의학석사 학위논문

제대혈 가스 분석의 임상적 의의

Clinical implication of umbilical cord blood gas analysis

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이 논문을 의학석사학위 논문으로 제출함

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Abstract

Title: Clinical implication of umbilical cord blood gas analysis

Introduction: Umbilical cord blood gas analysis (UC-BGA) is used as an evaluation index for newborns. This study aimed to confirm lactate levels according to gestational age (GA), the correlation between umbilical cord blood glucose and infant blood glucose levels and analyze the usefulness of UC-BGA to evaluate delayed umbilical cord clamping (DCC).

Methods: We retrospectively reviewed the charts of all infants born at Ulsan University Hospital from January 2014 to December 2023. We collected data on the UC-BGA and infants' initial arterial blood gas analysis (A-BGA) results, such as pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), bicarbonate (HCO_3^-), base excess blood (BEB), total carbon dioxide (TCO_2), oxygen saturation (O_2Sat), hematocrit, glucose, and lactate levels. Using these values, a comparison between immediate cord clamping (ICC) and DCC in infants aged 34 weeks or older was performed over the target period of 2 years before and after DCC implementation.

Results: There were 3133 infants with UC-BGAs and 1664 with initial A-BGAs. Lactate levels gradually decreased up to GA 33 weeks and then gradually increased to term; however, the increase in lactate levels with increasing GA did not show a clear correlation. For glucose levels, a positive correlation was observed (r=0.415, p<0.001) between umbilical cord blood glucose and infant blood glucose levels, and it was observed that when the cord blood glucose level increased by 1mg/dl, the infants' glucose level increased by 0.430mg/dl. In the DCC group (n=740), pCO_2, BEB, HCO_3^-, TCO_2, and glucose levels significantly decreased, and pO_2 and O_2Sat levels significantly increased compared to those in the ICC group (n=764). No significant differences were observed in pH, hematocrit, and lactate levels.

Conclusions: A UC-BGA's use as a predictive factor was confirmed by validating its correlation with infant blood glucose levels and benefits of DCC were confirmed through respiratory parameters measured via UC-BGA.

Key words: delayed cord clamping, cord blood gas analysis, lactate, hypoglycemia

차 례

그림목차

표목차

Introduction

To determine the infant's condition at delivery, several methods are considered. The Apgar score is representatively used to evaluate the condition of infant at delivery [1]; however, it relies on subjective judgment, and its relationship with the prognosis of preterm or term infants is often inaccurate [2]. Accordingly, various studies have recently attempted to evaluate the use of umbilical cord blood gas analysis (UC-BGA) as a predictive tool [3].

A UC-BGA can provide important information regarding an infant's condition. In particular, the acid-base status and lactate levels have been shown to reflect the infant's aerobic and anaerobic intrauterine metabolism; therefore, the fetus's well-being in the uterus can be assessed [4]. A unified reference value has been proposed for lactic acid; however, due to changes in the physiological state of the fetus with advancing gestational age (GA), there may be inaccuracies in assessing the fetal condition, suggesting a need for improvements in these reference values.

Hypoglycemia observed early in life is common in infants and is critical because it is a crucial factor that determines hospitalization and increases the risk of developmental delays later in life. To prevent complications, blood glucose levels are measured within 1 hour after birth in infants born to mothers with gestational diabetes mellitus and in low birth weight infants, as these groups are at higher risk. UC-BGA can help predict these risks. Accordingly, we hypothesized that if an infant blood glucose levels could be predicted through UC-BGA, early intervention could reduce various complications caused by hypoglycemia.

Delayed cord clamping (DCC) is recommended to perform at birth. The effectiveness of DCC is known for enhancing breathing stability, providing a smooth transition of circulation, and facilitating placental transfusion [5-7]. The benefit of DCC can be confirmed through UC-BGA.

Therefore, this study aimed to analyze the usefulness of UC-BGA from various aspects. We aimed to proposed a reference range for lactate levels according to GA, and evaluate its usefulness as a predictor of the correlation between cord blood and the infant glucose levels and investigate the effect of DCC on UC-BGA.

Methods

Study participants

We retrospectively reviewed charts from January 2014 to December 2023. We investigated all infants born at Ulsan University Hospital. Neonatal demographic variables, including GA, birth weight, Apgar scores, mode of delivery, sex, body temperature at admission, and need for resuscitation, were collected from medical records.

Additionally, we collected UC-BGA and initial arterial blood gas analysis (A-BGA) results including pH, partial pressure of carbon dioxide (pCO_2), partial pressure of oxygen (pO_2), total carbon dioxide (TCO_2), oxygen saturation (O_2Sat), bicarbonate (HCO_3^-), base excess blood (BEB), hematocrit, lactate and glucose levels.

Lactate levels were analyzed according to gestational age. Glucose of UC-BGA and A-BGA were compared. Changes in UC-BGA and A-BGA following DCC implementation was analyzed in infants with gestational age 34 weeks or older and the target period was each 2 years before and after DCC implementation.

The study protocol was reviewed and approved by the Institutional Review Board of the Ulsan University Hospital. (#2024-05-042)

Statistical analysis

Data are presented as mean ± standard deviation (SD) or medians and as frequencies and percentages (%) for categorical variables. We compared demographic data using Student's t-test and categorical variables using the chi-square test or Fisher's exact test, as appropriate. To establish a reference range of GA-dependent lactate levels, we calculated percentile values in each group using the Lambda-Mu-Sigma method with the gamlss package. We performed Pearson's correlation analysis to confirm the correlation between cord blood and infant blood glucose levels. All tests of significance were two-sided, and *p*-values of less than 0.05 were used to indicate statistical significance. We performed all statistical analyses using SPSS (ver. 21, IBM Co., Armonk, NY, USA).

Results

As a result of data collection, 3857 infants were identified, with 3133 cases of UC-BGA and 1664 cases of initial A-BGA. BGA results included lactate and glucose levels. The baseline characteristics of the included infants are shown in Table 1. The mean GA is 36.22±2.88 weeks, and body weight was 2714.0±681.4g. The mean 1min and 5min Apgar scores were 7.5±1.6 and 8.8±1.1. Regarding the mode of delivery, vaginal delivery accounted for 45.6% cases, and cesarean section accounted for 54.4% cases. The sex ratio was similar at 51.8% males and 48.2% females.

Table1. Baseline characteristics of participants

	Mean±SD or N (%)
Gestational age (weeks)	36.22±2.88
Body weight (g)	2714.0±681.4
Apgar 1min	7.5±1.6
Apgar 5min	8.8±1.1
Delivery	
Vaginal delivery	1,758 (45.6)
Cesarean section	2,099 (54.4)
Sex	
Male	1,997 (51.8)
Female	1,860 (48.2)
Body temperature (℃)	36.81±0.52
Resuscitation	
Not done	2,870 (74.4)
Done	987 (25.6)

Data are presented as mean ± standard deviation

Gestational age (GA) dependent lactate levels in umbilical cord blood

A total of 3133 infants had lactate levels obtained through UC-BGA and classified according to GA. The distribution of cord blood lactate levels relative to GA is shown in Figure 1. The number of infants up to 33 weeks of age was very small (400 of 3133 patients), and most were born beyond 33 weeks of gestation. Lactate levels gradually decreased up to 33 weeks of gestation and then gradually increased until term age (Figure 1). However, the increase in lactate levels with increasing GA did not show a clear correlation. The means ± SDs, range, and reference range of lactate levels and the number of infants at each GA are shown in Table 2.

Figure 1. Scatterplot of the lactate value according to gestational age (weeks).

10%, 50%, and 90% were indicated according to each percentile. The best-fit curve of lactate value is marked solid line.

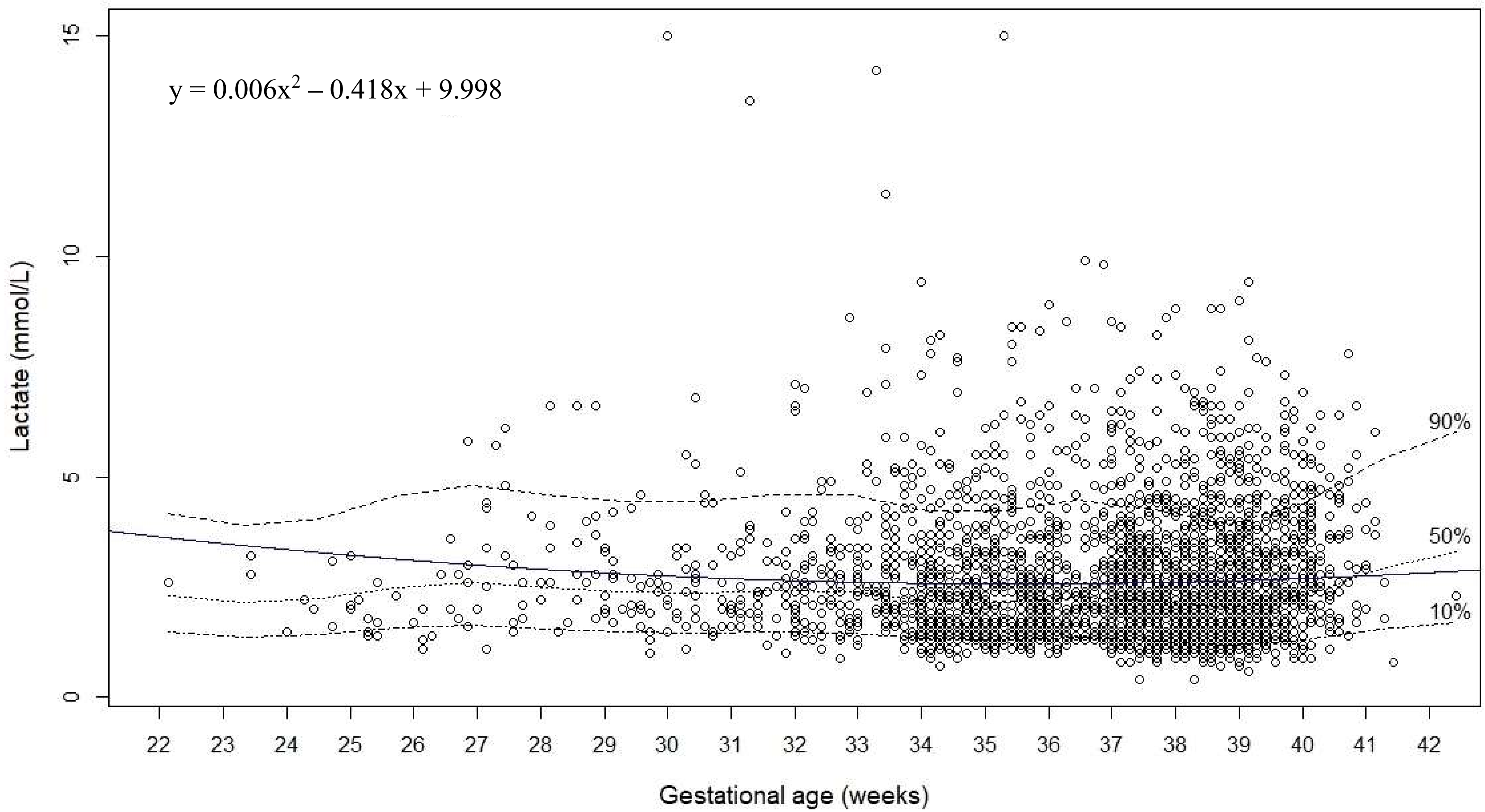

Table 2. Estimate reference ranges of lactate at each gestational age

Gestational age (weeks)	N	Mean±SD (mmol/L)	Range (mmol/L)	5%	10%	25%	50%	75%	90%	95%
22~23	3	2.87±0.31	2.60-3.20	1.33	1.49	1.81	2.30	3.05	4.16	5.22
24~25	17	2.00±0.56	1.40-3.20	1.24	1.38	1.68	2.15	2.85	3.89	4.86
26	15	3.13±3.08	1.10-13.40	1.28	1.43	1.75	2.24	2.98	4.06	5.06
27	18	3.16±1.46	1.10-6.10	1.42	1.59	1.95	2.50	3.34	4.56	5.67
28	20	3.37±1.59	1.50-6.60	1.48	1.65	2.03	2.61	3.51	4.79	5.95
29	30	2.48±0.87	1.00-4.60	1.40	1.57	1.93	2.49	3.36	4.60	5.72
30	39	3.10±2.34	1.10-15.00	1.33	1.49	1.84	2.39	3.23	4.45	5.54
31	43	2.78±1.89	1.00-13.50	1.30	1.47	1.81	2.36	3.21	4.44	5.55
32	88	2.70±1.43	0.90-8.60	1.32	1.49	1.85	2.42	3.30	4.59	5.76
33	127	3.05±1.83	1.10-14.20	1.30	1.46	1.82	2.39	3.28	4.58	5.77
34	318	2.49±1.33	0.70-9.40	1.17	1.33	1.65	2.18	3.01	4.23	5.35
35	311	2.61±1.57	1.00-15.00	1.15	1.30	1.63	2.16	3.00	4.22	5.35
36	233	2.68±1.52	1.00-9.90	1.20	1.36	1.71	2.28	3.17	4.47	5.64
37	546	2.58±1.34	0.40-8.60	1.12	1.28	1.63	2.19	3.04	4.26	5.34
38	714	2.37±1.35	0.40-8.80	1.02	1.18	1.51	2.04	2.84	3.95	4.88
39	437	2.72±1.47	0.60-9.40	1.12	1.30	1.71	2.33	3.24	4.42	5.37
40	162	3.24±1.33	0.90-7.80	1.32	1.57	2.10	2.90	4.01	5.38	6.41
41~42	12	3.11±1.38	0.80-6.00	1.39	1.71	2.35	3.30	4.55	6.00	7.03

Correlation between cord blood and infant glucose levels

A positive correlation was observed between cord blood and infant blood glucose levels (r=0.415, $p<0.001$). When the cord blood glucose level increased by 1mg/dl, the infant glucose level increased by 0.430mg/dl.

Comparison between immediate cord clamping (ICC) and delayed cord clamping (DCC)

From September 2019 to September 2023, there were a total of 2198 infants who were at least GA 34 weeks. The numbers of infants in the target period of ICC and DCC were 909 and 949, respectively; among them, those with UC-BGA results were included. There were 1858 infants with a GA of 34 weeks or more born over a total of 4 years, 2 years before and 2 years after the implementation of DCC.

The characteristics of the ICC and DCC subgroups are shown in Table 3-1. The 1min and 5min Apgar scores was higher in the DCC group than in the ICC group, and no significant differences were observed between the ICC and DCC subgroups in the characteristics studied.

A total of 764 of the 909 infants in the ICC group and 740 of the 949 infants in the DCC group had UC-BGA data (Table 3-2). In the DCC group, pCO_2, BEB, HCO_3^-, TCO_2, and glucose values significantly decreased, and pO_2 and O_2Sat values significantly increased. No significant differences were observed in pH, hematocrit, and lactate values between the ICC and DCC groups.

There were 333 and 339 infants with initial A-BGA data in the ICC and DCC groups, respectively (Table 3-3). In the DCC group, pO_2 and lactate values significantly decreased, whereas those of pCO_2, hematocrit, and bicarbonate significantly increased. No significant differences were observed in pH and glucose values.

Table 3-1. Baseline characteristics of immediate cord clamping and delayed cord clamping group

	ICC (N=764)	**DCC (N=740)**	***p*-value**
Gestational age (weeks)	36.86±1.78	36.77±1.66	0.292
Body weight (g)	2836.8±559.9	2830.5±538.0	0.823
Apgar 1min	7.5±1.4	8.1±1.1	<0.001
Apgar 5min	8.9±1.0	9.1±0.8	<0.001
Delivery			0.011
Vaginal delivery	283 (37.0)	228 (30.8)	
Cesarean section	481 (63.0)	512 (69.2)	
Sex			0.326
Male	390 (51.0)	359 (48.5)	
Female	374 (49.0)	381 (51.5)	
Body temperature (°C)	37.27±11.94	37.12±12.44	0.813
Resuscitation			0.102
Not done	609 (79.7)	564 (6.2)	
Done	155 (20.3)	176 (23.8)	

Data are presented as mean ± standard deviation or number (%).
A *p*-value of <0.05 was considered significant for all analyses.

Table 3-2. Comparison of cord blood gas analysis between immediate cord clamping and delayed cord clamping group

	ICC (N=764)	**DCC (N=740)**	***p*-value**
pH	7.30±0.28	7.32±0.07	0.055
pO_2 (mmHg)	28.86±48.23	37.06±53.30	0.002
pCO_2 (mmHg)	50.50±11.42	47.22±10.15	<0.001
Hct (%)	45.28±7.53	45.94±7.25	0.082
BEB (mM/L)	-1.62±2.89	-2.34±2.77	<0.001
HCO_3^- (mM/L)	25.26±3.38	24.17±3.19	<0.001
TCO_2 (mM/L)	26.38±3.88	23.63±3.94	<0.001
O_2Sat (%)	29.00±26.48	43.61±27.52	<0.001
Glucose (mg/dl)	74.83±19.87	68.59±21.55	<0.001
Lactate (mmol/L)	2.46±1.47	2.44±1.14	0.704

Data are presented as mean ± standard deviation.
A *p*-value of <0.05 was considered significant for all analyses.
Abbreviations: Hct, Hematocrit; BEB, Base Excess Blood; TCO_2, Total Carbon Dioxide; O_2Sat, Oxygen Saturation.

Table 3-3. Comparison of infants initial arterial blood gas analysis between immediate cord clamping and delayed cord clamping group

	ICC (N=333)	**DCC (N=339)**	***p*-value**
pH	7.29±0.09	7.29±0.07	0.682
pO_2 (mmHg)	70.09±30.52	64.42±27.44	0.011
pCO_2 (mmHg)	45.88±10.43	47.80±9.97	0.015
Hct (%)	51.50±6.18	54.27±6.94	<0.001
BEB (mM/L)	-4.59±3.39	-4.08±2.66	0.029
HCO_3^- (mM/L)	22.08±3.17	22.85±2.66	0.001
TCO_2 (mM/L)	21.70±3.89	20.03±2.41	<0.001
O_2Sat (%)	87.40±13.67	89.75±11.70	0.017
Glucose (mg/dl)	69.17±30.41	65.15±35.94	0.118
Lactate (mmol/L)	3.40±2.21	2.62±1.39	<0.001

Data are presented as mean ± standard deviation.
A *p*-value of <0.05 was considered significant for all analyses.
Abbreviations: Hct, Hematocrit; BEB, Base Excess Blood; TCO_2, Total Carbon Dioxide; O_2Sat, Oxygen Saturation.

Discussion

We found that there was no significant difference in lactate levels depending on gestational age, and the glucose level of the UC-BGA could be used to predict the infant glucose level after birth. Following the implementation of DCC, improvement in respiratory parameters were confirmed through UC-BGA.

Gestational age (GA) dependent lactate levels in umbilical cord blood

Lactate is an end product of anaerobic metabolism, and its production increases under anaerobic conditions, making it an essential component of metabolic acidosis [8, 9]. Therefore, lactate level measurement in cord blood may be a suitable alternative or supplement to pH measurement to assess fetal oxygenation during labor and delivery [10]. However, lactate levels increase physiologically, at least from 34 weeks and beyond, as the GA increases and pregnancy progresses, and a stationary umbilical cord blood lactate cutoff to define lacticemia might give false-positive or false-negative diagnoses [10]. This could lead to incorrect diagnoses when assessing perinatal morbidity and condition of infants, which may also result in exclusion. For example, Kitlinski et al. found a 25% false-positive rate of acidosis when a stationary cutoff of 7.10 for cord arterial pH was used instead of a GA-dependent cutoff at mean minus 2 SDs [10, 11]. Therefore, we attempted to prevent false-positive or false-negative diagnoses by presenting differential reference values according to the GA and attempted to present reference values according to GA through data analysis. However, the lactate values reported in this study, with advancing GA, did not reveal a significant increase in the umbilical cord lactate concentrations. Because the number of infants from 22 to 33 weeks was small compared to the total number of infants, and the distribution range was diverse. As shown in Figure 1, lactate levels tended to decrease until the GA of 33 weeks and increase thereafter, but the difference was not significant enough to be presented as a reference value. However, it is believed that new results can be obtained if additional analyses are performed after adjusting for confounders, such as the GA, mode of delivery, and condition at the time of delivery.

Correlation between cord blood and infant glucose levels

Neonatal hypoglycemia is the most common metabolic derangement in the neonatal period, accounting for nearly one-fifth of all neonatal admissions in late preterm and term infants [12]. It has traditionally been thought that there is a strong correlation between fetal and maternal glucose levels, with increases in maternal glucose levels leading to high fetal glucose and insulin levels, increased glucose consumption, and fetal growth [13-15]. However, recent studies suggested that fetal glucose consumption also influences placental glucose transfer [16, 17]. While a healthy term fetus consumes approximately 10% of the available glucose per liter in the fetal–placental circulation, this will likely be higher in pregnancies complicated by growth restriction, maternal diabetes mellitus, or intrauterine stress [16]. Therefore, we aimed to confirm the correlation by examining the glucose level in umbilical cord blood, as it reflects the glucose utilization in the fetal-placental unit.

Our study confirmed a significant correlation between umbilical cord blood and infant blood glucose levels. However, to gain significance as a predictive tool, it is crucial to determine whether hypoglycemia actually occurred in the target infant and establish the cutoff value of hypoglycemia to be used in the analysis and patient's outcomes.

Comparison between immediate cord clamping (ICC) and delayed cord clamping (DCC)

We found that in the DCC group, pCO_2 values significantly decreased, and pO_2 values significantly increased in the UC-BGAs. This finding may be explained by the fact that infant started self-breathing while the umbilical cord was unclamped; therefore, DCC allows the infant to continue self-breathing, receiving oxygen and effective ventilation resulted in improved respiratory indicators [18]. Previous studies have consistently reported that DCC in very preterm infants was well tolerated, and the majority established spontaneous respiration during DCC; breathing benefits from DCC were also reported [19-22].

However, in this study, there was no analysis of whether oxygen requirements, tracheal intubation, or surfactant use were reduced. Therefore, it would be beneficial to conduct a correlation study.

A delay in cord clamping permits placental transfusion, reported to increase the infant blood volume by 30% and the supply of red blood cells by 60%, providing the infant with a further 40 mg of iron [23, 24]. For term infants, several randomized controlled trials have reported the beneficial effects of DCC on infant hemoglobin levels at birth or at different follow-up durations and demonstrated a subsequent reduction in anemia without unacceptable side effects [25]. Ceriani et al. found that DCC of term infants for 1 or 3 min improved venous hematocrit levels measured 6 hours after birth within a physiological range and decreased the prevalence of neonatal anemia without any harmful effects on the infants or mothers [26]. For preterm infants, in a randomized unblinded controlled trial of preterm infants with a GA of 24–28 weeks, Oh et al. found a higher venous hematocrit value at 4 hours of age after in DCC (30–45 s) versus ICC (< 10 s), indicating that DCC led to effective placental transfusion at birth [27]. Furthermore, for preterm infants born between 27 and 31 6/7 weeks of GA, DCC for 60 s had significant benefits in terms of an increase in hematocrit compared to that with ICC (< 10 s) [28]. In this way, many studies have shown that DCC is beneficial for preterm and term infants in terms of increasing hematocrit values. However, in this study, there was a numerical increase, and no statistical significance was found in hematocrit values between the ICC and DCC groups in their UC-BGA results. Interestingly, Ertekin et al. found that DCC for up to 90–120 s in term infants did not affect the hematologic status at birth but improved the hemoglobin, hematocrit, and iron levels in the second month without serious complications [29]. Although we implemented a 60 s delay in cord clamping, the infants' initial A-BGA results showed an increase in hematocrit, which was a statistically significant result. Therefore, it seems crucial to investigate the positive effect by reviewing the hemoglobin and hematocrit levels of infant at 2 months or later.

This study had some limitations. First, the records did not accurately identify whether the UC-BGA was arterial or venous. Second infants with various characteristics were not properly classified according to their demographics. It is necessary to set a target by analyzing the mode of delivery, maternal medical history, and causes of emergency delivery, which may affect infants' UC-BGA results.

The major advantage of our study is the assessment of a large number of patients from a single medical institution and the evaluation of the various effects of DCC on infants in the future, as well as whether lactate or glucose levels can be used as biomarkers to reduce the risk of acidosis stress or hypoglycemia in infants. UC-BGA confirmed that DCC can be safely performed not only in term infants but also in late-term premature infants. It is important to demonstrate that this can be achieved.

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국문요약

제목 : 제대혈 가스 분석의 임상적 의의

연구배경 및 목적 : 제대혈 가스 분석은 신생아 평가지표로서 사용된다. 본 연구에서는 제대혈 가스 분석의 임상적 의의를 보고자 제대혈 가스 분석 결과를 통해 재태 연령에 따른 젖산 농도의 참고치를 제시하고 제대혈 혈당치와 신생아 혈당치의 상관관계를 분석하고자 하였다. 또한 지연 제대 결찰의 이점을 확인하고자 하였다.

연구방법 : 2014 년 1 월부터 2023 년 12 월까지 울산대학교병원에서 태어난 모든 신생아의 기록을 후향적으로 분석하였다. 신생아들의 제대혈 가스 분석 결과를 통해 pH, 이산화탄소분압, 산소분압, 중탄산염, 염기과잉, 총 이산화탄소, 산소포화도, 적혈구 용적, 젖산, 혈당치를 수집하였다. 그 중 즉시 제대 결찰과 지연 제대 결찰을 비교하기 위해서 34 주 이상의 신생아를 대상으로 지연 제대 결찰 실시 전후 2 년의 기간을 분석하였다.

연구결과 : 제대혈가스분석 결과는 3133 건, 최초 동맥혈가스분석 결과는 1664 건이 수집되었다. 젖산 수치는 재태 주수 33 주까지 점진적으로 감소한 다음 만삭 주수까지 점차 증가하는 양상을 보였다. 그러나 재태 주수 증가에 따른 젖산 수치의 증가는 명확한 상관관계를 나타내지 않았다. 제대 혈당 수치와 신생아 혈당 수치는 양의 상관관계를 보였고 ($r=0.415$, $p<0.001$) 제대혈 혈당이 1mg/dl 증가하면 아기의 혈당의 0.430mg/dl 증가하는 것으로 나타났다. 지연 제대 결찰군에서는 즉시 제대 결찰군에 비해 이산화탄소분압, 염기과잉, 중탄산염, 총 이산화탄소, 혈당치가 유의하게 감소하였고, 산소분압, 산소포화도는 유의하게 증가하였다. pH, 적혈구 용적, 젖산 값에서는 유의한 차이가 관찰되지 않았다.

결론 : 제대혈가스분석을 통해 제대혈 혈당치와 신생아 혈당치의 상관관계를 확인하여 예측인자로서의 활용가능성을 확인하였고, 지연 제대 결찰시 호흡 지표의 개선을 확인하였다.

중심단어 : 지연 제대 결찰, 제대혈가스분석, 젖산, 저혈당