Volume 15 (4), 2013

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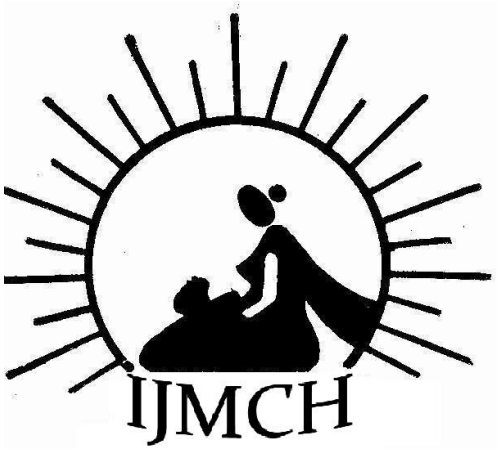

INDIAN JOURNAL OF MATERNAL AND CHILD HEALTH

To establish a correlation between umbilical cord blood bilirubin levels and the development of subsequent hyperbilirubinemia in healthy term newborn ABO incompatible infants of blood group “O” mothers.

Predictive Value of Umbilical Cord Blood Bilirubin Level for Subsequent Hyperbilirubinemia in ABO Incompatibility

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ABSTRACT

Objectives: To establish a correlation between umbilical cord blood bilirubin levels and the development of subsequent hyperbilirubinemia in healthy term newborn ABO incompatible infants of blood group "O" mothers.

***Subject & Methods**:* One hundred consecutive healthy full term offsprings of ABO incompatible pregnancies and 30 controls resulting from O-O pregnancies were studied. Blood group and serm bilirubin estimations were carried out on cord blood and bilirubin estimation was further done at 36 hours of life.

***Results**:* Out of 100 cases in study group 33(33%) developed hyperbilirubinemia whereas only one (3.3%) out of 30 cases in control group developed hyperbilirubinemia. Majority of cases with hyperbilirubinemia i.e. 20 (60.6%) out of 33 cases, had cord bilirubin values between 2.5 to 2.99 mg/dl. Mean cord bilirubin values were significantly higher (2.27 $\pm$U 0.76) in study group as compared to compared to control group (1.55 $\pm$ 0.33).

Conclusion : It is concluded that in ABO incompatibility the cord bilirubin value $\geq$ 2.5 mg/dl can serve as a useful cutoff limit for the later development of hyperbilirubinemia.

Key words: ABO Incompatibility; Hyperbilirubinemia; Cord blood bilirubin; Newborns

INTRODUCTION

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in neonates[1].Identifying among all newborns those few at risk to develop marked hyperbilirubinemia is a clinical challenge [1,2]. Although up to 60 percent of term newborns have clinical jaundice in the first week of life, few have significant underlying disease [3,4]. Common risk factors for hyperbilirubinemia include fetal-maternal blood group incompatibility, prematurity, and a previously affected sibling[5,6]. In the expanding list of conditions causing neonatal icterus gravis, blood group incompatibility still remains the most common & important cause of icterus of potential severity[5]. Hemolytic disease related to ABO incompatibility is a major risk factor for severe hyperbilirubinemia in the 2004 AAP practice guidelines[7].For all practical purposes it is limited to infants of blood group A or B born to mothers who are blood group O[8,9,10,11].Heterospecificity of mother

& child with respect to blood group- A, B & O, is common. The gene incidence for ABO in a given population has been estimated at between 20-25 % in all pregnancies[12,13].
Despite the difficulty in predicting its development,symptomatic ABO hemolytic disease does occur,often with clinica jaundice detected within the first 12 to 24 hours of life;hence, the term "icterus praecox" was ascribed to this condition by Halbrecht in 1944[14].
Because of the relative infrequency of severe ABO disease, the urgency for predictive criteria in this disease have been slow in forthcoming.
With increasing emphasis on initiation of breast feeding soon after birth & threreafter early discharge of babies, it is very important to predict, within 24 hours of birth, the probability of subsequent hyperbilirubinemia.
Various workers have tried to identify the newborn likely to develop hyperbilirubinemia by monitoring serial serum bilirubin levels after birth or by measuring bilirubin levels of cord blood [1,2,15,16,17,18,19].Routine screening of all ABO-incompatible cord blood has been recommended and remains common practice in some nurseries[11,18]. Our study was designed to test the reliability of umbilical cord blood bilirubin levels in predicting the development of subsequent hyperbilirubinemia in ABO incompatible babies of blood group O mothers.
Hyperbilrubinemia for the purpose of study was defined as a serum bilirubin level greater that or equal to 10mg/dl upto 36 hrs. of age and was derived from the hour specific nomograms for term babies given by bhutani et al[18].

MATERIAL AND METHODS

This was a prospective study. One hundred consecutive healthy term newborns of heterospecific pregnancies (cases)and 30 healthy term newborns of homospecific pregnancies(controls) were studied.
Cord blood was obtained from all consecutive newborns with groups O mothers.
The bilirubin level and blood groups were carried out in each sample. In those cases where the newborn was found to have a blood group other than O, bilirubin estimation was carried out at 36 hrs.If clinically significant jaundice appeared earlier in any baby,then serum bilirubin levels were done earlier also. If any baby was taken into nursery for phototherapy, further bilirubin estimations were done according to the nursery protocol.
Bilirubin levels were estimated by using semiautomatic analyzer RA 50 (miles India Ltd) using the method of Jendrassik and Grof. Blood groupings were done using the standard slide agglutination method.**I**

Statistical Methods:

All the data obtained during our study was analyzed by statistical attribute test. Chi square test and t-test was applied and level of probability calculated.
Permission for human studies from institutional review board and ethics committee was duly taken.

RESULTS

Table 1 shows the comparison of the cord bilirubin levels between study & control group. In study group cord bilirubin levels were significantly higher than those in control group. Only one out of 30 cases in control group developed significant hyperbilirubinemia, as compared to 33 our of 100 cases in study group. This difference was statistically significant (Table 2).

An analysis of the usefulness of umbilical cord blood bilirubin level as a predictor of late development of hyperbilirubinemia is presented in Table 3.

The Probability that a new born with cord bilirubin level higher than or equal to 2.5 mg/dl would later develop hyperbilirubinemia (predictive valve positive) was 87.09%. The predictive value negative, the probability of non development of hyperbilirubinemia given a cord bilirubin less that or equal to 2.5 mg/dl was 91/3%. If a child developed hyperbilirubinemia, the probability that the cord bilirubin was higher than or equal to 2.5 mg/dl was 81.18% (sensitivity of the test). Given a new born with non-development of hyperbilirubinemia, the probability that the cord bilirubin was less than or equal to 2.5 mg/dl was 92.38% was 92.38% (specificity of the test).

Table 1: Comparison of cord bilirubin levels between study and Control group

	Study Group (n=100)	**Control Group (n=30)**	**t test**	**p value**
Mean	2.278	1.555	2.4597	<0.10
SD	0.7615	0.3351		

Table 2: Distribution of cases in study and control group according to development of hyperbilirubinemia (SB≥10mg/dl upto 36 hours)

S.Bilirubin upto 36 hrs.	Study group (n=100)		Control group (n=30)		Chi square	P value
	Number	%	Number	%		
<10mg/dl(n=96)	67	67	29	96.7	9.036	<0.0026
≥10mg/dl(n=34)	33	33	1	3.3		

Table 3: Predictive value of umbilical cord blood bilirubin levels for later development of significant hyperbilirubinemia

	≥4.5 mg/dl	≥4.0 mg/dl	≥3.5 mg/dl	≥3.0 mg/dl	≥2.5 mg/dl	≥2.0 mg/dl	≥1.0 mg/dl
Predictive Value positive	100	100	100	100	87.09	68.0	35.05
Predictive Value negative	69.07	72.04	73.62	76.40	91.30	100	100
True positive rate (Sensitivity)	9.90	21.21	27.27	33.37	81.18	100	100
True negative rate (specificity)	100	100	100	100	92.68	75.75	4.99

Table 4: Relationship of severe hyperbilirubinemia & cord bilirubin level ≥4mg/100ml

Cord bilirubin (mg/100ml)	**Serum bilirubin levels upto 36 hours of age(mg/100ml)**		**Chi square**	**P value**
	<15	**≥15**		
<4	93	0	70.286	<0.0001
≥4	1	6		

Relationship of Severe hyperbilirubinemia(bilirubin level≥15mg/100ml upto 36 hours of life) with Cord bilirubin level ≥4mg/100ml is shown in table 4. Out of 100 patients included in the study, 6 developed severe hyperbilirubinemia & in all of these 6 cases, cord bilirubin level was greater than or equal to 4 mg/dl.

Only one case with cord bilirubin ≥4mg/dl did'nt develop severe hyperbilirubinemia.

DISCUSSION

In the spite of several years of research, many aspects of neonatal jaundice remain an enigma to the treating physician. Since the introduction of Rh. Immunoglobulin there has been a decline in hemolytic disease of the newborn due to Rh incompatibility and ABO hemolytic disease of newborn has become the most common cause of neonatal jaundice requiring therapy. ABO hemolytic disease is found almost exclusively among infants of group O mothers[8,10,11]

Halbrect first reported a possible association between ABO incompatibility and neonatal jaundice[14]. Rosenfield was the first to note marked preponderance of group O mothers of infants having ABO hemolytic disease of newborn[20]. Various authors have studied the incidence of clinically significant jaundice in ABO hemolytic disease of newborn. Tovey et al in their study found incidence of deep jaundice (Serum bilirubin >10mg/dl) in 1% of ABO compatible babies and 8% of incompatible babies[21]. Dufour and Monogham in their study found clinically significant jaundice (serum bilirubin >12mg/dl) in 6.5% of ABO compatible newborns and 22% of ABO incompatible newborns[22]. In our study, we found clinically significant jaundice in 3.3% of ABO compatible newborns and 33% of ABO incompatible newborns (Table 2).

Jhonstone studied serum bilirubin values of 1353 cord blood samples & found the values to be significantly higher in heterospecific than homospecific pregnancies [23].

Zuelzer and Kaplan in their study also found the combined average cord bilirubin values of O-A and O-B groups to be higher than those of O-O groups[12]. In our study also we found the mean cord bilirubin values to be significantly higher in ABO heterospecific that ABO homospecific pregnancies (Table 1).

Robinson et al reported that cord bilirubin levels above 3 mg/dl were highly suggestive of ABO disease[24].

The value of measuring cord bilirubin level in ABO incompatibility has been investigated by Risemberg et al who found that all infants with cord bilirubin levels higher that 4 mg/dl developed significant jaundice[8]. In contrast, Haque showed that the cord bilirubin levels are unreliable in predicting hyperbilirubinemia in ABO compatibility[25].

In our study, a correlation between the level of cord bilirubin and development of subsequent hyperbilirubinemia was observed (Table 3). We also found that all the 6 cases of severe hyperbilirubinia (Serum bilirubin $\geq$ 15 mg/dl upto 36 hrs.) had cord biliruin levels $\geq$ 4 mg/dl (Table 4).

However there are some limitations of the study like number of cases and controls enrolled were less. In future a study with more number of subjects (cases as well as controls) can be done to see for the reproducibility of our study.

CONCLUSION

It is already known that cord blood bilirubin levels can help in predicting subsequent hyperbilirubinemia in Rh incompatibility but there are only few studies in cases of ABO incompatibility. From our study it is concluded that in ABO incompatibility a cord bilirubin level greater than or equal to 2.5 mg/dl can serve as a useful cutoff limit for the later development of hyperbilirubinemia . This knowledge will influence a decision of early discharge from hospiral vs. prolonged observation of babies born to blood group O mothers.

Competing Interests
We declare that we don't have any financial or non financial competing interests.

Funding: None

Authors' contributions
Both the authors contributed to the conception of the study and were involved in writing, revising and approving the final draft of the manuscript.

Acknowledgement We are thankful to Dr N N Purohit, Professor Pediatrics for his constant guidance and moral support.
Permission for human studies from institutional review board and ethics committee was duly taken.

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