EVALUATION OF CORD BILIRUBIN FOR DEVELOPMENT OF SIGNIFICANT HYPERBILIRUBINEMIA IN HIGH-RISK TERM NEONATE

By

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ABSTRACT

Introduction: *Neonatal jaundice occurs in approximately 60% of term newborns. Although risk factors for neonatal jaundice have been studied, all the suggested strategies are based on various newborn tests for bilirubin levels.*

Aim Of Work: *to evaluate Cord Bilirubin for the development of significant hyperbilirubinemia in high-risk term neonates.*

Patients & Methods: *This is a Case control study that was conducted at Al-Azhar university hospitals from May 2023 to Dec 2023, including 100 term neonates met the inclusion criteria, evaluated for cord bilirubin at birth, 70 of them have had high risk features for developing pathological jaundice like ABO & RH incompatibility (study group (group1)), while 30 patients didn't have risk factors (control group- (group 2)), all patients were subjected to ABO group, CBC, CRP, reticulocytes, Coombs test and Cord bilirubin at 24 hrs. then peripheral samples for 3 successive days for total, direct and indirect bilirubin.*

Results: *Of 70 high risk term neonates, 44 of them had maternal UTI, 16 had ABO incompatibility and 10 had RH incompatibility, 56 of them were females (80%), while 14 were males (20%). On the other hand, control group included 7 females (23.3%) and 23 males (76.7%). The mean gestational age ±38.3 weeks and range between 37 to 42 weeks with standard deviation (SD) ±1.350. The mean birth weight of babies enrolled in our study ±3.09 kg with a range from 1.5 kg to 4.2 kg with SD±0.557. Newborns delivered by caesarean section were 88.6% and rest by spontaneous vaginal or assisted vaginal delivery, mean cord bilirubin for group (1) and (2) were 5.4±0.5 ,*

1.1±0.14 mg/dl respectively , p=0.001, while peripheral total bilirubin in the 3rd day was 8.77±0.13, 1.13±0.16 mg/dl respectively, P=0.001.

Conclusion: *Measuring cord bilirubin in high-risk term neonates is crucial, valid and highly sensitive method for the early detection of significant hyperbilirubinemia. More trials needed to be conducted to emphasize the importance of cord bilirubin measurement. More risk factors should be studied specially at the antenatal period to evaluate if there is correlation between this period and developing hyperbilirubinemia or not.*

Keywords: *Cord Bilirubin, Hyperbilirubinemia, High risk neonates.*

INTRODUCTION

Jaundice in the newborn has presented a diagnostic challenge to clinicians for millennia. Because virtually every newborn infant has an elevated serum bilirubin in comparison with the normal adult and more than 50% are visibly jaundiced during the first week of life, the physician's first challenge is to differentiate pathology from variations within the normal range. Today, clinicians are faced with critical therapeutic decisions as well; treatment should be instituted only when benefit will accrue **(Enweronu-Laryea et al., 2022)**.

Neonatal jaundice occurs in approximately 60% of term newborns. Although risk factors for neonatal jaundice have been studied, all the suggested strategies are based on various newborn tests for bilirubin levels **(Guedalia et al., 2022)**.

Jaundice caused by hyperbilirubinemia is a common phenomenon during the neonatal period. Population-based studies evaluating assessment, management, and incidence of jaundice and need for phototherapy among otherwise healthy neonates are scarce. We prospectively explored these aspects in a primary care setting via assessing care as usual during the control phase of a stepped wedge cluster randomized controlled trial **(Guedalia et al., 2022)**.

Neonatal jaundice is a leading cause of hospitalization in the first week of life worldwide. It is a major cause of hospital neonatal intensive care unit admission and readmissions during the neonatal period. Jaundice in the newborn has a reported incidence between 60% to more than 90%. Every year, about 1.1 million babies develop severe hyperbilirubinemia encephalopathy (which is one of the complications of neonatal jaundice) and most of these people

reside in Sub-Saharan Africa (SSA) and South Asia.

The aim of work of our study is to evaluate Cord Bilirubin for the development of significant hyperbilirubinemia in high-risk term neonates.

Sample size calculation:

The sample size is calculated according to the following equation:

Necessary Sample Size =

$$\frac{(Z-score)2\,x\,StdDev\,x\,(1-StdDev)}{(marging\ of\ error)2}$$

(Keogh et al.2009).

with 16% standard deviation alpha error of 0.10 &prediction of 90%. It included 26 patients for control group and 68 patients for study group.

Ethical Consideration:

- Approval by the ethical committee of the Pediatrics department at the Faculty of Medicine at Al-Azhar University under the registration number was obtained before the study.
- Patients were enrolled in the study after getting informed oral and written consent from their parents.
- Patient data confidentiality was preserved during all study procedures.
- The patient and parents have the right to withdraw at any time.
- There was no conflict of interest regarding the study or publication.
- There is no financial support or sponsorship.
- We ensure that the participants are not physically or psychologically harmed during the study.

Inclusion Criteria:

1. Term Neonates of both sexes.
2. High risk factor for neonatal jaundice (RH incompatibility& ABO incompatibility and maternal UTI).

Exclusion Criteria:

1. Preterm neonates <37 weeks GA.
2. Neonates without risk factor for hyperbilirubinemia
3. Presence of congenital anomalies.

PATIENTS AND METHODS

This is a Case control study that was conducted on 100 term neonates recruited from Al-Azhar

university hospitals from May 2023 to Dec 2023.

All the studied patients and control group was subjected to the following:

I. Perinatal history taking:

- Pre-natal history for: (mother blood group, RH factor, maternal DM and hypertension, previous delivery with neonatal jaundice) .
- Thorough natal history: type of delivery: whether spontaneous vaginal delivery or CS.
- Thorough postnatal history: APGAR score, Ballard score, baby admitted on NICU or not.

II. Thorough clinical examination: vital signs, anthropometric measures, signs of respiratory distress, and systemic review.

III. Laboratory assessment: for high risk babies: cord bilirubin, ABO group & RH, CBC, ESR, CRP, reticulocitic count, Coomb's test (direct and indirect) , then follow up of S.bilirubin peripherally at

- 24 hours.
- 48 hours.
- 72 hours.

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Numerical data were tested for the normal assumption using Kolmogorov Smirnov test. Comparison of numerical variables between the study groups was done using Student's t test for independent samples for comparing 2 groups of normally distributed data and/or large enough samples, and one way analysis of variance (ANOVA) test with post hoc multiple 2-group comparisons when comparing more than 2 groups of normally distributed data and/or large enough samples. Kruskal Wallis test was used when comparing not-normal numerical data. For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is less than 5. Two-sided p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program IBM SPSS (Statistical Package for the Social Science; IBM Corp, Armonk, NY, USA) release 22 for Microsoft Windows.

RESULTS

Our results were summarized in the following tables.

Table (1): The demographic characteristics of the studied cases

Variable	Group (1) (no = 70)	Group (2) (no = 30)	P value
Mode of delivery			
S.V.D.	8(11.4%)	3(10%)	0.834*
CS	62(88.6%)	27(90%)	0.324*
Sex			
Male	14(20%)	23(76.7%)	0.001**
Female	56 (80%)	7(23.3%)	0.005**
Sibling with neonatal jaundice (n/ %)			
Present	10(14.3%)	0	0.001**
Absent	60(85.7%)	30(100%)	0.986

This table showed that there was no statistically significant difference regarding mode of delivery, males were predominant in control group unlike females for study group. On the other hand, the history of neonatal jaundice for siblings was associated with **Group (1)** significantly.

Table (2): Clinical findings of the studied groups

Variable	Group (1) (no = 70)	Group (2) (no = 30)	P value
Vital signs mean ± SD.			
Heart rate (B/M)	143.7±21.6	135.9 ±8.4	0.06*
Respiratory rate (C/M)	45.2±8.8	46.8±9.2	0.42*
Mean ABP (mm Hg)	55.3±13.4	59.4±12.3	0.21*
Temperature (C˚)	36.4±0.5	36.9±0.8	0.34*
Clinical finding			
pallor	14(20%)	27(90%)	0.001**
jaundice	56 (80%)	3(10%)	0.005**
Poor feeding	65(92.8%)	9(30%)	0.001**

This table shows significant difference regarding pallor, jaundice, and poor feeding, while insignificant difference regarding HR, RR, Bl. Pressure, and temperature between **Group (1)** and **Group (2)**.

Table (3): The laboratory characteristics of the studied cases

	Group (1) (no = 70)	Group (2) (no = 30)	P value
Hemoglobin (mean ±SD)	10.5±2.08	11.7±1.23	0.004**
WBCs count (mean ±SD $\times 10^3$)	12.09± 3.05	4.6± 1.41	0.007*
CRP	47.3±23.7	4.2±0.2	0.001**
ESR	59.5±3.2	10.6±2.5	0.002**
Cord bilirubin 1st day	5.4±0.5	1.1±0.14	<0.0001**
Peripheral total bilirubin 2nd day	5.3±.3	1.1±0.15	<0.0001**
Peripheral total bilirubin 3rd day	5.06±0.9	1.2±0.18	<0.0001**
Peripheral total bilirubin 4th day	8.77±0.13	1.13±0.16	<0.0001**

This table shows significant difference regarding all lab. finding between **(Group 1)** and **(Group 2)**.

Table (4): Outcome in both groups

Variable	Group (1) (no = 70)	Group (2) (no = 30)	P value
Pathological jaundice Presence	19 (27.1%)	1(3%)	0.001**
Improvement after phototherapy			
Yes	19 (27.1%)	1(3%)	0.001**
No	0	0	0.005**

This table shows that the improvement was 100 percent in both groups on phototherapy.

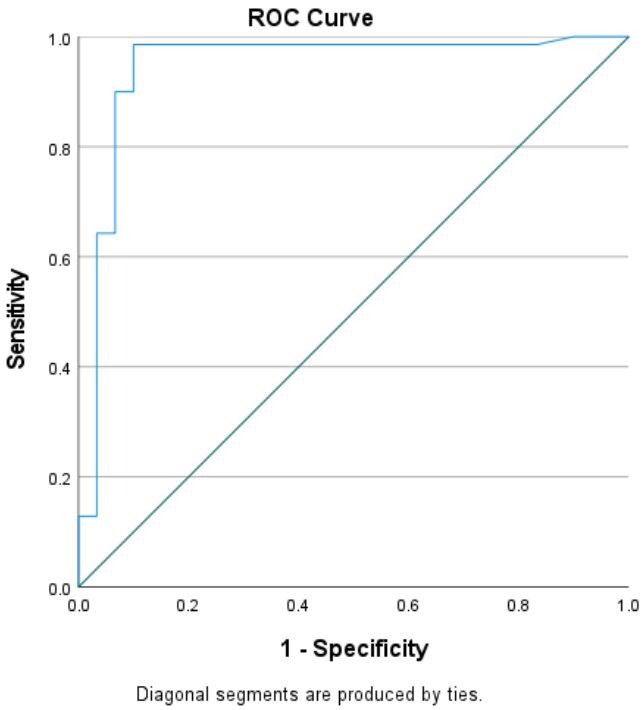

Figure (1): ROC Curve analysis of cord bilirubin

Table (5): ROC curve analysis between cord bilirubin in both groups

Cord bilirubin	Cord bilirubin at birth			
	Negative		**Positive**	
	No.	**%**	**No.**	**%**
	30	30.0	70	70.0
Cut off value	1.7250			
Sensitivity	98 %			
Specificity	97%			
AUC	.945			
CI 95%	(.881,.976)			
P value	<0.001*			

DISCUSSION

Hyperbilirubinemia is a common and, in most cases, benign problem in the neonatal period that is often physiologic, and interventions are not usually necessary. Over 50% of all newborn infants become visibly jaundiced. Infants become clinically jaundiced when the bilirubin level reaches about 80 μmol/L **(Stephens et al., 2018)**.

On the other hand, neonatal jaundice is an important clinical feature as it may be a sign of an underlying disorder (i.e. hemolytic anemia, infection, an inborn error of metabolism or liver disease). In severe cases, high unconjugated hyperbilirubinemia can be deposited in the brain, particularly in the basal ganglia, causing kernicterus **(Chen et al., 2021)**.

Early discharge of the healthy-term newborns after delivery has become a common practice because of both medical and social reasons as well as economic constraints. Universal follow-up within 1–2 days of early discharge (often an unattainable goal in low-income countries), umbilical cord bilirubin (uCB) concentration at birth, routine pre-discharge serum bilirubin, and transcutaneous bilirubin measurements, as well as the universal clinical assessment of risk factors for developing jaundice, are various strategies to predict significant hyperbilirubinemia. Despite these suggested measures, hyperbilirubinemia is still the most common cause of readmission during the early neonatal period **(Perme et al., 2016)**.

The current study aimed to evaluate the Cord Bilirubin as a risk factor for development of significant hyperbilirubinemia in high-risk term neonate.

This was a case control study that was done at Al-Azhar university hospitals for 100 neonates (70 term neonates at high risk for hyperbilirubinemia (group 1) & 30 control (group 2)).

Our results agree with the study done by **Hamdi et al., (2012)**, who showed no significant difference among his studied groups regarding the mode of delivery, whether vaginal delivery or cesarean section that is agree with our study. The same results were found in the study done by **(Abd El Moktader et al., 2020)**, showing no significant difference regarding the mode of delivery.

In our study, our results showed that **Group (1)** included 70 patients, 56 of them were females (80%), while 14 were males (20%). On the other hand, **Group (2)** included 7 females (23.3%) and 23 males (76.7%), with statistically significant difference.

The study showed that there was no statistically significant difference between both groups regarding heart rate and respiratory rate.

Regarding the antenatal history, we found that in **Group (2)**, no previous delivery with

neonatal jaundice, while in **Group (1)** there was previous delivery with neonatal jaundice. It may indicate that neonatal hyperbilirubinemia is associated with positive family history of neonatal jaundice.

In our study, regarding lab parameters, there was statistically significant difference regarding HB, CRP and ESR, between **Group (1)** and **Group (2)**.

This is also in harmony with **Anand et al. (2016)** who aimed to assess cord bilirubin as a predictor of neonatal hyperbilirubinemia. They reported that there was no significant difference based on the mode of delivery **(Anand et al., 2021)**.

Babies delivered by caesarean section had significant lower values of cord bilirubin as compared to babies delivered vaginally which was explained due to decreased placental transfusion during caesarean section **(Shao et al., 2023)**.

In our study, longitudinal measurements of cord bilirubin over 72 hours showed a notable upward trend in the study group from 5.4959 initially to 8.7720 at 72 hours, whereas levels remained stable between 1.16 and 1.1603 in the control group. This indicates that measuring cord bilirubin in neonatal jaundice is mandatory daily. ROC analysis demonstrated high accuracy of cord bilirubin, with a sensitivity of 98%, specificity of 97%, and area under the curve of 0.945 based on the optimal cutoff of 1.7250, which categorized 30% as test negative and 70% as test positive. The significant p-value and narrow 95% confidence interval (0.881, 0.976) confirmed that cord bilirubin is a highly sensitive and valid method for distinguishing between infants with versus without neonatal jaundice.

In the study group of **El-Gendy et al. (2013)**, at cut-off value of 2.73 mg/dl, with 100% sensitivity and 90% specificity, 71.4% of males developed significant hyperbilirubinemia **(El-Gendy et al., 2013)**.

Our results were in agreement with the study done by **Kardum et al (2021)** who found that a clear relation between cord serum bilirubin and the development of hyperbilirubinemia with a sensitivity of 90% and a negative predictive value of 99.1%. **(Kardum et al., 2021)**.

Also, our results were in agreement with study done by **Jones et al. (2017)**, who demonstrated that jaundiced newborns presented higher umbilical cord blood bilirubin levels than newborns without

clinical jaundice, and he proved the possibility of defining a newborn risk group for developing neonatal hyperbilirubinemia at birth **(Jones et al., 2017)**.

There is an association between bilirubin levels in cord blood & later neonatal bilirubin concentration. Mean bilirubin levels in cord blood range from 1.4 to 1.9 mg/dl & elevated cord bilirubin levels was associated with an increased risk of hyperbilirubinemia **(Anand et al., 2016)** and **(Anand et al., 2021)**.

Our results are in accordance with those of **Şahan et al. (2023)** who recorded that the mean CB among high-risk group is significantly higher compared with the group with no risk **(ŞAHAN et al., 2023)**. However, **Ipek et al. (2012)** recorded a mean CB of 2.05 ± 0.98 mg/dl. The difference between our results, which shows a higher level, and other studies may be owing to higher percentage of ABO and Rh incompatible cases in our study (33.3%) than in others **(Ipek et al., 2012)**.

CONCLUSION

Measuring cord bilirubin in high-risk term neonates is crucial, valid and highly sensitive method for the early detection of significant hyperbilirubinemia.

RECOMMENDATION

- More trials needed to be conducted to emphasize the importance of cord bilirubin measurement.
- More risk factors should be studied specially at the antenatal period to evaluate if there is correlation between this period and developing hyperbilirubinemia or not.

LIMITATIONS

- Difficulty in follow up of high-risk group.
- Refusal of some mothers to share the study.
- Difficult frequent sampling.

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