



Is Umbilical Cord Arterial Lactate a Predictive Indicator of Term Neonate Well-being?

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ABSTRACT

Objective: This research was conducted with a medical records-based, retrospective design to examine the predictive value of umbilical cord lactate measurement as an early indicator of well-being and severe conditions in term neonates.

Materials and Methods: The study sample consisted of 81 term neonates with a gestational age of ≥ 37 weeks who experienced respiratory distress and were treated and monitored in the neonatal intensive care unit, and who had a cord arterial blood gas measurement performed at birth. The data were retrospectively collected from hospital records.

Results: The umbilical cord arterial lactate value was associated with the pH level and analysis revealed that it predicted a low Apgar score, commonly used as a wellness assessment of a neonate ($p < 0.05$). The lactate value was significantly high at birth in neonates with meconium aspiration syndrome and premature rupture of membranes in comparison with the pH and other cord gas parameters, suggesting that it may be an early predictor of distress. Receiver operating characteristic curve analysis determined that the lactate value was a more sensitive measurement than pH in predicting a low first-minute Apgar score. It was also found that as the lactate level increased, the length of hospitalization increased.

Conclusion: The results suggested that cord lactate is at least as predictive as the Apgar score and the pH level as an early means to determine severe conditions in neonates. Lactate might be a useful variable for clinicians at first-level hospitals to consider in their decision to refer a patient to a secondary or tertiary neonatal intensive care unit before the clinical situation deteriorates.

Keywords: Apgar score, lactate, neonate, pH, well-being

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INTRODUCTION

The Apgar score is the best known and most widely used method to provide a rapid assessment of the clinical status of a neonate (1). This quick evaluation performed shortly after birth has been in use for about 60 years, however, it is now recognized that it might be influenced by factors such as prematurity, congenital abnormalities, gestational age, medication, and the type of anesthesia administered to the mother (2–4). It has been suggested that while the Apgar score is useful for distinguishing normal neonates from weak infants, a more sensitive assessment may be needed (3, 5). Perinatal hypoxia is a dangerous and potentially severe condition that is difficult to fully assess at birth. Most neonates born with hypoxia symptoms and a low Apgar score or acidemia detected in the cord blood analysis recover in the neonatal period with appropriate attention and monitoring. However, intrauterine problems emerging days or weeks before the birth can cause severe neurological sequelae, long-lasting morbidity, and even death (6, 7). Therefore, an accurate determination and proper treatment of intrapartum hypoxia in the early postnatal period is significant in order to prevent possible complications (7).

Evaluation of umbilical arterial blood gas parameters is another method that can be used to differentiate neonates with a risky or low Apgar score from seriously hypoxic and acidemic neonates (8, 9). Cord gas analysis includes the direct measurement of pH, partial oxygen (pO_2), partial carbon dioxide (pCO_2), lactate, and base excess (BE) (8). The umbilical cord pH value can be a valuable measurement to help determine a clear diagnosis of birth asphyxia and referral for neonatal assistance in complicated or extended births (depressed) infants (9). However, the influence of other parameters is still uncertain. Recent studies have noted that the lactate value is another objective indicator that might be used in the assessment of neonates (8, 10, 11).

Perinatal hypoxia is a critical condition caused by a lack of oxygen supply followed by increased anaerobic metabolism (10, 6). As a result of reduced oxygen in body tissues, the pH level decreases in umbilical cord arterial blood and the level of lactate increases (10). Lactate is an end-product of anaerobic metabolism. Glucose breaks down into pyruvate, which is converted into lactate and hydrogen ions under hypoxic conditions (12). Data from animal models have demonstrated that the fetal lactate level increased sooner in hypoxia and persisted longer than low pH after normoxia was established (13). Umbilical cord arterial lactate, the main source of lactate in fetal circulation, is a direct representation of fetal acidosis in the fetus itself (3, 10).

Table 1. Characteristics of the study neonates (N=81)

Features	Number (n)	Percent (%)
Gender		
Female	40	49.4
Male	41	50.6
Birth type		
Normal birth	32	39.5
Caesarean section	49	60.5
Diagnosis		
MAS	12	14.8
TTN	41	50.6
Pneumonia	19	23.5
Sepsis	5	6.2
PROM	4	4.9
Cord entanglement		
Yes	5	6.2
No	76	93.8
Deep tracheal aspiration		
Applied	2	2.5
Not applied	79	97.5
Positive pressure ventilation		
Applied	11	13.6
Not applied	70	86.4
Type of treatment administered		
Oxygen hood	35	43.2
CPAP	36	44.5
Mechanical ventilation	10	12.3
Length of stay in the hospital (days)		
1–7	46	56.8
8–16	35	43.2

CPAP: Continuous positive airway pressure; MAS: Meconium aspiration syndrome; PROM: Premature rupture of membranes; TTN: Transient tachypnea of the newborn

The objective of this study was to examine whether lactate may be a predictive indicator of severe conditions and of well-being in term neonates. The research questions were:

1. Is umbilical cord blood lactate concentration a predictive parameter of severe conditions in term neonates?
2. Is there a relationship between umbilical cord arterial lactate and the Apgar score or other cord gas parameters in the assessment of term neonate well-being?

MATERIALS and METHODS

Prior to beginning, ethical approval was obtained from the Yozgat Bozok University Clinical Research Ethics Committee on May 30, 2018 (no: 2017-KAEK-189_2018.05.30_19).

This research was conducted as a medical records-based retrospec-

tive study with a descriptive correlational analysis at a university hospital in Central Anatolia. The study population consisted of 248 neonates delivered at term/mature in a university hospital and monitored in the neonatal intensive care unit (NICU). The sample studied included 81 term infants born between January 2017 and January 2018 with a gestational age of ≥ 37 weeks who experienced respiratory distress, received oxygen therapy, were monitored in the NICU, and who had a cord arterial blood gas measurement performed at birth.

The data were retrospectively collected from the hospital birth records. The demographic and medical variables were retrieved from the neonate data collection form. The demographic variables used were gender, gestational age at birth, type of birth, and measurements of birth weight, length, and head circumference. The medical variables examined were diagnosis, treatment applied, length of hospital stay, Apgar score, cord blood gas parameters, and arterial lactate values. Umbilical cord blood is routinely sampled by the assistant physician immediately after birth. A segment of the umbilical cord is isolated using 2 clamps and needle aspiration of arterial blood is performed using a heparinized syringe. Analyses is performed within 30 minutes and the blood gases and lactate are measured using a whole blood automatic analyzer.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 22.0 software (IBM Corp., Armonk, NY, USA) was used to analyze data. Sociodemographic data were presented as percentage (%), median value (with minimum and maximum), and mean \pm SD ($\bar{x} \pm SD$). The distribution of numerical variables was assessed using the Shapiro-Wilk normality test and Q-Q plotting. The Kruskal-Wallis test was used to compare numerical data, and the Dunn-Bonferroni test was applied as a post-hoc test in pairwise comparisons to determine significance. Spearman correlation analysis was used to evaluate the relationship between lactate and other variables. A *p* value of < 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to determine the selectivity of lactate. An area under the curve (AUC) value of ≥ 0.70 was considered a good predictive value.

RESULTS

In this study group, 50.6% of the neonates were male and 60.5% were a cesarean delivery. In all, 50.6% were followed up with a diagnoses of transient tachypnea of the newborn (TTN), 23.5% with pneumonia, 14.8% with meconium aspiration syndrome (MAS), 6.2% with sepsis, and 4.9% with premature rupture of membranes (PROM). Oxygen was administered using an oxygen hood in 43.2% of the neonates, continuous positive airway pressure (CPAP) was used in 44.5%, 12.3% required mechanical ventilation, and 43.2% stayed in the hospital for 8–16 days (Table 1).

The mean gestational age of the neonates was 38.26 ± 1.13 weeks. Examination of the anthropometric measurements revealed a mean birth weight of 3185.98 ± 563.62 g, length of 49.32 ± 2.88 cm, and a head circumference of 34.33 ± 1.35 cm. The mean first and fifth minute Apgar score was 7.77 ± 1.81 and 9.02 ± 1.08 , respectively. The mean cord arterial blood gas parameters were pH: 7.26 ± 0.12 , BE: -6.85 ± 4.36 mmol/L, HCO_3^- : 19.70 ± 2.93

Table 2. Anthropometric measurements, Apgar score, and cord blood parameters of the study neonates (N=81)

Features	Mean±SD	Median (Min–Max)
Anthropometric measurements		
Gestational age (weeks)	38.26±1.13	38.20 (37.0–41.10)
Length (cm)	49.32±2.88	49.00 (41.00–53.00)
Weight (g)	3185.98±563.62	3170.00 (2330–4925)
Head circumference (cm)	34.33±1.35	34.50 (32.00–37.00)
Apgar score		
1 minute	7.77±1.81	8.00 (1.00–9.00)
5 minute	9.02±1.08	9.00 (6.00–10.00)
Cord blood measurements		
pH	7.26±0.12	7.29 (6.89–7.47)
BE (mmol/L)	-6.85±4.36	-5.30 (-19.30–0.10)
HCO ₃ (mEq/L)	19.70±2.93	20.25 (12.60–24.40)
pCO ₂ (mmHg)	44.64±11.39	42.90 (24.00–89.20)
pO ₂ (mmHg)	35.30±17.63	31.60 (10.80–79.30)
Lactate (mmol/L)	4.01±2.47	3.15 (1.10–11.96)

SD: Standard deviation; Min: Minimum; Max: Maximum; BE: Base extract; HCO₃: Bicarbonate; pCO₂: Partial carbon dioxide pressure; pO₂: Partial pressure of oxygen

mEq/L, pCO₂: 44.64±11.39 mmHg, pO₂: 35.30±17.63 mmHg, and lactate: 4.01± 2.47 mmol/L (Table 2).

The cord blood gas and serum lactate levels are presented in Table 3 according to diagnosis. The mean pH, BE, HCO₃, pCO₂, and pO₂ values of the neonates in the TTN, MAS, pneumonia, sepsis, and PROM groups demonstrated no significant difference. The lactate value was, however, significant, with higher serum lactate values in the MAS and PROM groups (p<0.05).

Table 4 provides the mean cord blood gas parameters according to the type of oxygen treatment delivered. There was a significant difference in the cord blood gas pH values according to the method of oxygen therapy (mechanical ventilator, CPAP, or hood) (p<0.05). The Dunn-Bonferroni test revealed a significant difference between the mechanical ventilator and CPAP groups, and the mechanical ventilator and hood groups (p=0.012; p=0.048, respectively). A significant difference was also seen in the BE values of the neonates (p<0.05). Furthermore, there was a significant difference between the group that received mechanical ventilation and CPAP, and between the mechanical ventilation and hood groups (p=0.005; p=0.041, respectively). In addition, a significant difference was observed between the groups in pCO₂ value: the group receiving mechanical ventilation had a higher mean value than that of the CPAP or hood group (p=0.043, p=0.049, respectively). There was no significant difference between the groups in terms of HCO₃ or pO₂ values according to the type of oxygen treatment. The comparison of lactate values indicated that the mean serum lactate of all 3 groups was high, but the difference between groups was not significant (p>0.05).

The relationship between umbilical cord arterial lactate and other blood gas parameters, Apgar score, and other parameters is illustrated in Table 5. In terms of assessing the well-being of the

Table 3. Distribution of average lactate and blood gas parameters according to the diagnosis of the study neonates

Variables	PROM		MAS		Pneumonia		Sepsis		TTN		Test KW	p
	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)		
pH	7.24±0.15	7.21 (7.10/7.45)	7.20±0.15	7.21 (6.89/7.41)	7.27±0.09	7.26 (7.05/7.39)	7.32±0.08	7.34 (7.21/7.42)	7.27±0.12	7.31 (6.90/7.47)	3.759	0.440
BE mmol/L	-6.37±5.89	-5.70 (-14.20/0.10)	-9.48±5.17	-8.50 (-18.40/-4.40)	-5.90±3.33	-5.20 (-13.70/-1.60)	-5.24±1.66	-5.0 (-8.00/-3.80)	-6.69±4.40	-4.80 (-19.30/-1.10)	5.115	0.276
HCO ₃ mEq/L	20.62±3.65	21.25 (15.70/24.30)	17.98±3.13	17.40 (13.30/23.80)	20.41±2.69	20.30 (15.70/24.30)	20.12±1.18	19.90 (18.90/22.10)	19.79±2.96	20.50 (12.60/24.40)	4.707	0.319
PCO ₂ mmHg	50.67±13.06	50.85 (34.50/66.50)	47.82±16.10	43.45 (28.80/89.20)	44.64±8.91	41.80 (33.50/67.00)	39.50±9.06	36.80 (29.70/50.10)	43.76±10.88	42.80 (24.00/79.60)	2.858	0.582
PO ₂ mmHg	35.57±16.29	41.20 (11.80/48.10)	39.17±20.66	31.60 (15.90/76.40)	31.80±17.27	24.90 (13.90/79.30)	41.56±14.31	45.70 (22.20/56.00)	34.83±17.82	31.0 (10.80/76.80)	2.601	0.627
Lactate mmol/L	4.81±1.89	5.13 (2.24/6.77)	6.73±3.53	6.05 (1.59/11.96)	3.49±2.10	2.81 (1.35/7.90)	3.69±1.34	3.80 (1.74/5.52)	3.38±1.85	2.77 (1.10/8.68)	11.920	0.018

SD: Standard deviation; Min: Minimum; Max: Maximum; KW: Kruskal-Wallis test; BE: Base extract; CPAP: Continuous positive airway pressure; HCO₃: Bicarbonate; MAS: Meconium aspiration syndrome; PCO₂: Partial carbon dioxide pressure; PO₂: Partial pressure of oxygen; PROM: Premature rupture of membranes; TTN: Transient tachypnea of the newborn

Table 4. Distribution of lactate and blood gas parameters according to the type of oxygen treatment

Variables	Mechanical ventilator		CPAP		Oxygen hood		Test KW	P
	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)	Mean±SD	Median (Min/Max)		
pH	7.21±0.13	7.25 (6.89/7.40)	7.30±0.10	7.37 (7.05/7.47)	7.33±0.05	7.33 (7.22/7.41)	10.628	0.005
BE (mmol/L)	-8.86±4.82	-8.80 (-19.30/-1.10)	-5.38±3.56	-4.60 (-16.20/0.10)	-4.98±1.95	-4.70 (-9.90/-2.90)	11.297	0.004
HCO ₃ (mEq/L)	18.72±3.20	18.70 (12.60/24.40)	20.51±2.65	21.0 (13.30/24.30)	20.29±1.82	20.50 (17.60/23.20)	5.934	0.051
PCO ₂ (mmHg)	48.77±13.16	47.90 (30.60/89.20)	41.95±9.30	41.75 (24.00/66.50)	39.36±5.45	41.00 (28.80/45.10)	7.351	0.025
PO ₂ (mmHg)	33.82±18.92	28.85 (10.80/76.80)	34.80±14.13	35.65 (11.60/68.90)	41.94±23.04	35.0 (18.50/79.30)	1.173	0.556
Lactate (mmol/L)	4.57±2.82	4.04 (1.10/11.96)	3.68±2.26	3.06 (1.35/11.55)	3.22±1.42	2.90 (1.63/5.24)	1.950	0.377

SD: Standard deviation; Min: Minimum; Max: Maximum; KW: Kruskal-Wallis test; BE: Base extract; CPAP: Continuous positive airway pressure; HCO₃: Bicarbonate; PCO₂: Partial carbon dioxide pressure; PO₂: Partial pressure of oxygen

Table 5. The relationship between umbilical cord arterial lactate and some other parameters

Parameters	Lactate (mmol/L)	
	rho	p
pH	-0.600	< 0.001
BE (mmol/L)	-0.691	< 0.001
HCO ₃ (mEq/L)	-0.569	< 0.001
pCO ₂ (mmHg)	0.409	< 0.001
pO ₂ (mmHg)	0.053	0.654
Apgar 1 minute score	-0.372	0.001
Apgar 5 minute score	-0.292	0.012
Gestational age	0.431	< 0.001
Gestational weight	0.179	0.116
Hospital stay (days)	0.632	< 0.001

BE: Base extract; HCO₃: Bicarbonate; PCO₂: Partial carbon dioxide pressure; PO₂: Partial pressure of oxygen

Table 6. ROC curve analysis area under the curve for lactate and pH for low Apgar

Variables	Area	SE	Asymptotic sig.	Asymptotic 95% interval	
				Lower bound	Upper bound
pH	0.254	0.097	0.012	0.063	0.445
Lactate	0.772	0.084	0.006	0.607	0.937

ROC: Receiver operating characteristic; SE: Standard error

newborn and predicting severe neonatal outcomes, a strong negative relationship was found between the lactate measurement and the pH and BE values (respectively, rho=-0.600, p<0.001; rho=-0.691, p<0.001). There was a moderate negative meaningful relationship to HCO₃ (rho=-0.569, p<0.001), and a positive meaningful relationship to CO₂ (rho=0.409, p<0.001). There was a negative relationship to the Apgar first and fifth minute scores (rho=-0.372, p=0.001; rho=-0.292, p=0.012, respectively) and a moderate positive relationship to gestational age (rho=0.431, p<0.001). Additionally, a good positive correlation was found between the length of stay in the hospital and the lactate level (rho=0.632, p<0.001).

The ROC curve analysis of lactate and pH levels as a predictive indicator of a low first-minute Apgar score (≤5) can be seen in Figure 1. The 0.772 AUC determined in this study (p<0.05, 95% confidence interval: 0.607–0.937) was categorized as a good value (Table 6).

DISCUSSION

Objective evaluation of the physical condition of newborns during the postnatal period is important; healthcare professionals must be able to recognize deviations from normal and perform the appropriate interventions. The aim of the current study was to determine whether the umbilical cord lactate value was a predictive indicator in the evaluation of the well-being of term neonates, as well as the relationship of the lactate value to other cord blood gas parameters and the Apgar score.

The term neonates studied were hospitalized in the NICU due to respiratory distress with pneumonia, TTN, MAS, sepsis, or PROM. Hakan et al. (14) determined that 126 of 257 neonates hospitalized in the neonatal unit followed up due to respiratory distress were most often treated with an oxygen hood or CPAP, while 12.3% of term neonates received mechanical ventilation therapy.

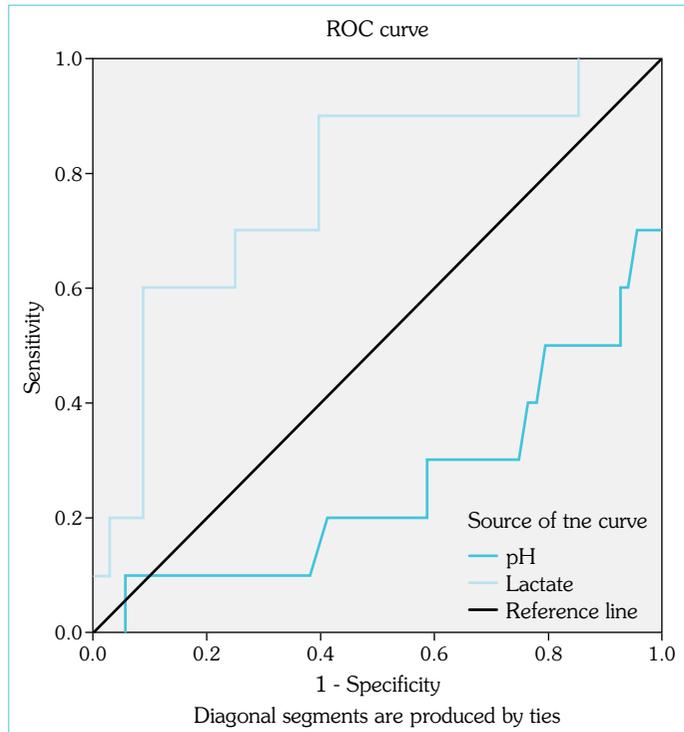


Figure 1. The receiver operating characteristic (ROC) curve of lactate and pH as a predictive indicator of a low Apgar score

In recent years, it has been noted that in addition to the Apgar score, umbilical cord blood gas values may be a reliable and objective method to assess fetal oxygenation and the acid-base level in the evaluation of serious conditions in neonates (3, 8, 10). Before, during, or after labor, various factors affect gas passage in utero-placental circulation and changes in umbilical cord blood gas parameters (15). In our study, while comparison of the cord blood gas and lactate level according to the diagnosis of the neonates revealed no significant difference in terms of pH, PCO_2 , PO_2 , HCO_3 , or BE values, the umbilical artery lactate value was higher in the neonates with MAS and PROM. Lactate may be a more sensitive measurement to determine the morbidity of term neonates than pH or other cord blood gas values. Since lactate is a direct product of anaerobic metabolism, it is produced earlier in cases of hypoxia. Therefore, changes in the lactate value can be detected sooner than a low pH value (12, 16). In addition, a high umbilical cord blood lactate value is a specific marker of metabolic acidosis, which is associated with more neonatal complications than respiratory acidosis (17, 18). Tuuli et al. (8) also reported that umbilical cord arterial lactate was more specific than pH in the prediction of neonatal morbidity. Mazouri et al. (19) found that an increase in lactate in the umbilical cord blood indicated MAS severity and could be used to distinguish between thick meconium and thin meconium in amniotic acid. Sun and Yu (20) investigated the clinical value of lactate to predict the prognosis of neonatal sepsis and determined that their group with a poor prognosis had a higher lactate level than the good prognosis group. Özkiraz et al. (21) found that a lactate measurement might be useful for clinicians at first-level hospitals in decision-making to refer a TTN patient to a secondary or tertiary level neonatal intensive care unit before the clinical situation worsened (21). Similarly, Farragy and Soliman

(22) found that lactate could be used for early diagnosis of TTN and early treatment, offering the chance of a better prognosis.

Although we did not determine a specific cutoff point for the umbilical cord blood gas value in our study, it was observed that the mean pH of the umbilical artery at the birth of the neonates whose postpartum clinical condition deteriorated varied between 7.20 to 7.32, and the mean lactate level varied between 3.38 ± 1.85 and 6.73 ± 3.53 mmol/L. Anaerobic glycolysis, which increases as a result of tissue hypoxia, causes lactic acid production in tissues. Six hours after birth, the lactate concentration in the umbilical arterial blood of healthy term and preterm infants is often <2.5 mmol/L (23). In similar studies on the subject in the literature, lactate threshold values suggested for predicting adverse outcomes in neonates vary between 3.2 and 10.0 mmol/L (8, 24–27). Tuuli et al. (8) reported a cutoff value for term neonates that predicted adverse outcomes of 7.25 for pH and 3.9 mmol/L for arterial lactate. Labrecque et al. (27) found that the best cutoff lactate concentration to predict a pH <7.20 was 4.9 mmol/L, with a sensitivity of 82% and a specificity of 90% (27). In their study analyzing 2554 single births, Gjerris et al. (28) suggested a lactate cutoff level of 8 mmol/L for intrapartum asphyxia. Einikyte et al. (10) determined cutoff values for pH and lactate of 7.234 and 5.9 mmol/L, respectively. Our findings were consistent.

Our results indicated that the neonates who received mechanical ventilation had the lowest umbilical artery pH value at birth ($p < 0.05$). Similarly, the base deficit and PCO_2 values were higher in this group ($p < 0.05$). Although it did not reach the level of significant difference, the mean umbilical cord arterial lactate value was high in the neonates who received mechanical ventilation. Similarly, the length of hospital stay demonstrated a positive relationship to lactate level. The values observed at birth appear to be valuable predictive factor for the clinical condition of neonates.

In the present study, there was a relationship between the umbilical cord arterial lactate measurement, low Apgar first- and fifth-minute scores, and the pH value. Lactate was found to more sensitive as an indication of severe conditions than pH for neonates with a first-minute Apgar score of ≤ 5 . Gjerris et al. (28) found a significant relationship between lactate in arterial cord blood and pH. A cohort study demonstrated that arterial cord blood lactate measurement was as effective as pH in detecting depressed neonates at birth (29). Similar to our findings, Einikyte et al. (10) found that arterial lactate was as effective as pH, and that umbilical cord blood lactate was more specific than pH. Westgren et al. (24) also found a significant relationship between lactate concentration and fetal pH, and suggested that lactate values could predict a low Apgar score. In their systematic review, Allanson et al. (7) reported that umbilical cord lactate was an effective measure of fetal acidosis and could be used to predict neonatal outcome. Neacsu et al. (18) found that lactate was a better predictor of adverse neonatal outcomes than pH. In contrast, Marti Gamboa et al. (30) observed a similar predictive capability of adverse neonatal outcomes for pH and lactate values. Our findings also revealed a relationship between lactate and gestational age. Wiberg et al. (29) observed that lactate was at least as good as base deficit to reflect impaired condition at birth, and best when gestational age-adjusted values were used. Future research may focus on determining lactate cutoff values according to gestational age to predict severe conditions.

Study Limitations

The small number of cases is the primary limitation of this study. The neonatal unit in which the study was conducted is part of a secondary hospital; most patients were referred to units with additional facilities in other provinces.

CONCLUSION

The umbilical cord arterial lactate measurements of term neonates in this study were associated with the pH value and the Apgar score, and the lactate value predicted a low Apgar score. The umbilical cord arterial lactate value was higher at birth in neonates with MAS and PROM, which cause perinatal hypoxia. The lactate in arterial cord blood would appear to be a predictive parameter for the early detection of neonates whose clinical picture may deteriorate during or after labor.

While the results seen thus far are intriguing, larger trials with a control group are needed to establish the true benefit of the prognostic value and usefulness of lactate level measurements to determine a prognosis in cases of neonatal sepsis, TTN, and pneumonia, for example, as well as correlations between lactate level and disease severity. Nonetheless, evaluation of umbilical cord arterial lactate in the early assessment of the well-being of neonates is recommended in order to prevent misvaluation of infants exposed to severe asphyxia and thus, inadequate treatment. Furthermore, lactate level assessment is recommended to prevent complications that may develop due to perinatal hypoxia, to reduce the number of neonates needing mechanical ventilation, and to protect and improve neonate health by reducing long-term hospitalization with early and effective treatment. Additionally, lactate evaluation might be useful for clinicians at first-level hospitals in decision-making about appropriate referral to a secondary or tertiary level NICU before the clinical situation worsens.

Ethics Committee Approval: The Bozok University Clinical Research Ethics Committee granted approval for this study (date: 30.05.2018, number: 2017-KAEK-189_2018.05.30_19).

Informed Consent: Not applicable, since this study is a medical records-based retrospective study.

Peer-review: Externally peer-reviewed.

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