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Original Article

The comparison of umbilical cord arterial blood lactate and pH values for predicting short-term neonatal outcomes

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ABSTRACT

Objective: Current clinical practice of assessing neonatal condition is based on evaluation of umbilical cord arterial blood pH value rather than lactate. However, evidence shows that lactate is direct and more predictive measurement than pH or at least of equal importance. This study is to assess and compare umbilical cord arterial lactate and pH values for predicting short-term neonatal outcomes.
Materials and methods: A retrospective cohort study was conducted at the tertiary level hospital, were arterial umbilical cord blood sampling was collected according to the standard procedures. Neonatal morbidity was registered if at least one of the following conditions was noted: Apgar score at 1 min after delivery was 6 or lower, resuscitation performed, including assisted ventilation and requirement of admission to neonatal intensive care unit. Mothers–newborns pairs were allocated into two groups: newborns exposed to perinatal hypoxia (group 1) and observed as healthy newborns (group 2). Receiver operating characteristics curves (ROC) were generated to assess the predictive ability of pH and lactate for the short-term neonatal outcomes.
Results: 901 neonates born at $\geq$37 weeks of gestation were included. Newborns exposed to perinatal hypoxia (group 1) encompassed 39 (4.3%) patients, and observed as healthy (group 2) – 862 (95.7%). Arterial umbilical cord blood pH in group 1 was 7.160 ± 0.126 as compared to 7.314 ± 0.083 in group 2; $p < 0.001$. Mean arterial lactate was significantly higher in group 1 than group 2 (6.423 ± 2.335 as compared to 3.600 ± 1.833; $p < 0.001$). The difference between areas under ROC curves representing pH and lactate was not significant (0.848 and 0.831 respectively; $p = 0.6132$).
Conclusion: Umbilical cord arterial lactate and pH predicted short-term neonatal outcomes with similar efficacies.

Introduction

Perinatal hypoxia is a serious condition caused by oxygen supply insufficiency for tissue energy requirements that is followed by increased anaerobic metabolism [1]. If the process continues, the maintenance of the energy balance is disturbed. The products of anaerobic metabolism, such as lactate and hydrogen ions, accumulate and overpower the buffer capacity of arterial blood [2]. Goldaber et al. and Ross et al. researches have revealed that neonatal complications are more often associated with metabolic rather than respiratory acidosis [3,4]. Respiratory acidosis usually presents in the early stages of insufficient blood supply to the fetus by hypoxemia and hypercapnia, which cause a reduction in pH, but a base excess remains normal [3–6]. In the late stage of fetal hypoxia, when insufficiency of oxygen supply is prolonged, metabolic products rise to the presence of metabolic acidosis [5]. Subsequently, diminished oxygen supply and acidosis can lead to organ failure with a probability of permanent tissue damage, therefore, objective assessment of neonate's metabolic status is essential [3–6].

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Epidemiology of perinatal hypoxia and newborns short-term outcomes are not extensively analysed in recent scientific studies. Even though, most neonates with acidemia will not have a severe outcomes, cases with acidotic newborns still deserve examination. The analysis of short-term neonatal outcomes would enable medical staff to differentiate between healthy neonates and those who need further clinical examination. Currently used diagnostic criteria: umbilical cord arterial blood pH and lactate are considered to be the standard biomarkers for the evaluation of fetal hypoxia and predictors of neonatal morbidity [7,8].

Accordingly, it is advised that physicians or midwives attempt to obtain arterial samples in order to evaluate whether a neonate was exposed to perinatal hypoxia [9]. Cord gas analysis includes direct measurement of pH, pO_2, pCO_2, lactate and calculation of base excess using various algorithms [2]. Umbilical cord arterial pH falls and lactate increases when the products of anaerobic metabolism overpower the buffer capacity of the fetuses arterial blood due to diminished availability of oxygen to the body tissues [2].

In clinical practice pH is more commonly used than lactate as an indicator of neonatal condition. It is important to note that pH and base excess require more blood and complex equipment than is needed for lactate measurement [10]. Furthermore lactate can be measured using a handheld apparatus, which requires less blood and makes it lower-cost, easier maintenance [10]. These features show lactate to be superior to pH or other parameters [10]. Moreover, various studies have showed that lactate might be a more predictive measurement for neonatal morbidity than pH or at least of equal importance [5,9,11,12].

Therefore, we conducted a study to test the hypothesis that umbilical cord arterial blood lactate is a superior biomarker than pH to predict short-term neonatal outcomes.

Materials and methods

A retrospective cohort study was conducted at the tertiary referral centre The Obstetrics and Gynaecology Centre of Vilnius University Hospital Santariskiu Clinic from 1 January, 2015 to 31 March, 2015. The study was conducted under permission of Bioethics Committee of Vilnius University hospital Santariskiu Clinic. All women who agreed to participate in the study signed informed consent.

Neonates were eligible for the study if they were singleton, born at term (gestational age of ≥37 weeks) and women have agreed to participate in the study. The main exclusion criteria were multifetal pregnancy, fetal anomalies suspected or diagnosed antenatally and those women who refused to take part in the research; sample size estimation a priori was not performed.

Pregnancies were dated by woman's last menstrual period and were confirmed with first or second trimester ultrasonography [2]. Demographic and relevant clinical data were collected from the patient's records.

Umbilical cord arterial blood was collected according to the standard procedure: from double-clamped cord segments after neonatal delivery. Samples were collected by trained midwives into heparinized syringes. Thereafter blood gases and lactate were measured using automated analyser (ABL90 FLEX Radiometer) located in the labor and delivery ward. Obtained data was recorded in a newborn's notes. Apgar score was determined by a trained midwife, an obstetrician or a neonatologist.

Neonatal morbidity was counted if at least one of the following conditions was noted after birth: Apgar score at 1 min was 6 or lower, resuscitation performed (suctioning of secretions from the airways, breathing stimulation, free flow oxygen, assisted ventilation (continuous positive airway pressure (CPAP), positive pressure ventilation (PPV), intubation), chest compressions, administration of drugs) and requirement of admission to neonatal intensive care unit.

Then women were allocated into two groups: those with neonates, who had at least one condition or procedure performed (group 1 or newborns exposed to perinatal hypoxia) and those, whose neonates were considered as healthy (group 2). Both groups were compared with respect to maternal background factors (age, parity, gravidity, mode of delivery and anesthesia applied) and neonatal characteristics (gender, weight). Neonatal weight was evaluated (either normal, small for gestational age (SGA) or large for gestational age (LGA)) using charts, adjusted for gestational age and gender based on Lithuanian population [13].

The data was analysed statistically using a statistical software packages (IBM SPSS Statistics 21.0 and MedCalc Statistical Software 17.5). Baseline continuous data is shown as means and standard deviations (SD); dichotomous data is presented as numbers and percentage. Differences between groups were analysed with the Student t test and categorical data with chi-square or Fisher's exact test as appropriate. Normality of distribution of the continuous variables was confirmed using the Kolmogorov–Smirnov test. Comparisons of continuous data with a skewed distribution were performed using the nonparametric Mann–Whitney U test. Receiver operating characteristics (ROC) curves were generated to assess the predictive ability of umbilical arterial pH and lactate for the short-term neonatal outcomes. Predictive characteristics of lactate and pH were defined using Youden Index. The criterion for statistical significance in this study was a level of 0.05.

Results

In total, 936 births were registered during the study period. It was estimated that 901 women delivered singletons without fetal anomalies at ≥37 weeks of gestation. Women with twins or higher order multiples (n = 35) were excluded from the study. Of these 901 births majority of the women underwent spontaneous vaginal delivery 70.1% (n = 632), 25.2% (n = 227) delivered by caesarean section and 4.7% (n = 42) by operative vaginal delivery.

Among 901 neonates, 39 (4.3%) had at least one of the following: 1 min Apgar score ≤6 (n = 26, 2.9%), had resuscitation (n = 36, 4.0%) including assisted ventilation (n = 32, 3.6%) performed, were transferred to neonatal intensive care unit (n = 15, 1.6%) and were included into group 1 (newborns exposed to perinatal hypoxia). Overall, 4 (0.4%) responded well to primary resuscitation actions (suctioning of secretions from the airways, breathing stimulation, free flow oxygen) and 32 (3.5%) required more advanced resuscitation like assisted ventilation (CPAP, PPV, intubation) at birth. The rest 862 (95.7%) newborns, considered as healthy, were included into group 2. Table 1 shows that there were no significant differences in baseline characteristics between neonates exposed to perinatal hypoxia and those considered as healthy with the exception of gestational age. Using nonparametric statistical

Table 1
Comparison of the baseline characteristics of the newborns (N = 901).

Characteristics	I group N = 39	II group N = 862	p
Weight (g)	3633.1 ± 533.8	3553.5 ± 485.8	0.576
Male	23 (59.0%)	446 (51.8%)	0.416
Female	16 (41.0%)	415 (48.2%)	0.416
SGA[a]	6 (15.4%)	71 (8.2%)	0.135
LGA[b]	9 (23.1%)	122 (14.2%)	0.158
Gestational age (weeks)	39.8 ± 1.0	39.4 ± 1.0	0.038

[a] SGA – small for gestational age.
[b] LGA – large for gestational age.

Table 2
Comparison of the baseline characteristics of the studied women (N = 901).

Characteristics	I group N = 39	II group N = 862	p
Age (years)	31.24 ± 5.30	30.97 ± 5.31	0.879
Primiparous	29 (74.4%)	450 (52.2%)	0.008
Primigravida	24 (61.5%)	385 (44.7%)	0.048
Spontaneous vaginal delivery	11 (28.2%)	621 (72.0%)	<0.001
Operative vaginal delivery	10 (25.6%)	32 (3.7%)	<0.001
Cesarean section	18 (46.2%)	209 (24.3%)	0.004
Epidural anesthesia	17 (43.6%)	218 (25.3%)	0.015

analysis, neonates in group 1 had higher gestational age (39.8 ± 1.1 weeks versus 39.4 ± 1.0 weeks, p = 0.038).

Baseline characteristics of the women, who were included in the final analysis were evaluated and compared between group 1 and group 2 (shown in Table 2). Women in both groups were of similar age. Mothers of newborns exposed to perinatal hypoxia were significantly more often primiparous and primigravidae. There was a significant difference in the number of epidural anesthesia in group 1 compared with group 2 (n = 17, 43.6% versus n = 218, 25.3%; p = 0.015) and operative vaginal deliveries performed (n = 10, 25.6% versus n = 32, 3.7%; $p < 0.001$). Women in group 1 also underwent more caesarean sections (n = 18, 46.2% versus n = 209, 24.2%; p = 0.004).

Average arterial lactate and pH were significantly different in group 1 and 2 (shown in Table 3). The pH value for group 1 was 7.160 ± 0.126 compared to 7.314 ± 0.083 for group 2; $p < 0.001$. Mean arterial lactate was higher in neonates exposed to perinatal hypoxia (6.423 ± 2.335 versus 3.600 ± 1.832; $p < 0.001$).

The ROC curves in Fig. 1 illustrate similar predictive capacity. The area under ROC curve representing pH predictive value was slightly higher than the area representing lactate (0.848 and 0.831 respectively), but the difference was statistically insignificant (p = 0.613). Table 4 shows that lactate is more specific as compared to pH (87.4% and 84.2% respectively), whereas pH was more sensitive than lactate (71.8% and 65.8% respectively). The optimal cutoff value for lactate was >5.9 mmol/l, it was <7.234 for pH.

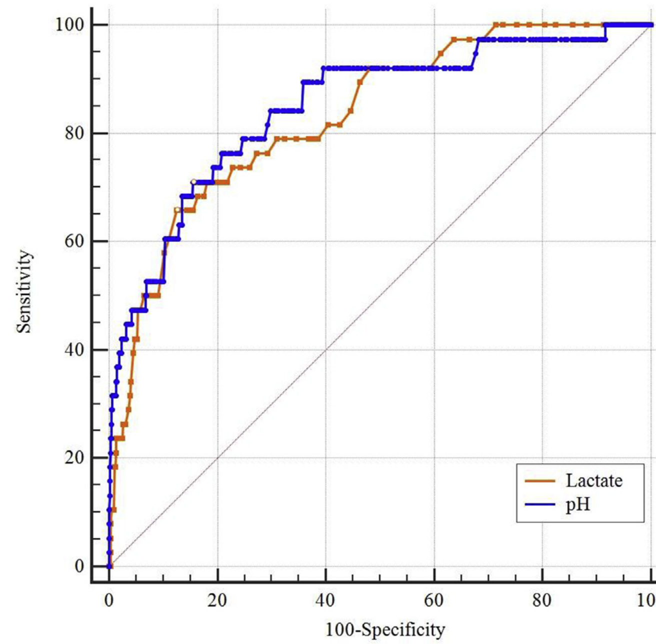

Fig. 1. ROC curve of lactate and pH for predicting short-term neonatal outcomes.

Discussion

Perinatal hypoxia is a condition caused by disturbed blood gas exchange during the intrapartum period can lead to severe complications affecting various organ systems. Different criteria have been used to predict neonatal morbidity due to hypoxia. Apgar score is a well-known method to quickly assess the health of a newborn and used since 1952. However, it is not recommended to solely rely on one factor and it is advised that medical staff attempt to obtain umbilical cord arterial and venous blood samples in order to test for the metabolic products of anaerobic respiration and therefore evaluate whether a neonate was exposed to hypoxia [2,9].

The prevalence of short-term neonatal outcomes after exposure to perinatal hypoxia is rarely discussed in the literature. As per study results performed by Tuuli et al. the incidence of composite neonatal morbidity such as neonatal death, hypoxic encephalopathy, meconium aspiration syndrome, need of hypothermic therapy, endotracheal intubation and mechanical ventilation is estimated as 1.1% [2] In our study, 4.3% of neonates were considered as exposed to perinatal hypoxia with no severe outcomes (neonatal deaths, meconium aspiration syndrome or neonates eligible for therapeutic hypothermia) registered. The results of the prevalence of perinatal hypoxia found in our study need to be considered with providence due to different inclusion criteria and severity of hypoxia of enrolled neonates. In our cohort 3.5% required more advanced resuscitation like assisted ventilation (CPAP, PPV, intubation) at birth performed by neonatologist. However, 1.6% neonates were admitted to neonatal intensive care unit, following need of more close observation and assisted ventilation. Although most neonates in our study did not have severe consequences, the events that resulted in the acidosis could be considered as mild hypoxia.

There were no significant differences in baseline characteristics between neonates exposed to perinatal hypoxia and those considered as healthy with the exception of gestational age. Wiberg et al. in their populations based study of 17 876 newborns confirms, that level of lactate increases significantly since 34 week of gestation and beyond [14].

Maternal factors and mode of delivery have influence on neonates' umbilical blood gas status. It is well known that the first delivery is longer than any subsequent one and Friedman proved this finding more than 60 years ago. Since then the Friedman curve has been used worldwide [15]. Interestingly enough, Zhang et al. found that in so called "contemporary population" the duration of labor in nulliparas has prolonged even more [16]. It has been demonstrated that the rate of cervical dilation from 4 to 6 cm was

Table 3
Average lactate and pH values in neonates groups.

Value	I group N = 39	II group N = 862	p
pH	7.160 ± 0.126	7.314 ± 0.083	<0.001
Lactate	6.423 ± 2.335	3.600 ± 1.833	<0.001

Table 4
pH and lactate cutoff values; predictive characteristics for short-term neonatal outcomes.

Characteristic	Lactate	pH
Cutoff value	>5.9 mmol/L	<7.234
AUC	0.831 (0.805–0.855)	0.848 (0.826–0.873)
Sensitivity	65.8 (48.6–80.4)	71.8 (55.1–85.0)
Specificity	87.4 (85.0–89.6)	84.2 (81.6–86.6)

much slower than previously described by Friedman, despite the fact that more labors are being treated with oxytocin for augmentation. The possible maternal reasons are suggested to be older age and higher body mass index [16]. Nevertheless, the second stage of labor contributes the most to the fetal lactate level: the longer it continues, the higher the lactate level appears [17].

Epidural analgesia use for labor has increased dramatically since the 1960s. Epidural anesthesia is known to cause a transient utero-placental insufficiency due to increased maternal and fetal temperatures and hence a less oxygen delivery to the tissues of fetus. Decreased maternal systemic vascular resistance reduces maternal systolic blood pressure. The latter may lead to utero-placental insufficiency and increased production of lactate in neonatal tissues [17].

The present study indicates that group 1 women significantly more often were primiparous and primigravidae, underwent epidural anesthesia, had more instrumental vaginal deliveries and caesarean sections. Probably the most proper way to describe the pathway of neonatal hypoxia would be a chain of cross-linked events. Utero-placental insufficiency leads to fetal hypoxia and lactate production. Certain factors may adversely affect utero-placental function such as prolonged progression of the first labor stage. This may cause oxytocin administration for augmentation. Subsequently stronger and more painful contractions potentially increase the requirement of epidural anesthesia. Both oxytocin and epidural, on their own might influence increase in lactate level in a neonates [17]. Therefore, the delivery of the first child causes the longer second stage of labor, increased use of oxytocin and epidural as well as higher frequency of abnormal cardiotocography followed by more operative deliveries or emergency caesarean sections [17]. Due to various factors influencing the process of labor at the same time, further investigations may disclose the underlying metabolic differences that could account for the changes in acid–base status of the neonates.

Umbilical cord arterial blood gas is a valuable tool for assessing impaired neonatal condition [7,8]. In current clinical practice pH is used more often than lactate, although the latter has the advantage of requiring less blood and simpler equipment requiring less blood and simpler equipment [2,10,11,18–20]. Suidan et al. reported that arterial cord blood pH reflects maternal acid base balance and it accounts only to a minor degree for the fetal acidosis at the time of delivery. Whereas umbilical cord arterial lactate is a direct representation of fetal acidosis since the major source of lactate in the fetal circulation is the fetus itself [21]. Wiberg et al. in a large cohort study demonstrated that arterial cord blood lactate is at least of equal value as pH and base deficit when predicting a depressed neonatal condition at birth [11]. However, we discovered that lactate is as effective as pH rather than superior. Moreover, our data has shown that umbilical cord blood lactate is a more specific than pH, but less sensitive measure of short-term neonatal outcomes.

Fairly recently published large cohort study by Tuuli et al. has showed different mean umbilical cord arterial lactate and pH values as well as cut-off values for term pregnancies: cut-off value for pH was 7.25 and 3.9 mmol/l for lactate [2]. Labrecque et al. in their study have measured cord blood pH and lactate concentrations and reported that the best cut-off lactate concentration to predict a pH $\leq$7.20 was 4.9 mmol/l with a sensitivity of 82% and a specificity of 90% [22]. Ramanah et al. compared fetal scalp lactate, neonatal cord blood gas (pH and lactates) and Apgar scores and have shown significant scalp lactate and pH correlations with cord blood pH value <7.10 and lactates >6.35 mmol/l for prediction of hypoxia [23]. Grerris et al. analysed 2554 singleton deliveries and suggested a lactate cut-off level of 8 mmol/l for intrapartum asphyxia and demonstrated umbilical cord arterial lactate to be more correct indicator of fetal asphyxia at delivery than pH and base excess [24]. Kruger et al. performed a larger study of 1709, they found that lactate at >4.8 mmol/l had greater sensitivity and specificity compared to pH value and recommended using lactate value of 4.8 mmol/l as the test for fetal hypoxia [25]. Our findings were compatible with these studies. The cut-off values for pH and lactate were 7.234 and 5.9 mmol/l respectively. We calculated the sensitivity of 65.8% and specificity of 87.4% for the lactate cut-off value of 5.9 mmol/l.

It is important to note that even though various studies state similar cutoff points, the slight variations in the values cause different judgment on the concept of normality and abnormality leading to clinical uncertainty and the necessity to continue investigations in this field [5,26].

Unfortunately, the results of this research might not be applicable to pre-term births. However, it is necessary to enlarge study population in the future studies including pre-term births and long-term neonatal outcomes.

The main strength of this research was a large unselected population rather than simply a hypoxic cohort. However, no severe neonatal outcomes such as meconium aspiration syndrome or severe hypoxic ischemic encephalopathy were registered during the research period. This could be the reason for the variations of the cut-off values in different studies as compared to ours.

Conclusion

Umbilical cord arterial lactate and pH predicted neonatal outcomes with similar efficacies, showing lactate to be equally important in acidosis evaluation of a newborn.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

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