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**ORIGINAL RESEARCH** **OBSTETRIC ANESTHESIA**

# Comparison of the effects of normal and cesarean delivery methods and general and spinal anesthesia techniques on the inflammatory response

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## ABSTRACT

**Background:** Childbirth induces an inflammatory response that varies with the delivery mode and anesthesia type. This study investigates how normal delivery (ND) versus cesarean section (CS) under spinal anesthesia (SA) or general anesthesia (GA) affects inflammatory markers, including mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR).

**Methods:** This retrospective study included patients who underwent ND or CS at a tertiary care hospital in Turkey between 2013 and 2017. Patients with significant illnesses were excluded. Patients were categorized into three groups: CS-SA, CS-GA, and ND. Blood samples were taken preoperatively and 24 h postpartum to measure MPV, NLR, and PLR.

**Results:** The mean age was 27.8 ± 3.8 years. Hemoglobin and platelet counts decreased significantly in all groups, while NLR increased. PLR increased in the CS-SA and CS-GA groups but not in the ND group. MPV decreased significantly only in the CS-SA group. Postoperative NLR, PLR, and MPV showed significant differences between the groups, with the highest response in the CS-GA group.

**Conclusion:** Cesarean section under general anesthesia is associated with a higher inflammatory response compared to spinal anesthesia or normal delivery. Normal vaginal delivery results in the lowest inflammatory response.

**Keywords**: Cesarean Section; Anesthesia, Spinal; General; Inflammatory Response; Neutrophil-to-Lymphocyte Ratio

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## 1. INTRODUCTION

The rate of births by cesarean section (CS) has increased significantly in recent years, accounting for almost one-third of all births in the United States [1]. Anesthesia, which can be administered in various types, is an integral part of the cesarean birth procedure. Medical advances have significantly increased the safety of anesthesia, leading to a significant reduction in associated mortality rates. As a matter of fact, the mortality rate associated with general anesthesia (GA) has fallen to less than one in 200,000 to 300,000 cases [2].

Significant changes occur in the immune system during surgery and anesthesia due to factors such as the scale of the surgery, patient characteristics, medications administered, and blood transfusions. This adaptive response includes the release of immune mediators due to surgical trauma, which may be further affected by the types of anesthesia and surgical methods chosen [3–5]. Clinicians often evaluate the inflammatory status of patients through parameters, including C-reactive protein, fibrinogen, and pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α). However, these high-cost tests are typically performed in specialized laboratories that are not easily accessible [6]. In contrast, markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) are practical and cost-effective alternatives for assessing inflammation associated with various diseases [6, 7].

Although changes in MPV, NLR, and PLR values in the context of preterm labor or pregnancy have been examined in the literature, studies on the role of different types of anesthesia in modulating these inflammatory markers are limited [8, 9]. Therefore, it remains unclear how the type of anesthesia used for birth may affect inflammatory responses. Preliminary evidence suggests that spinal anesthesia (SA) may minimize systemic inflammation by targeting only the lower body, as evidenced by more stable MPV, NLR, and PLR values, thus mitigating the broader inflammatory effects seen with general anesthesia. Preliminary evidence suggests that spinal anesthesia (SA) may minimize systemic inflammation by targeting only the lower body, as evidenced by more stable MPV, NLR, and PLR values, thus mitigating the broader inflammatory effects seen when general anesthesia is performed.

### Objective of the study:

The main goal of this study is to compare the impact of different types of anesthesia with CS and ND on inflammatory markers, specifically MPV, NLR, and PLR. The study seeks to ascertain which anesthesia technique and delivery method result in reduced inflammatory response, providing valuable insights into optimal clinical practices for minimizing inflammation during childbirth.

# 2. METHODOLOGY

## 2.1. Study Design

This study was designed as a retrospective single-center study. The study protocol was approved by the XXX University Ethics Committee (Protocol Number: 18920478-050.01.04/E.103300, Approval No: 2017/14, Approval Date: 06.09.2017).

## 2.2. Population and Sample

The study population consisted of patients who underwent ND or CS at XXXX University Hospital, a tertiary care hospital in Turkey, between 2013 and 2017. Patients' data were accessed from their medical records. Patients who had significant illnesses such as hypertension, diabetes, cardiovascular disease, chorioamnionitis, preeclampsia, and fever, have been using corticosteroids or medications that affect the immune system, had a history of alcohol consumption, and had various concomitant diseases, including infections, hematological, renal, rheumatological, and oncological diseases were excluded from the study. Of the remaining patients, those who were assigned American Society of Anesthesiologists (ASA) class I or II status and thus had normal health or mild systemic disease were included in the study. We categorized the patients into three groups according to the mode of delivery they underwent and the type of anesthesia administered in the case of CS delivery: CS-SA, CS-GA, and ND, that is, term delivery (36-42 weeks of gestational age) with head presentation. We chose our sample size to be 75 patients in each group since group sizes typically ranged from 70 to 100 in previous studies evaluating inflammatory markers [12, 13]. In the end, we included 225 patients in our sample, with 75 patients in each study group.

## 2.3. Anesthesia Protocol

Patients in the CS-SA group were administered SA from the L2-L3 or L3-L4 intervertebral space using a 26-G spinal needle while they were in a sitting position. 0.5% hyperbaric bupivacaine was injected into their subarachnoid space, followed by sensory block testing using the needle method. Patients’ blood pressure was measured every 5 minutes after SA. Their hypotension was recorded in the event that systolic blood pressure was less than 90 mmHg or decreased more than 20% of their baseline systolic blood pressure, in which case they were administered 10 mg ephedrine IV [10].

Patients in the CS-GA group were preoxygenated with 100% $O_2$ and given 2 mg/kg propofol and 0.6 mg/kg rocuronium IV before the induction of GA. During the induction of GA, patients were intubated after controlled ventilation with 6% $O_2$ using an appropriate mask. Patients were ventilated with 50% air and 50% $O_2$ with 2% sevoflurane at 6 L/min throughout the anesthesia procedure. Patients were given 1 μg/kg fentanyl after delivery. Patients’ inhalation of active ingredients was stopped after the last skin suture, and they were started on manual ventilation with 100% $O_2$. All parameters were measured and recorded in accordance with the latest versions of relevant guidelines.[11]

 

### 2.4. Blood Sample Collection

Per institutional guidelines, blood samples were taken preoperatively from the antecubital vein between 8 and 10 in the morning after 12-hour fasting, and 24 hours postpartum. The collected blood samples were analyzed using the Beckman Coulter LH 780 instrument system (Beckman Coulter, Inc., CA, USA), fluorescence flow cytometry, and the electrical bioimpedance method.

**Table 1. Patient Demographics and Surgical Duration Across Different Delivery Modalities**

| | Group ND (n = 75) | Group SA (n = 75) | Group GA (n = 75) | p-values |
|---|---|---|---|---|
| **Age (yr)†** | 27.31 ± 4.46 | 27.55 ± 3.93 | 28.8 ± 3.05 | > 0.05** |
| **Body mass index (kg/m²) §** | 29 [20 – 42] | 29 [22 – 43] | 29 [19 – 45] | 0.663*** |
| **Operation time (min)†** | - | 57.6 ± 6.8 | 54.0 ± 7.1 | > 0.05* |

*ND: Normal delivery, SA Spinal Anesthesia, GA: General Anesthesia,*

*†: Mean ± Standard Deviation*

*§: Median [Min.-Max.]*

**. Independent Samples T-Test*

***. One-Way ANOVA test,*

****. Kruskal Wallis test.*

### 2.5. Data Collection

Patients' demographic characteristics, including age, weight, and height, were obtained from their medical records. Patients' body mass index (BMI) values were calculated by dividing their weight (kg) by the square of their height ($m^2$). In addition, patients' surgical details, including the duration of CS and laboratory test results, including preoperative and postoperative hemoglobin (Hb), neutrophil, lymphocyte, platelet counts, and MPV values, were recorded. We calculated composite indicators NLR and PLR by dividing the neutrophil and platelet counts by the lymphocyte count, respectively. We recorded the MPV, NLR, and PLR values at the time of admission to the hospital for delivery and 24 hours postpartum.

### 2.6. Statistical Analysis

We analyzed the collected data using the SPSS 20.0 (Statistical Product and Service Solutions for Windows, Version 20.0, IBM Corp., Armonk, NY, US, 2011) software package. The descriptive statistics obtained from the collected data were expressed as mean ± standard deviation values in the case of continuous variables determined to conform to the normal distribution, e.g., hemoglobin platelet count, as median with minimum and maximum values in the case of continuous variables determined not to conform to the normal distribution, e.g., NLR, PLR, MPV, and as numbers and percentage values in the case of categorical variables. The normal distribution characteristics of numerical variables were analyzed using the Kolmogorov-Smirnov test. In comparing the differences in the variables' pre- and post-delivery numerical values, a paired sample t-test was used for numerical variables determined to conform to the normal distribution, and the Wilcoxon signed-rank test was used for numerical variables determined not to conform to the normal distribution. In comparing the study groups, i.e., ND, CS-SA, and CS-GA, the Mann-Whitney U test with Bonferroni correction with probability (P) < 0.017 was used. The overall threshold for statistical significance was set at P < 0.05.

## 3. RESULTS

The distribution of demographic characteristics by the study groups is given in Table 1. Accordingly, there was no significant difference between the groups in demographic characteristics, BMI value, and duration of CS (p>0.05). The distribution of laboratory test results by the study groups is given in Table 2. Accordingly, hemoglobin (Hb) level and platelet count decreased significantly in all groups, whereas NLR value significantly increased (P < 0.05). PLR value increased in the CS-SA and CS-GA groups (P < 0.001) but not in the ND group (P = 0.376). Although the MPV value decreased in all groups, only the decrease in the CS-SA group was significant (P = 0.012). There was no significant difference in preoperative NLR, PLR, and MPV values between the groups. On the other hand, significant differences were found between the groups in postoperative NLR (P < 0.001), PLR (P = 0.003), and MPV (P = 0.019) values, with median NLR significantly higher in the CS-GA group (P < 0.001).

## 4. DISCUSSION

There are only a limited number of studies in the literature on changes in the levels of inflammatory markers such as MPV, NLR, and PLR in women who underwent ND or CS under different types of anesthesia.[14, 15] These studies show that the type of anesthesia administered changes the inflammatory response, as reflected in NLR, PLR, and MPV levels. Similarly, we found significant increases in NLR and

PLR levels in the SA and GA groups and only an increase in NLR level in the ND group, suggesting a more natural course of decrease in inflammatory response within 24 hours after delivery.

It has been reported that GA leads to a greater increase in the levels of inflammatory markers due to its systemic effect, which triggers a broader inflammatory cascade, compared to the localized effect of SA.[15,16] This effect includes activation of the neuroendocrine system during and after surgery, releasing cytokines such as IL-6 and TNF-α, and natural killer cell responses.[17]

inflammatory response was more intense in women who underwent CS under GA.

Although inflammation is essential for tissue repair, too much of it can be detrimental.[17] Our finding that the NLR value in the GA group increased significantly more than the other groups may indicate an increased susceptibility to infection due to the transient inflammatory surge associated with GA.[14] The immune response to surgery depends on both surgical trauma and neuroendocrine stress.[3,17,19] Attenuated cortisol, catecholamine, and IL-6 responses to SA suggest a milder stress reaction.[15,18]

**Table 2: Comparative Evaluation of Hematological Parameters Pre- and Post-Delivery by Anesthesia Method**

| | Group ND (n = 75) | Group SA (n = 75) | Group GA (n = 75) |
|---|---|---|---|
| **Hemoglobin (*g/dL*) †** | | | |
| Pre | 12.0 ± 1.36 | 12.0 ± 1.15 | 11.8 ± 1.14 |
| Post | 10.0 ± 1.2 | 10.6 ± 1.2 | 10.8 ± 1.14 |
| ***p**** | **< 0.001** | **< 0.001** | **< 0.001** |
| **Platelet (*K/mm³*)†** | | | |
| Pre | 230.3 ± 59.6 | 225.8 ± 67.6 | 228.8 ± 70.6 |
| Post | 201.8 ± 57.6 | 196.1 ± 61.2 | 197.7 ± 64.5 |
| ***p**** | **0.011** | **0.018** | **0.018** |
| **NLR §** | | | |
| Pre | 4.3 [1.8 – 17.1] | 3.7 [1.4 – 29.7] | 4 [1.9 – 10.5] |
| Post | 6.6 [2.3 – 20.9] | 8.0 [2.9 – 30.2] | 10.4 [2.4 – 46.0] |
| ***p***** | **< 0.001** | **< 0.001** | **< 0.001** |
| **PLR §** | | | |
| Pre | 115.6 [57.4 – 285.7] | 111.7 [39.0 – 453.3] | 107.5 [41.7 – 280.9] |
| Post | 111.9 [41.7 – 365.6] | 120.7 [52.8 – 380.0] | 142.9 [45.9 – 576.7] |
| ***p***** | 0.376 | **0.003** | **< 0.001** |
| **MPV §** | | | |
| Pre | 8.5 [5.9 – 11.3] | 8.8 [6.6 – 12.9] | 8.9 [5.3 – 13.9] |
| Post | 8.3 [6.7 – 11.0] | 8.5 [6.8 – 11.8] | 8.7 [6.1 – 12.5] |
| ***p***** | 0.064 | **0.012** | 0.149 |

*NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, MPV: Mean platelet volume, ND: Normal delivery, SA Spina*
*†: Mean ± Standard Deviation,*
*§: Median [Min.-Max.],*
**. One-Way ANOVA,*
***. Kruskal Wallis-H test,*
****. Paired t-test,*
***** Wilcoxon test*

Anesthesia can modulate these inflammatory responses. As a matter of fact, current evidence shows that SA may be preferred to minimize the neuroendocrine stress response.[15,16,18] Similarly, our findings show that the

Pregnancy itself significantly alters maternal hormone levels in the context of the interplay between anxiety, stress, and birth biology.[20, 21]

 

Significantly higher NLR, PLR, and MPV values in the GA group than in other groups underscore the physiological adaptation to surgical stress [5, 15, 20]. NLR increases as neutrophils increase and lymphocytes decrease due to anesthesia-induced immunosuppression [5], prioritizing immediate inflammation over cellular immunity. The increase in PLR, which reflects the increase in platelets and decrease in lymphocytes due to coagulation and tissue repair, indicates a stress response. The increase in MPV indicates greater platelet activation and size, which is crucial for rapid coagulation. These changes collectively represent an acute physiological shift towards immediate defense and healing mechanisms, temporarily suppressing certain immune functions to mitigate surgical trauma.[22]

In particular, suppression of cellular immunity is a critical inflammatory response to surgical stress, potentially compromising host defenses.[4, 15, 19] The presence of marked neutrophilia and lymphopenia may indicate a higher postoperative infection risk. These leukocytic changes have been linked to inflammatory mediators like IL-6 and neutrophilia, lymphopenia, and elevated NLR values associated with morbidity or mortality in various conditions.[5, 8, 12] High baseline NLR values may predict poor prognosis and also postoperative morbidity in patients with malignancy.[23] NLR, which can be determined within the scope of peripheral blood leukocyte count, is a simple and cost-effective clinical tool.

The study's primary limitation was its retrospective design. As a reason, retrospective design may introduce bias since the data collected from existing records, and certain variables, such as the duration of normal vaginal delivery, could not be precisely controlled. Secondly, the fact that postoperative blood values were measured only at the 24-hour mark may not have fully depicted the course of the inflammatory response. Thirdly, potential confounding factors such as medications or variations in surgical technique were not taken into account. Further prospective studies with larger samples and more frequent postoperative measurements are needed to corroborate this study's findings and better understand the temporal dynamics of inflammation following the administration of different types of anesthesia. Additionally, our follow-up period was limited. Hence, longer-term studies are required to assess the persistence of inflammatory responses and their clinical implications. Lastly, more of the markers and pathways involved in the inflammatory response could be evaluated.

Postoperative inflammatory markers were the highest in the Group CS-GA, followed by the Group CS-SA, and lowest in the Group ND.

## 5. CONCLUSION

CS under GA is associated with a higher inflammatory response compared to SA or ND. Normal vaginal delivery results in the lowest inflammatory response. These findings suggest that SA may be preferred over GA for CS to minimize inflammation. Further research with larger sample sizes and more frequent postoperative measurements is needed to corroborate these findings and explore the long-term implications of different anesthesia techniques on inflammatory responses.

## 6. ETHICAL COMMITTEE APPROVAL

The study protocol was approved by the XXX University Ethics Committee (Protocol Number: 18920478-050.01.04/E.103300, Approval No: 2017/14, Approval Date: 06.09.2017).

## 7. DATA AVAILABILITY

The numerical data is available with the corresponding author and can be provided on request.

## 8. CONFLICT OF INTEREST

All authors declare that there was no conflicting interests.

## 9.AUTHORS CONTRIBUTION:

EUH: Concept, statistics, collection of patient data,

BA: conducted the study, edited the manuscript

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