanying anesthetic procedure may cause a temporary or permanent regression in cognitive function in the early postoperative period. However, better cognitive performance could not be proved in the sugammadex patients compared to the neostigmine patients. No prior studies comparing the cognitive performance of sugammadex and neostigmine patients were found.

Calculating the sample size for an 80% strength required each group to include 64 patients, for a total of 128; however, exclusion criteria meant that the study was completed with 87 patients. Limitations in terms of the project duration meant that backup groups were not included. This was the most important limitation of the study. In addition, postoperative cognitive evaluation was completed only during the early period. As a result, the effects of sugammadex on cognitive function were compared only in the early period. Another limitation of the study was that low doses of sugammadex (2 mg/kg) were used. As a result, the effect of high-dose (16 mg/kg) sugammadex on POCD development is unknown.

In conclusion, evaluating cognitive function after an operation is complicated; the many independent risk factors and multitude of evaluation tests add to the difficulty.

Sugammadex is a very new agent. Further studies that include more detailed statistical analysis, different doses of sugammadex, and larger sample sizes are needed to fully understand the effects of this agent on cognitive function in the late postoperative period.

Conflicts of interest

The authors declare no conflicts of interest.

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