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Original Article

The Maternal, Cord Blood and Neonatal Serum Ischemia-Modified Albumin Levels in Different Modes of Delivery

Farklı Doğum Şekillerinde Anne, Kordon Kanı ve Yenidoğanda Serum İskemi-Modifiye Albümin Düzeyleri

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Abstract

Background: Human serum albumin modifies in response to ischemic events and affinity of N-terminal decreases for metal especially for cobalt. This modification results in the formation of ischemia modified albumin (IMA). The IMA rises immediately after ischemic event and remains high for several hours after cessation of ischemia. The purpose of this study was to investigate the effects of mode of delivery on the IMA levels in mothers and their term infants, and to determine which mode causes much oxidative stress.

Study Design: The cases were grouped according to the mode of delivery: vaginal delivery group (VD, n=40) and cesarean group (C/S, n=40). The serum samples were collected from mothers before delivery (pre-delivery), from the cord blood (CB) and from the infants at the 24th hour after birth according to the following criteria: (1) singleton live birth, (2) gestational age between 37- 41 6/7 weeks, (3) birth weight of 2500 and 4000 g, and (4) Apgar scores ≥ 8 at 5 min. The IMA levels of both groups were compared.

Results: The pre-delivery serum IMA levels were similar between two groups. The cord blood IMA levels were significantly higher in C/S group than those with VD group (0.694±0.113 vs 0.642±0.084, p=0.021). The serum IMA levels were higher in infants born by C/S compared with those born by VD, but the result was not statistically significant.

Conclusion: Our results showed the IMA levels in infants and cord blood was influenced by the way of delivery and supported that oxidative stress is reduced in vaginally delivered infants.

Keywords: Cord blood; Ischemia modified albumin; mode of delivery; newborn

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Öz

Amaç: Serum albumini iskemik olaylara yanıt olarak değişir ve N-terminalinin kobalt metaline afinitesi azalır. Bu modifikasyon sonucu iskemi modifiye albümin (IMA) oluşur. IMA, iskemik olaydan hemen sonra yükselir ve iskeminin sonlanmasından sonra birkaç saat yüksek kalır. Bu çalışmanın amacı, doğum şeklinin annelerde ve term bebeklerde İMA düzeylerine etkisini araştırmak ve hangi doğum şeklinin daha fazla oksidatif strese neden olduğunu belirlemektir.

Gereç ve Yöntem: Vakalar doğum şekline göre vajinal doğum grubu (VD, n=40) ve sezaryen grubu (C/S, n=40) olarak gruplandırıldı. Annelerden doğum öncesi, kordon kanından ve bebeklerden doğumdan sonraki 24. saatte serum örnekleri belirlenen kriterlere uyan vakalardan alındı; (1) tekil canlı doğum, (2) gebelik yaşı 37-41 6/7 hafta arası, (3) 2500 ve 4000 gr doğum ağırlığı ve (4) 5. dakikada Apgar skoru ≥ 8. Her iki grubun İMA düzeyleri karşılaştırıldı.

Bulgular: Doğum öncesi serum IMA seviyeleri iki grup arasında benzerdi. Kordon kanı IMA düzeyleri C/S grubunda VD grubuna göre anlamlı olarak yüksekti (0,694±0,113'e vs 0,642±0,084, p=0,021). C/S ile doğan bebeklerde serum IMA seviyeleri, VD ile doğan bebeklere göre daha yüksekti, ancak sonuç istatistiksel olarak anlamlı değildi.

Sonuç: Bulgularımız bebeklerde ve kord kanında IMA düzeylerinin doğum şeklinden etkilenebileceğini ve VD ile doğan bebeklerde oksidatif stresin azaldığını desteklemektedir.

Anahtar Kelimeler: İskemi Modifiye Albumin; Doğum Şekli; Kord Kanı; Yenidoğan

1. Introduction

Pregnancy is a physiological condition in which oxygen demand and energy requirement increases. This increase in oxygen uptake and storage are expected to increase the level of oxidative stress (1). Several factors during the adaptation of the newborn to the extrauterine life also cause an increase in oxidative stress and oxygen radicals. Oxygen radicals in newborns cause tissue damage via lipid peroxidation (2). The mode of delivery is also a condition that affects the oxidant status in the newborn. There are many studies in which oxidative stress markers have been studied. Although some of these studies show that the mode of delivery does not affect oxidative stress, recent studies have reported high total oxidant status and reduced total antioxidant capacity, especially with planned cesarean delivery (3-6).

Ischemia modified albumin (IMA) is formed as the result of accumulated free radicals from ischemic tissue and is used as a specific and sensitive marker for ischemic process (7). The IMA rises immediately after ischemic event and remains high for several hours after cessation of ischemia. It was firstly described as a new biomarker in myocardial ischemia (8). Current studies propose IMA as a marker for the early identification of oxidative stress in differential clinical conditions such as chronic kidney disease, hyperlipidemia and diabetes (9,10). Increased IMA levels have been reported in cord blood related to fetal distress, hypoxia, preeclampsia and complicated births (11-14). Besides elevated IMA levels have been detected in newborns with necrotizing enterocolitis, sepsis, anemia of prematurity, patent ductus arteriosus and transient tachypnea (15-18).

In literature, some biomarkers are compared between modes of delivery including; a-tocopherol, cortisol, uric acid, thiol–disulfide homeostasis, total antioxidant capacity and oxidant status (3,5,19). It was reported that the cord blood (CB) IMA levels were significantly higher in cases of cesarean (CS) compared to cases of vaginal delivery (VD) in normal and intrauterine growth restricted pregnancies (12). The aim of the present study is to investigate the effects of mode of delivery on the IMA levels in mothers, cord blood and term infants, and to determine which mode causes much oxidative stress.

2. Methods

This prospective study was conducted in University of Health Sciences, Etlik Zubeyde Hanım Women's Teaching and Research Hospital between June 2017 and October 2017.

Patient population

The healthy mothers with uneventful pregnancy and their healthy babies were enrolled in this study. Healthy pregnant women were considered to be eligible if; i. Gestational age between 37–$41^{6/7}$ weeks, ii. Singleton pregnancy, iii. Absence of chronic-gestational disease and any infectious risk factor including preterm premature rupture of membranes more than 18 hours, iv. Elective CS delivery without general anesthesia, iv. VD without induction of labor or anesthesia. After birth mother-infant pair was included in the study if birth weight of 2500 and 4000 g, and Apgar scores ≥ 8 at 5 min. If the neonate was admitted to NICU, and advanced resuscitation had been performed (positive pressure ventilation, intubation, chest compression or medication), the mother–infant pair was excluded from study.

Gestational age was determined according to the menstrual history or obstetrical findings. The participants were grouped according to the labor and mode of delivery: group VD (n=40)

and group CS (n=40) with scheduled CS and delivery. Antenatal and postnatal characteristics including maternal age, mode of delivery, gestational age, birth weight, gender, and 5-min Apgar scores were recorded. The study was approved by the Institutional Ethics Committee (Date: 06.05.2016, Number: 2016/3), and written informed consent was obtained from both the mother for herself and the parents for neonates before enrollment.

Samples and IMA analysis

We obtained three samples of 2 ml from included mother-infant pairs; 1. pre-delivery (before delivery), 2. cord blood (CB), and infant at 24th postnatal age. Each sample was centrifuged at 3600 rpm for 10 min and the supernatants were stored in Eppendorf tube at -80 °C until analysis. Albumin concentrations were measured by bromocresol green (BCG) method. IMA concentrations were assessed as described by Bar-Or et al (20). This colorimetric assay measures the cobalt (Co2+) binding facility of human albumin in serum. 50 µL water solution with % 0.1 cobalt chloride (CoCl2.6H2O) was mixed with 200 µL serum and kept dark for ten minutes. Subsequently, 50 µL of dithiothreitol (DTT) solution (1.5 mg/mL H2O) was added. After two minutes, 1.0 mL of 0.9% NaCl was supplemented to trim the reaction. The blank was prepared similar to the exclusion of DTT. Specimen absorbencies were assessed at 470 nm. IMA concentration was obtained with the difference between samples measured with and without DTT, and reported in absorbance units (ABSU). The pre-delivery, CB and infant serum IMA levels in VD and CS groups were compared.

Statistical analysis

Statistical analyses were conducted using SPSS version 17.0 (SPSS Inc., Chicago, IL). Student's t-tests and Mann–Whitney U-tests were used to compare continuous parametric and nonparametric variables, respectively. The X2 test was used to compare categorical variables. Spearman's and Pearson's correlation coefficients were used to determine the relationships between variables for nonparametric and parametric data, respectively. Data were expressed as mean ± SD or as percentages; p values ≤.0.5 (two-tailed) were considered significant

3. Results

During study period, 109 eligible mothers were identified. Seventeen mothers were excluded due to lack of informed consent, 7 infants due to requirement of advanced resuscitation, and five mothers as their infants were admitted to the NICU due to respiratory distress and feeding difficulties. A total of 80 healthy mothers (CS group, n=40 and VD group, n=40) and their babies were included.

The clinical and demographic features were similar in both groups (Table 1) [the age of the mothers (p=0.082), the number of delivery (p=0.179), birth weight (p=0.099), gestational age (p=0.095), and gender of newborns (p=0.503)]. The parameters indicated that pre-delivery IMA levels did not differ among pregnant women with regards to mode of delivery (P>0.05) (Table 2). The CB IMA levels were significantly higher in CS group

Table 1. The demographic features of the mothers and their newborns

	Vaginal delivery (n=40)	Cesarean section (n=40)	p
Maternal age (years)*	27.5 (19-41)	30.5 (20-38)	0.082
Number of delivery ≥3 (n, %)	17 (42)	17 (42)	0.179
Gender, mean ±SD, (male/female)	18/22	22/18	0.503
Gestational age* (weeks)	39 (37-41)	39 (37-40)	0.095
Birth weight (g), mean ±SD	3258±44.4	3371±52	0.099

*Values are presented as median (minimum–maximum)

Table 2. The pre-delivery, cord blood and infant serum IMA levels

	Vaginal delivery (n=40)	Cesarean section (n=40)	p
Pre-delivery serum IMA levels (ABSU)	0.77±0.11	0.74±0.085	0.069
Cord blood IMA levels (ABSU)	0.642±0.08	0.694±0.11	**0.021**
Infant serum IMA levels (ABSU)	0.83±0.099	0.87±0.1	**0.057**

ABSU: Absorbance units
Values are presented as mean (± SD)

than those with VD group (0.694±0.113 ABSU vs 0.642±0.084 ABSU, P=0.021). The infant serum IMA levels were higher in infants born by CS compared with those born by VD (0.87±0.099 ABSU vs. 0.83±0.1 ABSU, P=0.057), however the difference was not statistically significant.

The CB and infant serum IMA levels were similar in male and female infants (CB: p=0.336, infant serum: p=0.981). There were no significant correlation between three IMA levels and maternal age [pre-delivery: r=0.113, p=0.320; CB: r=0.164, p=0.145; infant serum: r=0.04 p=0.973], gestational age [pre-delivery: r= 0.076, p=0.501; CB r=-0.106, p=0.346; infant serum:r=-0.029, p=0,801], and birth weight [pre-delivery: r=0.060, p=0.594; CB:r=-0.056, p=0,619; infant serum: p=0.180, p=0.110].

4. Discussion

Albumin is the most abundant serum protein and is a strong extracellular antioxidant. Serum IMA is the result of the modification of serum albumin because of oxidative stress and concurrently produced superoxide radicals that appear during ischemic events absence tissue specify (21). The elevated serum IMA levels in neonatal period has been investigated in increasing number of clinical conditions in neonatal period. We presented here the serum IMA levels associated with mode of delivery in mothers, arterial CB, and term infants.

Pre-delivery serum IMA levels are important to evaluate the effect of labor itself in pregnant women. Increase in oxygen requirement and production of many pro-oxidants and vasoactive substances, and activation of maternal coagulation and inflammation occurs physiologically in pregnancy. As a result of these conditions, elevated serum IMA levels, was reported in normal pregnancy (22). It was also reported that elevated IMA levels in complicated pregnancies such as intrauterine growth retardation, hypertensive disorders, and abnormal placental development (23-25). In our study, we found that IMA levels were similar in mothers before delivery. This result may suggest that presence of labor does not affect oxidative stress in pregnant women.

Several maternal, fetal and environmental factors can surge oxidative stress during postnatal transition. Furthermore, the mode of delivery itself can also affect both mother and fetus and increase reactive oxygen radicals and ischemic events. Clinicians taking care of newborns must be aware that newborns have reduced protection against oxidative stress as to lower levels of plasma antioxidant systems and the balance between oxidative stress and antioxidant systems may vary according to the mode of delivery (2).

Effect of mode of delivery on oxidative stress was investigated in limited number of studies which concluded in conflicting results. Adekanle et al. and Wilinska et al. reported that mode of delivery dose not effect oxidative stress (3,4). In another study, the authors attributed the normal oxidative stress markers in elective CS cases to short duration of the delivery and absence of the contraction of skeletal and uterine muscles (26). On the contrary, recent studies stated that elevated oxidative stress markers are related with inadequate antioxidant response and/or depletion of antioxidants because of excessively high oxidative stress in elective C/S compared with VD (6,27). Iacovidou et al. also reported that IMA levels were higher in cases of cesarean section compared to vaginal delivery (12). In addition it was showed that CB IMA levels were higher in the general anesthesia cases compared to regional anesthesia cases attributed to hypotension. Supporting these results, we showed that CB IMA levels were higher in elective CS compared to VD. In addition we found a slight increase in infant serum IMA levels infants born by C/S compared to born by VD. Cesarean section may have contributed to increase of ischemic events and oxidative stress by intrauterine hypoperfusion resulting from anesthesia during CS and hypotension.

Although data about CB gas analysis and maternal arterial blood tension was missing in our study, our results demonstrated that low IMA level in CB and infant serum may indicate protective effect of labor and VD on oxidative stress. It may be more informative to study IMA levels in the presence of CB pH and lactic acid values; however, it is not a common practice for our unit to study CB gasses in uneventful deliveries. Although the pre-delivery serum IMA levels are important to evaluate the effect of labor itself in pregnant women, we are aware that the design of our study is unable to answer the exact importance of presence of labor in the oxidative system balance. Thus future prospective studies designed to evaluate effect of labor on oxidative stress response in both mother and newborn are required.

In conclusion, our study indicated an association between the mode of delivery and IMA levels in cord blood. These results can be ascribed to less exposure of neonates to insults like acidosis, hypoxia, ischemia and free radical damage during VD. Delivery by CS may have contributed to increase of oxidative stress markers and also ischemic events by several factors such as surgery, anesthesia, and inspired oxygen.

Author contribution

Study conception and design: DUI, SU, ÖE; data collection: DUI, SU, YAR; analysis and interpretation of results: DUI, ND, ÖE, AYB; draft manuscript preparation: DUI, SU, ND, AYB. All

authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Etlik Zübeyde Hanım Gynecology Training and Research Hospital Ethics Committee (Protocol no. 2016/3 / 06.05.2016).

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Conflict of interest

The authors declare that there is no conflict of interest.

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