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Impact of Patent Ductus Arteriosus and Subsequent Therapy with Ibuprofen on the Release of S-100B and Oxidative Stress Index in Preterm Infants

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Statistical Analysis C
Data Interpretation D
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Background: Hemodynamically significant patent ductus arteriosus (hsPDA) leads to injury in tissues/organs by reducing perfusion of organs and causing oxidative stress. The purpose of this study was to evaluate the oxidant/antioxidant status in preterm infants with hsPDA by measuring the total antioxidant capacity and total oxidant status and to assess neuronal damage due to oxidant stress related to hsPDA.





Material/Methods: This prospective study included 37 low-birth-weight infants with echocardiographically diagnosed hsPDA treated with oral ibuprofen and a control group of 40 infants without PDA. Blood samples were taken from all infants, and then the total antioxidant capacity (TAC), total oxidant status (TOS), and S-100B protein levels were assessed and oxidative stress index was calculated before and after therapy.

Results: The mean pre-therapy TOS level and oxidative stress index (OSI) value of the patients with hsPDA were significantly higher, but TAC level was lower than in the control group. There were no statistically significant differences in the mean post-therapy values of TOS, TAC, OSI, and S-100B protein between the two groups.

Conclusions: hsPDA may cause cellular injury by increasing oxidative stress and damaging tissue perfusion; however the brain can compensate for oxidative stress and impaired tissue perfusion through well-developed autoregulation systems to decrease tissue injury.

MeSH Keywords: **Antioxidants • Ductus Arteriosus, Patent • Oxidative Stress • S100 Calcium Binding Protein beta Subunit**

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Background

The left-to-right shunt in hemodynamically significant patent ductus arteriosus (hsPDA) in premature newborns leads to alveolar edema and decreased lung compliance by increasing pulmonary blood flow and capillary permeability. Under this condition, the infant potentially requires more oxygen and higher mechanical ventilation support [1]. Furthermore, hsPDA may cause hypoperfusion of vital organs, leading to pathologies such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and acute renal insufficiency [2,3]. In addition, intraventricular hemorrhage (IVH) resulting from sudden change in pressure and damage to the white matter may be caused by defective perfusion of the brain [4,5]. Although hsPDA is definitely related to these morbidities, its causative role has not been fully determined [6]. Patients with congenital heart diseases that lead to hypoperfusion, ischemia, and chronic hypoxia cannot meet the biological requirements of the tissues and are strongly confronted with oxygen radicals [7]. To prevent the adverse effects of free radicals and oxidants such as lipid peroxidant, the body activates antioxidant defense mechanisms that include: glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase [8]. In the first days of life, premature infants have higher concentrations of hydroperoxide in their erythrocyte membrane and lower antioxidant defense compared with those of term infants [9]. S-100B protein and neuron-specific enolase (NSE) are the most valuable biochemical markers of neuronal damage and glial activation in premature infants [37]. S-100B is a calcium-binding protein found particularly in Schwann and astroglial cells [10]. It increases after head trauma, subarachnoid hemorrhage, paralysis, and cardiac pathologies, resulting to neurologic damage [11].

The purpose of this study was to evaluate the oxidant/antioxidant status in preterm infants with hsPDA by measuring the total antioxidant capacity (TAC) and total oxidant status (TOS) and to assess the neuronal damage due to oxidant stress related to hsPDA.

Material and Methods

Patient population

The study included 77 infants of the same age group and gestational age hospitalized with the diagnosis of prematurity and respiratory distress syndrome in the Newborn Intensive Care Unit of Yüzüncü Yil University Teaching Hospital, Van, Turkey. The infants were divided into 2 groups. The first group included 37 infants, presumably ≤ 32 weeks of gestational age, diagnosed with hsPDA between day 3 and 7 using electrocardiography (ECHO). The second group included 40 infants with no hsPDA on ECHO examination. The clinical severity of hsPDA was

determined according to the PDA scoring system recommended by McNamara et al. [12]. Initially, all patients received fluids at a dose of 70–80 cc/kg/day; on subsequent days the fluid was gradually increased by 10–20 cc/kg/day, reaching a maximum of 150 cc/kg/day. The exclusion criteria for the study were congenital malformations, major congenital cardiac anomaly, genetic or metabolic disease, contraindication for the use of ibuprofen (oliguria or serum creatinine level >150 $\mu\text{mol/L}$ or platelet count $<75 \times 10^9/\text{L}$), and patients who refused to participate in the study. Seven of the patients initially included in the study were thereafter excluded: 2 of the patients had unstable phase III or greater intraventricular hemorrhage, 3 patients had unclosed PDA after ibuprofen therapy, and 2 patients died of sepsis during the study period. Before the initiation of the study, signed permission forms from the families of the infants and approval from the Ethics Council of the University were obtained.

Clinical and laboratory data

The study was performed in a prospective manner. The decision for therapy of the newborns diagnosed with hsPDA was made by a neonatologist. The SpO₂, arterial blood pressure, and support ventilation of the newborns were closely followed-up. The cranial ultrasonographies of all patients were performed on postnatal day 1 and 5 by a neonatologist experienced in transfontanel ultrasonography. Complications such as IVH, BPD, and NEC were recorded. BPD was diagnosed according to the diagnostic criteria of the U.S. National Institutes of Health [13]. After taking basal blood samples, the patients in the test group received a single dose ibuprofen via orogastric catheter (10 mg/kg/day on day 1; 5 mg/kg/day on day 2; 5 mg/kg/day on day 3). Twelve hours after the third dose of ibuprofen, the patients were reassessed with ECHO, and once again blood samples were taken from those who's PDA had closed. The blood samples were taken either from the umbilical venous catheter or from the peripheral veins, centrifuged at 5000 rpm for 10 min, and the sera obtained were kept at -80°C until the time of analysis.

Echocardiographic evaluation of patent ductus arteriosus

The patients included in the study were evaluated using ECHO in short and high parasternal axis. Echocardiography was performed once or more than once according to the clinical course of each patient. We used color Doppler echocardiography system with a Vivid S6 6s sector probe (GE Healthcare, GE Medical Systems, Horten, Norway). The diagnosis of hsPDA was reached and ibuprofen therapy was started upon the determination in echocardiographic parasternal long axis, left atrial/aortic root ratio of ≥ 1.4 mm/kg [2], enlargement of left ventricle, holodiastolic retrograde flow in the descending aorta; and a pulse-waved Doppler turbulent systolic and diastolic flow on the ductus and abnormal antegrade diastolic flow. Tachycardia ($\geq 160/\text{min}$) and hypotension (less than tenth

percentile according to birth weight and age) were evaluated as clinical findings supporting the diagnosis of hsPDA.

Calculation of total antioxidant capacity

The plasma TAC level was measured using a new automated measurement system developed by Erel [14], which uses hydroxyl radical, one of the most effective biological radicals produced. For measurements, as Reagent 1, the existing ferrous ion solution [o-dianisidine (10 mM), ferrous ion (45 AM) in the Clark and Lubs solution (75 mM, pH 1.8)] was mixed with Reagent 2-hydrogen peroxide [H₂O₂ (7.5 mM) in the Clark and Lubs solution]. The sequentially produced brown-colored dianisidiny radical cation and the radicals produced by the hydroxyl radical are strong radicals. Using this method, the antioxidant effect of the sample on a strong free radical produced by hydroxyl radical was measured. The tests gave perfect results at values under 3%. The results are expressed as mmol Trolox Equiv. L-1.

Calculation of total oxidant status

The plasma TOS level was measured using a new automated measurement system developed by Erel [15]. Oxidants present in the sample oxidize the ferrous ion-o-dianisidine complex to ferric ion. The oxidation reaction is mediated by glycerol molecules amply found in the reaction area. The ferric ion forms an orange-colored complex with the xylenol molecule in an acidic setting. The color saturation, which can be measured spectrophotometrically, is based on the total quantity of oxidant substances in the specimen. The results were calibrated with hydrogen peroxide and expressed in terms of micromolar hydrogen peroxide equivalent per liter (1 mol H₂O₂ Equiv. L-1).

Oxidative stress index

The oxidative stress index (OSI) was taken as the percentage ratio of TOS values to TAS values. Before making the calculations, the values in the TAC test were converted into micromolar values, as in the TOS test. The results were calculated using the formula OSI (arbitrary unit) = TOS (μmol H₂O₂ equivalent/L)/TAS (mmol Trolox equivalent/L) × 10, and the calculated values were defined as random units [15].

Serum S100B measurement

The serum S-100B level was measured using an electrochemiluminescence immunoassay kit (ECLIA, Roche Diagnostics, Germany).

Statistical analyses

The results of groups with normal distribution are presented as mean ±SD, and the median was used to present results that showed abnormal distribution. The chi-square test was used

Table 1. Important perinatal and neonatal clinical characteristics.

Characteristic	Group 1 (n=30)	Group 2 (n=40)
Birth weight (g)	1456±299	1440±329
Gestational age (wk)	29.9±1.9	30.4±1.8
Male sex, n (%)	14 (46.7)	20 (50)
Antenatal steroids, n (%)	24 (80)	33 (82)
Apgar score, median (range)		
1 min	5 (2–7)	5 (2–8)
5 min	7 (5–9)	8 (5–9)
PDA score, n (%)		
C3 (Moderate)	20 (66.6)	NA
C4 (Severe)	10 (33.4)	NA
Age at PDA diagnosis (day)	4.2±1.4	NA
Surfactant, n (%)	18 (60)	23 (57.5)
Dopamine, n (%)	20 (66.7)	19 (47.5)
Postnatal hydrocortisone, n (%)	2 (6.7)	0 (0)
Hematocrit (%)	38.2±3.4	36.4±4.2
Delivery, n (%)		
Cesarean section	27 (90)	38 (95)
Spontaneous vaginal delivery	3 (10)	2 (5)
Average duration of mechanical ventilation (day)*	4.3±2.7	2.3±1.5

NA – not applicable. Plus-minus values are means ±SD. PDA score is from McNamara and Sehgal [12]. * The mean duration of mechanical ventilation support in the PDA group was significantly longer than that in the control group (p<0.001).

to evaluate demographic data between the 2 groups. To determine significant differences between the groups, the unpaired t-test for data with normal distribution and Mann-Whitney U test for data with non-normal distribution were used. In comparing pre-therapy with post-therapy, the paired t-test for data with normal distribution and Wilcoxon test for data with non-normal distribution were performed. To determine the relationship between the variables, for each group, Pearson and Spearman correlation coefficients were used. The p values <0.05 of the obtained results was accepted as statistically significant. For statistical analysis, SPSS 12.0 (SPSS Inc, Chicago, IL) was used.

Results

Clinical findings

The clinical, perinatal, and natal features of the hsPDA patients (test group) and the control group patients are shown

Table 2. Comparison of mean pre-treatment TOS, TAS, OSI, and S-100B protein values of the patient and control groups.

Variables	Pre-treatment (n=30)	Control (n=40)	p
TOS, $\mu\text{mol Trolox equivalents/L}$	15.2 \pm 7.50	8.94 \pm 6.80	0.001
TAC, $\mu\text{mol H}_2\text{O}_2$ equivalents/L	2.00 \pm 0.43	2.23 \pm 0.38	0.023
OSI, unit	0.79 \pm 0.43	0.41 \pm 0.32	<0.001
S-100B protein ($\mu\text{g/L}$)	0.92 \pm 1.00	0.92 \pm 1.04	0.449

The t test for independent samples was used. Data are expressed as mean \pm standard deviation. Significance was defined as $p \leq 0.05$. TOS – total oxidant stress; TAS – total antioxidant status; OSI – oxidative stress index.

Table 3. Comparison of mean post-treatment TOS, TAS, OSI, and S-100B protein values of the patient and control groups.

Variables	Post-treatment (n=30)	Control (n=40)	p
TOS, $\mu\text{mol Trolox equivalents/L}$	10.1 \pm 5.6	8.94 \pm 6.8	0.434
TAC, $\mu\text{mol H}_2\text{O}_2$ equivalents/L	2.42 \pm 0.44	2.23 \pm 0.38	0.062
OSI, unit	0.43 \pm 0.24	0.41 \pm 0.32	0.268
S-100B protein ($\mu\text{g/L}$)	0.92 \pm 1.04	0.77 \pm 0.48	0.447

The t test for independent samples was used. The data are expressed as mean \pm standard deviation. Significance was defined as $p \leq 0.05$. TOS – total oxidant stress; TAS – total antioxidant status; OSI – oxidative stress index.

Table 4. Comparison of the pre-treatment and post-treatment serum TOS, TAS, OSI, and S-100B protein values of the patients.

Variables	Pre-treatment (n=30)	Post-treatment (n=30)	p
TOS, $\mu\text{mol Trolox equivalents/L}$	15.2 \pm 7.5	10.1 \pm 5.60	<0.001
TAC, $\mu\text{mol H}_2\text{O}_2$ equivalents/L	2.00 \pm 0.43	2.42 \pm 0.44	<0.001
OSI, unit	0.79 \pm 0.43	0.43 \pm 0.24	<0.001
S-100B protein ($\mu\text{g/L}$)	0.92 \pm 1.00	0.92 \pm 1.04	0.845

The paired samples t test was used. Significance was defined as $p \leq 0.05$. TOS – total oxidant stress; TAS – total antioxidant status; OSI – oxidative stress index.

in Table 1. There were no significant differences between the two groups in terms of birth weight, birth week, sex, antenatal steroid use, Apgar score, surfactant therapy, type of delivery, and inotropic support, but the mean duration of mechanical ventilation support in the PDA group was significantly longer than that in the control group ($p < 0.001$).

TAC, TOS, OSI, and S-100B protein values

The mean pre-therapy values of TOS and OSI in the test group were significantly higher, but TAC values were lower than those in the control group ($p = 0.001$, $p < 0.001$, and $p = 0.023$, respectively). The S-100B protein levels in both groups were similar (Table 2).

There were no significant differences between the test and control groups in terms of mean post-therapy values of TOS, TAC, OSI, and S-100B protein ($p > 0.05$) (Table 3).

When the pre-therapy TOS, TAC, and OSI values were compared with the post-therapy values, the TOS and OSI values were significantly higher, but TAC values were found to be significantly lower ($p < 0.001$ for all values). The S-100B protein levels in both groups were similar (Table 4).

Discussion

In this study, we evaluated how hsPDA, a cause of significantly increased morbidity and mortality in infants, affected the

body's total antioxidant capacity, total oxidant status, and serum S-100B level, which is one of the most important markers of cerebral damage.

Infants encounter oxidative stress because they are born into a hyperoxic surrounding after a relatively hypoxic fetal life. The effect of oxidative stress, as well as other factors (decreased prostaglandins E₂ and I₂ and role of platelets), enables the ductus arteriosus to physiologically close within the first 3 days of life [2,16]. In case of PDA, the high requirement for oxygen leads premature infants who are normally prone to oxidative stress to encounter more free oxygen radicals. The oxidant defense mechanism and antioxidant enzymatic system are increasingly activated towards the last weeks of pregnancy; hence, the antioxidant capacity of premature infants is thought to be low [17,18]. Another study [19] reported that serum antioxidant enzyme activity in premature infants was lower than that in term infants, but oxidant markers were found in similar quantities in both groups of infants. In the test group, the pre-therapy TAC levels were lower than the post-therapy and TAC levels of the control group, and the patients with hsPDA had significantly higher levels of TOS and OSI than those in the control patients. The marked decrease in TOS and OSI levels in hsPDA patients after therapy was related to decreased exposure to free oxygen radicals secondary to the closure of PDA. The free oxygen radicals damage the proteins, carbohydrates, lipids, and nucleic acids in the cell membranes [20]. Free oxygen radicals are natural reactive components that are continuously produced in the body and which have positive as well as negative effects. The body needs a strong antioxidant system in order to limit the negative effects of these radicals. The antioxidant system consists of enzymes (catalase, glutathione peroxidase, and superoxide dismutase), vitamins (Vitamin A, E, and C), uric acid, and glutathione. When the balance between the oxidant and antioxidant systems is upset in favor of oxidants, various disorders emerge due to increased oxidative stress [21]. Rokicki et al. [22] reported that in patients with congenital heart disease with left-to-right shunt, there is a low antioxidant system, but a high oxidant system (with the exception of uric acid). Ercan et al. [21], in their study of 91 patients, reported that serum TAC, TOS, and OSI levels in cyanotic congenital heart disease patients were higher than those in acyanotic congenital heart disease patients and the control group. The same study [21] found no statistically significant differences between the acyanotic congenital heart disease patients (19 cases of ventricular septal defect, 5 cases of atrial septal defect, and 6 cases of PDA) and control patients in terms of TAC, TOS, and OSI levels. Particularly in patients with PDA, the increase in free oxygen radicals caused by high oxygen requirement may lead to an imbalance between oxidants and antioxidants in infants in who the antioxidant system has not yet fully developed. The increasing prevalence of complications such as IVH, BPD, NEC, periventricular leukomalacia, and

white matter damage in PDA with no apparent reason might be due to this imbalance. It was reported that BPD developed later in patients with high levels of peroxidase in urine and tracheal lavage specimens [23,24]. Another study [25] reported high values of TOS and OSI in BPD patients. Aydemir et al. [26] found quite high levels of serum TOS and OSI in patients with NEC, but TAC levels similar to those of the control group. Left ventricular volume overload and steal phenomenon due to PDA leads to decreased perfusion and oxygenation of vital organs such as the brain. Since the cerebrovascular autoregulation capacity of the immature brain is not fully developed and the present partial autoregulation tends to be easily upset, the brain is more prone to injury [27]. The critical oxygen level required for sufficient oxygenation of the premature infant's brain is not yet fully known. PDA in premature infants has been reported to be related to IVH and periventricular leukomalacia, and this negative effect of PDA might cause neurodevelopmental disorders [28–31]. Such critical reports on PDA have consequently led to the conclusion that PDA should be closed as soon as possible. Therefore, based on ECHO findings on the first day of life, surgical ligation performed in the delivery room, and medical treatment with indomethacin or ibuprofen have been widely used as therapies for PDA [32,33]. With the introduction of near-infrared spectroscopy (NIRS), which measures regional cerebral tissue oxygen saturation, the effect of PDA on the cerebral oxygenation of very premature infants could be measured [34]. Determination of cerebral oxygenation and oxygen extraction by using NIRS showed that cerebral oxygenation and fractional tissue oxygen extraction (FTOE) were decreased in PDA patients, but more injury to the immature brain tissue could be prevented by early diagnosis, appropriate treatment, and providing cerebral oxygenation. In contrast to the report that indomethacin, through vasoconstriction, harms tissue oxygenation and thereby causes tissue damage [35], another study [34] found that low cerebral tissue perfusion oxygenation already present did not worsen after indomethacin therapy. Another study that used a similar methodology [36] reported that sudden changes in pressure after surgical ligation were more prominent than after conservative and indomethacin therapy; however, there was no relationship between hsPDA and worsening neuroimaging abnormalities before and after therapy. In our study, when the test cases were compared with control cases and pre-therapy test cases were compared with post-therapy test cases, the S-100B levels, which are expected to rise in direct tissue damage, did not show significant changes.

Conclusions

The presence of hsPDA in premature infants, in who the oxidant defense mechanism is not fully developed, causes increase in total oxidant status and oxidative stress index, which leads

to tissue/organ damage. We determined that in patients with hsPDA no significant cerebral injury developed before or after therapy. To determine the rate of cerebral damage in patients with hsPDA, there is a need for studies with larger number of patients to assess the correlation between the results obtained from devices such as NIRS, which measures local tissue oxygenation and serum NSE, and S-100B levels accepted to be the best markers of cerebral damage.

Limitations of the study

1. A small number of patients were included.
2. We did not measure NSE level, which is another important parameter to measure cerebral damage.

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35. 3. Devices such as NIRS that measure local tissue oxygenation were not available.

Contribution to the literature

1. The study demonstrated for the first time that in hsPDA patients, oxidant stress responsible for tissue damage is significantly increased.
2. Although oxidant stress index rises significantly in hsPDA patients, it does not cause cerebral damage.

Statement

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