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Comparison the effects of sugammadex and neostigmine/atropine on cognitive functions in bariatric surgery patents: Randomized controlled trial

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The study was approved by Malatya Inonu University Clinical Studies Ethics Committee (2015/178).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: A recently introduced drug, sugammadex, can be a good alternative to conventional neuromuscular blockade reversal agents, such as neostigmine. This choice is of great importance, especially in the patients in whom it would be wise to avoid cholinergic side effects. The aim of this study was to compare the effects of sugammadex and the combination of neostigmine/atropine on post-operative cognitive dysfunction in bariatric surgery patients.

Methods: This randomized controlled trial included a total of 90 patients with American Society of Anesthesiologists (ASA) I–III physical status and body mass index >30 who were scheduled for elective sleeve gastrectomy were recruited for the study after obtaining ethics committee approval. Written consent was obtained from each patient. The exclusion criteria consisted of several parameters: lack of consent, co-existing muscular diseases, and severe cardiovascular diseases (New York Heart Association [NYHA]). The patients were randomly divided into two groups, and the randomization was performed by the investigator using previously prepared envelopes. In both groups, Mini Mental State Examination (MMSE) was performed before the operation. The patients' memory, attentive executive functions, and motor skills were evaluated as part of a control cognitive evaluation. After the operation while in the post-anesthesia care unit and when the Modified Aldrete Recovery Score was ≥9, the MMSE evaluation was repeated one and six hours later.

Results: The pre-operative MMSE results were similar in both groups. In the post-operative period, MMSEpo, MMSEpo1, and MMSEpo6 values were not significantly different between the groups. When a detailed examination of MMSEpo data was performed, it was determined that the MMSE scores were 20–25 in 14 patients (32.6%) in Group N/A and six patients (14.6%) in Group S. In Group N/A, the percentage of patients with MMSE 20–25 was significantly higher than that of Group S (X2=3.807; P=0.046).

Conclusion: In this study, sugammadex produced less effects on cognitive functions when compared with neostigmine/atropine combination. The neostigmine/atropine combination produced mild effects on cognitive functions in the first hour of recovery.

Keywords: sugammadex, neostigmine, atropine, cognitive dysfunction, bariatric surgery

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Introduction

Sugammadex is a γ-cyclodextrin that is used to encapsulate aminosteroidal non-depolarizing neuromuscular blocking drugs (NMBDs), such as rocuronium and vecuronium. With hydrophobic cores and hydrophilic peripheral chains, NMBDs becomes trapped inside the sugammadex molecule, and a rocuronium–sugammadex complex is formed. This inert complex leads to a reduction in the concentration of rocuronium in the neuromuscular cleft without affecting muscarinic functions and is mainly excreted via urine [1]. It has a high molecular weight, so it has a very low blood-brain barrier transfer [2]. It also has no direct effects on cholinergic transmission [3].

Neostigmine is an anticholinesterase that is used for reversal of NMBDs for over 40 years. It consists of a quaternary ammonium group and provides a covalent bonding to acetylcholinesterase which is lipid insoluble and cannot pass through the blood-brain barrier (BBB) [4]. They cause a rise in the level of acetylcholine (Ach) in the postsynaptic membrane by inhibiting acetylcholinesterase reversibly [5]. It causes some muscarinic effects that can be prevented by adding an anticholinergic drug during blockade reversal [4]. Atropine can rapidly cross the BBB and has been associated with mild post-operative memory deficits; its toxic doses are associated with excitatory reactions [6].

Post-operative cognitive dysfunction (POCD) refers to an impairment in a person’s concentration, memory, language use, and social communication and is especially common after major surgery [7,8]. The etiology of POCD remains unclear, but many factors are blamed to be its cause. Recently, it’s emphasized that the imbalance of the neurotransmitters, such as acetylcholine (Ach), serotonin, and glutamate during the peri-operative period can be a cause of POCD [9]. Ach, especially, has serious effects on cognitive functions, and it is thought that the defect in the acetylcholinergic system can be the reason behind POCD [10]. The effect of the nicotinic system on learning, memory, and cognition has previously been shown in human and animal studies [11].

The mini mental state examination (MMSE) is a widely used test among the elderly population to evaluate the cognitive status of these patients. It was first described in 1975 by Folstein et al. [12] and designed as a screening test for evaluating cognitive status. The test measures, orientation to time and place, short term memory, attention span, ability to solve problems, language, comprehension, and motor skills. The scoring is straight forward and even can be done at home.

In this study, we hypothesized that sugammadex may yield better cognitive functions with less adverse airway effects in bariatric surgery patients when compared with neostigmine/atropine combination, which are the most commonly used reversal agents for neuromuscular blockade.

Materials and methods

After obtaining the local ethics committee approval (Malatya Inonu Unıversity Clinical Studies Ethics Committee, 015/178), 90 patients with American Society of Anesthesiologists (ASA) I–III physical status who were scheduled for elective sleeve gastrectomy were recruited for this randomized controlled study. Written informed consent was obtained from all the patients. The sample size was determined due to power analysis. It was carried out using the G*power program 3.1.9.4 version. According to the mean difference and standard deviation in MMSE scores during the post-operative period and at baseline, to achieve the power of the study as 80% with 0.05 alpha error and 0.50 effect size, 44 and 45 patients should have been included in the neostigmine/atropine and sugammadex groups, respectively. The closed envelope method was used for the patient assignment, and the patients were divided into two groups with 45 patients in each group.in terms of the use of neuromuscular block reversal: (1) Group N/A and (2) Group S. Neostigmine/atropine combination was used in the Group N/A, and sugammadex in the Group S for reversal. Patients under the age of 18 and those with congestive heart failure, history of previous neuropsychiatric disorder, cardiac arrest, and/or stroke were excluded. Patients with ASA physical status IV and above patients who met difficult intubation criteria were also excluded from the study. Two patients in Group N/A and four in the Group S did not complete the study because of surgical complications. Each patient was pre-medicated with intravenous (IV) metochlopramide 10 mg and ranitidine 50 mg 30 min prior to the surgical procedure. An 8-h fasting period was ensured for the patients.

In the surgical theatre, routine monitoring, including electrocardiography (ECG), pulse oximetry (SpO_2) and non-invasive blood pressure (NIBP), was provided. Neuromuscular block monitoring was performed by a TOF-WATCH®SX (Organon Teknika B V, Netherlands). Forehead temperature probes were used for patients’ temperature measurements. During the entire procedure, fluids were warmed, and an underbody warming blanket (Bair Hugger 63500, 3M Health Care, Nauss, Germany) was used to keep patients’ body temperature at 36 to 36.5 °C. Anesthesia was induced with propofol 2 mg kg^{-1}, fentanyl 1 µg kg^{-1}, and rocuronium 0.6 mg/kg. The dosing regimen was selected according to ideal body weight. An endotracheal tube with an internal diameter of 8.5 and 7.5 mm was used for males and females, respectively. Following intubation, an orogastric tube was inserted and free drainage was allowed after aspiration.

Anesthesia was maintained with one minimum alveolar concentration desflurane (6%) with 40% oxygen in air. Volume-controlled mechanical ventilation was used for both groups, and the ventilation parameters were set as a tidal volume of 6 mL kg^{-1} according to ideal body weight at a rate of 10 to12 min^{-1} and adjusted to maintain an end-tidal carbon dioxide ($EtCO_2$) between 30 and 45 mm Hg. The high initial fresh gas flow rates (6 L min^{-1}) were reduced to 4 L min^{-1}.

After Veress needle insertion from the lower abdomen pneumoperitoneum was obtained, the intra-abdominal pressure was maintained at 8 to10 mm Hg in the supine position. The patient was put in a reverse-Trendelenburg position with the patient’s head raised about 30° from the horizontal line after which the gastrectomy was performed.

In Group N/A, neostigmine 0.04 mg kg^{-1} IV was used to reverse the neuromuscular blockade. Atropine 0.02 mg kg^{-1} IV was given to prevent muscarinic side effects. In Group S, sugammadex 2 mg/kg was used when a train-of-four of 25% (TOF 25) was reached. Extubation was performed after obtaining a TOF value of 90% (TOF 90). Tenoxicam 20 mg IV and tramadol 1 mg kg^{-1} were used for post-operative analgesia. Heart rates, blood pressures, SpO_2 values, and body temperatures of the patients were closely followed and maintained within physiological ranges.

In both groups, MMSE was performed before the operation: The patients' memory, attentive executive functions, and motor skills were evaluated as a control cognitive evaluation. For MMSE (total score 30) was used orientation (total 10 points), recording memory (total score 3), pay attention and count (total score 5), recursion (total score 3), language (total score 9). After the operation in the post-operative anesthesia care unit (PACU) and when the Modified Aldrete Recovery Score was ≥9, the MMSE evaluations were repeated one and six hours later (MMSEp: mini mental test pre-operative, MMSEpo: mini mental test post-operative, MMSEpo1: mini mental test post-operative 1st h, and MMSEpo6: mini mental test post-operative 6th h). The patients in both groups did not receive any pre-medications.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 20.0 software. Age, BMI, and MMSE were assessed using a Student's t-test between the groups. Assessment of data such as ASA and MMESpo patient numbers was done using a chi-squared or Fisher's exact test. The correlation between MMESpo data and surgical time, ASA, and BMI was assessed by Spearman's correlation. $P<0.05$ was considered significant.

Results

Demographic characteristics of the patients and surgery duration are presented in the Table 1. No significant differences between the groups were found.

Table 1: Demographic characteristics of the patients

	Group N/A (n=43)	Group S (n=41)	*P*-value
BMI (kg m^{-2})	47.69 (4.14) (40-56)	47.39 (5.13) (40-57)	0.770
Operation duration (min)	90.69 (17.71) (65–145)	89.51 (19.39) (65-135)	0.763
ASA (1/2/3)	14/28/1 (32.6/65.1/2.3)	21/19/1 (51.2/46.3/2.4)	0.436

BMI: body mass index, ASA: American Society of Anesthesiologist, Group N/A: Group neostigmine/atropine, Group S: Group sugammadex. BMI and operation duration were presented as mean (standard deviation) (min-max); ASA was presented as number (%).

The MMSE scores of the patients are presented in Table 2. No significant differences between the groups were found..

When a detailed evaluation of the post-operative MMSE scores was obtained, more patients with higher MMSE scores (such as 25–30) in Group S were when compared with Group N/A. This difference was statistically significant ($x^{2=}3.807$; $P=0.046$) as shown in Table 3. No residual cauterization was observed in any patient.

Table 2: MMSE scores of the groups

	Group N/A (n=43)	Group S (n=41)	*P*-value
MMSEp	30.00 (0.00) (30–30)	30.00 (0.00) (30–30)	-
MMSEpo	27.00 (2.93) (21–32)	27.35 (2.77) (21–30)	0.585
MMSEpo1	28.79 (1.54) (25–30)	29.05 (1.32) (26–30)	0.413
MMSEpo6	29.84 (0.37) (29–30)	29.88 (0.33) (29–30)	0.598

MMSEp, MMSEpo, MMSEpo1, and MMSEpo6: mini mental state examination pre-operative, post-operative, post-operative 1st h, and post-operative 6th h, respectively; Group N/A, Group neostigmine/atropine; Group S, Group sugammadex. MMSE data are presented as mean (standard deviation; min–max). The numbers are test points (see text for detailed information).

Table 3: MMSEpo data of the patients

MMSE Score	Group N/A (n=43)	Group S (n=41)	*P*-value
25–30	29 (67.4)	35 (85.4)	$x^{2=}3.807$ 0.046*
20–25	14 (32.6)	6 (14.6)	

MMSEpo: mini mental state examination post-operative. MMSE numbers are test points (see text for detailed information). The data for the groups indicate the patient numbers with percentage of them in the group given in the parentheses. *$P<0.05$.

Discussion

In this study, the effects of neostigmine/atropine combination and sugammadex on cognitive functions in morbidly obese patients who had undergone laparoscopic bariatric surgery were evaluated. Obesity has a significant impact on anesthesia procedures. Obesity and alterations due to obesity, which include changes in metabolic, cardiovascular, and pulmonary functions, can lead to an increase the risk of peri-operative mortality and morbidity [14]. We planned our study involving obese patients as they have greater peri-operative mortality and morbidity. Although the MMSEpo, MMESpo1, and MMSEpo6 scores were not significantly different, the number of patients with a total MMSE score of 20 to 25, a score that indicates minimally affected cognitive functions, was significantly higher in Group N/A when compared with Group S.

The difficulty with studies on cognitive dysfunction is the presence of many risk factors that may contribute to POCD. These risk factors include advanced age, comorbidities that effect cognitive functions, multiple drug usage, duration of anesthesia, level of education, post-operative infections, post-operative respiratory complications, type of surgery, intra-operative ischemia, and impairment in glucose, sodium, and potassium levels [15–17]. ASA I–III patients were included in the study to standardize conditions and risk factors associated with the patients. Body temperature and hemodynamic parameters were kept within physiological ranges throughout the operation. Propofol was used for induction, and desflurane for maintenance of anesthesia as these have been shown to be produce less adverse risks on the cognitive functions [18].

The general incidence of POCD is 5–15%, and it can increase to 62% in high risk patients [16]. The etiology of POCD still remains unclear, but many factors for this uncertainty are to blame. Recently, it was emphasized that imbalance in levels neurotransmitters, such as ACh, serotonin, and glutamate during the peri-operative period can be the cause of POCD. ACh, especially, has serious effects on cognitive functions, and defects in the cholinergic system and/or insufficient ACh production were blamed for POCD development [9]. The effects of the nicotinic system on learning, memory, and cognition were previously shown in human and animal studies [10]. Atropine was previously shown to cause mild cognitive disorder during the post-operative period in addition to causing the central anticholinergic syndrome. This process can be attributed to easy transfer of atropine across the BBB in addition to central and subcortical muscarinic receptor antagonism. Barbiturates lead two a reduction in Ach release and cause somnolence, amnesia, and hallucinations [19,20]. Thus, atropine may result in a decrease in MMSE scores during the first hour of recovery.

Piskin et al. [21] compared the effects of neostigmine and sugammadex following general anesthesia but could not demonstrate better results in cognitive functions in the sugammadex group. Batistaki et al. [13] concluded that no clinically important differences in the incidence of POCD after neostigmine or sugammadex administration in patients above 40 years could be detected. The results of our study are compatible with these findings, but in the detailed examination of MMSEpo data, more patients with minimally affected cognitive functions were found after receiving neostigmine compared to those receiving sugammadex.

Limitations

One limitation of the study was that sugammadex was used at a of 2 mg/kg. The effect of high dose sugammadex on cognitive functions is unknown. Studies can be initiated in this regard.

Conclusion

In conclusion, sugammadex and conventional neostigmine/atropine combination as reversal agents for neuromuscular blockade result in comparable effects on post-operative cognitive functions. Production of less early post-operative effects favor sugammadex, but whether the differences between the two agents has clinical significance should be questioned.

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