Relationship Between Hemodynamically Significant Ductus Arteriosus and Ischemia-Modified Albumin in Premature Infants

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Abstract Hemodynamically significant ductus arteriosus (hsPDA) may alter organ perfusion by interfering blood flow to the tissues. Therefore, in infants with hsPDA, hypoxia occurs in many tissues. In this study, we aimed to investigate the diagnostic significance of serum (ischemia-modified albumin) IMA levels as a screening tool for hsPDA, and its relation to the severity of the disease in the preterm neonates. For this purpose, seventy-two premature infants with gestation age <34 weeks were included in the study. Thirty premature infants with hsPDA were assigned as the study group and 42 premature infants without PDA were determined as the control group. Blood samples were collected before the treatment and 24 h after the treatment, and analyzed for IMA levels. IMA levels in the study group (1.26 ± 0.36 ABSU) were found to be significantly higher than control group (0.65 ± 0.12 ABSU) ($p < 0.05$). In infants with hsPDA, a positive correlation was found

between IMA and PDA diameter ($\rho = 0.876$, $p = 0.022$), and LA/Ao ratio ($\rho = 0.863$, $p = 0.014$). The cut-off value of IMA for hsPDA was measured as 0.78 ABSU with 88.89 % sensitivity, and 90.24 % specificity, 85.71 % positive predictive, 92.5 % negative predictive value [area under the curve (AUC) = 0.96; $p < 0.001$]. The mean IMA value of the infants with hsPDA before treatment was 1.26 ± 0.36 ABSU, and the mean IMA value of infants after medical treatment was 0.67 ± 0.27 ABSU ($p = 0.03$). We concluded that IMA can be used as a marker for the diagnosis and monitoring of a successful treatment of hsPDA.

Keywords Preterm · Newborn · Ischemia-modified albumin · Patent ductus arteriosus · Diagnosis

Introduction

Hemodynamically significant patent ductus arteriosus (hsPDA) is a common problem in the first week of life in the preterm infants [1]. PDA may lead to pulmonary congestion, heart failure, exacerbate respiratory distress syndrome, increase the need for assisted ventilation, pulmonary hemorrhage, chronic lung disease due to increased pulmonary flow, renal failure, necrotizing enterocolitis (NEC), and periventricular leukomalacia because of ductal sealing of blood from systemic flow, cerebral palsy, and retinopathy [2–4]. It is obvious that untreated PDA may alter organ perfusion by interfering blood flow to tissues [5]. Therefore, in infants who have hsPDA, hypoxia occurs in many tissues such as the brain, heart, lungs, liver, kidney, and bowels [6].

Ischemia modified albumin (IMA) is a modification of human serum albumin (HSA). N-terminal amino acids of

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HSA temporarily bind to transitional metals such as cobalt, nickel and copper. Hypoxia, acidosis or ischemia leads to a change in this region and reduces the binding capacity of HSA to these metals, resulting in IMA [7]. IMA rapidly increases within 5–10 min after the ischemic event and remains high for 30 min. It declines to baseline after 12 h, but it continues to rise if the ischemia persists [8]. Recent clinical studies suggested IMA as a new biochemical marker for the early diagnosis of myocardial ischemic events and cerebrovascular accidents [9–11]. In newborns, recent studies have demonstrated that IMA levels increase in hypoxic events and sepsis [11–14]. However, there are limited data in the literature about the relationship between IMA and hsPDA in preterm neonates with hsPDA. Therefore, the main aim of this study was to evaluate the diagnostic significance of serum IMA levels as a screening tool for detecting hsPDA and its relation to the severity of the disease in the preterm neonates.

Methodology

Study Population

We conducted a prospective study between June 2013 and February 2014 in the newborn intensive care unit (NICU) of Erzurum Nene Hatun Maternity Hospital and Erzurum Regional Research and Training Hospital in Turkey. Our study was approved by the Ethic Committee of Erzurum Research and Training Hospital and informed consent was obtained from each family prior to the study. Echocardiography was done for newborns between 25 and 34 gestational weeks, and those with hsPDA were included in the study group. Gestational age was determined based on the last date of maternal menstruation, fetal ultrasonography findings or the New Ballard Scoring system [15]. Prenatal, natal and postnatal medical history of infants, demographic, clinical and radiological data was recorded. Infants with potential asphyxia history such as placental detachment, severe deceleration of antenatal heart beats and/or detection of asphyxia through clinical and conventional laboratory findings, significant somatic anomalies, abnormal fetal karyotype, severe congenital heart disease, hypoalbuminemia, intrauterine growth retardation, and chorioamnionitis proven by clinical or laboratory findings were excluded from our study. During the study period, infants in the study group were excluded if they had sepsis detected by positive C-reactive protein (CRP) and blood culture, congenital metabolic disease, necrotizing enterocolitis (NEC) before the management of PDA. Infants who were born less than 34 weeks of gestation without hsPDA were included in our study as the control group. Infants who had respiratory distress syndrome were administered

surfactant (200 mg/kg body weight; Curourf[®], Chiesi Ltd., Parma, Italy) via endotracheal route. Each of the infants in the study group received oral ibuprofen (Dolven, Zentiva, Istanbul, Turkey) (initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 h) for the management of hsPDA. However, infants who had feeding intolerance and/or contraindications for enteral feeding were administered intravenous ibuprofen (Pedeia, Orphan Europe SARL, France) (initial dose: 10 mg/kg, followed by 5 mg/kg at 24 and 48 h). Infants whose PDA was not closed were given an additional ibuprofen treatment for 3 days.

Evaluation of Infants for hsPDA

Echocardiography (ECO) was performed for premature infants (<34 weeks of gestation) weighing <1000 g and infants weighing >1000 g for PDA. Two-dimensional color Doppler echocardiography was performed using a GE Vivid 7 Pro, 10S transducer (GE Healthcare, Salt Lake City, UT, USA), and patients who had echocardiographic evidence of PDA postnatally at 48–96 h were followed in the NICU. Echocardiographic criteria for the diagnosis of PDA were included as a duct size >1.5 mm and a left atrium-to-aortic root (LA:Ao) >1.5 and/or left-to-right shunting of blood, or end-diastolic reversal of the blood flow in the aorta [16].

Blood Sampling

In the study group, blood samples were obtained immediately before commencing of ibuprofen treatment and 24 h after treatment by direct venipuncture. Blood samples were obtained on postnatal days 3–6 from infants in the control group. IMA was measured in the sera of infants in all groups.

Ischemia Modified Albumin Assay

Blood samples were collected in simple tubes containing no preservatives or separation gels, and centrifuged 30–45 min after collection. Obtained serum samples were refrigerated at -80°C . Frozen samples were mixed thoroughly after thawing and centrifuged before analysis. Samples containing a trace amount of hemolysis were discarded. Colorimetric assay was developed to screen human serum samples for decreased cobalt binding to albumin. The assay method involved adding 15 microliter of 0.1 % cobalt chloride (Sigma, $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$) in H_2O to 50 microliters of serum, gently mixing, and waiting 10 min for adequate cobalt-albumin binding. Fifty microliters of dithiothreitol (DTT) (Sigma, 1.5 mg/ml H_2O) was added as a colorizing agent and the reaction was quenched 2 min later by adding 1.0 mL of 0.9 % NaCl. Using an ELISA reader at 450 nm (Bio-Tek ELX 800 Absorbance microplate reader, Bio-Rad, USA and Bio-Tek ELx50

microplateauto strip washer, Bio-Rad, USA) color development with DTT was compared to a serum-cobalt blank without DTT and reported in absorbance units (ABSU).

Statistical Analysis

All data were analyzed using SPSS ver. 20 (SPSS, Inc., Chicago, IL). The Student's *t* test was used for comparing quantitative data, as well as descriptive statistical methods (mean and standard deviation). The Kolmogorov–Smirnov test was used to determine if the sample values suited to a normal distribution. Paired-Sample Test was used to assess changes between parameters with a normal distribution such as IMA of infants in the study and control groups. The Yates continuity correction test (Yates corrected Chi squared test) was used to compare qualitative data. Spearman's correlation analysis was used to evaluate correlations between parameters. Diagnostic screening tests to determine the cut off for IMA (sensitivity, specificity, positive predictive value, negative predictive value) and ROC curve analysis was used. All quantitative results were reported with 95 % confidence intervals, and a *p* value. *p* < 0.01 and <0.05 was considered significant.

Results

Seventy-three infants were included in our study; 34 in the study group and 42 in the control group. Three infants were excluded from the study because of severe pulmonary

hemorrhage during medication, and 1 infant was excluded because of NEC. Therefore, the study was completed with 30 infants in the study group. No significant difference was found between the groups in terms of gender, gestational age, birth weight and modes of delivery (*p* > 0.05). Demographic characteristics of both groups are shown in Table 1.

Twenty-two (73.3 %) infants in the study group and 29 (69.1 %) infants in the control group were administered surfactant due to respiratory distress syndrome. The mean duration on mechanical ventilation was 9.5 ± 11.6 (range 0–52) days and mean duration on NCPAP was 6.9 ± 8.6 (range 0–42) days in the study group. The mean duration on a mechanical ventilation was 6.4 ± 11.6 (range 0–18) days and the mean duration on NCPAP was 4.7 ± 8.2 (range 0–28) days in the control group. There were statistically significant differences between groups in terms of duration on mechanical ventilation and duration on NCPAP (*p* = 0.006, and *p* = 0.012, respectively). The mean duration of oxygen administration was 19.3 ± 14.0 (range 5–55) days in the study group and 5.5 ± 4.6 (range 0–11) days in the control group. There was a statistically significant difference between the groups in terms of duration of oxygen administration (*p* < 0.001). The mean duration of hospital stay was also longer in the study group than control group (38.5 ± 16.3 , range 8–65 days vs. 24.3 ± 11.7 , range 2–35 days, respectively; *p* < 0.001). The mean PDA diameter of infants was 2.14 ± 0.54 (range 1.5–3.0 mm) and LA/Ao ratio was 1.9 ± 0.2 (range 1.6–2.3). Clinical features of the patients are shown in Table 1.

Table 1 Demographic and clinical characteristics of the groups

Variables	Study group (n = 30) mean $\pm$ SD	Control group (n = 42) mean $\pm$ SD	<i>p</i>
Gender			
Female, n (%)	13 (48.2 %)	20 (47.6 %)	0.324
Male, n (%)	14 (51.8 %)	22 (52.4 %)	0.586
Gestasyon (week), (range)	29.6 ± 2.6 (25–34)	30.3 ± 2.0 (27–34)	0.218
Birth weight (gram), (range)	1820 ± 285 (860–2300)	1875 ± 310 (1150–2400)	0.560
Mode of delivery			
Vaginal, n (%)	12 (44.4 %)	23 (54.8 %)	0.085
C/S, n (%)	15 (55.6 %)	19 (45.23 %)	0.088
Surfactant use, n (%)	22 (73 %)	29 (69.1 %)	0.076
PDA diameter	2.14 ± 0.54 (1.5–3.0)	0	NA
LA/AO ratio	1.9 ± 0.2 (1.6–2.3)	0	NA
Duration of mechanical ventilation (day), (range)	9.5 ± 11.6 (0–52)	6.4 ± 11.6 (0–18)	<0.05*
Duration of NCPAP (day), (range)	6.9 ± 8.6 (0–42)	4.7 ± 8.2 (0–28)	<0.05*
Duration of oxygen application	19.3 ± 14.0 (5–55)	5.5 ± 4.6 (0–11)	0.000*
Duration of Hospitalization (day), (range)	38.5 ± 16.3 (8–65)	24.3 ± 11.7 (2–35)	0.000*

C/S cesarean section, PDA patent ductus arteriosus, LA/AO left atrium/aort ratio, NCPAP nasal continuous positive airway pressure, NA not applicable

* *p* < 0.05 were considered to be significant

Fig. 1 Representing, ischemia-modified albumin (IMA) levels of hemodynamically significant Patent Ductus Arteriosus (hsPDA) and the control group; IMA levels of hsPDA group before and after medical treatment

The mean IMA values of the hsPDA group was 1.26 ± 0.36 ABSU (range 0.77–1.48), and the mean IMA values of control group was 0.65 ± 0.12 (range 0.23–0.82) ABSU. There was a statistically significant difference between the study and control groups in terms of IMA values ($p = 0.013$) (Fig. 1). Moreover, there was no correlation between IMA values and gestational age, birth weight, and duration of ventilation, NCPAP, or oxygen administration in the study group. Moreover, in infants with hsPDA, a positive correlation was found between IMA and PDA diameter ($\rho = 0.876$, $p = 0.022$), and LA/Ao ratio ($\rho = 0.863$, $p = 0.014$).

There were 17 (56.7 %) infants with ≤ 29 weeks of gestational age and 13 (43.3 %) infants with >30 weeks of gestational age. Mean IMA level was 1.20 ± 0.28 ABSU (range 0.48–1.56) in infants with ≤ 29 weeks of gestational age. Furthermore, mean IMA level was 1.20 ± 0.38 ABSU (range 0.36–1.42) in infants with >30 weeks of gestational age. There was no significant difference between infants according to gestational age ($p = 0.845$).

Logistic regression analysis was performed for IMA serum levels for the prediction of hsPDA. The cut-off value of IMA for hsPDA was measured as 0.78 ABSU with 88.89 % sensitivity, and 90.24 % specificity, 85.71 % positive predictive, 92.5 % negative predictive value [area under the curve (AUC) = 0.96; $p < 0.001$]. The area under the curve was 93.6 % and the standard error was 3.3 % (Fig. 2). There was a statistically significant association between the groups on this cut-off value ($p < 0.01$). The ODSS ratio for IMA was 74.00 (95 % CI 15.202–360.215).

The mean IMA value of the infants with hsPDA before treatment was 1.26 ± 0.36 ABSU (range 0.77–1.48). However, the mean IMA value of infants after medical treatment was 0.67 ± 0.27 ABSU (range 0.72–1.12). These findings were considered to be statistically significant ($p = 0.03$) (Fig. 1).

Fig. 2 ROC curve showing the predictive value of serum ischemia-modified albumin (IMA) levels in the diagnosis of hemodynamically significant Patent Ductus Arteriosus (hsPDA) in preterm newborn

Discussion

In our present study, we have evaluated the serum levels and the efficacy of IMA in infants with hsPDA. To the best of our knowledge, our study will be the first reported study evaluating neonatal IMA levels in hsPDA. Our results described the relationship between IMA levels and hsPDA which showed an association with hypoxia and oxidative stress in newborns with hsPDA. Our results showed that IMA levels were significantly higher in infants with diagnosed hsPDA. In this study, we described that sensitivity, predictive value and AUC values of IMA in PDA were significantly higher than the control group. Additionally, we showed that IMA levels decreased after appropriate

treatment of PDA. Therefore, we suggested that IMA may be a useful marker for distinguishing severity of PDA in preterm infants which may possibly results in serious clinical adverse outcomes in early days of life.

Hemodynamically significant PDA in preterm infants can have significant clinical consequences through causing hypoperfusion and hypoxia due to the ductal steal phenomenon in many organs, particularly the brain, especially during the recovery period from respiratory distress syndrome [3–6, 17]. In a study conducted with very low birth weight (VLBW) infants, tissue oxygenation was measured using near-infrared spectroscopy, has shown that infants with hsPDA requiring surgical correction were at high-risk for alterations in cerebral oxygenation, while cerebral oxygenation of infants who were administered indomethacine or who received conservative treatment remained relatively stable [18]. In another study, preterm infants with <32 weeks of gestation, the mean arterial blood pressure and regional cerebral oxygen saturation were significantly lower in PDA infants compared with controls, and oxygenation improved after treatment of the PDA [19]. Therefore, it is obvious that hsPDA is very important for appropriate blood delivery and further oxygenation for the vital organs in preterm infants. In this present study, IMA levels were determined significantly higher infants with hsPDA. Current results show that hsPDA is an important contributing factor for hypoxia in preterm infants, and IMA can be used to display hypoxia in infants with hsPDA.

The relationship between IMA and asphyxia and/or hypoxia has been investigated in many studies, although the mechanism of IMA generation remains unexplained. It has been suggested that IMA is a modification of serum albumin, resulting from oxidative stress and concurrently produced superoxide-free oxygen radicals that occur during ischemic events regardless of tissue specificity [7–10, 13]. Recently, some studies have reported that IMA is related to various ischemia-related conditions, such as acute coronary syndrome, ischemia of the liver, brain, kidney, and bowel in adults [10, 19, 20]. IMA is accepted as a highly specific marker for myocardial ischemia, since IMA levels remain high during an ischemic event [8]. In the newborn period, few studies have determined that IMA are higher in perinatal asphyxia and complicated deliveries are associated with fetal distress, hypoxia, and oxidative stress indicating that IMA levels may be a good marker for the diagnosis of asphyxia in newborns [12, 13, 21–23]. Furthermore, recent studies have reported that serum IMA levels are sensitive and effective marker for the diagnosis, monitoring, treatment and followup of different diseases in newborn such as NEC, transient tachypnea of newborn [14, 24].

Because of augmented left-to-right shunt through the PDA, pulmonary blood flow increases and leads to pulmonary edema and overall worsening of cardiopulmonary

status. As a result, it therefore causes prolonged ventilation with the potential risks of volutrauma, barotrauma, and hyperoxygenation, that are strongly associated with the development and severity of bronchopulmonary dysplasia/chronic lung disease. Furthermore, increased left-to-right shunting through the ductus may also increase the risk of intraventricular hemorrhage, necrotizing enterocolitis, adverse neurodevelopmental outcomes, multiorgan failure and death [2, 4, 5, 17]. In this study, we determined that acute transient hypoxia appeared in infants with hsPDA. We thought that hypoxia mainly occurred because of PDA and its deleterious effects. As we obviously can see that preterm infant in the control group did not have long term respiratory compromises, long term respiratory support and higher IMA levels after birth. Higher IMA levels in preterm infants with hsPDA suggested that preterm infants with PDA may suffer from clinical hypoxia/asphyxia. And also, PDA further led to increase severity of respiratory distress and caused to long duration of respiratory support/oxygen administration and hospital stay. Based on our findings, the serum level of IMA can reliably differentiate hsPDA from no PDA state in preterm neonates. Moreover, in infants with hsPDA, a positive correlation was found between IMA and PDA diameter and LA/Ao ratio. Therefore, in this case, increased IMA levels could warn the attending physicians about hsPDA in NICU, and echocardiography may be avoided.

Hemodynamically significant PDA in preterm infants should be treated to avoid adverse outcomes which threat this particular population [16, 17]. In this study, infants who had hsPDA were administered ibuprofen. After successful treatment and closure of PDA, the serum level of IMA dropped dramatically to the level of no PDA state and this makes the serum level of IMA a valuable tool for the therapeutic monitoring. This may reduce the number of echocardiograms and eliminates the concern about recurrent or persistent PDA after the treatment. Additionally, decrease of the serum level of IMA to its normal level may indicate a successful treatment.

Conclusion

In the current study, IMA level was proved to be a good predictor for ductal intervention. In infants with PDA diagnosed by echocardiography and increased serum IMA levels, intervention may be required. Moreover, after appropriate treatment, decrease of the serum level of IMA to its normal level may indicate a successful treatment. Measurement of IMA is an easy and inexpensive test. However, clinical studies are insufficient for its use in routine practice in infant with hsPDA.

Compliance with Ethical Standards

Conflict of interest All authors have no conflict of interest.

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