

Does sugammadex decrease the severity of agitation and complications in pediatric patients undergoing adenotonsillectomy?

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ABSTRACT

الأهداف: تقييم فعالية عقار سوغاماداكس في الحد أو القضاء بعد العملية الجراحية من مستويات الهياج، والمضاعفات التنفسية المبكرة والغثيان/القيء في الأطفال الذين يخضعون لاستئصال اللوزتين والغدانيات.

الطريقة: اشتملت الدراسة على 70 مريضاً (الفئة العمرية= 5-13 أعوام) خضعوا لاستئصال الغدانيات واللوزتين والغدانيات في عيادة الأنف والأذن والحنجرة، جامعة سقاريا، سقاريا، تركيا خلال الفترة من مايو 2015م وسبتمبر 2017م. تم اختيارهم بصورة عشوائية من المرضى في مجموعة سوغاماداكس (المجموعة S) ونيوستجمين+الأترابين (المجموعة N)؛ كل مجموعة تحتوي على 35 مريض. قمنا بتسجيل وتقييم كلا من الوقت لنزع الأنبوب، ومستويات الهياج بعد العملية الجراحية، ومضاعفات ما بعد الجراحة في وقت مبكر. وقُيِّمت البيانات من كلا المجموعتين إحصائياً ومقارنتها.

النتائج: كان وقت نزع الأنبوب بشكل ملحوظ أقصر في المجموعة S من المجموعة N القيمة الإحصائية ($p > 0.05$). كانت درجات الإثارة خلال الانتعاش أقل بكثير في المجموعة S من المجموعة N ($p > 0.05$). المزيد من المضاعفات لوحظت في المجموعة N عن المجموعة S؛ عدد المرضى الذين ظهرت لديهم أعراض السعال والغثيان/القيء في المجموعة S إحصائياً أقل بكثير ($p > 0.05$).

الخاتمة: أظهرت هذه الدراسة أن استخدام عقار سوغاماداكس وقت أقل للتعافي وأقل هياج بالمقارنة مع الاستخدام التقليدي لعقار نيوستجمين+الأترابين في إبطال الانسداد العصبي العضلي بعد استئصال اللوزتين والغدانيات.

Objectives: To evaluate the effectiveness of sugammadex in reducing or eliminating postoperative agitation levels, early respiratory complications and nausea/vomiting in children undergoing adenotonsillectomy.

Methods: A total of 70 patients (age range: 5-13 years) who underwent an adenotonsillectomy in the Otolaryngology Clinic, Sakarya University, Sakarya, Turkey between May 2015 and September 2017 were included in the study. The patients were randomized into a sugammadex group (Group S) and a neostigmine + atropine (Group N); each group contained 35 patients. Time to extubation, postoperative agitation levels, and early postoperative complications were evaluated and recorded. Data from both groups were statistically evaluated and compared.

Results: The time to extubation was significantly shorter in Group S than Group N ($p < 0.05$). Agitation scores during recovery were significantly lower in Group S than Group N ($p < 0.05$). More complications were observed in Group N than in Group S; the number of patients seen coughing and experiencing nausea/vomiting in Group S was statistically significantly lower ($p < 0.05$).

Conclusion: This study demonstrated that the use of sugammadex results in less time to recovery and less agitation in comparison to conventional administration of neostigmine + atropine in the reversal of neuromuscular blocking after adenotonsillectomy.

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Adenotonsillectomy is one of the most common surgical procedures in otolaryngology practice. It is often performed under general anesthesia in children ranging in age from 4 to 7 years, with an indication of recurrent infection or obstruction.¹ Depending on the adenotonsillectomy, many complications may develop in the perioperative and postoperative surgical period. Since this surgery is frequently performed in the pediatric age group, agitation and pain that occur during and after the recovery period are significant problems for children.² Common perioperative and postoperative complications during adenotonsillectomy include bleeding, respiratory adverse events, postoperative nausea and vomiting, postoperative agitation (emergence delirium [ED]), and pain. Agitation is one of the major problems encountered during recovery, especially in children, and the frequency is reported to be 18-80%.^{3,4} The agitation experienced during recovery from anesthesia can cause a patient to harm himself/herself and his/her environment; it can also result in pain and bleeding, and prolonged recovery time.⁵ It has been reported that ED increases the possibility of airway complications.⁶ Therefore, reduction of agitation is important for avoiding possible airway complications after adenotonsillectomy.

Neostigmine is the agent that is most often preferred for the reversal of the neuromuscular blockade performed with acetylcholinesterase inhibitors used during the general anesthesia protocol. However, delayed recovery and prolonged curarization can be seen in the postoperative period after the use of these drugs.⁷ Sugammadex, a newly developed modified cyclodextrin, is a selective binding agent that rapidly and completely reverses the effects of rocuronium, a neuromuscular blockade agent.⁸ Sugammadex has been shown to significantly shorten the time to extubation, especially in pediatric patients, during reversal of the neuromuscular blockade. Clinical trials have shown that sugammadex has few side effects and is a fast-acting binding agent in the reversal of rocuronium-induced muscle blocking.^{9,10}

We hypothesized that the use of sugammadex during reversal of the neuromuscular blockade would be advantageous in terms of increasing patient comfort and reducing postoperative agitation levels; thereby, reducing the early postoperative complications of

patients undergoing adenotonsillectomy. Therefore, this study aimed to compare the use of sugammadex and neostigmine in pediatric patients undergoing adenotonsillectomy in terms of their impact on postoperative agitation level, early respiratory complications and nausea/vomiting.

Methods. This prospective controlled randomized, double-blinded study was conducted at Sakarya University Medical Faculty Training and Research Hospital, Sakarya, Turkey between May 2015 and September 2017. Faculty of Medicine Review Board, Kocaeli University (KOU-KAEK 2015/53) approved the study. The study was performed in accordance with the Declaration of Helsinki.

A total of 70 patients, with an age range of 5 to 13 years, who underwent adenotonsillectomy with recurrent/chronic tonsillitis or obstructive sleep apnea in the Otolaryngology Clinic, Medical Faculty, Sakarya University, Sakarya, Turkey were included in the study. Patients with a history of allergy to any medication used during general anesthesia, known neurological diseases, asthma, and bleeding diathesis were excluded from the study. Written consent and verbal consent were obtained from the legal guardians of the patients, who were blinded to the groups that participated in the study. Allocation of the patients to the groups was performed using computerized numbers (Excel; Microsoft, Redmond, WA, USA) by an anesthesiologist who did not participate in the study. Patients were randomized into a sugammadex group (Group S) and a neostigmine + atropine group (Group N); each group consisted of 35 patients. The same surgical procedure was used for all patients. Adenoid tissue was excised by curetting with adenotome. No analgesic infiltration of the tonsillar fossa was performed before surgery; the tonsillectomy was performed using the cold dissection method. Hemorrhage was controlled by bipolar cauterization at the surgical site after excision. All patients were hospitalized for the first 24 hours in our Otolaryngology Clinic. Patients who did not develop any complications, such as bleeding, were discharged after 24 hours. After surgery, all the patients in each group were administered antibiotics (amoxicillin-clavulanate syrup 40 mg/kg, 2 times for one week) plus paracetamol syrup (15 mg/kg, as needed). All patients were started on oral intake 4-6 hours after the operation.

Patients were monitored for pulse oximetry (SpO₂), heart rate (HR), electrocardiogram, cutaneous temperature, and noninvasive arterial blood pressure after being taken to the operating room. Monitoring of neuromuscular function at the adductor pollicis muscle

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was performed using a TOF-Watch SX (Schering-Plough, Swords, Co. Dublin, Ireland) acceleromyograph device. A pair of electrodes were placed 2-3 cm apart through ulnar nerve trace of the left wrist, and a transducer was placed over the left thumb. In both groups, the anesthesia induction of the patients was provided by intravenous administration of 2 mg/kg of propofol, 2 mg/kg of fentanyl, and 0.6 mg/kg of rocuronium bromide. For both groups of patients, maintenance of anesthesia was provided by 1-2% sevoflurane (MAC 0.8-1) in a mixture of air-oxygen (50% oxygen) and fresh gas flow at 2 L/min using the anesthesia workstation (Perseus® A500, Dräger, Lübeck, Germany). Heart rate and oxygen saturation values of the patients were followed and recorded by the anesthesiologist during the operation. Mean values of all patients were compared. In the perioperative period, 15 mg/kg intravenous (iv) paracetamol was used for postoperative analgesia. After surgery, while the train-of-four (TOF) count was 2/4, the residual muscle relaxation was antagonized with 2 mg/kg intravenous sugammadex + 0.01 ml/kg saline in Group S and 0.02 mg/kg neostigmin+0.01 mg/kg atropine in Group N. At the moment of 90% of TOF inhalation gases were ceased, and patients were extubated when spontaneous breathing was adequate (adequate respiratory rate according to the age; tidal volume >4 ml/kg; SpO₂ maintained above 95%), hemodynamics were stable and upper airway reflexes were fully recovered. Tracheal extubation time (from discontinuing anesthetics until extubation), duration of anesthesia (from the injection of anesthetic until discontinuation), and duration of the operation (from the injection of anesthetic until the patient's discharge from the operating room) were recorded for each patient. The patients were transported from the operating room to the post-anesthesia care unit (PACU) when they started breathing spontaneously. The patients were observed by blind personnel (nurses, anesthesiologist or doctors) in operating room and PACU. Their observations were recorded in terms of agitation levels and complications that may occur after extubation. Patients were taken to service room after 30-minute observation if no problem developed.

We assessed the postoperative agitation level with the Pediatric Anesthesia Emergence Delirium (PAED), which provides a score from 0 to 20, during the first 15 minutes in PACU (T0) and first (T1) hour after extubation at service room. Evaluations also were made at fourth (T4), eighth (T8) and twelfth (T12) hours of post-extubation to evaluate the negative state related to postoperative agitation and complications. The scores of each item were summed to obtain a total PAED scale score.

We also evaluated the patient's early postoperative respiratory complications such as hypoxemia, laryngospasm and apnea that may occur during the recovery period immediately after extubation. In addition, the patients' complaints of nausea and cough that may occur due to increased respiratory activity were evaluated. For desaturation, the blood oxygen level was considered to be <92 for a prolonged period of 30 seconds. For treatment, positive pressure ventilation and bronchodilator drugs were performed. The absence of any respiratory activity for 30 seconds was defined as the acceptance criteria for apnea. Laryngospasm was defined as the presence of increased respiratory effort and paradoxical chest movements.¹¹ Nausea/vomiting was considered positive even once seen during the recovery or follow-up period. The presence of persistent cough immediately after extubation or during follow-up in the child was considered positive. All complications were recorded according to the follow-up period at PACU and the first 24-hour observation at otolaryngology service.

Statistical analysis. Power analysis using the Gpower computer program was used to calculate the sample size. Power analysis calculation based on the values in previous studies on related to postoperative ED.^{12,13} In order to find a significant difference between measurements and estimated risk reduction, it was found that there should be at least 35 patients in each group while the power of 80% and an alpha level of 0.05. Categorical data were given as number (n) and percentage (%) and continuous data as mean+standard deviation. The normal distribution of categorical and continuous data was carried out by Kolmogorov Smirnov test. The unpaired t test was used to compare the mean times of extubation. Comparison of non-parametric data between sugammadex group and neostigmine + atropine group was performed by Mann Whitney U test. Chi-square and Fisher exact tests were used to compare categorical data. Values of $p < 0.05$ were considered statistically significant. All analysis were performed by Statistical Package for Social Sciences, version 23.0 (IBM Corp, Armonk, NY, USA).

Results. There were 35 patients in each group. The mean age of the patients in Group S was 6.63 ± 2.14 . Of the patients in this group, 19 were male (54.3%) and 16 were female (45.7%). The mean age of the patients in the neostigmine + atropine group was 6.58 ± 2.44 . Of the patients in this group, 14 were male (38.9%) and 22 were female (61.1%). The mean weight was 27.1 ± 6.7 at Group S and 28.0 ± 5.7 at Group N. There was no statistical difference between the groups in terms

of age, gender, weight, anesthesia time, surgery time, HR mean, and oxygen saturation mean (Table 1). Time to extubation was in the range of 4-7 and averaged 4.88 ± 0.86 in Group S, and in the range of 6-12 minutes averaged 8.83 ± 1.79 minutes in Group N (Table 2). The mean time to extubation in Group S was significantly shorter than Group N ($p < 0.001$) (Table 2).

When we evaluated the agitation levels; the mean agitation scores were 8.86 ± 1.4 in Group S and 12.25 ± 2.52 in Group N at T0. Mean values in the T1 were 6.26 ± 2.17 in Group S and 8.39 ± 2.57 in Group N. In Group S, agitation scores at T0 and T1 were significantly lower than Group N ($p < 0.001$). There was no significant difference between the 2 groups in terms of the mean of values at the T4, T8, and T12 hours (Table 3).

All complications were higher in Group N than in Group S. Transient laryngospasm and oxygen desaturation was seen as an early postoperative respiratory complication in 2 of the patients in Group N. In Group S, laryngospasm was not seen in any patient, only one patient had transient oxygen desaturation. Then, the oxygen saturation returned to normal with continuous oxygen. The number of patients with persistent cough after extubation was higher in Group N. There was no statistically significant difference between the 2 groups. However, the number of patients who observed nausea/vomiting in Group S statistically significantly lower (Table 4).

Discussion. Our study has shown extubation times and agitation levels of patients were significantly lower in the postoperative period than neostigmine-atropine group when sugammadex was used in pediatric patients who underwent adenotonsillectomy. It was also found that nausea and vomiting complaints decreased with the use of sugammadex in terms of postoperative early complications.

Steroidal neuromuscular blocking agents (NMBA) such as rocuronium and vecuronium are frequently used to provide muscle relaxation in general anesthesia. However, the pharmacokinetic and pharmacodynamic effects of NMBAs in pediatric patients differ from adults. Therefore, prolonged curarization effects and residual paralysis due to NMBAs are more common in children.¹⁴ Sugammadex is a new pharmacological agent that reverses neuromuscular blockade by a mechanism different from other acetylcholinesterase inhibitors. Sugammadex form a complex with NMBAs and bind to nicotinic receptors in the neuromuscular junctions and provide reversal of the neuromuscular blocking.⁸ Clinical trials have shown that sugammadex is a fast, effective and low-side effects binding agent in the reversal of rocuronium-induced muscle blocking.^{15,16}

Emergence delirium in children after general anesthesia is quite common and its incidence varies between 18-80%.^{3,4} The factors are affecting ED; age, preoperative anxiety, premedication, anesthetic agents during general anesthesia, adjuvant agents, rapid waking,

Table 1 - Patient characteristics and perioperative data of 70 patients.

Characteristics	Group S (n=35)	Group N (n=35)	P-value*
Age: years \pm SD	6.63 ± 2.14	6.58 ± 2.44	0.37
Gender (n/%)			
Female	16 (45.7)	14 (38.9)	0.221
Male	19 (54.3)	21 (61.1)	
Weight; kg \pm SD	27.1 ± 6.7	28.0 ± 5.7	0.284

*Mann Whitney U test. Group S - sugammadex + saline group, Group N - neostigmine + atropine group, SD - standard deviation

Table 2 - The comparison of the mean values of anesthesia time, surgery time, extubation time, and preoperative findings of 70 patients.

Variables	Group S (n=35)	Group N (n=35)	P-value*
Anesthesia time (min)	33.73 ± 5.3	34.63 ± 4.5	0.715
Surgery time (min)	30.45 ± 2.74	32.11 ± 3.04	0.378
Extubation time (min)	4.82 ± 0.85	8.83 ± 1.79	< 0.001
Heart rate	102.42 ± 15.7	100.8 ± 8.28	0.90
Oxygen saturation (%)	98.62 ± 1.16	98.72 ± 1.18	0.942

*Independent t-test. Group S - sugammadex + saline group, Group N - neostigmine + atropine group, SD - standard deviation

Table 3 - The comparison of Pediatric Anesthesia Emergence Delirium results in times.

Time	Group S	Group N	P-values*
T0	8.86 ± 1.4	12.25 ± 2.52	< 0.001
T1	6.26 ± 2.17	8.39 ± 2.57	< 0.001
T4	4.92 ± 1.35	5.32 ± 1.52	0.658
T8	2.72 ± 1.72	3.26 ± 2.11	0.315
T12	1.94 ± 1.26	2.83 ± 2.23	0.073

*Mann Whitney- U test, values are given as mean \pm standrd deviation. Group S - sugammadex + saline group, Group N - neostigmine + atropine group

Table 4 - The comparison of the frequency of early postoperative complications in 2 groups.

Complication	Group S	Group N	P=value*
Coughing	1	7	0.054
Oxygen desaturation	1	2	0.572
Laryngospasm	0	2	0.157
Nausea/vomiting	1	9	0.048
Apnea	0	1	0.321

*Chi-square test and Fisher exact test, Group S - sugammadex + saline group, Group N - neostigmine + atropine group

during awakening presence of parents, pain, and type of surgery.¹⁷ The used anesthetic drugs and postoperative muscle relaxant drugs are of great importance in the occurrence and control of the agitation. While ED has not been observed very often in the previous years due to the widespread use of halothane, the use of short-acting new volatile anesthetics, such as sevoflurane and desflurane, the incidence increased.¹⁸ Likewise, late recovery due to neuromuscular blockage also increases the risk of agitation development.¹⁹ The patient's postoperative agitation and residual neuromuscular block may cause difficulty in postoperative care and aspiration and, consequently led to respiratory complications. Sugammadex is a pharmacological agent that reverses residual neuromuscular block (NMB) without cholinergic side effects, and decreases the rates of postoperative respiratory complications compared to similar drugs. In literature, there are studies evaluating the efficacy of various anesthetic drugs on emergence agitation in patients undergoing pediatric adenotonsillectomy surgery, but there is no controlled study with Sugammadex.^{20,21} In the study by Pieters et al²¹ the effects of propofol and sevoflurane on the ED were investigated, but there was no significant difference in PAED score between the 2 groups. Decreased agitation is also thought to be advantageous in terms of reducing the trauma that can occur in the oral surgical field in patients undergoing adenotonsillectomy surgery. Based on this hypothesis, we also suggest that sugammadex may be effective in reducing agitation in children undergoing adenotonsillectomy in our study. We prefer PAED scoring method in the evaluation of emergence agitation because the most commonly used method of evaluating ED is PAED in literature.^{17,22} In addition, PAED was used in previous studies in our clinic, the participants were more familiar with this evaluation scale. Similar studies were considered in determining the timing of the evaluations.²³ In our study, PAED scores at the fifteenth minute and the first hour were significantly lower in Group S than Group N ($p=0.001$).

Carron et al¹⁶ found that sugammadex provided faster extubation compared to neostigmine and that the risk of postoperative residual curarization was less with sugammadex. Jones et al²⁴ showed that the time to reverse the effects of sugammadex and NMB and the time to reach 0.90 TOF was 18 times shorter than neostigmine. They also stated that sugammadex was well tolerated and no side effects were recorded.

In our study, it was determined that the time to extubation in the sugammadex group were significantly shorter than the control group. The mean duration of extubation was approximately 9 minutes in the neostigmine group and 4 minutes in the sugammadex group. In a Cochrane database²⁵ containing similar studies, it was stated that sugammadex significantly shortened the time of extubation and reach to maximum TOF ratio. Our results are similar to the literature in this respect.^{25,26} Another advantage of the reduced agitation and shortening recovery period is the shorter discharge time of the operation room. There may also be delayed transfer of patient to the wards due to prolonged neuromuscular blockade in the postoperative period. This will be especially advantageous for both anesthetists and surgeons in clinics dealing with pediatric surgery, especially in a large number of patients.

In addition to the complications that may occur due to surgery, the problems that can develop due to general anesthesia are also of great importance in pediatric patients who underwent adenotonsillectomy. The rate of major respiratory complications following adenotonsillectomy surgery in pediatric cases varies between 5-20% in the literature. These complications can be defined as severe airway obstructions that is requiring positive airway pressure, re-intubation or pharmacological intervention.^{11,27} Minor respiratory complications have been reported to occur in 10-30% of children and include hypoxemia, hypercapnia and transient apnea.²⁸ Age and prolonged time to extubation are among the risk factors for the development of respiratory complications in children undergoing adenotonsillectomy surgery.^{11,27} Therefore, the shortening of time to extubation with the use of sugammadex is also effective in reducing the possible complications. In the present study, no major respiratory complication or bleeding occurred in any of the children, but all other complications are lower in the Group S than the Group N. These values are only statistically significantly lower in terms of nausea/vomiting. We thought that this difference may be due to muscarinic side effects of neostigmine.

The only disadvantage of using sugammadex is that it is relatively expensive. When the drug is first marketed, it is available at a higher cost and it can be supplied at more affordable prices today. However, the sugammadex vial may also be used in divided doses when stored under sterile conditions. Pediatric anesthesiologists can offer one ampoule of sugammadex

in 4 children with an average of 25 kg.^{29,30} With the use of sugammadex, operation rooms can be used more efficiently by reducing the recovery time and agitation levels of the patients. This reduces the disadvantage that may occur due to the high price of the drug. In addition, sugammadex eliminates the possible complications of residual curarization leads to a reduction in the associated additional costs.

Study limitations. The neuromuscular monitoring continued only until the patient left the operation room. Neuromuscular monitoring has more detailed information on residual curarization that could be sustained for at least one hour in the PACU. Another points that may be deficient are the preoperative anxiety levels; and pain scores were not evaluated. The fact that patients were not evaluated separately according to age groups were considered another deficiency. In addition, there was no multivariate analysis for confounders.

In conclusion, sugammadex is beneficial in pediatric patients undergoing adenotonsillectomy, especially reduction of postoperative agitation and in terms of shortening of time to extubation. Further studies with larger groups are needed to assess the effectiveness of reducing agitations levels.

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