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The Impact of Anesthesia Choice on Maternal and Fetal Outcomes in Pregnant Women with COVID-19 Undergoing Cesarean Sectio

Esra Adıyeke[1*], Nurten Bakan[1]

1 Sancaktepe Martyr Prof. Dr. İlhan Varank Training and Research Hospital Department of Anesthesiology and Reanimation, Istanbul, Turkey.

Abstract

Background: Cesarean section (C/S) is frequently considered by the obstetricians for delivery in pregnant women with COVID-19. However, there is little data concerning the mode of anesthesia, whether general (G) or regional (R). This study aimed to compare general and regional anesthesia concerning the maternal and fetal outcomes in pregnant COVID-19 women undergoing C/S.

Methods: Twenty-three consecutive pregnant women with COVID-19 admitted for delivery with C/S in our institute were enrolled in this retrospective analysis. All C/S procedures and anesthesia were performed by the same surgical team and the anesthesiologist. Subjects were divided into two groups according to the anesthesia procedure which was left to the anesthesiologist's and obstetrician's discretion. The difference in laboratory tests, length of hospital stay, maternal ICU admission, and 1st and 5th minute APGAR scores was the primary outcome measure of this study.

Results: There were no significant differences between the groups concerning fever, oxygen saturation, D-dimer, ferritin, C-reactive protein, leukocyte count, mean platelet volume and neutrophil to lymphocyte ratio. However, subjects receiving general anesthesia had higher procalcitonin at admission (1.2 ± 0.5, ng/mL vs. 0.6 ± 0.4, ng/mL, p=0.010). However, length of hospital stay was significantly longer in subjects receiving general anesthesia compared to those receiving regional anesthesia (18.5 ± 6.2 days vs. 12.6 ± 4.2 days, p=0.016). Moreover, 1st (6.1 ± 0.8 vs. 7.6 ± 0.5, p=0.011) and 5th minute (7.2 ± 1.4 vs. 8.9 ± 1.3, p=0.026) APGAR scores of the neonates born to mothers receiving general anesthesia were significantly lower compared to those born to mothers receiving regional anesthesia.

Conclusions: Both regional and general anesthesia provide similar changes in surrogate markers of inflammation, and D-dimer. The length of the hospital stay was significantly higher in women undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S. Moreover, the 1st and 5th minute APGAR scores were significantly lower in neonates born to mothers undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S.

Key words: COVID-19, pregnancy, cesarean, general anesthesia, regional anesthesia

***Corresponding Author:** Esra Adıyeke, Sancaktepe Prof. Dr. İlhan Varank Training and Research Hospital Department of Anesthesiology and Reanimation Emek Mahallesi, Namık Kemal Street. No:54, PK:34785 Sancaktepe / İstanbul, Turkey. **Phone:** +90 216 606 33 00 **E-mail:** dresradiyeke@gmail.com **Received:** Sep, 2020. **Accepted:** Jan, 2021.

Introduction

COVID-19, a multisystem disease that primarily affects the lungs. However, cardiovascular and thrombotic complications are also reported in patients with COVID-19. There are certain conditions including preexisting severe cardiovascular disease, advanced age, cystic fibrosis, severe asthma or severe chronic obstructive pulmonary disease (COPD), use of steroids or immunosuppressant drugs, which make individuals more vulnerable to be infected by COVID-19 (1). Pregnant women are also considered as having high risk for being infected by CVODI-19 or being subject to complications of COVID-19 (2, 3).

There are many unknowns for pregnant women during the coronavirus disease 2019 (COVID-19) pandemic. A number of physiological changes influencing immune system, respiratory system, cardiovascular function, and coagulation. The immune system adapts during pregnancy to allow for the growth of a semiallogenic fetus, resulting in an altered immune response to infections during pregnancy (4). The altered inflammatory response to viruses during pregnancy is thought to be mediated by a shift in CD4+ T cell population toward the Th2 phenotype over Th1, a decrease in circulating natural killer cells, a decrease in circulating plasmacytoid dendritic cells, and an increase in circulating progesterone levels (5, 6). Despite these changes in immunresponse it remains unclear whether these adaptations result in a higher susceptibility and/or morbidity or are, in fact, protective against COVID-19. In addition to immune changes, a hypercoagulable state which may complicate COVID-19 infection occurs during pregnancy and pregnant women with COVID-19 may have additive or synergistic risk factors for thrombosis (7).

Cesarean section is frequently considered by the obstetricians for delivery in pregnant women with COVID-19. However, there is little data concerning the mode of anesthesia, whether general or regional. Given the unfavorable effects of general anesthesia on pulmonary physiology, we hypothesized that utilization of regional anesthesia in this particular patients subset for delivery with C/S would provide better outcomes both for the mother and the neonates.

This study aimed to compare general and regional anesthesia concerning the maternal and fetal outcomes in pregnant COVID-19 women undergoing C/S.

Materials and Methods

Twenty-three consecutive pregnant women with COVID-19 admitted for delivery with C/S between April 2020, and August 2020 in our institute were enrolled in this retrospective analysis. C/S indication was based on the international guidelines if the following were existing: repeat cesarean delivery, obstructive lesions in the lower genital tract, pelvic abnormalities that preclude engagement or interfere with descent of the fetal presentation in labor, cardiac conditions that preclude Valsalva maneuver during a vaginal delivery, malpresentations, congenital malformations or skeletal disorders, infection, prolonged academia, placenta previa, placenta accrete, abnormal labor due to cephalopelvic disproportion. Diagnosis of COVID-19 was based on the Polymerase chain reaction (PCR) test which was performed upon admission. All

subjects provided informed consent. The study was approved by Institutional Ethical Committee and was conducted in accordance with the Helsinki Declaration.

All C/S procedures and anesthesia were performed in elective condition by the same surgical team and the anesthesiologist. General anesthesia was induced using propofol or sodium thiopental and maintained with sevoflurane. IV morphine, fentanyl and sometimes meperidine were used to manage perioperative analgesia. Spinal anesthesia was preferred as regional anesthesia in patients. Spinal anesthesia was performed with a spinal needle inserted through the L3–L4 interspace. Following the return of 3ml clear cerebrospinal fluid, 0.5% levobupivacaine (15 mg) was injected over 20–30 s through 25 G Whitacre/Quincke spinal needle. When requires, additional doses of levobupivacaine were administered during surgery. For postoperative analgesia, patients received 4000 mg of paracetamol (in four separate doses of 1000 mg). If necessary, three doses of 50 mg diclofenac were administered. Demographic and clinical characteristics, comorbid diseases including the presence of diabetes, hypertension, and cardiovascular disease and admission and discharge blood tests were compared between subjects undergoing general and regional anesthesia. All subjects underwent thorax computed tomography (CT) following C/S. Lung infiltrates >50% on thorax CT were recorded. Length of hospital stay (LOHS), maternal intensive care unit (ICU) admission, 1st and 5th minute APGAR scores and neonatal mortality were noted.

Primary endpoint

Subjects were divided into two groups according to the anesthesia procedure which was left to the anesthesiologist's and obstetrician's discretion. The difference in laboratory tests, LOHS, maternal ICU admission, and 1st and 5th minute APGAR scores was the primary outcome measure of this study.

Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Histograms and Q-Q plots were used to test the distribution of data. Continuous variables are presented as mean ± standard deviation or median (minimum-maximum) according to normal or abnormal distribution and categorical variables were presented as frequency (percentage). Independent samples t test and the Mann Whitney U test were used for comparison of the groups. Pearson chi-square test was employed in comparison of the categorical variables. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

A total of 23 pregnant women with COVID 19 (mean age 29.1 ± 6.2 years) who underwent C/S either under general anesthesia or regional anesthesia were included in this retrospective analysis. Subjects receiving general anesthesia or regional anesthesia were similar with respect to age and the presence of comorbid diseases. Demographic features and laboratory measurements of the study groups are listed in Table 1.

Table 1. Demographic and clinical characteristics and laboratory test of the groups

	General Anesthesia n=12	Regional Anesthesia n=11	p value
Age, years	31.9 ± 6.1	29.7 ± 5.4	0.377
Comorbid disease, n	1 (8.3%)	1 (9.1%)	0.739
Fever (admission, °C)	37.5 ± 0.6	37.0 ± 0.6	0.089
Fever (discharge, °C)	36.3 ± 0.2	36.4 ± 0.2	0.480
O^2Sat (admission, %)	89.4 ± 6.5	91.1 ± 2.8	0.417
O^2Sat (preC/S, %)	97.0 ± 2.3	97.9 ± 1.6	0.339
O^2Sat (discharge, %)	95.7 ± 1.0	96.8 ± 1.0	0.580
D-dimer (admission, mcg/mL)	1.37 ± 1.011	1.23 ± 0.76	0.719
D-dimer (discharge, mcg/mL)	0.50 ± 0.27	0.57 ± 0.22	0.540
Ferritin (admission, ng/mL)	698.9 ± 477.3	547.3 ± 382.8	0.414
Ferritin (discharge, ng/mL)	559.5 ± 345.5	523.2 ± 295.7	0.791
C-reactive protein (admission, mg/L)	19.0 ± 11.1	15.6 ± 8.1	0.413
C-reactive protein (discharge, mg/L)	1.31 ± 0.2	1.08 ± 0.1	0.751
Procalcitonin (admission, ng/mL)	1.2 ± 0.5	0.6 ± 0.4	**0.010**
Procalcitonin (discharge, ng/mL)	0.08 ± 0.07	0.10 ± 0.06	0.778
Leukocyte count (admission, $x10^3$)	11.4 ± 2.9	10.5 ± 2.3	0.396
Leukocyte count (discharge, $x10^3$)	8.7 ± 1.5	8.6 ± 1.1	0.800
Neutrophil % (admission)	76.2 ± 14.1	73.9 ± 10.8	0.659
Neutrophil % (discharge)	62.9 ± 7.5	62.8 ± 6.7	0.987
Lymphocyte (admission, $x10^3$)	0.69 ± 0.17	0.77 ± 0.22	0.328
Lymphocyte (discharge, $x10^3$)	1.61 ± 0.32	1.37 ± 0.43	0.056

MPV (admission, fL)	8.9 ± 0.7	9.0 ± 0.7	0.762
MPV (discharge, fL)	8.6 ± 0.7	8.6 ± 0.5	0.967
RDW % (admission)	13.5 ± 1.5	14.0 ± 1.9	0.561
RDW % (discharge)	13.1 ± 1.7	12.9 ± 0.6	0.803
NLR (admission)	12.5 ± 4.5	13.2 ± 3.9	0.704
NLR (discharge)	3.7 ± 1.5	4.3 ± 1.7	0.420
Hemoglobin (admission, g/dL)	10.7 ± 0.9	10.4 ± 1.3	0.588
Hemoglobin (discharge, g/dL)	12.0 ± 1.1	11.8 ± 1.0	0.615
Platelet count, (admission, x10^3)	221 ± 65	254 ± 69	0.256
Platelet count, (discharge, x10^3)	356 ± 83	331 ± 74	0.572
LOHS, days	18.5 ± 6.2	12.6 ± 4.2	**0.016**
ICU admission, n	2 (16.7%)	1 (9.1%)	0.534
>50 % Lung involvement, n	8 (66.7%)	5 (45.5%)	0.414
APGAR1st min	**6.1 ± 0.8**	**7.6 ± 0.5**	**0.011**
APGAR5th min	**7.2 ± 1.4**	**8.9 ± 1.3**	**0.026**
Neonatal mortality, n	1 (8.3%)	0 (0%)	0.522

LOHS: Length of hospital stay, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, RDW: Reticulocyte distribution width

There were no significant differences between the groups concerning fever, oxygen saturation, D-dimer, ferritin, C-reactive protein, leukocyte count, mean platelet volume and neutrophil to lymphocyte ratio. However, subjects receiving general anesthesia had higher procalcitonin at admission (1.2 ± 0.5, ng/mL vs. 0.6 ± 0.4, ng/mL, p=0.010). However, LOHS was significantly longer in subjects receiving general anesthesia compared to those receiving regional anesthesia (18.5 ± 6.2 days vs. 12.6 ± 4.2 days, p=0.016). Moreover, 1st (6.1 ± 0.8 vs. 7.6 ± 0.5, p=0.011) and 5th minute (7.2 ± 1.4 vs. 8.9 ± 1.3, p=0.026) APGAR scores of the neonates born to mothers receiving general anesthesia were significantly lower compared to those born to mothers receiving regional anesthesia. Maternal mortality did not occur in any of the groups. Neonatal mortality was observed in one neonate in the general anesthesia group.

Discussion

The present study purposed to investigate the maternal and fetal outcomes in pregnant women with COVID-19 who underwent C/S either under general or regional anesthesia. Our findings show that both groups have similar blood test results both on admission and discharge. However, length of hospital stay was significantly lower in subjects undergoing C/S with regional anesthesia.

Although extensive data concerning the risk of pregnant women for COVID-19 infection is limited, they are considered to be at high risk for severe forms of COVID-19 as a consequence of the altered immunity, and increased thromoembolic events (8). Moreover, physiological changes in cardiovascular and respiratory system (diaphragm elevation, high oxygen consumption, and mucosal edema) during pregnancy may increase the risk of severe COVID-19 infection in pregnant women. Recent experience from SARS infection indicates that women with SARS infection were more likely to ICU as well as the need for mechanical ventilation compared to general population (9).

In addition to obstetric measures, COVID-19 infection which has increased among pregnant women has become another bail-out indication for C/S for rapid delivery of the fetus and management of the mothers. However, owing to the respiratory changes occurring during pregnancy, the mode of anesthesia may increase the risk for more severe infection. There is currently few reports comparing the safety of general and regional anesthesia in pregnant women with COVID-19 infection who are scheduled for C/S. We hypothesized that diaphragm elevation, respiratory mucosal edema, and increased oxygen consumption preexisting in pregnant women could increase the risk for development of a more severe form of COVID-19 when general anesthesia was applied to these subjects during C/S.

Although previous data published before 2002's reported an increased morbidity and mortality in pregnant women undergoing C/S with general anesthesia, further evidence was unable to prove that general anesthesia was associated to increased mortality (10, 11). However, it is well known that general anesthesia may deteriorate pulmonary function in several ways. Many of the anesthetic agents used currently leads to a reduction in functional residual capacity as a consequence of the weakened muscle tone (12). The reduction in functional residual capacity and reduced lung volume further induces cyclic or constant airway closure and gas resorption behind occluded airways, resulting in atelectasis (13). Previous data have revealed that a 0.4-0.5-liter decrease occurs in resting lung volume following to the induction of general anesthesia independent form the route of the agent given either by inhalation or intravenously (12, 14). In addition, an average of 60 to 95 ml/cm H2O reduction is observed in the static compliance of the total respiratory system during general anesthesia (15). Accompanying premature closure of the airway during general anesthesia impedes ventilation, and with persisting perfusion, it causes a ventilation/perfusion mismatch leading to impairment in oxygenation during anesthesia. Finally, atelectasis occurs in up to 90% of all patients who underwent general anesthesia (16). Computed tomography-based studies have shown that 10-20% of the lung is regularly collapsed

at the base of the lung during uneventful anesthesia, even before a surgery has been carried out (17). These changes occurring during general anesthesia and resulting atelectasis may precipitate pulmonary dysfunction existing in COVID-19 patients.

This study is among the first reports comparing general and regional anesthesia of pregnant women with COVID-19 infection who are scheduled for C/S. Our findings show that both regional and general anesthesia provide similar changes in surrogate markers of inflammation, and D-dimer. Although not statistically significant, a higher trend was observed in oxygen saturation in women receiving regional anesthesia compared to those receiving general anesthesia. The length of the hospital stay was significantly higher in women undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S. As an important finding the 1st and 5th minute APGAR scores were significantly lower in neonates born to mothers undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S. Fortunately maternal mortality was not observed in any of the study subjects. The longer length of the hospital stay in women receiving general anesthesia than the women receiving regional anesthesia may be associated with the negative effects of general anesthesia on lung volume and resulting atelectasis. Consequently this may have influenced 1st and 5th minute APGAR scores of the neonates born to mothers undergoing C/S with general anesthesia.

There are several limitations concerning this study. First, the retrospective design may provide bias in comparison of the general and regional anesthesia in this particular patient subset. Second, our study population is consisting of limited number of subjects which impedes reaching a clear conclusion concerning the role of anesthesia choice in pregnant COVID-19 women undergoing C/S. Nevertheless, our data somewhat favoring the utilization of regional anesthesia rather than general anesthesia in these patients is one of the first reports comparing the two anesthesia techniques in pregnant women with COVID-19. Further prospective, randomized data with larger sample size is required to support the results derived from this study.

Conclusion

In conclusion, both regional and general anesthesia provide similar changes in surrogate markers of inflammation, and D-dimer. The length of the hospital stay was significantly higher in women undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S. Moreover, the 1st and 5th minute APGAR scores were significantly lower in neonates born to mothers undergoing C/S with general anesthesia compared to women receiving regional anesthesia during C/S.

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