



# Comparison of Pre and Postoperative Eosinophil/Lymphocyte and Basophil/Lymphocyte Ratio in Patients of Radical Robotic Prostatectomy who were Administered Sugammadex for the Reversal of Neuromuscular Blockade

## Nöromusküler Blokajın Geri Dönüşünde Sugammadex Uygulanan Radikal Robotik Prostatektomi Hastalarında Pre ve Postoperatif Eosinofil / Lenfosit ve Bazofil / Lenfosit Oranının Karşılaştırılması

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### ABSTRACT

**Objective:** Sugammadex is a new agent that is increasingly used in the recovery of neuromuscular blockade in anesthesiology practice. It has significant benefits, but is not risk-free.

The most important side effect is hypersensitivity. Since the ratio of eosinophil and basophil to lymphocyte (ELR and BLR) is suggested to be clinically appropriate in cases of hypersensitivity, it has been assumed that sugammadex reflects allergic character in ELR and / or BLR. In order to evaluate this hypothesis, we aimed to compare the preoperative and postoperative ELR and NLR of the patients.

**Material and Methods:** ASA I-II patients undergoing elective robotic radical prostatectomy were included in the study. Patient data were generated by scanning the electronic patient data system (SARUS). ELR and BLR were calculated from whole blood counts.

**Results:** A total of 46 patients (mean age 64.06±6.4 years) were included. ELR decreased significantly (p<0.001) in the postoperative period, but no significant difference was observed for BLR (p=0.124).

**Conclusion:** ELR and BLR have the potential to be useful tools as markers of sugammadex hypersensitivity. In our study, Sugammadex did not increase ELR and BLR rates significantly.

**Key Words:** Eosinophil lymphocyte ratio, Basophil lymphocyte ratio, Sugammadex, Hypersensitivity, Allergy, Anaphylaxis

### ÖZ

**Amaç:** Sugammadex, anesteziyoloji pratiğindeki nöromusküler blokajın iyileşmesinde giderek daha fazla kullanılan yeni bir ajandır. Önemli yararları vardır, ancak risksiz değildir.

En önemli yan etki aşırı duyarlılıktır. Eozinofil ve bazofilin lenfosit (ELR ve BLR) oranının, aşırı duyarlılık durumlarında klinik olarak uygun olduğu önerildiği için, ELR ve / veya BLR'de, sugammadexin alerjik karakterini yansıttığı varsayılmıştır. Bu hipotezi değerlendirmek için hastaların preoperatif ve postoperatif ELR ve NLR'lerini karşılaştırmayı amaçladık.

**Gereç ve Yöntemler:** Elektif robotik radikal prostatektomi yapılan ASA I-II hastaları çalışmaya dahil edildi. Hasta verileri, elektronik hasta veri sistemi (SARUS) taranarak üretildi. ELR ve BLR, tam kan sayımlarından hesaplandı.

**Bulgular:** Toplam 46 hasta (ortalama yaş 64,06±6,4 yıl) dahil edildi. ELR postoperatif dönemde anlamlı olarak azaldı (p <0,001), ancak BLR için anlamlı fark gözlenmedi (p=0,124).

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**Sonuç:** ELR ve BLR, sugammadex aşırı duyarlılığının belirleyicileri olarak faydalı araçlar olma potansiyeline sahiptir. Çalışmamızda Sugammadex, ELR ve BLR oranlarını anlamlı şekilde artırmadı.

**Anahtar Sözcükler:** Eozinofil lenfosit oranı, Bazofil Lenfosit oranı, Sugammadex, Hipersensitivite, Alerji, Anafilaksi

## INTRODUCTION

One of the contemporary agents of neuromuscular reversal that is used for recovery of neuromuscular block is sugammadex, which is a modified  $\gamma$ -cyclodextrin that selectively binds free molecules of neuromuscular blocking agent in the plasma (1). This is an encapsulating agent, which safely and rapidly reverses the effects of commonly used aminosteroid non-depolarizing agents, the rocuronium and vecuronium (2,3). The most prominent favorable effect of sugammadex in anesthesia practice is this immediate reversal of neuromuscular blockade in cases of unexpectedly difficult airway management to regain spontaneous ventilation (4). Although the usage of sugammadex has its benefits, there are also some risks related to its use. The most important concern for using sugammadex is its potential for causing hypersensitivity, which is a rare but important side effect (5). Other side effects are coughing, movement of a limb or the body, parosmia (abnormal sense of smell), and elevated urine levels of N-acetyl-glucosaminidase (6). Eosinophilia is defined as a peripheral blood eosinophil count higher than  $0.45 \times 10^9/L$  (7). The most commonly known causes of eosinophilia are allergic reactions and parasitosis. Eosinophils damage the tissue in which they are located with the proteins they contain such as: major basic protein, eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN), and eosinophil cationic protein (ECP) (8). Eosinophilic cationic protein is a significant parameter used in the monitorization of the activity of eosinophils in blood (8). Sensitivity of serum ECP activity is at 81.6% and its specificity is in the vicinity of 57.6% (9).

Basophil activation test (BAT) is used in the monitorization of the activity of basophil related inflammatory diseases (10). The test is based on detection of the rate of increase in the up-regulation of CD203<sub>c</sub> molecule, membrane glycoprotein-3, or CD63 that is in the structure of basophils in blood (10). BAT sensitivity is at 62% (36-92) and specificity is at 97% between (81-100) (11). Basophil BAS is among the main basic components that carry out the body's allergic reactions. Basophilia is defined as an abnormal accumulation of basophils (more than 1010 basophils per liter of blood), and is known to be associated with pruritus (itch) due to the release of histamine. Several studies have evaluated the prognostic roles of eosinophil to lymphocyte ratio (ELR) and basophil to lymphocyte ratio (BLR) for

allergic conditions, and reported that these parameters might have clinical relevance in patients with tendency to allergy (12, 13). Nevertheless, no studies were found in a literature search regarding the utilization of these markers for allergy or anaphylaxis arising from sugammadex use.

Under the light of these evidences, we hypothesized that an increase in ELR and/or BLR might reflect the allergic characteristic of sugammadex. To evaluate this update, we aimed to compare the preoperative and postoperative ELR and BLR of patients who received sugammadex for recovery of neuromuscular blockade.

## MATERIAL and METHOD

Data from a total of 46 patients were included in the study. The study population consisted of 46 patients between 44 and 75 years of age, who had undergone elective robotic assisted radical prostatectomy (RARP) operation, and sugammadex had been administered to reverse the neuromuscular blockade in all of the patients.

Patients were graded as ASA I or II according to the criteria of American Society of Anesthesiologists. This retrospective study was conducted at the Department of Antalya Education and Research Hospital, between 2017 and 2018. The Local Ethics Committee of Antalya Education and Research Hospital approved the study (2018-056).

After obtaining anesthesia, monitoring was ensured with electrocardiogram, intra-arterial and central jugular catheter pressure reading, pulse oximetry, capnography, neuromuscular blockade, and urine output. In the induction of anesthesia, intravenous propofol (3 mg/kg), rocuronium (0.6 mg/kg), remifentanyl (1  $\mu$ g/kg) were administered to the patients. For maintaining anesthesia, remifentanyl (0.5  $\mu$ g/kg/min) and 50% medical air and oxygen with desflurane (4-6 Mac) as the inhalation agent were used.

No clinical changes were detected in terms of tendency towards allergies or anaphylaxis related to the medications administered to the patients in the intraoperative or early postoperative periods following the anesthesia induction.

At the end of the operation, sugammadex (2 mg/kg) was administered to the patients to reverse the neuromuscular block. There were no clinically observed allergic reactions in the early postoperative period due to sugammadex administration.

Neuromuscular blocking agents that are traditionally non-depolarizing, such as Neostigmine, were not included in the study because of their limited and unpredictable activity during the reversal of blockades, their non-selectivity, and occurrences of unwanted autonomic responses.

Patients who were postoperatively transferred to the ICU, and patients with a history of allergies were not included in the study.

Comparisons were made between the ratios of the values of eosinophils, basophils, and lymphocytes in the control hemograms of the patients taken within the first 24 hours postoperatively, and those taken in the preoperative period.

### Statistical Analyses

Descriptive analyses were presented with the mean, standard deviation, median, minimum and maximum for numerical variables. Comparisons between 2 dependent groups were made with the Wilcoxon Signed Rank test. The correlations between numerical variables were analyzed with Spearman's rho test. A p value lower than 0.05 was considered as statistically significant. PASW 18.0 for Windows software was used for the analyses in this study.

### RESULTS

A total of 46 patients with a mean age of  $64.06 \pm 6.4$  were included in the study. The mean duration of anesthesia was 197.2 min. and the mean duration of surgery was 157.1 minutes. Liquid requirement of the patients was met with isolyte-s input and the urine output was monitored with an urethral catheter during the operation (Table I). Pre and postoperative ELRs ranged between 0-0.43 and 0-0.09, respectively. Pre and postoperative BLRs ranged between 0-0.06 and 0-0.83, respectively. The distributions of ELR and BLR are presented in Table II in detail.

The correlations between ELR, BLR and patient age are shown in Table III. Accordingly, there were no significant correlations between patient age and preoperative ELR ( $p=0.911$ ), postoperative ELR ( $p=0.930$ ), preoperative BLR ( $p=0.429$ ), and postoperative BLR ( $p=0.092$ ). The changes of ELR and BLR in the postoperative period are presented in Table IV. The comparisons between preoperative and postoperative values revealed that ELR decreased significantly ( $p<0.001$ ) in the postoperative

period, but no significant difference was observed for BLR ( $p=0.124$ ).

### DISCUSSION

Elevated levels of eosinophils in the blood do not indicate allergic disease by itself, and it is even possible to observe a drop in their level. In some cases such as medication allergies and eosinophilic pneumonia, no elevation of eosinophils occurs in the blood while elevation is observed in the target organs (8). Therefore an elevation or drop of the level of eosinophils is not considered significant by itself for the diagnosis of allergies (8).

**Table I:** Demographic data and study group.

Parameter	Mean value $\pm$ SD
Mean Age (years)	$64.06 \pm 6.4$
Anesthesia Time (min)	$197.2 \pm 17.4$
Operating Time (min)	$157.1 \pm 11.3$
Isolyte-S input (ml)	$1781.6 \pm 132.8$
Urine output (ml)	$397.1 \pm 47.6$
Bleeding (ml)	$238.2 \pm 31.4$

**Table II:** Distribution of patients' age, and pre- and postoperative ELR and BLR values.

	Mean $\pm$ SD	Median (min-max)
Preoperative ELR	$0.08 \pm 0.07$	0.06 (0-0.43)
Postoperative ELR	$0.01 \pm 0.02$	0 (0-0.09)
Preoperative BLR	$0.01 \pm 0.01$	0 (0-0.06)
Postoperative BLR	$0.03 \pm 0.13$	0 (0-0.83)

**Table III:** Association of ELR and BLR with patient age.

	Age	
	rho	p*
Preoperative ELR	-0.019	0.911
Postoperative ELR	-0.015	0.930
Preoperative BLR	-0.136	0.429
Postoperative BLR	0.285	0.092

\* Spearman's rho.

**Table IV:** Changes of ELR and BLR in postoperative period.

		Preoperative Median (min-max)	Postoperative Median (min-max)	p*
ELR	46	0.06 (0-0,43)	0 (0-0.09)	<0.001
BLR	46	0 (0-0.06)	0 (0-0.83)	0.124

\* Wilcoxon Signed Rank Test.

Alcohol consumption, Cushing syndrome, and stress are the main causes of low levels of eosinophils. In our patients, no complications such as bronchospasm or urticarious plaques related to the administration of medications were clinically observed.

We thought it would be appropriate to also compare the levels of basophils, which are rich in histamine content. Histamine is important in the pathogenesis of allergy and anaphylaxis. Vasodilatation and bronchospasm are among its most important effects. In our study, there was no significant increase in the BLR level.

To the best of our knowledge, this was the first study that evaluated the predictive value of ELR and BLR for sugammadex sensitivity in patients that underwent RARP surgery. Since ELR and BLR might have clinical relevance in allergic conditions of the organism, we evaluated their changes in postoperative period when compared to preoperative levels to assess sugammadex hypersensitivity. Our results showed that only ELR levels changed significantly, but this change was towards a decrease, which was not suggestive of a possible hypersensitivity to medications used during RARP procedure.

Theoretically, determination of hypersensitivity against sugammadex is a complex procedure, which is generally complicated with several factors. First, and the most important criterion for demonstrating an anesthetic agent as the primary cause of an anaphylactic reaction is demonstrating a temporal association between drug administration and the signs and symptoms of anaphylaxis (14, 15). Unfortunately, an anesthetized patient cannot display signs of anaphylaxis, or those signs might be hindered by surgical drapes. The only feature of a probable anesthetic anaphylaxis is generally sudden and unexplained cardiovascular collapse. Identification of potential markers such as ELR or BLR to predict this unfavorable complication should undoubtedly contribute a lot to anesthesiology practice.

According to the currently available literature data, true perioperative anaphylaxis mortality is up to 1.4% (16). Sugammadex is being more widely used in anesthesia applications, and should be used carefully with the background of this high prevalence of perioperative anaphylaxis rates. Several case reports have previously been published regarding anaphylaxis associated with sugammadex use (17-19). However, a recent study reported no significant increase in terms of hypersensitivity reaction in patients receiving sugammadex for reversal of neuromuscular blockade in comparison with patients receiving neostigmine (18).

Currently, there are no reports from Turkey, and likewise we have not observed any hypersensitivity reaction against sugammadex among our cases. In our study, the small number of cases and the lack of a control group should be considered as significant limitations. Based on the hypothesis of this study, our results were consistent with the assumption, and no increases in suggested markers of hypersensitivity have been detected in our analyses. Nevertheless, absence of an increase in ELR and/or BLR is not suggestive of any predictive value for sugammadex hypersensitivity since no cases were observed among our patients. These biomarkers should be evaluated in cases with proven sugammadex allergies for a definite conclusion about their predictive values.

## CONCLUSION

We investigated the effects of sugammadex on the eosinophil/lymphocyte ratio and basophil/lymphocyte ratio in blood due to its allergic side effects in this study.

Although there are publications concerning the allergic and anaphylactic potential of Sugammadex which is a new medication that reverses neuromuscular blockade, it must be taken into consideration that this can be a safe medication with very low side effects of allergy and anaphylaxis in pediatric and adult patients, and further studies must be conducted upon this subject.

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