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ARAŞTIRMA / RESEARCH

Do obstetric anesthesia methods have an impact on gastrointestinal system function in preterm infants?

Obstetrik anestezi yöntemlerinin preterm bebeklerde gastrointestinal sistem fonksiyonu üzerine etkisi var mı?

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Abstract

Purpose: The reason for gastrointestinal system (GIS) motility problems in premature infants is multifactorial and intestinal immaturity is the most important contributing factor. To investigate the effect of epidural (EA) or general anesthesia (GA) on GIS function and early neonatal morbidity in preterm infants delivered by cesarean section (CS).

Materials and Methods: This study was conducted in a single neonatal intensive care unit (NICU) between October 2011 and April 2015. Preterms ≤32 weeks and ≤1500g who were delivered by CS were enrolled in this study. Mode of anesthesia, demographic, clinical characteristics, first meconium passage time, meconium obstruction, use of drug for dysmotility and other preterm morbidities were evaluated.

Results: Three hundred and sixty four preterm infants were enrolled during the study period. Use of drug for dysmotility, time to first meconium passage, and meconium obstruction rate, were significantly higher in the GA group.

Conclusion: This was the first study in the literature that investigated the role of anesthesia methods, effect on preterm infant GIS motility. Anesthesia modalities during delivery may have an effect on GIS function in preterm infants.

Keywords:. Anesthesia method, meconium obstruction, motility, neonatal outcome, preterm infant

Öz

Amaç: Prematüre bebeklerde gastrointestinal sistem (GİS) motilite problemlerinin nedeni multifaktöriyeldir ve intestinal immatürite en önemli faktördür. Sezaryen (C/S) ile doğum yapan prematüre bebeklerde epidural anestezi (EA) veya genel anestezinin (GA) GİS fonksiyonu ve erken neonatal morbidite üzerine etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu çalışma Ekim 2011 ile Nisan 2015 arasında tek bir yenidoğan yoğun bakım ünitesinde (YDYBÜ) yapılmıştır. Bu çalışmaya C/S ile doğan ≤32 hafta ve ≤1500 g pretermler dahil edildi. Anestezi yöntemi, demografik, klinik özellikler, ilk mekonyum geçiş zamanı, mekonyum obstrüksiyonu, dismotilite için ilaç kullanımı ve diğer preterm morbiditeleri değerlendirildi.

Bulgular: Çalışma döneminde 364 preterm bebek kaydedildi. Dismotilite için ilaç kullanımı, ilk mekonyum geçiş zamanı ve mekonyum obstrüksiyonu oranı GA grubunda anlamlı olarak daha yüksekti.

Sonuç: Bu literatürde anestezi yöntemlerinin preterm bebeklerde GİS motilitesi üzerine rolünü araştıra ilk çalışmadır. Doğum sırasındaki anestezi yöntemleri, preterm bebeklerde GİS fonksiyonu üzerinde etkili olabilir.

Anahtar kelimeler: Anestezi metodu, mekonyum obstrüksiyonu, motilite, neonatal sonuç, preterm bebek

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INTRODUCTION

Anesthesia method used for the induction of cesarean section (CS) is known to affect some of neonatal outcomes immediate after birth. General anesthesia (GA) can be applied for mothers who has contraindications for regional anesthesia (RA) for cesarean section (CS). However, GA method may have concerning effects on newborn[1]. In general, GA is reserved for the most urgent cesarean deliveries. Guidelines and experts recommend RA such as spinal and epidural anesthesia (EA) for most CS[2]. Anesthesia for CS is selected according to the balance of benefits and harms on the mothers and babies[3]. When choosing the ideal anesthesia technique for cesarean section, attending physicians including anesthesiologists and gynecologists should consider deciding the technique that will cause the least damage to the mother and the fetus. However, there are some concerns about the side effects of the drugs used to induce anesthesia at the time of delivery on the fetus. Preterm infants are sensitive to maternally administered drugs because of the immaturity of enzyme systems related to drug metabolism, insufficient development of blood - brain barrier, low serum proteins and low drug - binding capacity. Different type of anesthetic drugs administered to the mother cause various effects on the infants including long-term neurodevelopmental at the delivery[4-6].

Postoperative gastrointestinal system (GIS) dysfunction occurs as predicted after major abdominal operations but can occur after operations in other parts of the body or sometimes even after minor surgery7. Immaturity and other perinatal factors have obviously deleterious effects, such as motility problems and feeding intolerance in the GIS, which is detrimental to the wellbeing of the preterm infant8. In addition, adverse effects have been determined related to general anesthesia and intestinal motility in adult studies as well as animal studies7,9-12. However, the impact of anesthesia on GIS functions of premature neonates is not well known. We aimed to compare the impact of EA versus GA on GIS functions in preterm infants.

MATERIALS AND METHODS

Sample

This retrospective study was conducted in a single neonatal intensive care unit (NICU) between October 2011 and April 2015. This is a 30-bed level 3-4 NICU that is part of a perinatal center performing 3000 annual high risk deliveries. The trial was approved by the Human Research Local Ethics Committee (Ankara University Faculty of Medicine Clinical Research Ethics Committee, Date: 23.03.2015, number of the approval: 05-213-15). Infants data were obtained from the hospital medical records. According to our unit protocol, written informed consent was obtained for each patient immediately on admission for invasive procedures. Infants with a gestational age of ≤32 weeks, birth weight of (BW) ≤1500g (VLBW, very low birth weight) and delivered by CS with either EA (Group 1) or GA (Group 2) were included in the study unless they had any exclusion criteria.

Infants delivered by normal vaginal route or who were small for gestational age, infants of preeclamptic or diabetic mothers or exposed to antenatal magnesium sulphate, infants with GIS anomalies or with a diagnosis of early neonatal sepsis were excluded from the study because of having adverse effects on GIS motility. Breastfeeding and maintenance procedures were performed in the same way in both groups.

Demographic and clinical features

Birth weight, gestational age, maternal age, Apgar scores (1 and 5 minute), umbilical arterial blood gases pH, delivery room resuscitation, duration of mechanical or non-invasive ventilation and oxygen requirement period, late onset sepsis (LOS), patent ductus arteriosus (PDA) (with either medical or surgical therapy), necrotizing enterocolitis (NEC; staging according to Bell[13]) (stage ≥2), intraventricular hemorrhage (IVH; staging according to Papile[14]) (grade ≥3), retinopathy of prematurity (ROP; defined according to the International Classification[15]) requiring laser therapy, bronchopulmonary dysplasia (BPD; defined by need for supplemental oxygen at 36 week of postconceptional age[16]), time to first meconium passage, meconium obstruction[17], use of drug (domperidone) for dysmotility, day of full enteral feeding, duration of NICU stay and mortality were recorded. Domperidone 0.75 mg kg per day was administered to patients with GIS motility problems and was used until regular spontaneous defecation was provided[18].

The indications for either GA or EA were decided by the anesthesiologist and the obstetrician according to current clinical guidelines and patient approval of the

method[19,20]. The anesthetic procedures were performed by an experienced and qualified anesthetist.

General anesthesia

General anesthesia induction was implemented when contraindications were existed to decide neuraxial anesthesia and/or according to the patients' requests for GA. The anesthesia protocol was performed by following certain steps. Briefly: oro-facial mask were applied for pre-induction oxygenation regimen of 4 or 5 vital-capacity breaths of pure oxygen. Subsequently, a dose of 2 mg kg of propofol were administered intravenously flowing induction of 0.6 mg kg of rocuronium bromide through endotracheal tube. Patients were subjected to a mixture of 50% nitrous oxide and 50% oxygen with sevoflurane (a 0.5 minimum alveolar concentration) by mechanical ventilation support. Mothers were kept in the left 15° lateral tilt position until the time of delivery.

Epidural anesthesia

Epidural anesthesia was inducted by using a 16- or 18-gauge needle (Portex Tuohy) through the L2–L3 intervertebral space. After the needle was placed, the position was checked by aspiration, and an mixture of 3 mL of 2% lidocaine plus bicarbonate at the concentration of 1 mEq per 20 mL of lidocaine were applied as a test dose. The study drug was injected as incremental boluses. After the test dose was applied, it was waited for 5 minutes in order to see adverse outcomes. If side effects were not observed, fentanyl at 1-2 mcg/kg (a total maximum dose of 50 µg/kg) and 20 mL maximum doses of 2% lidocaine were administered. Sensory block level was tested with pin-prick test at two minute intervals. The "pinprick test" or a cold sensation assessment was implemented by using an ethyl chloride spray 15 min after the procedure at the metameric levels of S1–L2 to T10 in order to test the height of the neural blockade. The target block height was defined as the T6 level coincided with the xiphoid line. Eventually, no more anesthetic agent was injected when this target was achieved. Each born premature infants was evaluated by experienced specialist neonatology. Neonatal resuscitation was performed according to current guidelines. Then, infants were admitted to the NICU.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 15 for Windows (SPSS Inc., St. Louis, MO) was used for statistical analysis, and p value < 0.05 was considered significant. The t-test and Mann-Whitney U-test were implemented to compare two groups according to normality of data. Categorical variables were analyzed by using Pearson chi-square tests. Continuous variables were stated as mean ± standard deviation (SD), and median (minimum-maximum). Categorical variables were expressed as percentage and frequency.

RESULTS

Three hundred and sixtyfour infants met the inclusion criteria (Figure1). Two hundred sixtytwo patients in the epidural anesthesia group and 102 patients in the GA group were included in the study. There were no significant differences between the two groups in terms of BW (EA vs GA, 1087.4 ± 287 g vs 1051.5 ± 323 g), gestational age (EA vs GA, 28.4 ± 2 weeks vs 28.5 ± 2 weeks), maternal age, 1st and 5th minute Apgar score, delivery room resuscitation, duration of mechanical, non-invasive ventilation and oxygen requirement, LOS, PDA, NEC (stage ≥2), ROP required laser therapy, IVH (grade ≥3), BPD, day of full enteral feeding, duration of NICU stay and mortality ($p>0.05$) (Table 1).

Timing of first meconium passage (EA vs GA, 14.2 ± 12.1 hours vs 19.3 ± 11.7 hours) and meconium obstruction (EA vs GA, 31% vs 46%) were high in the GA group (respectively, $p=0.012$, $p=0.018$). Domperidon administration (EA vs GA, 16% vs 55%) was high in infants exposed to GA ($p<0.001$). Furthermore, umbilical arterial blood pH (EA vs GA, 7.26 ± 0.07 vs 7.31 ± 0.06) was significantly lower in infants subjected to EA ($p=0.021$) (Table 1).

DISCUSSION

In this study, the incidence of meconium obstruction was high and first meconium passage time were longer in infants exposed to GA. Motility problems was high in infants subjected to GA. For infants VLBW, umbilical arterial blood pH was lower in the EA group.

Studies investigating mortality and early respiratory outcomes of neonates revealed no difference between both methods of anesthesia[21,22]. The effect of anesthesia modality on premature morbidities were not evaluated before. Our data revealed no significant difference between the groups in terms of

respiratory support, preterm morbidities (BPD, IVH, ROP, and NEC), NICU stay and mortality after CS with GA or EA.

These results suggested that anesthesia induction methods during delivery might be effective on short term neonatal outcomes.

Table 1. Demographic characteristics and neonatal outcomes of the study groups

Variables	Study groups		
	Group 1 (Epidural Anesthesia) (n=262)	**Group 2 (General anesthesia) (n=102)**	**P**
Birth weight, g (mean±SD)	1087.4 ± 287	1051.5 ± 323	0.084
Gestational age, weeks (mean±SD)	28.4 ± 2	28.5 ± 2	0.125
Maternal age, (mean±SD)	23 ± 14.6	24 ± 13.8	0.417
Apgar score 1. minute, median (minimum-maximum)	7 (1-9)	7 (1-8)	0.183
Apgar score 5. minute, median (minimum-maximum)	8 (5-10)	8 (3-9)	0.078
Delivery room resuscitation, n (%)	88 (33)	48 (47)	0.241
Umbilical arterial blood gases, pH (mean±SD)	7.26 ± 0.08	7.31 ± 0.07	**0.021***
Mechanical ventilation time, day, (mean±SD)	3.6 ± 12.7	5.1 ± 9.4	0.284
Non-invasive ventilation time, day, (mean±SD)	4.7 ± 5.8	5.5 ± 7.5	0.714
Oxygen requirement period, days, (mean±SD)	23.1 ± 23.2	25.4 ± 26.3	0.580
Late onset sepsis, n (%)	81 (30.9)	35 (34.3)	0.204
PDA (with either medical or surgical therapy), n (%)	63 (24)	15 (14.7)	0.105
NEC (stage ≥2), n (%)	28 (10.6)	11 (10.7)	0.644
ROP required laser therapy, n (%)	46 (17.5)	19 (18.6)	0.612
IVH (stage ≥ 3), n (%)	47 (17.9)	18 (17.6)	0.815
BPD, n (%)	65 (24.8)	25 (24.5)	0.698
The first meconium passage time, hours, (mean±SD)	14.2 ± 12.1	19.3 ± 11.7	**0.012***
Meconium obstruction, n (%)	81 (31)	47 (46)	**0.018***
Use of drug for dysmotility, n (%)	42 (16)	56 (55)	**<0.001***
The day of full enteral feeding, (mean±SD)	11 ± 7.2	14.1 ± 9.2	0.172
Duration of NICU stay, days, (mean±SD)	42.2 ± 19.8	46.1 ± 21.3	0.414
Mortality, n (%)	49 (18.7)	18 (17.6)	0.211

n, number of the subjects; BPD; Bronchopulmonary dysplasia, IVH; Intraventricular hemorrhage, NEC; Necrotizing enterocolitis, NICU; Neonatal intensive care unit; PDA; Patent ductus arteriosus, ROP; Retinopathy of prematurity, SD, standard deviation

Respiratory depression was found more frequently in newborns born with GA[23,24]. As in our study, assisted ventilation requirement was similar in both groups[25,26]. Low first and fifth minute Apgar scores noted either after GA or EA were related to neonatal depression after CS in some studies[26-28]. However, the studies mentioned above were on term infants. There are also conflicting data on neonatal outcomes of infants subjected to different anesthesia modalities. As in our results, the anesthesia method may not affect the Apgar score[22,25,29].

Some studies reported that anesthesia method did not affect umbilical arterial pH in infants whose mothers were exposed to either anesthesia modality[26,27,30]. In our study, mean umbilical arterial pH levels were lower in the EA group. It may be speculated that during RA, hypotension due to autonomic effects leads to decreased utero-placental perfusion and intervillous blood flow and as a result fetal hypo-perfusion and fetal acidemia may occur. On the other hand, there are a few studies stating that RA leads to high mean umbilical arterial pH values[26,31,32]. Hypotension can also occur during induction of general anesthesia. However, it is more common in EA[3,6,28]. Although, the prevalence of maternal hypotension during caesarean section is higher, term babies may tolerate placental blood perfusion difficulties due to maternal hypotension[33]. However, lack of data is existed for this condition in preterm infants. Furthermore, there are more likely to be a longer time interval between induction of EA to time to delivery than with GA. This may cause to the lower pH in the EA group[23].

These conflicting data may be due to unpredictable effects of anesthesia, cause of anesthesia indication, experience of the surgeon and proficiency of the anesthetist, antenatal risks, the duration to start the anesthesia until the time of birth and compounding morbidities in neonates with different gestational age and BW. Furthermore, data related to GIS outcomes of VLBW infants who are subjected to different anesthesia techniques, EA or GA, was not present.

Anesthetic agents on the newborn infants depends on the concentration of the drug reaching the fetus as well as related to drug levels in maternal and fetal blood[34]. Almost all of the inhaled anesthetics are depressants and show depressive effects in the respiratory system in preterm infants[23,35,36]. In addition, commonly used anesthetic medications may cause GIS motility problems[9-12,37]. In a study conducted by Somri and colleagues declared that recovery of intestinal function were shown to be faster, and postoperative abdominal distension was found to be lower in neonates anesthetized with RA when compared to GA[36].

Desmet et al and De Corte et al studied the effect of volatile anaesthetics on intestinal motility during laparoscopic surgery[12,38]. There were significant less peristaltic waves in the sevoflurane- based anaesthesia group. Even though, the reason for GIS motility problems in premature infants is multifactorial. Intestinal immaturity is the most important contributing factor[8,39]. We found that GIS motility problems, first meconium passage time, meconium obstruction, and drug administration for dysmotility were higher in infants exposed to GA. We suggest that commonly used drugs for GA may affect GIS motility in VLBW neonates. In addition, Acidosis was more prominent in the blood gas in the EA group. These data suggested that the placental passage of volatile anesthetics might have a significant influence on GIS functions. In order to determine the effect of anesthesia during delivery on GIS in preterm infants, follow-up of them is particularly important. In addition, we found that birth anesthesia negatively affected GIS in preterm infants in the early period. However, no effect was detected on the long term period.

We are aware of the limitations of our study. The limitation of our study was its retrospective nature. Another limitation was that we did not have the information about the duration to start the anesthesia until the time of birth, detailed medical history, hypotension data and the indications for CS. Usually, GA is applied for the urgent cesarean deliveries. In our study, the number of patients with emergency C / S could not be evaluated. Therefore, there is likely an inherent difference between the fetuses in these 2 groups. Future prospective randomized controlled trials will be better in determining the effects of EA versus GA on GIS and morbidities in preterms. Since the effects of anesthesia modality on comorbidities especially related to GIS were unknown in preterm infants, we thought that our results were meaningful.

General anesthesia during CS delivery may adversely affect preterm infant GIS motility and umbilical arterial pH. As far as we know, this was the first study in the literature that investigated the role of anesthesia methods, effect on preterm infant GIS motility. Therefore, clinicians may consider anesthesia methods when evaluating GIS symptoms in preterm infants.

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