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Effects of sugammadex on platelet levels and platelet-to-lymphocyte ratio in morbidly obese patients undergoing sleeve gastrectomy

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Abstract

Sugammadex is known to have minimal effects on coagulopathy. The aim of this study was to analyse the changes in platelet levels and platelet-to-lymphocyte ratio (PLR) in preoperative and postoperative periods in morbidly obese patients. This retrospective study included a total of 86 morbidly obese patients with a Body Mass Index (BMI) of >40 kg/m^2 and with an American Society of Anaesthesiologists Classification score (ASA) III undergoing elective laparoscopic sleeve gastrectomy (LSG). Patient data were obtained from patient files and electronic health records system (SARUS). The patients were allocated into two groups namely sugammadex (Group S) and neostigmine (Group N). Preoperative and postoperative (12th hour) hemogram recordings of the patients were examined. Compared to preoperative levels, there was a significant decrease in the postoperative platelet and lymphocyte values of patients in Group S ($p<0.001$) whereas postoperative PLR values were significantly increased ($p<0.001$). The comparison of the preoperative and postoperative values of patients in Group S according to gender showed no significant difference ($p>0.05$). Although sugammadex causes a decrease in the platelet and lymphocyte levels in the postoperative period similar to neostigmine, a relatively higher decrease in lymphocyte levels caused an increase in PLR values. None of the morbidly obese patients, who were administrated sugammadexn (2 mg kg^{-1}) via intravenous administration, underwent reoperation in the postoperative period due to coagulopathy.

Keywords: Sugammadex; platelet count; lymphocyte count; platelet-to-lymphocyte ratio; blood coagulation disorders

Introduction

Sugammadex is a new selective medication with a structure of modified gamma cyclodextrin that is used to reverse neuromuscular blockade caused by aminosteroid muscle relaxants [1]. Gamma cyclodextrin in its structure is a cyclic oligosaccharide formed by bacterial digestion of starch and used as solubilizers and stabilizers in various pharmaceutical and food products [2]. Oligosaccharides have various effects on blood components [3]. Oligosaccharides are known to inhibit platelet aggregation as well as exhibiting a mild anticoagulation effect by blocking the intrinsic coagulation pathway [3]. Furthermore, oligosaccharides have no effect on such complement activation and platelet activation as C3a and C5a [3]. There are also studies reporting that sugammadex prolongs prothrombin time (PT) and activated partial thromboplastin time (APTT) [4,5]. Sugammadex has been shown not to cause any major and minor bleeding in the postoperative period in morbidly obese patients [5].

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Although platelet-to-lymphocyte ratio (PLR) has been used in studies to estimate the prognosis of some cancer diseases such as nasopharyngeal carcinoma [6], urothelial carcinoma [7], small cell lung cancer [8], laryngeal squamous cell carcinoma [9], and hepatocellular carcinoma [10] in the literature, the number of studies investigating its effect on coagulopathy is limited. In light of all this information, we aimed to compare the preoperative and postoperative platelet levels and PLR according to gender to examine the effect of sugammadex on coagulopathy in morbidly obese patients who underwent sleeve gastrectomy.

Materials and Methods

Study Population

This retrospective study study was performed in compliance with the Declaration of Helsinki in the period from the year 2017 to 2018 and the Antalya Training and Research Hospital Ethics Committee Approval was obtained from our tertiary hospital before starting the study (Date of Approval-Protocol No: 2018-9/2). Patient data were obtained from patient files and electronic health records system (SARUS). Data of a total of 95 patients were analyzed. The study included a total of 86 morbidly obese patients with a Body

Mass Index (BMI) of >40 kg/m^2 and with an American Society of Anesthesiologists Classification score (ASA) III undergoing elective laparoscopic sleeve gastrectomy (LSG) (mean ± SD: 35.12±12.7 years, 75.6% were females). Patients with systemic disease other than morbid obesity were excluded from the study. The patients were allocated into two groups namely sugammadex (Group S) and neostigmine (Group N).

In our retrospective study, it was determined that 0.05 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine were administered intravenously to the patients in Group N, and 2 mg kg^{-1} sugammadex was administered to the patients in Group S to reverse neuromuscular blockade. In 5 patients, the drug used to reversal of the neuromuscular block was excluded because the drug was unknown. Since 4 mg kg^{-1} sugammadex was used in 4 patients, it was not included in the study.

Anesthesia Technique

After electrocardiography (ECG) and peripheral oxygen saturation (SpO_2) monitoring, general anesthesia was induced through the intravenous administration of 2% lidocaine (1mg/kg) to reduce the propofol-induced pain. After induction with propofol (3mg/kg) and fentanyl (1µg/kg), rocuronium (0.6mg/kg) was administered for muscle relaxation. A 50% air-oxygen, remifentanil infusion (0.5 µg/kg/min) and desflurane inhalation (1 MAC) were applied to maintain anesthesia. After inserting the orogastric catheter, end-tidal carbon dioxide ($EtCO_2$) was monitored using capnography. The patients were given the reverse-Trendelenburg position when the bispectral index (BIS) was 40–60 and 15 mmHg intra-abdominal insufflation pressure was applied. All patients received an intravenous infusion of Ringer's lactate (1000–1500 mL) throughout the surgery. This protocol was applied to all patients by the same surgical and anesthesia team.

Surgical Technique

In the sleeve gastrectomy technique that was used in the first group operated in 2017-2018, the patient was placed in the French (European) position, the surgeon stood between the legs in abduction, the first assistant stood on the left of the patient and the cameraman on the right of the patient, and entering the abdomen by a Veress needle at the distance of approximately 8-14 cm from the sternum xiphoid notch (depending on the distance between the umbilicus and xiphoid) and 1 cm left lateral of the linea alba, 14 mmHg intraperitoneal insufflation was achieved. An 36-Fr silicone bougie was inserted into the stomach under vision, passed through the pylorus and ensured to fit properly in the lesser curvature. The first 4.1mm (green) 60-mm linear stapler was placed at a distance of 2 cm to the pylorus by giving a 15-25 degree external angle through the 12-mm trocar on the right side of the patient not to create a stricture in the incisura and fit the base of the stapler in 2 cm to the pylorus. The second stapler was placed again through the right trocar as 4.1 mm (green) with an internal angle of 45 degrees. The third stapler 3.8mm (gold), 4th and if necessary 5th-6th cartridges as 3.5 mm (blue) were placed through the 12-mm trocar without angulation. Fundus resection was performed by preserving 1 cm HIS angle in the gastroesophageal junction. After the resection, the 36-Fr bougie was pulled out under vision and the presence of any twisting was checked. The mean operative time of the patients was 55 minutes.

Assessments

Age, sex, preoperative and postoperative (12 hours) platelet (low: 0-150 10^3 / mm³, high:> 450 10^3 / mm³) and lymphocyte levels (low: 0-1.16 10^3 / mm³, high:> 3.18 10^3 / mm³) and PLR values were calculated, and intragroup and intergroup comparisons were recorded. Power analysis could not be performed since there is no study in the literature investigating the side effects of sugammadex on platelets.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corporation, Armonk, NY, USA). Pearson chi-square test was used for categorical variables. The conformity of the data to normal distribution was evaluated with the Shapiro-Wilk test. The Mann–Whitney U test and Student's t test were used for the analysis of non-normally and normally distributed numerical data, respectively. Postoperative and preoperative parameters were compared using the Wilcoxon signed-rank test. Data were expressed as number (n), percentages (%), mean±standard deviation (SD) or median (min-max). A p value of <0.05 was considered statistically significant.

Results

There was no statistically significant difference between the gender distribution, age and mean BMI and ringer's lactate values of the groups (p>0.05) (Table 1).

Compared to preoperative levels(platelets count:300 10^3/mm³) lymphocytes count: 2.6 10^3/mm³), there was a significant decrease in the postoperative platelet and lymphocyte values(platelet count: 276.5 10^2, lymphocytes count: 1.7 10^3/mm³) of patients in Group S (p<0.001) whereas postoperative PLR(115108.7- 139722.2, respectively) values were significantly increased (p<0.001). Similarly, compared to preoperative levels(platelet count: 293.5 10^2, lymphocytes count: 2.3 10^3/mm³), there was a significant decrease in the postoperative platelet and lymphocyte values (260.5 10^2, 1.8 10^3/mm³, respectively) of patients in Group N (p<0.05) whereas postoperative PLR(123009.05-160573.5 respectively) values were significantly increased (p=0.018) (Table 2).

The decrease in the lymphocyte levels(-1 10^3/mm³ (-3.1-0.8)) in Group S was found to be higher than Group N(-0.5 10^3/mm³ (-2.3-1.4)) (p=0.041, p<0.05) (Table 3).

A significant decrease was observed in postoperative platelet and lymphocyte levels(291 10^3/mm³, 1.7 10^3/mm³ respectively) of female patients compared to preoperative levels(306 10^3/mm³, 2.6 10^3/mm³ respectively) (p<0.05) whereas PLR(121560.46, 175087.72 respectively) was found to significantly increase after the surgery (p=0.001, p<0.05). Similarly, a significant decrease was observed in postoperative platelet and lymphocyte levels(247 10^3/mm³, 2 10^3/mm³ respectively) of male patients compared to preoperative levels(274 10^3/mm³, 3.4 10^3/mm³ respectively) (p<0.05) whereas PLR was found to significantly increase after the surgery (p=0.028) (Table 4).

The comparison of the preoperative and postoperative values of patients in Group S according to gender showed no significant difference (p>0.05). (Table 5).

Table 1. Comparison of the demographic data of the patients

	Total (n=86)	Group S (n=42)	Group N (n=44)	p
Age	35.2±12.7(17–70)	33.2±10.8(19–60)	37.1±14.2(17–70)	0.152
Gender (Male/Female)	21(24.4)/65(75.6)	12(28.6)/30(71.4)	9(20.5)/35(79.5)	0.381
BMI	45.3±5.7(35–62.5)	45.7±5.9(37–62.5)	44.9±5.5(35–60.6)	0.491
Ringer's lactate (ml)	1250±75(1.175-1.325)	1243±78(1.165-1.321)	1252±45(1.207-1.297)	0.258

Data are presented as n (%), mean±SD (min-max). SD: standard deviation, BMI: Body Mass Index Student's t-test, Pearson's chi-square test

Table 2. Intergroup comparison of preoperative and postoperative values

	Group S (n=42)	Group N (n=44)	p
Preop Platelet	30010^3/mm³(152000–550000)	293500(186000–564000)	0.269
Postop Platelet	276.510^2/mm³(68000–418000)	260.510^2/mm³(162000–455000)	0.574
p	<0.001	<0.001	
Preop Lymphocyte	$2.6\ 10^3$/mm³ (1.7–5)	2.310^3/mm³ (1.5–4.4)	0.069
Postop Lymphocyte	1.710^3/mm³ (0.9–3.2)	1.810^3/mm³ (0.6–4)	0.527
p	<0.001	0.001	
Preop PLR	115108.7(44705.88–220000)	123009.05(64137.93–245217.39)	0.586
Postop PLR	139722.2(52631.6–360000)	160573.5(59428.6–338333.3)	0.931
p	<0.001	0.018	

Preop:Preoperative Postop:Postoperative Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Wilcoxon signed-rank test, Mann-Whitney U test. PLR: Platelet-to-lymphocyte ratio.

Table 3. Intragroup comparison of the differences in the parameters

	Group S (n=42)	Group N (n=44)	p
Platelet difference	-3910^3/mm³(-254000–147000)	-310^3/mm³(-121000–60000)	0.163
Lymphocyte difference	-110^3/mm³(-3.1–0.8)	-0.510^3/mm³(-2.3–1.4)	0.041
PLR difference	43923.38(-105037.04–205384.62)	23090.08(-97238.1–219833.33)	0.308

Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Mann-Whitney U test.

Table 4. Comparison of preoperative and postoperative values between genders in Group S

	Female (n=30)	Male (n=12)	p
Preop Platelet	30610^3/mm³(208000–550000)	27410^3/mm³(152000–356000)	0.010
Postop Platelet	29110^3/mm³(102000–418000)	24710^3/mm³(68000–301000)	0.028
p	0.001	0.023	
Preop Lymphocyte	2.610^3/mm³ (1.7–4.9)	3.410^3/mm³ (2.1–5)	0.034
Postop Lymphocyte	1.710^3/mm³ (0.9–3.2)	210^3/mm³ (0.9–2.7)	0.276
p	<0.001	0.002	
Preop PLR	121560.46(51224.49–220000)	84232.46(44705.88–125217.39)	0.004
Postop PLR	175087.72(78461.54–360000)	130113.64(52631.58–229230.77)	0.024
p	0.001	0.028	

Preop:Preoperative Postop:Postoperative Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Wilcoxon signed-rank test, Mann-Whitney U test.

Table 5. Comparison of the differences in the parameters between genders in Group S

	Female (n=30)	Male (n=12)	p
Platelet difference	-3910^3/mm³(-254000–147000)	-4310^3/mm³(-152000–20000)	0.717
Lymphocyte difference	-0.95 (-2.8–0.8)	-1.1(-3.1–-0.2)	0.139
PLR difference	44432.9(-105037.04–205384.62)	38439.12(-67368.42–104013.38)	0.597

Data are presented as median (min- max). PLR: platelet-to-lymphocyte ratio Mann-Whitney U test.

Discussion

In the literature, the studies investigating the effect of sugammadex and neostigmine on platelet levels and PLR, which are among coagulation parameters, is very rare. In this retrospective cohort study, although postoperative platelet and lymphocyte levels were lower than the preoperative levels, an increase has been observed in the PLR values in both patient groups undergoing sleeve gastrectomy for morbid obesity, who were given sugammadex and neostigmine to reverse neuromuscular blockade. In a study investigating the effect of sugammadex and pyridostigmine on coagulation parameters, no difference was reported between the two drugs in terms of the decrease in postoperative platelet levels, similar to our study [11]. The significant increase in postoperative PLR values may be due to the fact that the decrease in lymphocyte levels is higher than the decrease in platelet levels. In comparative studies using different doses of sugammadex (2 mg kg^{-1} and 4mg kg^{-1}), no significant coagulopathy was reported and none of the patients were re-operated due to postoperative bleeding [11,12]. Similarly, none of our patients receiving sugammadex via intravenous administration were re-operated due to coagulopathy in the postoperative period. In patients who undergo anesthesia, lymphopenia and immunosuppression due to surgical stress may be observed [13]. In the present study, the decrease in the lymphocyte levels in Group S was found to be higher than Group N. Surgery has no effect on acute coagulopathy in rats [14]. In rats, the decrease in the release of neutrophils and platelets into the circulation after laparotomy has been reported to cause a 45% decrease in lymphocytes [14]. There are studies in the literature showing that clinical doses of desflurane have no effect on platelets[15]. In studies conducted in the literature, it was found that the antithrombotic effects of desflurane did not persist 1 hour after surgery [16]. In the present study, the relative decrease in the lymphocyte levels due to decreased platelet and lymphocyte levels has been found to cause increases in PLR values. In our study, the comparison of both groups in terms of gender has shown similar results. There was a significant decrease in the postoperative platelet and lymphocyte levels compared to preoperative levels whereas there was a significant increase in the postoperative PLR values. In a randomized prospective study comparing PT and aPTT values of neostigmine and Sugammadex, no statistically significant difference was observed between the results [17]. In a publication examining the interaction of sugammadex with various anticoagulants, it was concluded that sugammadex has a temporary effect on coagulation and is unlikely to increase the risk of bleeding [18]. In our study, anticoagulant medication was not administered to the patients in the first 12 hours postoperatively. In an observational study, the use of 2 and 4 mg kg^{-1} sugammadex was not associated with longer clotting time or decreased hemoglobin concentrations [11,12,19]. However, results in patients administered 16 mg kg^{-1} sugammadex are uncertain. [19]. In the light of these findings, the effects of sugammadex on thrombocyte and lymphocyte levels in morbidly obese patients who underwent sleeve gastrectomy are similar to those in the neostigmine group. The limitation of our study is that it is retrospective and the patient population is not large number. Although sugammadex has limited effects on platelet volume and coagulopathy, there is a need for studies that compare the thromboelastogram analysis and changes in the platelet levels in a larger population. The administration of sugammadex in doses higher than 2 mg kg^{-1} may increase the risk of lymphopenia in addition to the current surgical stress, and may predispose to infection in the postoperative period.

Conclusion

Although sugammadex causes a decrease in the platelet and lymphocyte levels in the postoperative period similar to neostigmine, a relatively higher decrease in lymphocyte levels caused an increase in PLR values. None of the morbidly obese patients, who were administrated sugammadex(2 mg kg^{-1}) via intravenous administration, underwent reoperation in the postoperative period due to coagulopathy. Prospective randomized controlled studies are needed to evaluate the effect of sugammadex on platelet values and coagulopathy.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
This study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and permission was obtained from Ethics Committee of Antalya Training and Research Hospital for the use of patient data for publication purposes (Date of Approval-Protocol No: 2018-9/2).

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