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Effect of Sugammadex on Postoperative Bleeding and Coagulation Parameters After Septoplasty: A Randomized Prospective Study

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Backround: Sugammadex is a reversal agent with well known advantages but it's effects on haemostasis and bleeding have been a topic of interest. Septoplasty is a common surgical procedure with postoperative respiratory complications and bleeding. The aim of this study is to investigate the effects of sugammadex on postoperative coagulation parameters and bleeding after septoplasty procedure.

Material/Methods: In this randomized controlled study, fifty patients were grouped into two groups; neostigmine (Group N) *vs.* sugammadex (Group S). For the evaluation of PT, aPTT and INR, blood samples were taken for at the postoperative 120th minutes and alteration of these values with respect to preoperative values were documented. Postoperative bleeding was measured by evaluating the amount of blood absorbed on the nasal tip dressing during 3 hours postoperatively.

Results: Postoperative bleeding amount was significantly higher in the Group S compared to Group N (p=0.013). No significant difference was observed between two groups according to coagulation parameters (PT; p=0.953, aPTT; p=0.734, INR; p=0.612).

Conclusions: Sugammadex was associated with higher amount of postoperative bleeding than neostigmine in septoplasty patients. In surgical procedures having high risk of bleeding the safety of sugammadex need to be verified.

MeSH Keywords: Airway Extubation • Anesthesia, General • Bleeding Time • Blood Coagulation • Neuromuscular Blockade

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1882 6 — 15

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Background

Acetylcholinesterase inhibitors are frequently used to reverse the effects of nondepolarizing neuromuscular blockers. However, acetylcholinesterase inhibitors have several disadvantages, such as development of residual blockade and hemodynamic adverse effects [1]. Sugammadex, a ϒ-cyclodextrin derivative, is a new reversing agent that has been in use recently. Sugammadex is preferred because of its advantages during extubation and recovery and low risk of residual blockade [2]. It has been known that with sugammadex some changes in coagulation parameters occurred without documented clinical consequences. There are still controversies about the relation between sugammadex and bleeding [3]. Septoplasty is an operative procedure with expected early postoperative respiratory complications and bleeding. These complications can be decreased with appropriate anesthesia methods [4]. The aim of the present study is to evaluate the effects of sugammadex on postoperative nausea-vomiting, pain, coagulation parameters and amount of postoperative bleeding.

Material and Methods

This prospective study was approved by local Ethics Committee (2013/411) and informed consents were taken from all participants. Fifty patients aged between 18 and 65 (mean age; 34.58) scheduled for septoplasty operation were included in the study. Operations were performed with the same technique by surgeons HK and MK. All patients were in the ASA I-II (American Society of Anesthesiologists) class. Patients taking antiaggregant/anticoagulant treatment, patients with history of bleeding disorder, patients with abnormal complete blood count and coagulation tests (prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)) were excluded from the study. Patients were randomized preoperatively in to two groups: Neostigmine (Group N, n: 26) and Sugammadex (Group S, n: 24). Randomization was performed by author NT using the previously prepared, sealed opaque envelopes. Randomization sequence was generated by using computer generated random numbers. Initially according to the power analysis (for α=0.05,desired power=95%) sample size was determined; 25 for each groups. Fifty-two envelopes prepared for probable sample loss (26 for Neostigmine and 26 for Sugammadex). Two patients in Group S were discarded (one patient didn't come to surgery and in one patient surgery was postponed because of recent upper respiratory tract infection). So study population included 26 patients in Neostigmine Group and 24 patients in the Sugammadex Group. When the patients arrived in the operating room, heart rate, noninvasive arterial pressure, pulse-oximeter, end-tidal carbon dioxide monitoring, and neuromuscular block monitoring (Train-of-Four (TOF) Watch SX monitor; Organon, Dublin, Ireland) were performed. Standard anesthesia protocol was applied: after induction with propofol 2–2.5 mg·kg^{-1}, rocuronium 0.6 mg·kg^{-1}, fentanyl 0.5 µg·kg^{-1}, patients were intubated when TOF=0 was obtained. Anesthesia was maintained with sevoflurane 2%, remifentanil 0.25 µg·kg^{-1}·min^{-1} infusion, 2l oxygen + 2l dry air with 0.8 ml·kg^{-1} tidal volume and freguency of 12/min to maintain end tidal volume CO_2 at 30–35 mmHg. For routine analgesia paracetamol infusion 1 g/100 ml was applied when 15 minutes left to the end of the surgery in all patients. Merocel (Medtronic, Xomed, FL, USA) intranasal packs were placed in both nasal passages. A separate nasal tip dressing was placed in the anterior part of the nose. At the end of surgery and when 2 responses were achieved on the TOF stimulation, one of the study drugs was administered intravenously. Neostigmine 0.05 mg·kg^{-1} + atropine 0.02 mg·kg^{-1} in Group N or sugammadex 2 mg·kg^{-1} (Bridion® 200 mg/2 ml, N.V. Organon Kloosterstraat 6, Holland) in Group S. When TOF ≥0.9 patients were extubated. After the extubation, mean arterial pressure (MAP; mmHg), mean heart rate (MHR; beats/min), peripheral oxygen saturation (SpO_2;%) and presence of nausea-vomiting and pain were documented in the postoperative recovery room. Evaluation of pain was performed according to Visual Analog Scale (VAS), and nausea-vomiting according to Likert Scale. Patients were discharged from the recovery room when Modified Aldrete Score was ≥0.9. Evaluation of pain was done before the patient left the recovery room. Amount of bleeding was measured by evaluating the blood leak on the nasal tip dressing during 3 hours postoperatively at 30 min intervals during first hour then every hour during the next 2 hours. Postoperatively nasal tip dressings were changed and amount of bleeding on the nasal tip dressing was measured by comparing the patients dressing with the previously 1, 2, 3, 4 and 5 milliliters blood soaked dressings. These measurements were done by the surgeon without knowing which drug was used and documented the result as milliliters for each time period. Blood samples were taken 120 minutes after administration of sugammadex or neostigmine for PT (seconds) and aPTT (seconds) measurements (half life of sugammadex is 120 minutes).

Hemostatic analyses

The blood samples for routine preoperative analysis were taken into citrate including tubes for PT and aPTT measurements. The blood samples were centrifuged at 2000×g for 10 minutes at 4^{0}C and plasma samples were studied immediately. PT and aPTT measurements were performed by original reagent on ERBA Analyser.

Statistical analysis

Shapiro-Wilk tests were used for normality assumption of data. Student t test was used for total bleeding, age and operation time. One-way ANOVA with repeated measure was

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Table 1. Age (years), gender, ASA and surgery duration (minutes) distribution of groups.

Groups	Age	Gender		ASA		Surgery duration
	Mean ±SD	Male	Female	ASA I	ASA II	Mean ±SD
N	35.19±11.76	15	11	18	8	49.42±10.61
S	33.92±13.19	16	8	16	8	45.63±9.47
P values	*P*=0.719	*P*>0.05		*P*>0.05		*P*=0.190

SD – standart deviation.

Table 2. SPO_2 (%) MAP (mmHg) and MHR (beats/min) distribution of groups.

Groups	SPO_2	MAP	MHR
	Mean ±SD	Mean ±SD	Mean ±SD
N	98.0±0.2	97.8±2	81.1±2.2
S	97.6±0.2	94.7±2.1	82.3±2.3
P values	*P*=0.276	*P*=0.280	*P*=0.697

SD – standart deviation.

Table 3. PT (sec) and aPTT (sec) values of groups.

Groups	PT		aPTT	
	Mean ±SD		Mean ±SD	
	Preoperative	Postoperative	Preoperative	Postoperative
N	11.6±1.4	12.5±1.7	29.4±4.9	30.4±4.8
S	11.8±1.8	12.7±1.9	29.5±4.5	29.6±4.8

SD – standart deviation.

used for MAP, MHR, SpO_2 and postoperative bleeding in different time periods (during first hour, second hour and third hours) and Fisher exact test was used for postoperative pain and nausea-vomiting.

Results

There was no difference between patient characteristics such as age (p=0.719), gender (p>0.05), surgery duration (p=0.190) and ASA classification (p>0.05) (Table 1). The groups were similar regarding the postoperative pain (p=0.848), nausea-vomitting (p=0.512). SpO_2 (p=0.276), MAP (p=0.280) and MHR (p=0.697) values of two groups were not different (Table 2). The preoperative and postoperative coagulation parameters (PT and aPTT) were presented in Table 3. The difference between preoperative and postoperative coagulation parameters (PT and aPTT) were calculated for each group to evaluate the change in coagulation parameters. Shapiro-Wilk test was used to show normal distribution of the data. To evaluate the change in coagulation parameters Mann-Whitney U test was used for comparison of groups. No statistical difference was found between PT (p=0.953) and aPTT (p=0.734) difference values of Group N and Group S (Table 4). The amount of postoperative bleeding measured by nasal tip dressings in Group S was significantly higher than Group N in all measurement time periods (p=0.024, Table 5). The average amount of total bleeding was 2.48 milliliters in neostigmine group and 4.13 milliliters in sugammadex group. The total amount of bleeding was also found significantly higher in Group S than Group N (p=0.033, Table 6).

Discussion

Septoplasty is a common operative procedure in otolaryngology that requires neuromuscular blockage and intubation when performed under general anesthesia. Bleeding and respiratory complications can be observed in the postoperative period [4]. Residual neuromuscular blockade is one of

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Table 4. Change in PT (sec) and aPTT (sec) values (Postoperative PT-Preoperative PT and Postoperative aPTT-Preoperative aPTT).

	Groups	Median	IQR	Min	Max	P values
PT	N	0.50	0.73	–1.30	6.30	0.953
	S	0.55	1.03	–1.40	5.20	
aPTT	N	1	3.08	–9.60	10.8	0.734
	S	0.40	3.88	–10.7	7	

IQR – interquartile range.

Table 5. Postoperative bleeding amount (in milliliters) measured by nasal tip dressings.

Bleeding	Groups	n	Mean ±SD	95% Confidence Interval	
				Lower	Upper
Postop. 1st hour	N	26	0.96±1.3	0.48	1.44
	S	24	1.56±1.2	1.07	2.06
Postop. 2nd hour	N	26	0.90±1.3	0.36	1.44
	S	24	1.42±1.5	0.86	1.97
Postop. 3rd hour	N	26	0.62±0.6	0.29	0.94
	S	24	1.16±1.0	0.81	1.50

SD – standart deviation; p=0.024; all measurement times.

Table 6. Total amount of bleeding amount (in milliliters) measured by nasal tip dressings.

Groups	n	Mean ±SD	P value	95% Confidence Interval	
				Lower	Upper
N	26	2.5±2.7			
			0.033	–3.171	–0.138
S	24	4.1±2.7			

P value; for Student t-Test.

the undesired effects of acetylcholinesterase inhibitors for the reversal of nondepolarizing neuromuscular blockade [1]. It is preferred mainly because of its advantages over neostigmine during extubation and recovery period and should take place in the anestesia drawer [5]. Clinical trials on healthy volunteers has shown that sugammadex is a safe agent with rare and mild side effects [6]. There are no reported data about interaction of sugammadex with laboratory tests except coagulation parameters (PT, aPTT, INR,) and progesterone level. These reported interactions have been reported at blood levels achieved after administration of 16 mg·kg^{-1} sugammadex. However clinical significancy of these findings is unknown since number of clinical trials have been insufficent [7]. According to the information supplemented by the European Medicines Agency, administration of 4 and 16 mg·kg^{-1} of sugammadex in healthy volunteers resulted in maximum and mean prolongations of the aPTT by 17% and 22%, respectively and PT by 11% and 22%, respectively. And these mean aPTT and PT prolongations were limited and of short duration (≤30 minutes) [8]. Soon after the sugammadex administration, prolongation of coagulation time has been reported recently [9]. De Kam et al. reported that after administration of sugammadex at doses 4 and 16 mg·kg^{-1}, a dose-dependent, limited, temporary, and clinically irrelevant prolongation in PT and aPTT was observed. They stated that this effect may be related to decrease in Factor Xa activity but later they did not find any effect of sugammadex on Xa activity in patients pretreated with heparin [10]. In another study conducted by same authors on 26 healthy volunteers, aspirin and sugammadex were administered together and no clinically relevant reduction in platelet aggregation was observed. They also stated that sugammadex was well tolerated by volunteers [11]. Raft et al. conducted a retrospective study performed in patients at high risk of postoperative bleeding (laparotomy for cancer

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surgery requiring suction drains) and they concluded sugammadex at doses of 2 and 4 mg·kg^{-1} was not associated with increased bleeding measured by amount of blood in suction drains and dressings. Despite its limitations because of retrospective design, this study has been a remarkable study in this field [3]. In 2014 Rahe et al. in a study of patients undergoing joint surgery, compared the PT and aPTT levels of patients given sugammadex, neostigmine with glycopyrrolate or atropine or placebo/spontaneous recovery and they found limited levels of increase and reported there was no other increase in incidence of bleeding [12]. Haemostatic mechanisms must work both for coagulation and prevention of thrombosis during surgical procedures. Although routine preoperative assessment with coagulation tests (PT, aPTT, platelet count) is recommended, it is not always possible to identify coagulation disorders and determine the postoperative bleeding risks [13]. Preoperative coagulation tests (platelet count, PT and aPTT) were normal in our study population. Sugammadex has an elimination half-life of 100–150 minutes so blood samples were taken 120 minutes after administration of sugammadex for PT and aPTT measurements in all patients [14]. We did not investigate the postoperative platelet count since sugammadex has no reported effect on platelet count and aggregation [15]. This is the limitation of our study. We found no significant change of PT and aPTT values after administration of sugammadex or neostigmine. But amount of bleeding measured by nasal tip dressings was significantly higher in sugammadex group than neostigmine group without a change in PT and aPTT values. Anesthesiologist should consider the cons and pros of sugammadex use in patients with these risk factors. The transient increases in aPTT and PT and INR reported in the previous studies were primarily the result of reversal with 16 mg·kg^{1} sugammadex. We administered 2 mg·kg^{1} sugammadex and none of our patients needed an additional dose. This may explain why no increase in PT and aPTT was observed in our study. The increased amount of postoperative bleeding that we found in our study may be due to the fact that increased bleeding tendency can be observed without any change in standard coagulation tests [15].

Conclusions

In conclusion, our study demonsrated that sugammadex increases postoperative bleeding, but without significantly affecting PT and aPTT values. This study is one of the first to investigate the postoperative blood loss after sugammadex use. We think that future studies investigating the effects of sugammadex on haemostasis tests other than the routine coagulation tests can clarify the mechanisms leading to increased postoperative bleeding after sugammadex use. Our results need to be supported with clinical studies that will be designed with low- and high-dose sugammadex in different surgery types. Although life-threatening postoperative bleeding is uncommon after septoplasty, in operations like adenoidectomy and tonsillectomy, the safety of sugammadex as a reversing agent and the safe dose ranges need to be verified.

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