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Comparison of the changes in blood carboxyhemoglobin and bilirubin levels and their effects on neonatal hyperbilirubinemia in neonates born by cesarean section versus vaginal delivery

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Abstract

Aim: The study aimed to investigate whether there are differences in carboxyhemoglobin, bilirubin and hemoglobin values of neonates born by normal spontaneous vaginal birth (NSVD) (without anesthesia) and elective spinal cesarean section (CS) and its effect on neonatal jaundice.

Materials and Methods: A total of 110 healthy neonates without any risk factors for neonatal hyperbilirubinemia were included in the study. There were fifty-five neonates in both NVSD and spinal CS groups. COHb, bilirubin and Hb values which were measured from umbilical cord blood (as cord) and capillary blood taken from the heel 4-6 hours after birth (as post cord) were recorded.

Results: No statistically significant difference was found between the groups in terms of birthweight, maternal age, APGAR scores, and gender ($p>0.05$). There was a statistical difference between the groups according to the mean of gestational age, and it was observed that the mean of gestational age in spinal CS group was lower than in NSVD group (38.30 ± 1.2 and 39.16 ± 1.39 respectively) ($p=0.001$). Umbilical cord COHb levels in spinal CS group were higher than in NSVD group, but there was no statistically significant difference between groups (1.01 ± 0.15 and 0.99 ± 0.20 respectively, $p=0.22$). Furthermore, the differences between groups in term of mean of bilirubin and Hb levels in cord and post cord were not statistically significant (>0.05). But, it was determined that post cord COHb levels were higher than in NVSD group, and this difference was statistically significant ($p=0.028$). Additionally, it was found that the mean rank of COHb, bilirubin, and Hb in cord and post cord values were statistically significantly different between the groups ($p < 0.05$).

Conclusion: It should be kept in mind of that the anesthetic agent may also be a factor in bilirubin increases that occurs in neonatal hyperbilirubinemia without an underlying risk factor.

Introduction

Neonatal jaundice is a common problem in more than 80% of newborns, especially during the first week of life [1]. Pathological increases in bilirubin values and exceeding a certain level of blood bilirubin may cause neurotoxicity and lead to undesirable conditions such as kernicterus [1]. Therefore, early and appropriate management is very important for the prevention of long-term neurological sequelae.

To avoid this condition, especially in newborns with isoimmune hemolytic disease caused by blood group incompatibilities between mother and fetus, bilirubin levels and the rate of bilirubin increase should be closely monitored after birth. But, some newborns without an underlying risk factor or isoimmune hemolytic disease who had pathological high cord blood bilirubin values or bilirubin increase rates, need to be closely followed up and treated in the neonatal intensive care unit.

An increase in bilirubin levels, decrease in hemoglobin (Hb) values, direct Coombs test positivity, reticulocytosis, and hemolysis findings in peripheral smear are expected as an indicator of hemolysis in isoimmune hemolytic diseases [2]. Carboxyhemoglobin (COHb), one of the by-products of bilirubin metabolism can be used as another predictor of hemolysis and, consequently, of bilirubin production [2]. However, the heme-oxygenase enzyme, which plays a role in bilirubin metabolism, is affected and induced by many

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oxidative stresses such as sepsis, hypoxia, respiratory distress, or surgery, so bilirubin and COHb levels may also be affected by these conditions [3,4].

For this reason, the presence of pathological cord blood bilirubin values and bilirubin increase rates in healthy newborns without an underlying cause leaves a question mark in mind as to whether it may be related to birth anesthesia. In the literature, there are many studies investigating the relationship between COHb levels and neonatal hyperbilirubinemia [5-9]. However, we have seen that there are not enough studies in neonatal hyperbilirubinemia in which COHb, Hb, and bilirubin levels, type of delivery, and anesthetic agents are evaluated together. Therefore, we aimed to conduct a study in which changes in blood COHb, Hb, and bilirubin levels were investigated together to evaluate the effect of birth anesthesia on neonatal hyperbilirubinemia.

Materials and Methods

This retrospective cohort study was conducted at Karadeniz Technical University Medical School Department of Neonatology between 2017 and 2019. The study protocol was approved by the Karadeniz Technical University Institutional Ethics Committee.

A total of 110 healthy neonates without any risk factors for neonatal hyperbilirubinemia were included in the study. All study patients consisted of neonates who were born at 37-41 weeks of gestational age with an uncomplicated pregnancy and delivery.

The neonates were divided into two groups according to the type of delivery normal spontaneous vaginal delivery (NSVD) (without anesthesia) and elective spinal cesarean section (CS) (especially with the same anesthetic agent-bupivacaine).

Neonates who had sepsis, hypoxia, respiratory distress, or risk factors for hemolysis such as blood group incompatibilities (Rh, ABO, and/or subgroup incompatibilities, positive direct Coombs test result) were not included in this study (Figure 1).

Demographic characteristics (gestational age, birth weight, maternal age, APGAR scores, gender) and laboratory findings [blood groups of the neonates and mothers, results of direct Coombs test; COHb, bilirubin, and Hb values] were recorded. COHb, bilirubin, and Hb values were measured from umbilical cord blood (as cord) and capillary blood taken from the heel 4-6 hours after birth (as post cord). These parameters were measured using heparinized pipettes and in a blood gas analyzer (ABL 800, Radiometer GmbH, Copenhagen, Denmark).

Statistical analysis

All statistical analyses were analyzed in the IBM SPSS 22.0 environment (licensed by Karadeniz Technical University, Trabzon, Türkiye). Kolmogorov Smirnov test was used to evaluate the normal distribution. Continuous variables were expressed as means ± SD, and categorical variables were expressed as percentage and number. Categorical variables were analyzed with the Chi-Square test. The variables were tested with the Student's t-test or Mann-Whitney U test. Student's t-test (Mann Whitney U, if non-parametric) was used to compare means between independent two groups, and the Paired t-test (Wilcoxon Signed Rank test, if non-parametric) was used to compare means between dependent two groups. Spearman rank correlation analysis was used to test the relationship between variables (Table 1). Results were evaluated at a 95% confidence interval, and p-values less than 0.05 were considered statistically significant. Experimental (post-hoc; retrospective; posterior) power analysis was performed to calculate the realized power in the study. With a significance level of $\alpha = 0.05$ and an effect size of d = 0.5, the power of the study (1-β) was calculated as 0.83. The power of the sample was calculated in the G*Power 3.0.10 program environment.

Results

A total of 1,639 live births were born within the research interval. 110 neonates met the all criteria for this study and also had both capillary blood which was measured 4-6 hours after delivery and umbilical cord blood. There were fifty-five neonates in both of the groups. Demographic characteristics and laboratory findings of the study groups are shown in Table 2.

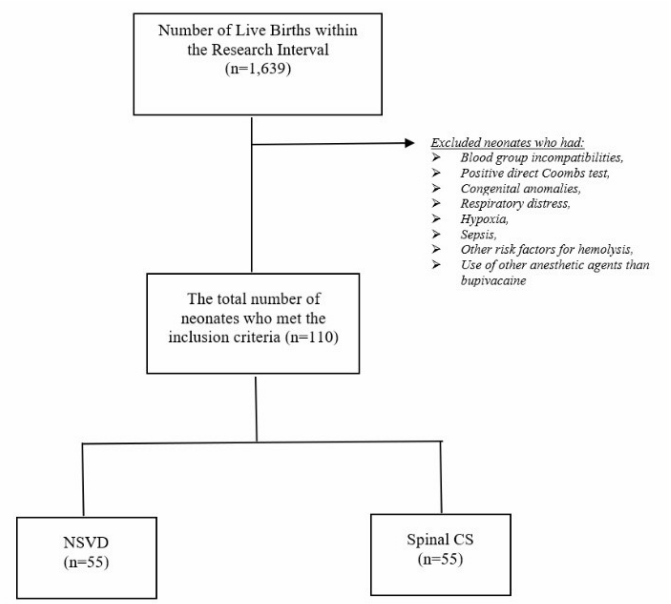

Figure 1. Patients flow diagram.

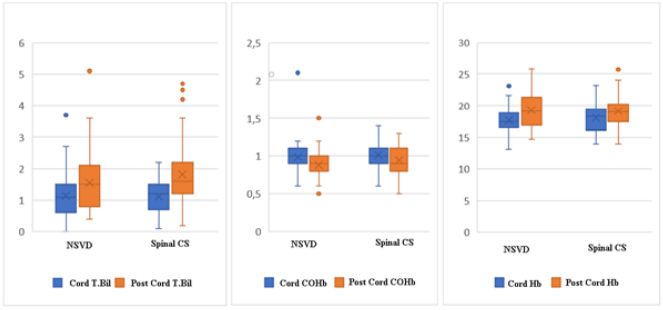

Figure 2. Distribution of COHb, bilirubin and Hb measurements in Cord and Post Cord (which was measured 4-6 hours after birth) blood gas.

Table 1. Relationship between variables.

Variables		Cord COHb	Post Cord COHb	Cord Hb	Cord T.bil	Post Cord Hb	Post Cord T.bil
Cord COHb	r	1					
	p	.					
Post Cord COHb	r	0.39**	1				
	p	0.001	.				
Cord Hb	r	-0.18	0.10	1			
	p	0.06	0.32	.			
Cord T.bil	r	0.18	0.09	-0.3**	1		
	p	0.06	0.35	0.01	.		
Post Cord Hb	r	0.15	0.13	0.49**	-0.36**	1	
	p	0.12	0.18	0.001	0.001	.	
Post Cord T.bil	r	0.06	0.17	-0.03	0.76**	-0.39**	1
	p	0.56	0.07	0.80	0.001	0.001	.
	n	110	110	110	110	110	110

r: Spearman rho, ** Correlation is significant at the 0.01 level (2-tailed).

Table 2. Demographic characteristics and laboratory findings of the neonates.

	All Patients	NSVD n=55	Spinal CS n=55	p
Gestational age (wk)	38.31 ± 2.96	39 (38-40)	38 (26-41)	0.001*
Maternal age (y)	28.3 ± 6.1	26 (17-39)	28 (37-39)	0.057*
Birthweight (g)	3161.9 ± 537.5	3227.6 ± 503.2	3096.3 ± 566.82	0.201**
Gender, n (%)				
Female	42 (38.2)	20 (36.4)	2 (40.0)	0.85***
Male	68 (61.8)	35 (63.6)	33 (60.0)	
Umbilical Cord Blood Sample (Cord)				
COHb (%)	0.99 ± 0.18	1 (0.90-1.10)	1 (0.90-1.10)	0.222*
Hb (g/dL)	17.86 ± 2.06	17.69 ± 1.93	18.02 ± 2.19	0.392**
T. Bil (mg/dL)	1.12 ± 0.61	1.13± 0.68	1.10 ± 0.53	0.852**
Capillary Blood Sample (Post Cord)				
COHb (%)	0.91 ± 0.18	0.90 (0.80-1.0)	0.90 (0.80-1.10)	0.028*
Hb (g/dL)	19.18 ± 2.54	19.27 ± 2.66	19.10 ± 2.44	0.754**
T. Bil (mg/dL)	1.68 ± 0.95	1.50 (0.80-2.10)	1.60 (1.20-2.20)	0.128*

Median(IQR), n(%), * : Mann Whitney U Test, **: Student t test, *** : Chi Square Test, p<0.05.
Abbreviations: COHb, Carboxyhemoglobin; CS, Cesarean Section; Hb, Hemoglobin ; NSVD, Normal Spontaneous Vaginal Delivery; T.bil, Total bilirubin.

Table 3. Comparison of umbilical cord and post cord results of COHb, T.bil and Hb values between in NSVD and spinal CS groups.

	NSVD (n=55)				Spinal CS (n=55)			
	Cord	Post Cord			Cord	Post Cord		
	Median(IQR)	Median (IQR)	z	p*	Median (IQR)	Median (IQR)	z	p
COHb (%)	1(0.9-1.1)	0.9(0.8-1.0)	-4.27b	0.001	1(0.90-1.10)	0.9(0.8-1.1)	-2.57b	0.010*
T.bil (mg/dL)	1.1(0.6-1.5)	1.5(0.8-2.1)	-5.44c	0.001	1.2(0.7-1.50)	1.6(1.2-2.2)	-5.51c	0.001*
Hb (g/dL)	17.4(16.5-18.8)	19.1(16.9-21.3)	-4.03c	0.001	18.3(16.1-19.5)	19.0(17.4-20.2)	-2.97c	0.003*

Median (IQR), Arithmetic mean ±standard deviation; * Wilcoxon Signed Rank Test; p<0.05; b, based on positive ranks; c, based on negative ranks; COHb, Carboxyhemoglobin; CS, Cesarean Section; Hb, Hemoglobin ; NSVD, Normal Spontaneous Vaginal Delivery; T.bil, Total bilirubin.

No statistically significant difference was found between the groups in terms of birthweight, maternal age, APGAR

scores, and gender (p>0.05).

There was a statistical difference between the groups according to the mean of gestational age, and it was observed that the mean of gestational age in the spinal CS group was lower than in the NSVD group (38.30±1.2 and 39.16±1.39 respectively) (p=0.001).

Umbilical cord COHb levels in the spinal CS group were higher than in the NSVD group, but there was no statistically significant difference between groups (1.01±0.15 and 0.99±0.20 respectively, p=0.22). Furthermore, the differences between groups in terms of mean bilirubin and Hb levels in cord and post-cord were not statistically significant (>0.05). However, it was determined that post-cord COHb levels were higher than in the NVSD group, and this difference was statistically significant (p=0.028) (Table 2).

Additionally, it was found that the mean rank of COHb, bilirubin, and Hb in cord and post-cord values were statistically significantly different between the groups ($p < 0.05$) (Table 3, Figure 2).

Discussion

In this study, we investigated neonates without hemolytic risk factors and other co-existing risk factors for jaundice, born by cesarean section or vaginal delivery affected COHb, Hb, and bilirubin levels. When cord and post-cord COHb levels were compared, although they tended to decrease in both groups, post-cord COHb values were found to be higher and statistically significant in the cesarean section group compared to the NSVD group. There was no statistically significant difference in terms of bilirubin and Hb changes. However, the mean rank of COHb, bilirubin, and Hb in cord and post-cord values were statistically significantly different between the groups ($p < 0.05$). It was also revealed that the values obtained as a result of the study were not clinically significant in terms of neonatal jaundice.

In the hemolytic process, mainly bilirubin load is formed due to excessive heme metabolism, on the other hand, the COHb molecule emerges as a by-product [7]. Many parameters of heme metabolism, such as bilirubin and COHb, were investigated for the early detection of phototherapy requirements in several studies [5-9]. Güney Varal et al. [8] investigated whether COHb levels could be an early predictor of the need for phototherapy in moderate and late preterm infants as classified who required and did not require phototherapy. The infants consisted of ABO and/or Rh incompatibility patients with positive and negative direct Coombs test (DCT). Consequently, they found that regardless of their DCT status, COHb measurement in moderate and late preterm newborns can simply be used to detect phototherapy requirements. The different aspects of this study from ours in that it also included newborns in the risk group and did not specify the newborn's mode of delivery.

Also, Tıraş et al [9] studied whether cord blood COHb levels in jaundiced term neonates with and without a positive direct Coombs test (DCT) and in healthy controls could be used as a predictor of severe hyperbilirubinemia. They could not prove that COHb levels were superior to DCT in anticipating the risk of developing severe hyperbilirubinemia in term infants.

In some of these studies, it has been examined if these parameters which were predictors for hyperbilirubinemia were related to especially anesthetic agents [10-16]. Clark and Landaw [10] showed that the effect of birth anesthesia, especially bupivacaine, was associated with neonatal hyperbilirubinemia. They also suggested that bupivacaine crosses the placenta, adheres to the erythrocyte membrane, and facilitates its hemolysis, resulting in neonatal hyperbilirubinemia. Similarly, Gale et al. [11] found that a significant association between high bilirubin levels and epidural anesthesia and CS in a study of 10,122 singleton neonates. In another study, it was emphasized that anesthesia technique can be among the factors that may affect neonatal jaundice [12].

However, some previous studies have not shown a relationship between different anesthetic agents and neonatal hyperbilirubinemia [13-16]. In 1987, Gale et al. [13] studied the rate of bilirubin production via measurement of COHb and bilirubin levels in 43 neonates and whether bupivacaine affected bilirubin and COHb levels. The results showed that bupivacaine did not affect neonatal jaundice. While neonates delivered with bupivacaine during vaginal birth or cesarean section were included in their study group, neonates born with other anesthetic agents were included in the control group. The presence of other anesthetic agents may be the reason why bupivacaine was not found to have an effect on neonatal jaundice in their study. However, in our study, the control group consisted of neonates born with NSVD who were healthy and did not receive any anesthetic agents during birth. Similarly, in another study, Alkan et al. [14] conducted by comparing the study group who were given various anesthetic agents during birth with the control group who were not given any anesthetic agent during NSVD, they found that anesthesia did not affect bilirubin levels during the first 24 hours. The difference between this study and from present study was that only transcutaneous bilirubin levels were investigated. However, we also examined the umbilical cord and post-cord COHb, bilirubin, and Hb values.

Conclusion

To our knowledge, this is the first study to compare the changes of COHb, bilirubin, and hemoglobin values in the first six hours of life among neonates who had no risk factors and were born by spinal CS versus NSVD. This study did not reveal any significant evidence of hemolysis since bilirubin levels did not increase pathologically and Hb values did not decrease. However, the mean rank of COHb, bilirubin, and Hb in cord and post-cord values were statistically significantly different between the groups. This study revealed that both cord and post-cord COHb means were higher in the spinal CS group than in the NVSD group, even though the difference in COHb mean in post-cord was statistically significant. Therefore, it should be kept in mind that the anesthetic agent may also be a factor in bilirubin increases that occur in neonatal hyperbilirubinemia without an underlying risk factor. Our study had limitations because the number of patients was not sufficient to make a definitive decision. Prospective studies

with larger sample sizes also include isoimmune hemolytic diseases and other anesthetic agents that are needed to better understand the effects of birth anesthesia on neonatal hyperbilirubinemia.

Conflict of interest

The author declared no conflict of interest.

Ethical approval

Ethics committee approval was received from the Karadeniz Technical University Institutional Ethics Committee (2023/173).

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