Annals of Clinical and Analytical Medicine
*Original Research*

# The effect of anesthesia method on the distribution of leukocyte elements and neutrophil/lymphocyte ratio in elective cesareane sections

Distribution of leukocyte

Selda Songur Dağlı[1], Recai Dağlı[2]
[1]Department of Obstetrics and Gynecology
[2]Department of Anaesthesiology and Reanimation, Kirsehir Ahi Evran University Faculty of Medicine, Kirsehir, Turkey

**Abstract**
Aim: In this study, we aimed to investigate whether the anesthesia method in cesarean sections (CS) affects the distribution of leukocyte elements and the neutrophil/lymphocyte ratio (NLR).
Material and Methods: In our retrospective study, 99 patients with general anesthesia (GA) and 87 patients with spinal anesthesia (SA) with elective CS were included. Preoperative and postoperative 24th-hour blood samples were evaluated. The distribution of leukocyte elements and NLR were compared preoperatively and postoperatively.
Results: The rate of neutrophils was 72.31% ± 6.25 preoperatively and 82.46 ± 4.96% postoperatively. This change was statistically significant (p = 0.00). There was no significant difference between the two groups in neutrophils, lymphocytes, monocytes, basophils, and NLRs in the postoperative period.
There was a significant difference in eosinophil distribution and eosinophil-lymphocyte ratio (ELR) between postoperative groups (p = 0.03, p = 0.04). In the postoperative period, the eosinophil rate was lower in the GA group.
Discussion: In CS anesthesia, there was no significant difference in leukocyte distribution and NLR rates between SA and GA in the postoperative period. Eosinophils and ELR were significantly different between the two groups.

**Keywords**
Anesthesia; Leukocyte; Neutrophil; Lymphocyte; Cesarean

DOI: 10.4328/ACAM.20696 Received: 2021-06-04 Accepted: 2021-07-13 Published Online: 2021-07-30 Printed: 2021-08-15 Ann Clin Anal Med 2021;12(Suppl 3): S323-327
Corresponding Author: Selda Songur Dağlı, Department of Obstetrics and Gynecology, Kirsehir Ahi Evran University Faculty of Medicine, Kirsehir, 40100, Turkey.
E-mail: seldasongurdagli@hotmail.com P: +90 5423160625
Corresponding Author ORCID ID: https://orcid.org/0000-0003-4887-4818

## Introduction

The neuroendocrine and immune systems are activated during trauma, surgery, ischemia, shock, infection, pregnancy. Acute changes occur in the white cell composition in the blood as a result of activation of the cellular and humoral immune system. Neutrophils, eosinophils, basophils increase, and lymphocytes decrease. In a study by Jilma et al., 4-6 hours after endotoxin, neutrophils increased by more than 300%, lymphocytes by 85% and monocytes by 96% reduced. The decrease in lymphocytes can last 2-7 days [1-3].

Neutrophilia and lymphopenia that develop in response to surgical or physiological stress are signs of a good prognosis. Neutrophil/lymphocyte ratio (NLR) has been defined as an indicator of physiological stress in recent years. These are easy, cheap and repeatable tests. It is predictive of post-diagnosis and pre-chemotherapy prognosis in cancer patients and is widely used in the clinic as a marker for systemic inflammation. In studies, patients with high NLR values have a better prognosis than those with low NLR values [4-7]. There are also studies for prognostic purposes in chronic diseases [8]. Recent literature has focused on creating community-based data and detecting thresholds to use NLR for prognostic purposes [9, 10].

There are many physiological changes during pregnancy and puerperium. In addition, when surgery and trauma caused by anesthesia are added along with a cesarean section (CS), the situation becomes even more complicated. There is an increase of more than 20 000/mm³ in the maternal white blood cell count during pregnancy and puerperium. These values are thought to be related to physiological stress during pregnancy [11, 12].

The effect of anesthesia on the immune system has been known for a long time [1]. The effects of anesthesia on surgical stress have been investigated. Today, studies examining the impact of CS anesthesia on NLR used for prognostic purposes are limited. We planned our research to provide data on this subject and to support the current literature.

In this study, we aim to investigate whether general (GA) and spinal (SA) anesthesia in cesarean affect NLR and the change in the distribution of leukocyte elements.

## Material and Methods

Ethical approval for this study was obtained from the local Ethics Committee of Ahi Evran University Faculty of Medicine (no: 2019-02 / 20). It was planned in accordance with the Helsinki guidelines.

*Research plan:*

This is a retrospective study. The data were obtained by examining patient files.

*Patient population:*

CS patients were examined in Kırşehir Training and Research Hospital between 03.03.2019 and 03.01.2020.

Inclusion criteria were as follows: 37-41 weeks of gestation, pregnant women with elective CS by GA or SA.

Exclusion criteria were as follows: any blood disease, postpartum atony development, placenta ablation, placenta adherence anomalies, pregnancies below 37 weeks or over 41 weeks, preeclampsia, pregnant women with eclampsia, intrauterine exitus fetus, chorioamnionitis, known infections (such as upper or lower respiratory tract) pregnant women who had a blood transfusion before or after the operation.

During the research period, we examined 210 elective CS made by the same surgeon in the clinic. We excluded from the study because of four preeclampsia-eclampsia, eight pregnant women below 37 weeks of gestation, three detachments, three blood transfusions, one twin pregnancy, and five pregnant women with missing data in their files.

Blood sampling was done before the operation and at the 24th hour after the operation. Leukocyte distribution, NLR and eosinophil/lymphocyte ratio (ELR) in the blood were evaluated. The patients were divided into two groups as GA and SA, according to CS anesthesia. For standardization, the data of CS cases performed by the same surgeon, patients who had similar procedures during GA and SA were included in the study. Data of 99 patients in the GA group and 87 patients in the SA group were evaluated.

Standard GA application: 2-3 mg/kg propofol, 0.6 mg/kg rocuronium was induced. Afterwards, endotracheal intubation was applied, and the surgical procedure was started. It is maintained with 4 L/min 50% O2-air mixture until the baby is delivered, then 1 µg/kg of fentanyl citrate and 50% O2-N2O mixture.

Standard SA application: A subarachnoid block L3-L4 or L4-L5 vertebral levels are applied with a 26G spinal needle (Atroucan®, Brown, Germany) 10 mg of Heavy bupivacaine. The surgical procedure is started when sensory block is achieved at the T4-T6 level. During the surgical process, 2 L/min O2 is applied with a nasal mask.

Paracetamol-tramadol Hcl vials are used for postoperative analgesia in both groups according to the patient's needs.

*Statistics*

Statistical analysis was performed using the SPSS 21.0 Windows (SSPS Inc., Chicago, IL, USA) program. In descriptive statistics, mean ± standard deviation, median (IQR) values, categorical data were expressed as number (n) and percentage (%). The compatibility of numerical variables to normal distribution was evaluated using the Shapiro-Wilk test. Student t-test, Chi-square and Mann-Whitney U tests were used for statistical analysis. The results were evaluated at a 95% confidence interval, and those less than $p < 0.05$ were considered statistically significant.

## Results

A total of 210 files were examined, but we analyzed data from 186 patients according to the inclusion and exclusion criteria.

The demographic data of the patients and duration of the operation, 1st and 5th-minute APGAR scores are shown in Table 1, and the distribution of cesarean indications in Figure 1. There was no significant difference between the two groups in terms of maternal age, gestational week, body mass index (BMI), and duration of the operation. Apgar scores were significantly higher in the SA group at the 1st and 5th minutes compared to the GA group ($p = 0.00$, $p = 0.00$).

Preoperative hemoglobin value (g / dl) was 12.09 ± 0.15 in the GA group, 12.27 ± 0.14 in the SA group, p<0.40; 10.78 ± 1.55 in the postoperative GA group, 10.92 ± 1.27 in the SA group, p <0.48. Preoperative hematocrit value (%) was 36.74 ± 0.36 in the GA group, 36.97 ± 0.33 in the SA group, p <0.63; postoperative GA: 32.81 ± 4.11, SA: 33.08 ± 3.36, p <0.62.

**Table 1.** Demographic data

| | General Anesthesia (n= 99) | Spinal Anesthesia (n= 87) | p |
|---|---|---|---|
| Maternal age | 28,58 ± 5.22 | 27.77 ± 5.69 | 0.31[a] |
| Gestation age (weeks) | 38.85 ± 0.95 | 38.95 ± 1.05 | 0.47[a] |
| BMI (kg/m$^2$) | 31.06 ± 4.57 | 31.48 ± 5.25 | 0.55[a] |
| Duration of operation (minute) | 27.36 ± 8.98 | 28.79 ± 9.39 | 0.29[a] |
| APGAR 1[st] minute | 8 (6-9) | 8 (7-9) | <0.001[b] |
| APGAR 5[th] minute | 9 (8-10) | 9 (8- 10) | <0.001[b] |

BMI: Body mass index
[a] Independent Samples T-Test, [b] Mann-Whitney U Test
Values are median (minimum-maximums) or mean ± standard deviation.

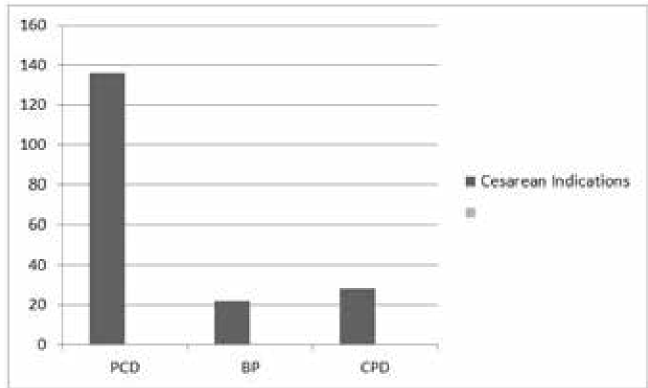


**Figure 1.** The distribution of cesarean indications.
PCD: Previous cesarean delivery, BP: Breech presentation, CPD: Cephalopelvic disproportion.

**Table 2.** The distribution of preoperative and postoperative leukocyte elements in the general anesthesia and spinal anesthesia groups

| | Preoperative | | | Postoperative | | |
|---|---|---|---|---|---|---|
| | General Anesthesia (GA) (n= 99) | Spinal Anesthesia (SA) (n= 87) | p | General Anesthesia (GA) (n= 99) | Spinal Anesthesia (SA) (n= 87) | p |
| Hemoglobin (g/dL) | 12.09 ± 0.15 | 12.27 ± 0.14 | 0.40[a] | 10.78 ± 1.55 | 10.92 ± 1.27 | 0.48[a] |
| Hematocrit (%) | 36.74 ± 0.36 | 36.97 ± 0.33 | 0.63[a] | 32.81 ± 4.11 | 33.08 ± 3.36 | 0.62[a] |
| Platelet (×10$^3$) | 232.27 ± 69.57 | 226.44 ± 61.44 | 0.54[a] | 205.10 ± 60.12 | 190.52 ± 51.70 | 0.80[a] |
| Neutrophil (%) | 72.26 ± 6.39 | 72.37 ± 6.14 | 0.90[a] | 83.20 (81.87- 83.65) | 83.10 (80.95- 83.28) | 0.68[b] |
| Lymphocyte (%) | 19.93 ± 6.01 | 19.77 ± 5.55 | 0.85[a] | 10.30 (0.20-29.40) | 9.90 (4.60-40.30) | 0.88[b] |
| Eosinophil (%) | 0.70 ± 0.62 | 0.86 ± 0.70 | 0.10[a] | 0.20 (0.00-2.00) | 0.30 (0.00-2.00) | 0.01[b] |
| Basophil (%) | 0.32 ± 0.14 | 0.34 ± 0.15 | 0.39[a] | 0.20 (0.00-0.60) | 0.20 (0.00-1.40) | 0.10[b] |
| Monocyte (%) | 6.52 ± 1.80 | 6.58 ± 1.76 | 0.39[a] | 5.89 ± 1.76 | 6.11 ± 1.70 | 0.37[a] |

[a] Independent Samples T-Test, [b] Mann-Whitney U Test
Values are median (minimum-maximums) or mean ± standard deviation.

**Table 3.** The comparison of NLR and ELR according to the type of anesthesia

| | Preoperative | | | Postoperative | | |
|---|---|---|---|---|---|---|
| | General Anesthesia (GA) (n= 99) | Spinal Anesthesia (SA) (n= 87) | p | General Anesthesia (GA) (n= 99) | Spinal Anesthesia (SA) (n= 87) | p |
| NLR | 3.7 (1.0-13.6) | 3.7 (1.4-17.1) | 0.37[b] | 8.40 ± 3.05 | 8.44 ± 3.26 | 0.93[a] |
| ELR | 0.028 (0.0-0.6) | 0.034 (0.0- 0.3) | 0.15[b] | 0.018 (0.0- 0.5) | 0.028 (0.0- 0.2) | 0.04[b] |

NLR: neutrophil /lymphocyte ratio, ELR: eosinophil/lymphocyte ratio.
[a] Independent Samples T-Test, [b] Mann-Whitney U Test
Values are median (minimum-maximums) or mean ± standard deviation.

Preoperative thrombocyte value (× 10$^3$) was 232.27 ± 69.57 in GA, 226.44 ± 61.44 in SA, p <0.54; Postoperative GA: 205.10 ± 60.12, SA: 190.52 ± 51.70, p <0.80. There was no significant difference in the hemoglobin, hematocrit, and platelet groups between the groups, preoperatively and postoperatively.

The preoperative neutrophil ratio in maternal blood was 72.31 ± 6.25%, while postoperative was 82.46 ± 4.96%. There was a significant difference between pre-and postoperative neutrophil ratios (p = 0.00).

Table 2 shows the distribution of preoperative and postoperative leukocyte elements in the GA and SA groups. Comparison of NLR and ELR according to the type of anesthesia is presented in Table 3.

Preoperative neutrophil (%) was 72.26 ± 6.39 GA, 72.37 ± 6.14 SA, p <0.90; lymphocyte (%) GA: 19.93 ± 6.01, SA: 19.77 ± 5.55, p <0.85; eosinophilia (%) GA: 0.70 ± 0.62, SA 0.86 ± 0.70, p <0.10; basophil (%)GA: 0.32 ± 0.14, SA: 0.34 ± 0.15, p <0.39; monocyte (%) GA: 6.52 ± 1.80, SA: 6.58 ± 1.76, p <0.39. In the postoperative period, no significant difference was found between the two groups in terms of neutrophil, lymphocyte, monocyte, basophil. Postoperative neutrophils (%) GA: 83.20 (81.87- 83.65), SA: 83.10 (80.95- 83.28), p <0.85; lymphocyte (%) GA: 10.30 (0.20-29.40), SA: 9.90 (4.60-40.30), p < 88; eosinophilia (%) GA: 0.20 (0.00-2.00), SA: 0.30 (0.00-2.00), p <0.01; basophil (%) GA: 0.20 (0.00-0.60), SA: 0.20 (0.00-1.40), p <0.10; monocyte (%) GA: 5.89 ± 1.76, SA: 6.11 ± 1.70, p <0.37. NLR in preoperative GA 3.7 (1.0-13.6), SA: 3.7 (1.4-17.1), p <0.37; postoperative GA 8.40 ± 3.05 in SA, 8.44 ± 3.26 SA, p <0.93. There was no statistically significant difference in NLR after surgery.

ELR in preoperative GA: 0.028 (0.0-0.6), SA: 0.034 (0.0-0.3), p<0.15; postoperative GA: 0.018 (0.0-0.5), SA: 0.028 (0.0-0.2), p<0.04.

When the postoperative GA and SA groups were compared, there was a statistically significant difference in eosinophil distribution and ELR. In the postoperative period, eosinophils decreased more in the GA group.

## Discussion

Surgical stress activates inflammation factors. We compared the effects of GA and SA in the group with systemic physiological changes such as pregnancy. When inflammation is stimulated, lymphocyte decreases and leukocyte increases. The release of mediators (such as IL-6) released from lymphocytes increases. It was observed that the wound healing was better when the postoperative NLR was high. Postoperative infection was observed less frequently in these patients [13, 14]. Like NLR, ELR is used as a prognostic factor in inflammation [15, 16]. High ELR was considered a good prognosis.

In our study, it was observed that ELR was significantly lower in the GA group.

We found that neutrophil ratios significantly increased in all cesarean sections in patients who GA and SA in CS. Our findings are similar to the change in leukocyte elements during stress in other surgeries [4, 5].

In our study, when the NLR values were compared, we found no statistically significant difference between the groups. Erbaş et al. observed that NLR values were statistically significantly lower in the SA group than in the GA group [17]. However, in this study, there is no information about the standardization of the surgical procedure. In our study, the control blood value obtained at the 24th hour after CS performed by the same surgeon was examined. In a stuy by Erbaş et al., control evaluations were made according to the blood results two hours after the operation.

Doğan et al. compared patients who underwent elective surgery under general and epidural anesthesia. However, in this study, the type of operation and the gender of the patients are not standardized. In this study, they concluded that epidural anesthesia affected the leukocyte distribution less than general anesthesia [18]. Our study was conducted only on pregnant women. There was no significant difference in leukocyte distribution in patients treated with GA or SA.

Aldemir et al. in their study, comparing propofol (intravenous) and desflurane (inhaler) anesthesia, found that the NLR was lower in the propofol group than in the desflurane group. Propofol had a positive but transient effect on NLR [19].

Karagöz et al. showed that the NLR rate was not affected by the mode of cesarean section anesthesia. In this study, plateletcrit was recommended to predict the prognosis, and in our research, ELR was recommended [20].

Surhonne et al.  found that in hernia surgery, NLR was higher in GA than in SA. Since our study included both pregnant women and only women with an average young age, it had a more specific group, which may be the reason for the difference  [21].

Dermitzaki et al. compared interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) values in patients undergoing general and neuraxial anesthesia to evaluate the anti-inflammatory response. As a result of the study, there was no significant difference between the two groups. According to this research, IL-6 levels also increase in postoperative patients regardless of the anesthesia type [22]. In contrast, in the study by Zura et al., a significant increase in IL-6 levels was found in patients who underwent GA compared with patients who underwent SA [23]. There was no difference in NLR in our study between the two anesthesia, and ELR was significantly lower in GA.

Adıyeke et al. showed that APGAR values at 1 and 5 minutes in SA were higher than GA with spinal anesthesia in pregnant women with COVID-19. In our study, in accordance with the literature, Apgar scores were higher  both at the 1st and 5th minute in the SA group [16, 24].

*Limitations*: Changes in leukocyte elements can be seen during the day, both due to the hormonal response whose level changes due to surgical stress and the diurnal rhythm. In addition, factors such as the change in personal analgesic need and the amount of analgesic administered, early feeding and early breastfeeding may cause changes in the anti-inflammatory response. Large-scale studies are required that take these factors into account.

***Scientific Responsibility Statement***

*The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.*

***Animal and human rights statement***

*All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.*

***Funding:*** *None*

***Conflict of interest***

*None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.*

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***How to cite this article:***
*Selda Songur Dağlı, Recai Dağlı. The effect of anesthesia method on the distribution of leukocyte elements and neutrophil/lymphocyte ratio in elective cesareane sections. Ann Clin Anal Med 2021;12(Suppl 3): S323-327*