

Comparing The Effects of Sugammadex and Neostigmine On Neuromuscular Block and Bispectral Index In Recovery From Intracranial Mass Resection Operations

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ABSTRACT

Neuromuscular recovery (NMR) is a critical part of recovery from general anesthesia. Neostigmine is a choline esterase inhibitor and one of the leading agents which are used for NMR from non-depolarizing neuromuscular block. Its effect depends on competitive antagonism of the neuromuscular blocking agent (NMB) in the neuromuscular junction (NMJ). Sugammadex is a new agent which has attracted attention with dramatically rapid NMR from non-depolarizing neuromuscular blocking agents (NDNMBAs). It effects via chemically antagonizing NMBAs.

In this study, effects of neostigmine and sugammadex concerning recovery from general anesthesia for intracranial mass excision operations were compared. Totally 60 patients were included in the study. Neostigmine was used for 30 patients, and sugammadex was used for 30 patients. Evaluation criteria were the train of four (TOF), bispectral index (BIS), Glasgow Coma Scale (GCS), Modified Aldrete Score (MAS), Ramsey Sedation Score (RSS), vital signs and existed complications.

It is observed that NMR and recovery from anesthesia were significantly shorter in the sugammadex group ($p<0,05$). It is also seen that the duration of attaining BIS level to 80 was significantly shorter in the sugammadex group but this result is attributed to the artifact of the rapidly increasing neuromuscular activity in the sugammadex group.

Conclusion: We suggest that both neostigmine and sugammadex are useful agents for NMR. Sugammadex has more advantages than neostigmine because of rapid onset of action without increased complications but much more studies are needed about sugammadex to take the place of neostigmine.

Key Words: Anesthesia, sugammadex, neostigmine, postoperative recovery

Introduction

Intracranial mass resection surgeries are critical and challenging operations because of the unique, complex and vulnerable structure of the brain. As a result of medical and technologic development, morbidity and mortality rates decreased dramatically over 20 years. Improved skills and knowledge of anesthesiologists have pretty much contribution on this success. Anesthetic evaluation of a patient before the surgery, preparing the patient for the operation, controlling vital functions of a patient who has an open cranium during the surgery and recovery at the end of the procedure are all critical steps and

requires perfect experience and knowledge. Especially recovery from general anesthesia is a challenging period which is convenient for possible catastrophic events. Hypoxia, hypercapnia, alterations of blood pressure or changes in heart rate may cause to increased intracranial pressure and thus irreversible neurological deficits and even mortality (1). Recovery from anesthesia may be divided into two categories: recovery from the hypnotics and recovery from muscle relaxants.

Recovery from the hypnotics mostly depends on the decreasing concentration of the volatile or intravenous hypnotic agent in the brain tissue after cutting off the anesthetic infusion or

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inhalation by time. Happily, recovery from the modern hypnotics happens in less than 15 minutes (2).

Recovery from the NMBA depends on the decreased concentration of the NMBA in the NMJ but complete NMR varies amongst individuals. Also, failed management of NMR may cause to awake and paralytic patients with sympathetic hyperactivity, increased blood pressure, increased heart rate, too weak skeletal muscles for respiration and too weak glossopharyngeal muscles for securing the airway from secretions. To prevent these complications rapid and effective NMR is tremendously essential.

Neostigmine is the most popular drug for recovering neuromuscular block after general anesthesia. It is a choline esterase inhibitor that prevents the catabolism of acetylcholine (ACh) in the NMJ which is the critical molecule for muscle contraction. It is a physiologic antagonist of NDNMBAs. Its effect starts in 5 minutes and peaks in 10 minutes. Its duration of action is about 1 hour. Although its recommended maximum dose is 0.08 mcg/kg, lower doses are generally effective (3). There are two basic compounds in its chemical structure. While carbamate compound provides covalent bound with ACh esterase, quaternary ammonium compound prevents dissolving in lipid tissue. Due to its non-lipophilic structure it cannot pass the blood-brain barrier and so that it has no central nervous system effect (4). It has anticholinergic adverse effects like bradycardia, hypotension, increased secretions, and bronchospasm because it's a cholinergic drug. The results of these side effects can be catastrophic particularly in critical patients. To prevent these undesirable adverse effects administering anticholinergic drugs like atropine or glycopyrrolate is a popular strategy in anesthesia practice.

Sugammadex is a new and promising drug in anesthesia practice with extremely rapid NMR which is a huge advantage both for post-anesthetic NMR and for urgent situations when tracheal intubation fails after muscle relaxant administered. It is a chemical antagonist of steroid type NDNMBAs (e.g., rocuronium, vecuronium, pancuronium). It bounds the NMBA molecule 1: 1 ratio and make a chemical complex with the capsule of the molecule and prevents its action in the NMJ (5). Sugammadex has no action on any other receptor or enzyme, so there is no need to use any other drug to prevent the adverse effects of sugammadex. Sugammadex has an extremely rapid onset of action. In a study including male

patients, it was observed that administering 8 mg/kg sugammadex 3 minutes after 0.6 mg/kg, rocuronium injection increased the train of four ratios (TOF) to 0.9 (which means complete recovery) in 2 minutes (6). In the same study when 4 mg kg⁻¹ sugammadex dose was used and 0.9 TOF ratio was achieved in less than 4 minutes. In another study, after surgery completed, at the moment that observing two twitches with TOF, 4 mg/kg sugammadex was administered and it has been noted that TOF ratio reached to 0.9 in 1.1 minutes (7).

Anticholinesterases have 'ceiling effect' that means after a level their efficacy cannot be increased with increasing the dose so they cannot take action at deep neuromuscular block situations in contrast to sugammadex.

Sugammadex is not effective for succinylcholine or benzylisoquinoline type NMBs because it cannot make chemical complexes with them (8). Sugammadex can make chemical bonds with few other drugs also but these interactions have no clinical value, and the interaction power is hundreds of times less than rocuronium. (9). In phase I and phase II studies, it has been observed that possible adverse effects of sugammadex are hypotension, coughing, nausea, vomiting, dry mouth, and parosmia. (6,7,10).

In this study, our purpose is to compare the clinical efficacies of two NMR drugs those are introduced above.

Materials and Methods

This study was performed in the neurosurgery theater of Ondokuz Mayıs University Faculty of Medicine Education and Research Hospital between 1st of January of 2014 and 30th of April of 2014. Intracranial, supratentorial mass resection cases are included in the study. Approval of the institutional ethics committee was obtained before the study. All patients who were planning to participate in the study were given detailed information about the research and written informed consent has taken. Patients between 18-65 years old, fully oriented and cooperated, Glasgow Coma Score 15, American Society of Anesthesiologists (ASA) risk score III or lower are included into the study. Patients who do not want to participate in the study, mentally disabled patients, pregnant, patients with allergy history, patients with late recovery history from previous anesthesia experiences and the ones who were planning to be followed in the intensive care unit

(ICU) after the surgery are not included in the study.

Totally 60 patients, 19 females and 41 males were included in the study. Patients were randomly divided into two groups via toss-up method. Neostigmine was administered for Group N, and sugammadex was administered for Group S. No anxiolytics were given before the anesthesia for preventing bias. After the patient was placed on the operation table, non-invasive blood pressure, pulse-oximetry and ECG monitorization performed and the initial values were recorded.

Following pre-oxygenation with 100% O₂ inhalation for 3-4 minutes, 50-100 mcg iv remifentanyl and 4-7 mg/kg thiopental sodium were administered. Following the induction of anesthesia, before administering the muscle relaxant, neuromuscular monitorization device (TOF Watch SX®, Organon, Dublin, Ireland) was connected and calibrated. Then 0.6 mg/kg iv rocuronium was administered, and the duration of achieving TOF ratio 0 (zero) has recorded. Arterial cannulation and central venous catheterization were applied for all patients. Tracheal intubation has performed following TOF count reached to 0. Maintenance of anesthesia has managed via 0.05-0.2 mcg/kg/min remifentanyl and 50-200 mcg/kg/min propofol iv infusion.

The doses of these drugs have adjusted simultaneously according to hemodynamical parameters of the patient. When hemodynamic parameters increased more than 20% of initial values, 10 mg of iv esmolol was administered and when this increase persists, 125 mg of iv thiopental was administered. When these parameters decreased more than 20% of initial values, 10 mg iv ephedrine was administered. Maintenance of neuromuscular blockade has managed via 0.3-0.6 mg/kg/h iv rocuronium infusion. The target of neuromuscular blockade has accepted TOF level is 0 and Post Tetanic Count (PTC) is less than 10 (deep NMB). When maximum rocuronium infusion is not enough, 0.15 mg/kg additional rocuronium bolus was administered. During the surgery, blood pressure, heart rate, peripheral oxygen saturation, body temperature, and central venous pressure values were followed and recorded. Intraoperative and postoperative complications and treatment methods were recorded. To prevent postoperative nausea and vomiting 10 mg of iv metoclopramide were administered for all patients.

When surgery ends, craniotomy is closed, and subcutaneous suturation was been started, infusion of rocuronium was ceased. Following that

the skull clamp was removed, infusions of both propofol and remifentanyl were terminated. BIS electrode was applied, and BIS score recorded at every 30 seconds. Simultaneously TOF monitorization applied and recorded at every 30 seconds. When TOF reached two twitches, 50 mcg/kg neostigmine administered for Group N and 2 mg/kg sugammadex administered for

Group S. Following administration of the reverse drugs, TOF and BIS scores were recorded at every 15 seconds. The duration that BIS score reached to '80' and TOF score to '90%' also recorded. When spontaneous respiration observed, patients were extubated and the time duration of starting of spontaneous ventilation recorded. Hemodynamically and respiratory stable patients were carried to the post-anesthetic care unit (PACU). Glasgow Coma Scale, Modified Aldrete Score (MAS), Ramsey Sedation Score (RSS), hemodynamic and respiratory parameters and existed complications were recorded at every 10 minutes following the study drug injection for 60 minutes. Patients were sent to the ward if vital signs are normal and MAS is 9 or higher. Patients were visited in the ward at 4th, 12th and the 24th hours following the operation and GCS were noted.

The results were analyzed using the Statistical Package for Social Sciences (SPSS) version 16.0. Student-T test was used for comparing definitive statistical methods and comparing quantitative data. Mann-Whitney-U Test was used for analyzing the parameters which do not show normal distribution. Chi-Square test was used for comparing qualitative data. P values lower than 0.05 were accepted as 'statistically significant.'

Results

There wasn't a significant difference between groups regarding demographic features (Table 1). American Society of Anesthesiologists (ASA) risk scores were also similar. While there were 11 ASA I, 13 ASA II and 6 ASA III patients in Group N, there were 12 ASA I, 8 ASA II, and 10 ASA III patients in Group S ($p=0.327$). There was no significant difference between groups regarding the duration of the surgery, anesthetic drug consumption, muscle relaxant consumption during the operation.

BIS values when study drugs have been injected were also similar. It was 38.9 ± 12.09 in Group N and 39.1 ± 10.5 in Group S ($p=0.955$). Mean duration of TOF value to reach 90% after injections of the study drugs was significantly

Table 1. Demographic features of patients

	Group N	Group S	P Value
Age	49.8± 11.9	51.6±12.0	0.554
Weight (kg)	76.56±12.7	75.7±13.5	0.814
Gender (M/F)	20/10	21/9	0.781

Table 2. Mean durations of TOF, BIS and spontaneous respiration parameters achieving to the target levels following injection of the study drugs. Results are given as ‘minutes’

	Group N	Group S	P value
TOF reaching 90%	10.37	3.5	<0,001
BIS reaching 80	13.9	9.2	0.005
Starting of spontaneous respiration	8.33	4.8	0.006

Table 3. Number of patients with Glasgow Coma Scores ‘15’ in the ward

	Group N	Group S	P value
4 th hour	21 (70%)	16 (53%)	0.288
12 th hour	22 (73%)	22 (73%)	1.000
24 th hour	27 (90%)	26(87%)	1.000

shorter in Group S. It was 10.37 ±4.0 minutes in Group N and 3.50±1.75 in Group S (p<0.001) (table2). Mean duration of BIS value to reach 80 after injection of the study drug was also significantly shorter in Group S. It was 13.9 ±7.0 minutes in Group N and 9.2±5.2 minutes in Group S (p=0.005) (table 2). Starting of spontaneous respiration was substantially shorter in Group S. It was 8.33±5.50 versus 4.80±3.90 minutes (p=0.006) (table 2).

There was no significant difference regarding post-anesthetic complications between groups. Happily, no major, life-threatening event occurred. No recurarization and no hypoxia were observed. No mechanical ventilation requirement needed after extubating any patient. Hypotension observed in 1 patient from each group and treated with 5 mg iv ephedrine. Postoperative hypertension found in 6 patients in Group N and 7 patients in Group S (p=0.754) and treated with 1 mcg/kg glycerol trinitrate. Postoperative tachycardia was observed in 3 patients of Group N and 2 patients of Group S (p=0.640) and treated with 10 mg iv esmolol. No bradycardia was observed. Postoperative pain as intense as requiring analgesic drug was seen in 9 patients in Group N and 7 patients in Group S (p=0.540). They were treated with 10 mg iv meperidine. No allergic reaction was observed. No vomiting was observed, but nausea has observed in 2 patients of Group N and 4 patients of Group S (p=0.667).

Those patients were treated with 5 mg additional iv metoclopramide.

We didn't observe a statistically significant difference regarding recovery scales (Figure 1,2,3). At 10th minute MAS of 2 patients of Group N has been reached to ‘9’ and 8 patients of Group S. The most significant difference was observed at the 10th minute, but even this was not statistically significant (p=0.083). MAS scores of Group S were superior to Group N at 20th, 30th and 40th minutes but there was no significant difference (Figure 1).

When we assessed RSS, we observed significant difference only at the 10th minute in favor of Group S. While only 3 patients' RSS were reached to 3 in Group N, 12 patients of Group S were reached to 3 (p=0.017) (Figure 2).

Concerning GCS, there was superiority of Group S at first 20 minutes. Mean GCS of Group N was 8.03±2.22 at 10th minute and 9.46±3.24 of Group S (p=0.049). At 20th minute mean score of Group N was 9.23±2.71, and Group S was 11.03±3.16 (p=0.016) (Figure 3). There was no significant difference in the other evaluation periods. GCS were similar in the ward (Table 3). Happily, there was no mortality in postoperative 30-day period.

Discussion

Anesthesia for intracranial mass excision surgery is critically important. Preoperative evaluation and

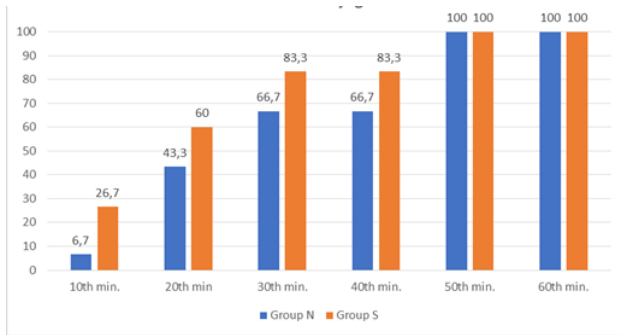


Fig.1. Percentage of patients reaching MAS to 9 in 60 minutes

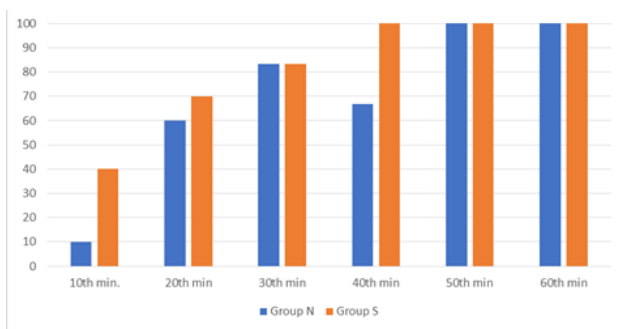


Fig.2. Percentage of patients reaching RSS to 3 in 60 minutes

preparation of the patient, anesthesia induction, maintaining anesthesia and recovery from anesthesia are all sensitive and critical steps. In this study, we focused on neuromuscular recovery period which is one of the critical parts of recovery from anesthesia. We studied two different drugs those are used for neuromuscular recovery. Neostigmine is a cholinesterase inhibitor that increases the acetylcholine level in the NMJ and enhances the contractibility of the muscle. It is a physiological antagonist of NDNMBAs. Sugammadex is a relatively new drug that is a chemical antagonist of steroid type NDNMBAs. Our purpose of this study was to compare these two drugs for clinical effects.

We performed the study on patients who would undergo intracranial, supratentorial mass excision surgery under general anesthesia. We did not include infratentorial surgeries because of conserving the study homogeneity.

Similar with other studies our results showed sugammadex enables rapid recovery. (11,12). Results of Sugammadex were better in the first 20 minutes. After 20 minutes although scores of sugammadex group were a little better, there was no statistically significant difference between sugammadex and neostigmine groups.

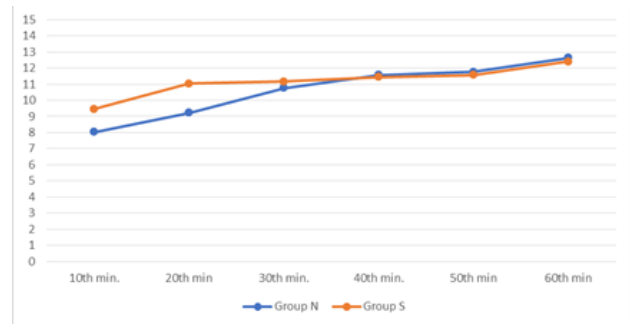


Fig.3. Mean GCSs of patients in 60 minutes

Our primary neuromuscular recovery criterion was TOF measurement. We administered the study drugs when TOF value reached to '2 twitches' and recorded the period between drug administration and TOF value to 90%. We observed significant superiority of sugammadex than neostigmine. Duration to 90% was 10.37 ± 4.0 minutes in Group N and 3.50 ± 1.75 minutes in Group S ($p < 0.001$). Our results were similar with other studies. Woo at al. included 128 patients in their study and administered sugammadex or neostigmine at second twitch appearance as the same as our study doses, and they observed that in sugammadex group mean duration to 90% TOF was 1.8 minutes and 14.8 min. in neostigmine ($p < 0.001$) (13). In another study that Geldner and Niskanen performed, they showed the superiority of sugammadex for recovery of deep neuromuscular blockade. They administered 4 mg/kg sugammadex or 50 mcg/kg neostigmine while post-tetanic count (PTC) was 1 or 2 and they showed that neuromuscular recovery by sugammadex is 3.4 times faster than neostigmine [14]. This study suggests sugammadex can be very beneficial in failed intubation cases.

Another evaluation criterion was resuming of spontaneous ventilation. We recorded the duration between the study drug administration and the first spontaneous breath of the patient. We observed a statistically significant advantage of sugammadex ($p < 0.006$). General accepted criteria for extubating are minimum 5 ml/kg tidal volume, inspiratory pressure more than -15 cm H₂O and respiration frequency more than 7/min. but we extubated our patients regardless of these criteria because of specific possible complications of intracranial surgeries (15). Reflex straining of an awake patient responding to the endotracheal tube may suddenly and remarkably increase the intracranial pressure and cause intracranial hemorrhage or cerebral herniation. When we observed first spontaneous breath, we extubated our patient, placed an oropharyngeal airway and

supported with mask ventilation. We did not record an additional 'duration of extubating.'

We observed our patients in PACU and recorded RSS, MAS, GCS. GCSs were significantly superior in sugammadex group in first 20 minutes. Following 20 minutes GCS results were similar between groups. MASs and RSSs were higher in Group S only in first 10 minutes. 10 minutes after study drug administration this difference disappeared. In a comprehensive study including 240 lower abdominal surgery patients Soyalp et al. reported mean duration of MAS reaching to 10 points is 16.69 ± 4.37 minutes in patients under desflurane anesthesia and lumbar epidural block while 20.67 ± 4.85 minutes in patients under desflurane plus remifentanyl anesthesia ($p < 0.001$) (16). In this study we recorded the duration of MAS reaching to 9 points rather than 10 because 9 is enough to send a patient from post-operative care unit to the ward. Additionally regarding to surgery type of our patients, reaching to 10 points could take hours, even days.

We followed our patients postoperative 24 hours in the ward, and we recorded GCSs and existed events. There was no significant difference between groups regarding GCSs and existed complications. Also, we followed up 1-month mortality rate and thanks to the dexterity of our surgeons we did not observe any mortality.

Corresponding to the results, we can suggest that sugammadex enables extremely rapid recovery compared to neostigmine. Its clinical effect is significant in first 20 minutes but following 20 minutes clinical conditions of the patients are similar with neostigmine. We recorded existed complications in both groups. Happily, we did not detect major hemodynamical or respiratory complication requiring reintubation or ICU admission. As shown above only a few acceptable and easily treatable complications occurred and there was no significant difference between groups. Phase I and II studies with sugammadex reported that most often adverse effects of sugammadex are hypotension, coughing, nausea and vomiting, dry mouth, parosmia and feeling of altered body temperature. Evaluation of safety data indicates sugammadex is well tolerated at doses up to 16.0 mg kg^{-1} (17).

Llaurado et al. described sugammadex has some advantages for pulmonary results. In their study including 160 obese, bariatric surgery patients, they reported a significantly higher number of patients requiring postoperative ventilation (5 versus 2 patients), as well as a significantly higher number of subjects with pathological

postoperative X-ray findings (26 versus 11 patients) (18). We did not observe pulmonary complications because we did not include respiratory high-risk patients and possibly due to our relatively small study population.

We also recorded BIS values. Our purpose of this evaluation was to search if we can observe the central nervous systemic effects of sugammadex. Our assessment criterion was to record the duration between drug administration and BIS value reaches 80. According to our results, BIS levels increased significantly faster in sugammadex group, but this is not enough to suggest sugammadex has central nervous effects and improves the activity of the brain because there was a correlation between TOF values and BIS values in both groups. In our opinion rapid increase on BIS value is because of the interference of increased tonicity and contractibility of the muscles on the skull (occipitofrontal muscle, corrugator supercilii muscle and other cranial muscles). To access through Blood-Brain Barrier (BBB) and to show some effects on the central nervous system in a patient, a drug must be smaller than 400-500 Dalton (Da). Sugammadex has a pretty large molecular structure with 2200 Da molecular weight and almost impossible to pass through BBB (19). We can also say that after binding the rocuronium molecule, the size of the complex is going to be much larger and cannot cross BBB. The results of a study that Dahaba et al. performed supports our suggestions about Sugammadex, Neostigmine and BIS values. They administered 4 mg/kg sugammadex or 50 mcg/kg neostigmine during continue propofol/remifentanyl anesthesia and showed that BIS values were significantly dependent on the presence of EMG activity (20).

In conclusion, sugammadex is a new and promising drug for anesthesia practice with rapid onset of action without increased complications but neostigmine is a reliable drug with almost half a century and millions of patient experience. We have so much knowledge and memories about neostigmine. For substituting neostigmine with sugammadex we need more and comprehensive studies.

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