Evaluation of total oxidant status/total antioxidant capacity and DNA damage in neonates with high lactate levels in umbilical cord blood gases

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Abstract. The relationship between elevated lactate levels, oxidative stress (OS) and DNA damage in neonates remains unclear; however, neonates with high lactate levels in umbilical cord gases may exhibit increased OS and DNA damage, thus serving as an indirect indicator of OS and DNA damage. The present study evaluated the relationship between elevated umbilical cord blood lactate levels, OS and DNA damage in term neonates. The present prospective, single-center study included 61 term newborns, categorized into a study group (n=38) with cord blood lactate levels of ≥5 mmol/l, and a control group (n=23) with lactate levels of <5 mmol/l. Blood samples of the study and control groups were obtained within the first 12 h for measurements of total oxidant status (TOS), total antioxidant capacity (TAC) and DNA damage. Second samples and measurements were obtained at 72-96 h after lactate levels fell to <5 mmol/l in the study group and samples for the control group were also obtained at postnatal 72-96 h for TOS and TAC measurements. Results in the first 12 h were referred to as TOS1/TAC1, while results at 72-96 h were referred to as TOS2/TAC2. The most accurate lactate cut-off for predicting pH ≤7.2 was 5.005 mmol/l (sensitivity, 92.9%; specificity, 48.9%). TOS1, TOS2, TAC1 and TAC2 levels were significantly higher in the study group (P<0.001). DNA damage was also higher in neonates with elevated lactate levels (P=0.01). Furthermore, lactate was negatively correlated with pH and base excess, and was positively correlated with DNA damage, TOS2 and TAC. In conclusion, these findings indicated that newborns with high umbilical cord lactate levels experience increased OS and DNA damage, even after lactate normalization. Therefore, lactate may serve as an indirect indicator of neonatal OS, warranting further investigation into its long-term implications.

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Introduction

Umbilical cord blood gas analysis, first proposed by James *et al* (1) in 1958 as a marker of intrapartum hypoxia, is now recommended in all high-risk deliveries by Armstrong and Stenson (2) and the American College of Obstetricians and Gynecologists Committee (3). As well as confirming the acid-base status of newborns at birth, umbilical cord blood gas gives immediate insight into perinatal events and potential longer-term risk such as neurodevelopmental impairments (4). Among its parameters, arterial lactate has consistently outperformed pH and base deficit (BE) in predicting early neonatal morbidity, hypoxic-ischemic encephalopathy (HIE) and the need for intensive care (5-11).

Oxygen is vital for all living organisms, yet it can exert harmful effects on cells by forming reactive oxygen species (ROS). Under normal physiological conditions, the body counteracts these deleterious effects via enzymatic and non-enzymatic antioxidant mechanisms (12). Neonates experience a significant oxidative stress (OS) burden during the transition from the intrauterine hypoxic environment to the relatively hyperoxic postnatal environment. This abrupt shift results in increased free radicals, which may contribute to oxidative tissue damage and play a crucial role in the pathogenesis of numerous neonatal disorders (13). The production of antioxidant enzymes commences in the fetal period, with a notable surge occurring in the last trimester (14). However, premature neonates may exhibit an inadequate antioxidant response, predisposing them to OS-related complications. OS can damage various cellular components, ultimately leading to DNA damage (15).

In neonates, lactate levels in umbilical cord blood gas are considered a key parameter in assessing hypoxic conditions. Several studies have indicated that elevated lactate

levels are associated with increased neonatal morbidity and mortality (5,6,11,16). Furthermore, OS and DNA damage markers have been linked in the development of neonatal diseases such as respiratory distress syndrome (RDS), intrauterine growth restriction, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC) and HIE (15-20).

Due to the fact that intrapartum lacticemia mirrors both the intensity and duration of tissue hypoxia, it has been hypothesized that neonates with high umbilical cord lactate levels may also demonstrate a parallel rise in systemic OS and early DNA damage. Establishing such a relationship would support the use of cord lactate as a pragmatic, rapidly available surrogate marker for oxidative injury and aid early risk stratification. Accordingly, the present study evaluated the relationship between neonates with elevated umbilical cord blood gas lactate levels, and markers of OS and DNA damage. The findings were compared with neonates exhibiting normal lactate levels to explore potential clinical implications, and to establish a better understanding of neonatal OS and its impact on perinatal outcomes.

Materials and methods

Study population. The present study was designed as a prospective study and focused on total oxidant status (TOS)/total antioxidant capacity (TAC) and DNA damage in neonates with high lactate levels in umbilical cord blood gas analysis. Cord blood gas analysis is routinely performed for all babies born at Haseki Training and Research Hospital (İstanbul, Türkiye). High lactate levels can cause anion-gap metabolic acidosis, with acidosis typically becoming concerning at lactate levels of ~45 mg/dl (5.0 mmol/l) (21). Labrecque *et al* (22) demonstrated by receiver operating characteristic (ROC) curve analysis that the best cut-off for prediction of a pH ≤7.20 is a lactate value of 4.9 mmol/l. Several studies have evaluated the definition of normal cord blood gases, but there is no global consensus (23-27). The Turkish Neonatal Society Guidelines recommend hospitalization and monitoring of newborns with serum pH <7.2, as this may affect cardiac contractility, cause pulmonary vasoconstriction, and be associated with pulmonary hypertension, hyperkalemia, tachypnea, lethargy and coma (28). Hence, neonates with lactate levels of ≥5 mmol/l in cord blood gas are routinely hospitalized and there is close follow-up for infants in the neonatal intensive care unit (NICU). Babies with lacticemia (elevated lactate without metabolic acidosis) or lactic acidosis (elevated lactate causing metabolic acidosis) in their cord blood gas are admitted to the NICU and are monitored for potential morbidities such as hypoglycemia, sepsis, hyperbilirubinemia and respiratory problems. The present study included newborn babies with lacticemia or lactic acidosis who did not develop any complications (such as sepsis, fever, hypoglycemia, jaundice, respiratory distress and asphyxia) during follow-up. Term infants born with a lactate level of ≥5 mmol/l in cord blood gas who were hospitalized in the NICU of Haseki Training and Research Hospital between August 31, 2022, and April 30, 2023, were enrolled in the present study. Infants of mothers with preeclampsia, infants of mothers with chorioamnionitis or fever (≥38˚C), and infants with fever, congenital heart disease, stage 2-3 HIE, hyperbilirubinemia, hypoglycemia, congenital malformation and septicemia were excluded. Additionally, infants whose second blood sample could not be obtained between 72 and 96 h after inclusion in the study were excluded. A total of 38 term infants for whom written informed consent was obtained from the parents were included as the study group.

The control group comprised consecutive healthy term newborns matched for gestational age with cord blood gas lactate levels of <5 mmol/l who had normal antenatal scans, were followed up at the maternity ward and were discharged without postnatal problems. A total of 23 term infants for whom written informed consent was obtained from the parents were included as the control group.

Demographic features such as sex, gestational week, birth weight, birth height, head circumference, 1- and 5-min Apgar scores and maternal features, such as maternal age, gravida and mode of delivery, were recorded for all infants.

Cord blood gas analysis. Newborns were handed to a pediatric physician or nurse after the first cord clamp was applied by obstetricians 30-40 sec after birth, following routine clinical practice. After a second cord clamp was placed at 4-5 cm from the navel, the physician or nurse performed the sampling and 1 ml blood was collected into Monovette lithium heparin tubes (Sarstedt, Inc.). The samples were transferred to the laboratory for cord blood gas analysis. The samples were promptly analyzed using a Siemens Rapidlab 1265 electrolyte and blood gas analyzer (Siemens AG). Newborns with a cord blood gas lactate level of ≥5 mmol/l who met the inclusion criteria were enrolled as the study group in the present study. The babies born with high lactate levels in the study group were routinely followed-up by monitoring blood gas analysis until the lactate level was <5 mmol/l after NICU admission. During this monitoring for a fall in lactate levels to <5 mmol/l, the change in lactate levels was referred to as Δlactate, which was calculated as 'baseline lactate level minus first lactate level <5 mmol/l'.

OS and DNA damage analysis. For neonates included in the study, blood samples were collected within the first 12 h after birth for follow-up and control purposes. The serum was separated for TAC and TOS analysis after centrifugation at 2,500 x g for 5 min at room temperature and stored at -80˚C for all samples. Blood gas analysis of newborns in the study group with lactate levels >5 mmol/l was routinely monitored until a fall to <5 mmol/l was observed. When the lactate levels were <5 mmol/l, the plans for the second sampling of TOS2 and TAC2 were made and samples were taken at the 72-96th h after lactate levels fell <5 mmol/l. Second sampling of TAC2 and TOS2 in the control group was performed according to the timing of cord blood gas analysis after 72-96 h. Blood samples were collected in yellow gel biochemistry tubes and were centrifuged at 2,500 x g for 5 min at room temperature, and then the supernatant was transferred to Eppendorf tubes for TAC, TOS and 8-hydroxy-2'-deoxyguanosine (8-OHdG) analyses. These samples were stored at -80˚C and transported on dry ice (-78.5˚C) for laboratory analysis. TAC and TOS samples taken at 12 h were labeled as TOS1-TAC1, and those collected at 72-96 h were labeled as TOS2-TAC2. 8-OHdG analysis of DNA damage was performed only on

the samples obtained within the first 12 h. TOS results were converted from pg/ml to U/ml for OS index (OSI) calculation, with OSI values derived from the TOS/TAC ratio (OSI1=TOS1/TAC1, OSI2=TOS2/TAC2). ΔTOS referred to TOS1 minus TOS2. ΔTAC referred to TAC1 minus TAC2. ΔOSI referred to OSI1 minus OSI2.

TAC analysis. TAC levels were measured using commercially available kits (cat. no. 201-12-2200; Rel Assay Diagnostics). The assay is based on a double-antibody sandwich ELISA principle. Briefly, serum samples and standards were added to wells pre-coated with human T-AOC monoclonal antibody, followed by 10 µl biotin-labeled T-AOC antibody (diluted with 120 µl standard diluent) and 50 µl streptavidin-HRP incubation for 60 min at 37˚C. After washing, Chromogen Solutions A and B were added for incubation for 10 min at 37˚C, and the reaction was stopped with stop solution. The optical density was measured at 450 nm within 15 min, and concentrations were calculated using a standard curve according to the manufacturer's protocol. The assay sensitivity was 0.5 U/ml, with an assay range of 0.7-85 U/ml, intra-assay CV (SD/mean x100) <8% and inter-assay CV <11%. TAC results are expressed in U/ml.

TOS analysis. TOS levels were measured using commercially available kits (cat. no. 201-12-5539; Rel Assay Diagnostics). The assay is based on an ELISA principle. Briefly, serum samples and standards were added to wells pre-coated with human TOS monoclonal antibody, followed by 10 µl biotin-labeled TOS antibody (diluted with 120 µl standard diluent) and 50 µl streptavidin-HRP incubation for 60 min at 37˚C. After washing, Chromogen Solutions A and B were added for incubation for 10 min at 37˚C, and the reaction was stopped with stop solution. The optical density was measured at 450 nm within 15 min, and concentrations were calculated using a standard curve according to the manufacturer's protocol. The assay sensitivity was 0.177 pg/ml, with an assay range of 0.2-60 pg/ml, intra-assay CV <10% and inter-assay CV <12%. TOS results were initially expressed in pg/ml and later converted to U/ml.

DNA damage analysis. DNA damage was assessed using a Human 8-OHdG ELISA kit (cat. no. 201-12-1437; Shanghai Sunred Biological Technology Co., Ltd.) based on a competitive ELISA. Briefly, serum samples and standards were added to wells pre-coated with human 8-OHdG monoclonal antibody, followed by 10 µl biotin-labeled 8-OHdG antibody (diluted with 120 µl standard diluent) and 50 µl streptavidin-HRP incubation for 60 min at 37˚C. After washing, Chromogen Solutions A and B were added for incubation for 10 min at 37˚C, and the reaction was stopped with stop solution. The optical density was measured at 450 nm within 15 min, and concentrations were calculated using a standard curve according to the manufacturer's protocol. The assay sensitivity was 0.558 ng/ml, with an assay range of 1-100 ng/ml, intra-assay CV <10% and inter-assay CV <12%. Results are expressed in ng/ml.

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp.). Descriptive statistics were presented as counts and percentages for categorical variables, while continuous variables were summarized using mean ± SD for normally distributed data and median (IQR: 25-75th percentile) for non-normally distributed data. Data normality was assessed using the Kolmogorov-Smirnov test. Categorical variables were compared between groups using Fisher's exact test due to small sample sizes. Continuous variables were compared between the study and control groups using the Mann-Whitney U test due to small sample sizes. For paired non-normally distributed numerical data Wilcoxon signed-rank test was applied (TOS1-2, TAC1-2, OSI1-2). Bonferroni corrections were performed after each of these tests. Correlation analysis between numerical variables was conducted using Spearman correlation analysis when parametric assumptions were not met. ROC curve analysis was performed to assess the predictive ability of cord blood gas lactate levels for identifying newborns with pH ≤7.2. The optimal cutoff value was determined using the Youden index, and sensitivity, specificity, positive predictive value and negative predictive value were calculated accordingly. P<0.05 was considered to indicate a statistically significant difference.

Based on the assumption that a large effect size difference (effect size, 0.8) between groups would be considered significant, the sample size was calculated to be 41 newborn for the study group and 21 newborn for the control group (total, 62 cases; power, 90%; significance level, P<0.05; patient:control ratio, 2:1).

Results

Study population. Of the 61 newborns included in the study, 32 (52.5%) were male, with a mean gestational week of 39.1±1.0 weeks, birth weight of 3,277±363 g, birth height of 51.6±2.0 cm and head circumference of 35.0±1.4 cm. The median 1-min Apgar score was 9 (IQR 8-9) and the median 5-min Apgar score was 10 (IQR 9-10) for all newborns. The study group had lower 1- and 5-min Apgar scores compared with the control group. When ROC curve analysis was performed for the cord blood gas lactate value of all newborns, the best lactate cut-off value for predicting pH ≤7.2 was calculated as 5.005 mmol/l with a sensitivity of 92.9% and specificity of 48.9% (Fig. S1). The mean lactate value of the study group (n=38) was 6.09±0.93 mmol/l, while that of the control group (n=23) was 2.64±0.63 mmol/l (P<0.001). Comparative demographic and maternal characteristics of the study and control groups, and cord blood gas data are given in Table I.

When the control blood gas values were obtained once the lactate levels of the study group fell to <5 mmol/l, the mean pH was 7.40±0.04, CO_2 35.2±4.8 mmHg, BE-2.0±2.3 mmol/l, HCO_3 22.6±1.9 mmol/l and lactate 3.1±0.8 mmol/l (minimum 1.23, maximum 4.70). The Δlactate value was 2.9±1.2 mmol/l and the mean percentage change in lactate value was 46.8±15.9% (data not shown).

OS and DNA damage. Comparisons made between the study and control groups are shown in Table II. TOS1 and TOS2 values were significantly higher in the study group compared with those in the control group. TAC1 and TAC2 values in the study group were also significantly higher when compared with those in the control group. In addition, DNA damage was

Table I. Comparison of demographic and maternal characteristics, and cord blood gas data of the study and control groups.

Variable	Study group (n=38)	Control group (n=23)	P-value
Demographic features			
Sex, n (%)			0.621
Female	19 (50)	10 (43.5)	
Male	19 (50)	13 (56.5)	
Gestational age, weeks[a]	39.2±1.0	39.1±1.0	0.895
Weight, g[a]	3,256±400	3,312±295	0.568
Height, cm[a]	51.4±2.1	52.0±1.8	0.255
Head circumference, cm[a]	34.9±1.6	35.2±1.2	0.328
Apgar score[b]			
1 min	8 (7-9)	10 (9-10)	0.007
5 min	9 (9-9)	10 (10-10)	0.019
Maternal features			
Maternal age, years[a]	26.3±6.2	28.9±5.6	0.106
Gravida[b]	2 (1-3)	3 (2-5)	<0.001
Mode of delivery, n (%)			0.232
Cesarean section	4 (10.5)	3 (13.0)	
Vaginal	26 (68.5)	19 (82.6)	
Assisted vaginal birth	8 (21.2)	1 (4.3)	
Cord blood gases[a]			
pH	7.23±0.08	7.35±0.04	<0.001
Lactate, mmol/l	6.09±0.93	2.64±0.63	<0.001
CO_2, mmHg	49.3±12.3	39.5±5.5	<0.001
HCO_3, mmol/l	17.4±1.8	20.6±1.4	<0.001
Base deficit, mmol/l	-7.6±2.1	-3.7±1.6	<0.001
Hemoglobin, g/dl	16.2±2.5	15.8±1.7	0.557
Hematocrit, %	48.1±4.6	46.6±5.0	0.250

[a]Data are presented as the mean ± SD; [b]data are presented as the median (IQR 25-75).

significantly higher in the study group compared with that in the control group. By contrast, there was no significant difference between OSI1 and OSI2 values in the study and control groups. ΔTOS (1.40±3.31 vs. 3.83±8.00; P=0.169), ΔTAC (2.90±8.98 vs. 1.39±6.81; P=0.847) and ΔOSI (0.01±0.16 vs. 0.10±0.37; P=0.783) were not significantly different between the study and control groups (data not shown). While the TOS2 value was significantly decreased in the study group and control group compared with the initial admission TOS1 value, TAC and OSI values did not change over time in both groups (Table II).

In all groups, the lactate level was negatively correlated with pH (ρ, -0.722) and BE (ρ, -0.699), and positively correlated with DNA damage (ρ, 0.257), TOS2 (ρ, 0.362; P=0.004), TAC1 (ρ, 0.326; P=0.01) and TAC2 (ρ, 0.329; P=0.01), but not with TOS1 (ρ, 0.183; P=0.158) (data not shown). Furthermore, there was a positive correlation between DNA damage and TOS1 (ρ, 0.699), DNA damage and TOS2 (ρ, 0.660), DNA damage and TAC1 (ρ, 0.619), and DNA damage and TAC2 (ρ, 0.784) in the study group (P<0.001 for all). TOS1 and 1-min Apgar scores were negatively correlated. Correlation analyses results of DNA damage, TOS1, TOS2, TAC1, TAC2, OSI1 and OSI2 in the study group are provided in Table III.

Discussion

In the present study, the relationship between elevated cord blood lactate levels (>5 mmol/l) and OS and DNA damage in term newborns was investigated. The results demonstrated that newborns with high cord blood lactate levels exhibited significantly increased TOS and TAC levels compared with those with lower lactate levels. Additionally, DNA damage was significantly higher in the high-lactate group. These findings suggested that elevated lactate levels in cord blood may be indicative of increased OS and potential cellular damage in neonates.

The optimum lactate cut-off value for predicting pH ≤7.2 in the present study was determined to be 5.005 mmol/l with a sensitivity of 92.9% and specificity of 48.9%. This is consistent with previous studies, such as those of Labrecque *et al* (22) and Ridenour *et al* (29); this previous study reported similar cut-off values for lactate in cord blood gas analysis to predict neonatal acidosis. In a previous study, cord blood lactate was shown to be at least as good as pH and BE for the evaluation of the development of perinatal asphyxia in newborns (6). Similarly, in other studies, the lactate value is accepted as an indicator of neurological complications such as tissue hypoxia

Table II. Comparisons of TOS1 vs. TOS2, TAC1 vs. TAC2, OSI1 vs. OSI2 and DNA damage in the study and control group.

Variable	Study group (n=38)	Control group (n=23)	P-value[a]
TOS1, U/ml	18.47±10.26	16.43±13.07	0.042
TOS2, U/ml	17.07±9.62	12.60±6.42	0.002
P-value[b]	0.04	0.002	
TAC1, U/ml	31.99±15.44	23.33±11.86	0.004
TAC2, U/ml	29.09±12.55	21.93±14.59	0.002
P-value[b]	0.572	0.402	
OSI1	0.59±0.13	0.71±0,43	0.844
OSI2	0.58±0.11	0,61±0.14	0.572
P-value[b]	>0.99	>0.99	
DNA damage, ng/ml	38.05±24.88	28.52±13.50	0.02

[a]Comparisons between study and control groups were made using the Mann-Whitney U test; [b]Comparisons of TOS1 vs. TOS2, TAC1 vs. TAC2 and OSI1 vs. OSI2 in the study and control group were made using the Wilcoxon signed-rank test. Bonferroni corrections were performed after each of these tests. Data are presented as the mean ± SD. TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index.

Table III. Correlation analyses of DNA damage, TOS1, TOS2, TAC1, TAC2, OSI1, and OSI2 in the study group.

	DNA damage		TOS1		TOS2		TAC1		TAC2		OSI1		OSI2	
Variables	ρ	P-value	ρ	P-value	ρ	P-value	ρ	P-value	ρ	P-value	ρ	P-value	ρ	P-value
TOS1	0.699	<0.001												
TOS2	0.660	<0.001	0.790	<0.001										
TAC1	0.619	<0.001	0.784	<0.001	0.714	<0.001								
TAC2	0.784	<0.001	0.735	<0.001	0.693	<0.001	0.694	<0.001						
OSI1	0.082	0.624	0.194	0.242	0.016	0.925	-0.345	0.034	0.042	0.802				
OSI2	0.028	0.866	0.291	0.077	0.484	0.002	0.243	0.142	-0.152	0.361	0.099	0.553		
Apgar (1-min)	-0.142	0.402	-0.340	0.040	-0.315	0.057	-0.167	0.324	-0.214	0.202	-0.050	0.768	-0.125	0.463
Apgar (5-min)	-0.151	0.371	-0.251	0.135	-0.238	0.157	-0.197	0.242	-0.220	0.191	-0.029	0.866	-0.153	0.365
pH	0.127	0.446	0.166	0.320	0.090	0.591	0.137	0.413	0.120	0.474	0.223	0.178	0.111	0.508
Base deficit	0.034	0.841	-0.078	0.646	-0.020	0.905	-0.078	0.645	0.002	0.991	-0.204	0.226	-0.140	0.410
CO_2	0.150	0.375	0.016	0.923	0.013	0.941	0.057	0.739	0.065	0.701	-0.026	0.878	0.019	0.911
HCO_3	0.146	0.396	0.029	0.869	-0.001	0.995	0.095	0.582	0.069	0.690	-0.011	0.949	0.081	0.637
Lactate	-0.032	0.848	-0.088	0.597	0.102	0.543	-0.006	0.971	-0.139	0.407	-0.189	0.255	0.184	0.269

TOS, total oxidant status; TAC, total antioxidant capacity; OSI, oxidative stress index.

and encephalopathy in the early neonatal period (30,31). An important advantage of using lactate instead of BE to assess acidosis in cord blood gas is that BE is a calculation or algorithm-dependent estimate; due to the methodological complexity involved in the calculation of BE, lactate may replace BE as an acid-base outcome parameter at birth, especially since lactate is a directly measured value (32). Lactic acid in fetal blood is thought to be primarily of fetal origin (33), when fetal acidosis is caused by maternal acidosis and lactic acid is produced by mechanisms other than those encountered during asphyxia, measurements of metabolic acidosis may not be specific. Studies have reported that increased maternal lactate production under conditions of labor and delivery may affect the rate of net transfer from fetus to mother. It is estimated that only 6% of fetal acidosis is due to maternal acidosis (30,34). In the present study, mothers with fever and severe infections such as chorioamnionitis were not included, so the presented results are not considered to be related to maternal acidosis. In the present study, cord blood gas lactate was correlated with pH and BE and it was thought that it may reflect the OS status of the newborn in the antenatal period and DNA damage better than BE or pH. The present study showed that TOS and TAC levels were higher in newborns with lactate levels of ≥5 mmol/l in cord blood gas compared

with those in newborns with lactate levels of <5 mmol/l. It has previously been shown that newborns are exposed to high levels of OS in the early postnatal period. However, in the present study, TOS was found to be higher in newborns with high lactate levels compared with in the control group in the present study, even when lactate levels had decreased to <5 mmol/l in the follow-up of these babies. In addition, although TOS2 had decreased compared to TOS1 in the study group, it was still significantly higher than the control group. These findings indicated that lactate levels may be valuable in terms of showing that these babies continue to be exposed to OS. Buonocore *et al* (35) investigated OS in premature newborns at birth and 7 days after birth, and the plasma levels of hypoxanthine, total hydroperoxide and advanced oxidation protein products were higher in hypoxic newborns at birth and on day 7 compared with those in control infants; these results were similar to those of the present study. Both oxidative and antioxidative parameters are elevated in neonates with birth asphyxia, which may represent an attempt to re-establish redox homeostasis in the immediate postnatal period. This dual elevation underscores the delicate balance between oxidative insult and defensive response in neonatal adaptation. Thus, data in the present study support the notion that a high-lactate environment not only reflects anaerobic metabolism but also initiates a systemic oxidative response, wherein both oxidant burden and antioxidant capacity are upregulated as part of a transient yet critical neonatal adaptation mechanism. Another key observation in the present study was the increased DNA damage in newborns with higher cord blood lactate levels. This may be an indirect indicator of enhanced OS in these infants. OS-induced DNA damage has been implicated in various neonatal conditions, including RDS, HIE, ROP and NEC (17-20). The persistence of OS despite the resolution of acidosis raises concerns regarding potential long-term effects on neurodevelopment, warranting further investigation.

Labor is an inherently oxidative process, and the intrauterine-to-extrauterine transition exposes newborns to a relatively hyperoxic environment (13). This exposure, combined with the physiological stress of birth, can lead to excessive free radical production (36). Free radicals can be produced by various mechanisms such as hypoxia, development of reperfusion after ischemia, hyperoxia, neutrophil and macrophage activation, mitochondrial dysfunction, the Fenton reaction, endothelial cell damage and prostaglandin metabolism (37,38). Neonates are at high risk for free radical damage as there is an imbalance between the antioxidant and oxidant-producing systems that causes oxidative damage. Neonatal plasma possesses antioxidant substances including several enzymes, proteins and vitamins (39), and ROS are removed from cells and tissues by the antioxidant mechanisms. The production of antioxidant enzymes starts during the fetal period and the levels of antioxidant enzymes and non-enzymatic antioxidant substances increase in the third trimester. In the present study, it was found that TAC levels were higher in newborns with cord blood gas lactate levels of >5 mmol/l than in newborns with lactate levels of <5 mmol/l.

A few studies have evaluated the neurodevelopmental outcomes of patients and their association with lactate levels in cord blood gas analysis. Yilmaz *et al* (40) evaluated the Ages and Stages Questionnaire, Third Edition, developmental screening questionnaire in infants with high cord lactate levels (>5 mmol/l) and low lactate levels (<5 mmol/l), and found that the high lactate group had lower fine motor, problem-solving and personal-social development scores compared with those in the normal lactate group. Furthermore, Malak *et al* (41) showed that cord blood gas was associated with low pH, sucking reflex, tonic neck reflex, attention deficit and general motor development according to the development score (Brazelton Neonatal Behavioral Assessment Scale, 4th edition). However, while no short-term neurological morbidity was observed in the present study, there are no data on the long-term neurodevelopmental outcomes of these newborns.

The present study has several strengths, including its prospective design and the homogeneous study population of term newborns. Multiple factors (such as infant sex, maternal age, gestational week, meconium in amniotic fluid and oxytocin use) have been reported to affect lactate levels in the literature; therefore, all the participants were matched according to gestational age. When the results of the present study were evaluated, it was shown that variables such as maternal age, infant sex and mode of delivery, which may affect lactate level, were similar in the study group and control group; however, there are some limitations. First, preterm newborns were not included, as they are already known to have increased OS, which could have confounded the results. Second, there is a lack of long-term neurodevelopmental follow-up data, which would have provided more insight into the clinical implications of the findings. Third, only a single 8-OHdG measurement was obtained within the first 12 h after birth to capture acute oxidative injury. Other perinatal studies have similarly used cord-blood 8-OHdG as an early marker of hypoxic damage (with samples taken at birth) (42,43) After initial resuscitation and lactate normalization, ongoing oxidative injury is expected to have subsided, so repeating 8-OHdG may not add clinically actionable information. Furthermore, 8-OHdG levels substantially fall over the first week of life, which may interfere with lactate decline (44). Finally, as a single-center study, the generalizability of the results of the current study may be limited.

In conclusion, the present study demonstrated that newborns with cord blood lactate levels of ≥5 mmol/l may experience increased OS and DNA damage compared with in those with lower lactate levels (<5 mmol/l). Notably, OS was shown to persist even after lactate levels decreased, highlighting the need for further research into the long-term consequences of perinatal OS. Future studies should focus on the neurodevelopmental outcomes of these infants and explore potential interventions to mitigate oxidative damage in the early neonatal period.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

BC contributed to design; acquisition, analysis and interpretation of data; and drafted and critically revised the manuscript. AY and DB contributed to acquisition and interpretation of data; and drafted and critically revised the manuscript. DK and HÇ contributed to analysis and interpretation of data; and drafted and critically revised the manuscript. ME contributed to design; analysis and interpretation of data; and drafted and critically revised the manuscript. BC and AY confirm the authenticity of all the raw data. All authors agree to be accountable for all aspects of work ensuring integrity and accuracy, and read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Haseki Training and Research Hospital, (approval no. 19/17; dated August 10, 2022). Written informed consent was obtained from the parents of all participants before their inclusion in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. James LS, Weisbrot IM, Prince CE, Holaday DA and Apgar V: The acid-base status of human infants in relation to birth asphyxia and the onset of respiration. J Pediatr 52: 379-394, 1958.
2. Armstrong L and Stenson BJ: Use of umbilical cord blood gas analysis in the assessment of the newborn. Arch Dis Child Fetal Neonatal Ed 92: F430-F434, 2007.
3. ACOG Committee on Obstetric Practice: ACOG committee opinion No. 348, November 2006: Umbilical cord blood gas and acid-base analysis. Obstet Gynecol 108: 1319-1322, 2006.
4. Cowley NJ, Owen A and Bion JF: Interpreting arterial blood gas results. BMJ 346: f16, 2013.
5. Wiberg N, Källén K, Herbst A and Olofsson P: Relation between umbilical cord blood pH, base deficit, lactate, 5-min Apgar score and development of hypoxic ischemic encephalopathy. Acta Obstet Gynecol Scand 89: 1263-1269, 2010.
6. Neacsu A, Herghelegiu CG, Voinea S, Dimitriu MCT, Ples L, Bohiltea RE, Braila AD, Nastase L, Bacalbasa N, Chivu LI, *et al*: Umbilical cord lactate compared with pH as predictors of intrapartum asphyxia. Exp Ther Med 21: 80, 2021.
7. Allanson ER, Waqar T, White C, Tunçalp Ö and Dickinson JE: Umbilical lactate as a measure of acidosis and predictor of neonatal risk: A systematic review. BJOG 124: 584-594, 2017.
8. Westgren M, Divon M, Horal M, Ingemarsson I, Kublickas M, Shimojo N and Nordström L: Routine measurements of umbilical artery lactate levels in the prediction of perinatal outcome. Am J Obstet Gynecol 173: 1416-1422, 1995.
9. Gaertner VD, Bassler D, Zimmermann R and Fontijn JR: Reference values for umbilical artery lactate by mode of delivery and gestational age: A retrospective observational study. Neonatology 118: 609-616, 2021.
10. Su TY, Reece M and Chua SC: Lactate study using umbilical cord blood: Agreement between Lactate Pro hand-held devices with blood gas analyser and evaluation of lactate stability over time. Aust N Z J Obstet Gynaecol 53: 375-380, 2013.
11. Gjerris AC, Staer-Jensen J, Jørgensen JS, Bergholt T and Nickelsen C: Umbilical cord blood lactate: A valuable tool in the assessment of fetal metabolic acidosis. Eur J Obstet Gynecol Reprod Biol 139: 16-20, 2008.
12. Cross CE, Halliwell B, Borish ET, Pryor WA, Ames BN, Saul RL, McCord JM and Harman D: Oxygen radicals and human disease. Ann Intern Med 107: 526-545, 1987.
13. Frank L and Sosenko IR: Development of lung antioxidant enzyme system in late gestation: Possible implications for the prematurely born infant. J Pediatr 110: 9-14, 1987.
14. Shim SY and Kim HS: Oxidative stress and the antioxidant enzyme system in the developing brain. Korean J Pediatr 56: 107-111, 2013.
15. Yu BP: Approaches to anti-aging intervention: The promises and the uncertainties. Mech Ageing Dev 111: 73-87, 1999.
16. Giovannini N, Crippa BL, Denaro E, Raffaeli G, Cortesi V, Consonni D, Cetera GE, Parazzini F, Ferrazzi E, Mosca F and Ghirardello S: The effect of delayed umbilical cord clamping on cord blood gas analysis in vaginal and caesarean-delivered term newborns without fetal distress: A prospective observational study. BJOG 127: 405-413, 2020.
17. Elkabany ZA, El-Farrash RA, Shinkar DM, Ismail EA, Nada AS, Farag AS, Elsayed MA, Salama DH, Macken EL and Gaballah SA: Oxidative stress markers in neonatal respiratory distress syndrome: Advanced oxidation protein products and 8-hydroxy-2-deoxyguanosine in relation to disease severity. Pediatr Res 87: 74-80, 2020.
18. Blok EL, Burger RJ, Bergeijk JEV, Bourgonje AR, Goor HV, Ganzevoort W and Gordijn SJ: Oxidative stress biomarkers for fetal growth restriction in umbilical cord blood: A scoping review. Placenta 154: 88-109, 2024.
19. Lembo C, Buonocore G and Perrone S: Oxidative stress in preterm newborns. Antioxidants (Basel) 10: 1672, 2021.
20. Perez M, Robbins ME, Revhaug C and Saugstad OD: Oxygen radical disease in the newborn, revisited: Oxidative stress and disease in the newborn period. Free Radic Biol Med 142: 61-72, 2019.
21. Ganetzky RD and Cuddapah SR: Neonatal lactic acidosis: A diagnostic and therapeutic approach. NeoReviews 18: e217-e227, 2017.
22. Labrecque L, Provençal M, Caqueret A, Wo BL, Bujold E, Larivière F and Bédard MJ: Correlation of cord blood pH, base excess, and lactate concentration measured with a portable device for identifying fetal acidosis. J Obstet Gynaecol Can 36: 598-604, 2014.
23. Gilstrap LC III, Hauth JC, Hankins GDV and Beck AW: Second-stage fetal heart rate abnormalities and type of neonatal acidemia. Obstet Gynecol 70: 191-195, 1987.
24. Gilstrap LC III, Leveno KJ, Burris J, Williams ML and Little BB: Diagnosis of birth asphyxia on the basis of fetal pH, Apgar score, and newborn cerebral dysfunction. Am J Obstet Gynecol 161: 825-830, 1989.
25. Goldaber KG, Gilstrap LC III, Leveno KJ, Dax JS and McIntire DD: Pathologic fetal acidemia. Obstet Gynecol 78: 1103-1107, 1991.
26. Winkler CL, Hauth JC, Tucker JM, Owen J and Brumfield CG: Neonatal complications at term as related to the degree of umbilical artery acidemia. Am J Obstet Gynecol 164: 637-641, 1991.
27. Lee JH, Jung J, Park H, Kim SY, Kwon DY, Choi SJ, Oh SY and Roh CR: Umbilical cord arterial blood gas analysis in term singleton pregnancies: A retrospective analysis over 11 years. Obstet Gynecol Sci 63: 293-304, 2020.
28. Yıldızdaş HY, Demirel N and İnce Z: Turkish neonatal society guideline on fluid and electrolyte balance in the newborn. Turk Pediatri Ars 53 (Suppl 1): S55-S64, 2018.
29. Ridenour RV, Gada RP, Brost BC and Karon BS: Comparison and validation of point of care lactate meters as a replacement for fetal pH measurement. Clin Biochem 41: 1461-1465, 2008.
30. Suidan JS, Antoine C, Silverman F, Lustig ID, Wasserman JF and Young BK: Human maternal-fetal lactate relationships. J Perinat Med 12: 211-217, 1984.
31. da Silva S, Hennebert N, Denis R and Wayenberg JL: Clinical value of a single postnatal lactate measurement after intrapartum asphyxia. Acta Paediatr 89: 320-323, 2000.
32. Wiberg N, Källén K and Olofsson P: Base deficit estimation in umbilical cord blood is influenced by gestational age, choice of fetal fluid compartment, and algorithm for calculation. Am J Obstet Gynecol 195: 1651-1656, 2006.

33. Otey E, Stenger V, Eitzman D, Andersen T, Gessner I and Prystowsky H: Movements of lactate and pyruvate in the pregnant uterus of the human. Am J Obstet Gynecol 90: 747-752, 1964.
34. Piquard F, Schaefer A, Dellenbach P and Haberey P: Is fetal acidosis in the human fetus maternogenic during labor? A reanalysis. Am J Physiol 261: R1294-R1299, 1991.
35. Buonocore G, Perrone S, Longini M, Vezzosi P, Marzocchi B, Paffetti P and Bracci R: Oxidative stress in preterm neonates at birth and on the seventh day of life. Pediatr Res 52: 46-49, 2002.
36. Buonocore G, Perrone S and Bracci R: Free radicals and brain damage in the newborn. Biol Neonate 79: 180-186, 2001.
37. McCord JM: Oxygen-derived free radicals in postischemic tissue injury. N Engl J Med 312: 159-163, 1985.
38. Kukreja RC, Kontos HA, Hess ML and Ellis EF: PGH synthase and lipoxygenase generate superoxide in the presence of NADH or NADPH. Circ Res 59: 612-619, 1986.
39. Gopinathan V, Miller NJ, Milner AD and Rice-Evans CA: Bilirubin and ascorbate antioxidant activity in neonatal plasma. FEBS Lett 349: 197-200, 1994.
40. Yilmaz A, Cebi MN, Yilmaz G, Karacaoglu G, Aydin SN, Perk Y and Vural M: Long-term neurodevelopmental effects of exclusively high cord lactate levels in term newborn. J Matern Fetal Neonatal Med 36: 2284115, 2023.
41. Malak R, Sikorska D, Rosołek M, Baum E, Mojs E, Daroszewski P, Matecka M, Fechner B and Samborski W: Impact of umbilical cord arterial pH, gestational age, and birth weight on neurodevelopmental outcomes for preterm neonates. PeerJ 9: e12043, 2021.
42. Kimura C, Watanabe K, Iwasaki A, Mori T, Matsushita H, Shinohara K and Wakatsuki A: The severity of hypoxic changes and oxidative DNA damage in the placenta of early-onset preeclamptic women and fetal growth restriction. J Matern Fetal Neonatal Med 26: 491-496, 2013.
43. Gane BD, Nandakumar S, Bhat BV, Rao R, Adhisivam B, Joy R, Prasad P and Shruti S: Biochemical marker as predictor of outcome in perinatal asphyxia. Curr Pediatr Res 17: 63-66, 2013.
44. Shoji H, Shimizu T, Shinohara K, Oguchi S, Shiga S and Yamashiro Y: Suppressive effects of breast milk on oxidative DNA damage in very low birthweight infants. Arch Dis Child Fetal Neonatal Ed 89: F136-F138, 2004.