

## The effects of midazolam and fentanyl on neonates in elective cesarean section

Comparison of the effects of fentanyl and midazolam on newborns

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### Abstract

**Aim:** As in all patients scheduled for surgery, obstetric patients may have both surgery and operating room fear, and secondary autonomic stress response may develop. To compare the effects of premedication with fentanyl or midazolam on maternal anxiety, tolerance of the birthing process, and central nervous system depression of the newborn.

**Material and Methods:** ASA II patients scheduled for elective cesarean section with spinal anesthesia who gave informed consent were randomized into two groups to receive either 0.025 mg/kg iv midazolam or 1 mcg/kg iv fentanyl. The APAIS score was recorded before and five minutes after premedication. Following the delivery of the newborn, the APGAR score was recorded at the first and fifth minutes, and the NACS score was recorded at the fifteenth minute. The primary outcome was a decrease in APAIS scores, the secondary outcomes were differences in APGAR and NACS scores.

**Results:** Data of 50 patients were analyzed. First-minute APAIS score was similar ( $19.3 \pm 5.3$  vs  $19.6 \pm 4.7$ ,  $p=0.82$ ), but the decrease at the fifth minute was more prominent in the midazolam group ( $10.8 \pm 3.8$  vs  $15.3 \pm 4.9$ ,  $p=0.001$ ). APGAR and NACS scores were similar ( $p=0.87$ ,  $p=0.58$ , and  $p=0.65$ , respectively).

**Discussion:** This study found that midazolam was more effective in reducing anxiety in uncomplicated pregnant patients with no apparent postdelivery depression in the newborn.

### Keywords

Preoperative Anxiety, Midazolam, Fentanyl, Cesarean Section, Newborn

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## Introduction

General and regional anesthesia can be applied in obstetric anesthesia. While choosing the anesthesia technique, ensuring the safety and comfort of both the mother and the baby to be delivered should be considered together.

In cesarean sections performed under general anesthesia, there is a risk of undesirable effects such as maternal aspiration of gastric contents, difficulty in intubation, fetal depression due to general anesthetics, low Apgar score and low NACS, fetal hypoxia and acidosis due to maternal hyperventilation, postpartum bleeding, postoperative pain, delayed mobilization, increased risk of thromboembolism, and delayed breastfeeding [1].

With the regional anesthetic approach, the mother can experience the moment of birth and breastfeed her baby early. In addition, the risks of intraoperative aspiration and difficulty in intubation are eliminated, and the depressant effect of anesthetic drugs in the newborn is avoided. While analgesia and early mobilization in the postoperative period are provided, the risk of thromboembolism and blood loss due to sympathetic blockage also decrease. At the same time, the neuroendocrine response to surgical stress is prevented, thus the need for anesthetics is reduced, making the work of the anesthesiologist easier [2]. Regional anesthesia has become an increasingly preferred method due to its high success rate [3].

Higher anxiety levels have been reported in patients who are young, female, who will undergo an operation for the first time, who have had previous bad anesthetic experience and have a fear of death [4].

With our study, we aimed to investigate at what doses midazolam and fentanyl can be used in premedication in order to relieve anxiety and pain caused by uterine contractions in the mother and to avoid negative effects on the baby.

## Material and Methods

This study was conducted with the approval of the local ethics committee of Karadeniz Technical University Faculty of Medicine (registration number: 2007/49). Patients who were planned for elective cesarean section by the Gynecology and Obstetrics Clinic and had regional anesthesia indication were informed about the study in the preoperative period and their consent was obtained. Fifty patients, aged 21-38 years, ASA II, were included in the study and randomly divided into two groups of 25 each, and Amsterdam Preoperative Anxiety and Information Scale (APAIS) tests were applied to the patients before premedication in the preoperative waiting room (APAIS 1st minute). Then, one group was premedicated with midazolam 0.025 mg/kg iv (Group M), and the other group with fentanyl 1 µg/kg iv (Group F). After 5 minutes, the "APAIS" score was repeated (APAIS 5th minute). After this evaluation, the patients were taken to the operating table.

Non-invasive arterial pressure (NIAP), peak heart rate (HR) and pulse oximetry (SpO<sub>2</sub>) were measured. Crystalloid fluid replacement was applied to the patients before the operation. The patients were followed up in the intraoperative and postoperative periods for complications such as loss of consciousness, nausea, vomiting, tremor and agitation.

For spinal anesthesia, a 22 G spinal needle was used in the

lateral decubitus position and 12.5 mg of levobupivacaine was administered intrathecally. The sensory block level was evaluated with cold-hot and pinprick tests. The operation was allowed to start when the sensory block was sufficient (thoracic 4 levels).

When the baby was delivered, the newborn was examined and APGAR scores were recorded at the 1st and 5th minutes. After basic neonatal care, and the umbilical cord was clamped and cut, "Neonatal Neurological and Adaptive Capacity Score (NACS)" was recorded at the 15th minute.

## Statistical analysis:

The data obtained, demographic data, mean and standard deviation

were evaluated with t-test and Mann-Whitney U test. The relationship between APGAR, APAIS and NACS scores was analyzed with the Chi-square test. Interpreting the results of the analysis,  $p < 0.05$  was accepted as an indicator of the significant difference, and  $p > 0.05$  as the indicator that the difference was not significant.

## Results

The pregnant women participating in the study were between the ages of 21-38. Midazolam was administered to one group (group M) and fentanyl to the other group (group F) for premedication. There was no statistically significant difference in terms of age and weight in demographic data of the groups. While there was no statistically significant difference in APAIS 1st minute score between the pregnant groups ( $p = 0.82$ ;  $p > 0.05$ ), there was a statistically significant difference between the APAIS 5th minute scores ( $p = 0.001$ ;  $p < 0.05$ ).

There was no statistically significant difference between the groups in terms of APGAR 1st and 5th minutes scores of the newborns ( $p = 0.87$ ;  $p > 0.05$ ). There was also no statistical difference between the groups in terms of NACS scores of the newborns ( $p = 0.65$ ;  $p > 0.05$ ). APAIS, APGAR and NACS scores of the groups were compared (Table 1).

**Table 1.** APAIS, APGAR and NACS scores

	GROUP M n = 25	GROUP F n = 25	P
APAIS 1. Min.	19,28±5,31	19,60±4,70	p=0,82
APAIS 5. Min.	10,76±3,76	15,32±4,9	p=0,001**
APGAR 1. Min.	8,48	8,52	p=0,87
APGAR5. Min.	25,96	25,04	p=0,58
NACS	26,42	24,58	P=0,65

(\*:  $p < 0.05$ , \*\*:  $p < 0.001$ )

## Discussion

Anxiety, which is common in patients who will undergo an operation, reaches its highest level in the preoperative preparation room. The study by Won-Sung Kim et al. reported that there is a strong relationship between anxiety in patients and hemodynamic changes [5]. In several studies, it was reported that anxiety started a few days before the operation and reached its highest levels just before the operation and two days after it [6].

It has been reported that levels of anxiety are higher in patients who are young, women, who have had previous bad anesthetic experience, who will undergo surgery for the first time, and those who have a fear of death [4].

Anxiety of the patient increases the peroperative stress response due to anesthesia and surgery, and affects the peroperative hemodynamics by activating the sympathetic nervous system. Thus, tachycardia, hypertension, arrhythmia and increased pain in the postoperative period can occur. Reducing anxiety with sedation makes easier the work of the anesthesiologist during induction, reduces the need for anesthetic drugs, and helps stabilize hemodynamics [7].

Nowadays, sedation is routinely used in regional anesthesia applications. However, due to the fear of possible depressant effects on the newborn, it is not applied at all or rarely applied in cesarean operations. Cesarean section is a surgery in which the expectant mother experiences anxiety and perioperative stress. Therefore, sedation becomes more important in cesarean section patients compared to other surgical patients. This is because vasoconstriction develops in uterine arteries as a result of the mother's stress and related autonomic response, and as a result, the risk of developing fetal distress increases.

There are many studies in the literature regarding the use of sedative drugs in regional anesthesia [8, 9]. However, there are a very limited number of studies on the use of midazolam and fentanyl in cesarean cases. Frölich et al. administered 1 mcg/kg iv fentanyl and 0.02 mg/kg iv midazolam to expectant mothers during skin cleansing for spinal anesthesia. Their study reported that a significant sedation was achieved in the group receiving a combination of midazolam and fentanyl compared to the placebo group; also there was no difference between the newborn APGAR and NACS scores [9].

In our study, patients undergoing a cesarean section were given 0.025 mg/kg iv midazolam or 1 mcg/kg iv fentanyl prior to delivery to the operation room. Such a time was chosen in order to suppress the increased anxiety in pregnant women, a special patient group, and to reduce the pain that may occur during spinal block procedure. In the study by Frölich et al., fentanyl and midazolam were applied just before the spinal anesthesia procedure [9].

In the study by Senel AC et al., 0.02 mg/kg midazolam was given as a premedication in cesarean section patients with extremely intense affectivity before cesarean. Sedation levels of these mothers and mothers in the placebo group, and the APGAR and NACS scores of the newborns were compared. It was observed that adequate sedation was achieved in mothers who were premedicated with midazolam compared to the placebo group, and there was no significant difference between the newborns from the two groups in terms of APGAR and NACS scores [10]. We aimed to provide sedation with different drugs and doses.

There are many cases of low muscle tone in newborns of pregnant women given diazepam until a few decades ago [11]. For this reason, anesthesiologists do not prefer pharmacological premedication because of the possible depressant effects due to sedation in the newborn. However, midazolam has been discovered after diazepam and has a shorter effect. Its effects on the newborn are also minimal [10]. Therefore, we aimed to show that midazolam can be safely used for sedation in

pregnant women who will undergo cesarean operation.

In a different study, it was observed that 90% of mothers fell asleep before the operation after administration of iv midazolam for sedation in cesarean operations under spinal anesthesia. They reported that there was no difference between these operations and the control group in terms of neonatal APGAR scores and umbilical vein pH values [9].

Frölich et al., in order to overcome concerns such as the decrease in tonus due to midazolam and the potential respiratory depression due to fentanyl, administered a single dose of midazolam and fentanyl during cesarian section and observed the clinical outcome in the patient and the newborn. In this study, it was determined that 0.02 mg/kg midazolam and 1 mcg/kg fentanyl did not cause maternal depression, did not impair breathing, but were doses that had a clinical effect [9]. Therefore, in our study, we considered the possibility of preoperative use of 0.025 mg/kg of midazolam, which is close to this dose and effective in our clinical practice, and 1 mcg/kg fentanyl due to its sedo-analgesia effect.

One of the reasons why deep sedation is not preferred in cesarean section operations performed under regional anesthesia is that the mother wants to see the baby born and remember that moment. The drug doses we determined were chosen as doses that would not cause amnesia in the mother, and the mother was not prevented from seeing her baby.

In order to ensure standardization in the study, all APGAR, NACS and APAIS scores were made by the same anesthesiologist. When the difference between the groups that received premedication with midazolam and fentanyl in the preoperative waiting room was evaluated, there was a statistically significant difference between APAIS scores. A statistically significant level of sedation was achieved in the mother in both the midazolam group and the fentanyl groups. Furthermore, higher levels of sedation were observed in the midazolam group. There was no statistically significant difference between the groups in our study in terms of APGAR (1st and 5th minutes) and NACS values of newborns.

As a limitation in our study, since some surgeons and patients did not want to participate in the study, the number of patients included in the study was low.

#### **Conclusion:**

The dosage and timing of the drugs we used provided a decrease in the anxiety of mothers, and we believe that it does not have any negative effect on newborns. We believe that there is a need for studies with more cases on this subject.

#### **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.*

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#### **Conflict of interest**

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#### References

1. Morgan GE Jr, Mikhail MS, Murray MJ, Larson CP. 3rd ed. *Clinical Anesthesiology*. New York: McGraw Hill; 2004. p. 830-1.
2. Papadopoulou E. Maternal stress-response during emergency cesarean section with general and spinal anesthesia. *Reg Anesth Pain Med* 2005(1); 30:72 DOI: 10.1136/rapm-00115550-200509001-00134
3. Kayacan N, Arıcı G, Akar M, Karslı B, Zorlu G. The Comparison of Different Regional Anesthetic Techniques on Hemodynamic Effect and Postoperative Analgesic Requirement for Cesarean Section T. *Klin.J. Gynecol Obs.* 2004; 14: 200-6.
4. Klopfenstein CE, Forster A, Gessel EV. Anesthetic assessment in an outpatient consultation clinic reduces preoperative anxiety. *Can J Anesth.* 2000; 47(6): 511-15.
5. Won-Sung Kim, Gyeong-Jo Byeon, Bong-Jae Song, Hyeon Jeong Lee. Availability of preoperative anxiety scale as a predictive factor for hemodynamic changes during induction of anesthesia. *Korean J Anesthesiol.* 2010; 58(4): 328-33.
6. Miller Ronald D. *Psychological preparation and preoperative medication in anesthesia*; 4th ed. Philadelphia, PA: Churchill Livingstone; 1994. p.1015.
7. Rama-Maceiras P, Gomar C, Criado A, Arizaga A, Rodriguez A, Marengo ML. Sedation in surgical procedures using regional anesthesia in adult patients: results of a survey of Spanish anesthesiologists *Rev Esp Anesthesiol Reanim.* 2008; 55(4):217-26.
8. Ahmed A, Khan FA, Hussain A. Comparison of two sedation techniques in patients undergoing surgical procedures under regional anaesthesia. *J Pak Med Assoc.* 2007; 57(11):548-52.
9. Frölich MA, Burchfield DJ, Euliano TY, Caton D. A single dose of fentanyl and midazolam prior to Cesarean section have no adverse neonatal effects. *Can J Anaesth.* 2006; 53(1):79-85.
10. Senel AC, Mergan F. Premedication with midazolam prior to caesarean section has no neonatal adverse effects. *Rev Bras Anesthesiol.* 2013; 64(1):16-21.
11. Haram K. "Floppy infant syndrome" and maternal diazepam (Letter). *Lancet* 1977;2: 612-3.

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