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Literature Review Article

Correlation of Cord Bilirubin Level in Newborns in O+ve Mothers with Neonatal Hyperbilirubinemia in Omdurman Maternity Hospital

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Abstract

Background*: Jaundice is the most common condition that requires medical attention in newborns. However, in some infants, serum bilirubin levels may raise excessively, which can be cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurologic sequelae in infants who survive (kernicterus), for these reasons, the presence of neonatal jaundice frequently results in diagnostic evaluation.*

ABO hemolytic disease of the newborn is the most common hemolytic consequence of maternofetal blood group incompatibility restricted mostly to non-group-O babies of group O mothers with immune anti-A or anti-B antibodies.

Objectives*: To find out the correlation of cord bilirubin level in newborn with ABO incomaptibility in group O+ve mother compared with neonatal hyperbilirubinemia*

Methods: This is discriptive comparative cross sectional study conducted during the period from Augast 2018 to January 2019 in Omdurman Maternal Hospital. Data collected, prepared, entered and analyzed using SPSS version 21.

Results*: This 100 studied participante regarding maternal age 53(53%) of the mothers of the studied neonates aged between 20 – 30 years and only 2(2%) aged above 40 years. The majority of the studied neonates 93(93%) delivered by cesarean section and 7(7%) by normal vaginal delivery. History of jaundice among the siblings of the studied neonates was reported in 18(18%), of them (n=18) 11(61.1%) received phototherapy, 1(5.6%) exchange transfusion and 1(5.6%) immunoglubin 1(5.6%) and 2(11.1%) their mothers not remember if the neonate received treatment or not. Male neonates were 53(53%) and females were 47(47%). Male to female ratio was 1.13: 1 .The majority of the studies neonates 75(75%) their birth weight was 2.5-3.5 kg, 15(15%) between 3.6 – 4.5 kg and 10(10%) less than 2.5 kg. 53(53%) of the studied neonates their blood group was O, 25(25%) A, 21(21%) B and 1(1%) AB. Compatibility found in 53(53%) of the neonates and incompatible in 47(47%). Cord bilirubin ≥ 2 mg/dl reported in 52(52%) of the studied neonates and <2 in 48(48%) . It should be noted that cord bilirubin > 2-3 mg/dl reported in 26(26%), > 3 – 4 mg/dl 17(17%) and > 4 – 5 mg/dl in 5(5%).During sampling clinically jaundiced neonates were 31(31%) and normal 69(69%).*

The majority of neonates who were clinically jaundice (n=31) 16(51.6%) received management in terms of observation and follow up, 14(45.2%) phototherapy and 1(3.2%) exchange transfusion (Table 4).

The majority of the studied neonates 84(84%) were not clinically pale,. Hb >= 12 mg/dl reported in 77(77%) of the studied neonates and < 12 mg/dl in 23(23%). Sensitivity of cord bilirubin in determination of neonatal jaundice against clinical assessment was 93.75%, specificity 70.59%, positive predictive value was 60%, negative predictive value 96% and accuracy 78% (P value = 0.003 < 0.05 significant). Cord bilirubin above 3 mg/dl significantly associated with ABO incompatibility (P value < 0.05).Frequency of neonate with ABO incompatibility was 47% in Omdurman Maternity Hospital.

Conclusion and recommendation: *In this study sensitivity of cord bilirubin in determination of neonatal jaundice against clinical assessment was 93.75%, specificity 70.59%, positive predictive value was 60%, negative predictive value 96% and accuracy 78% (P value = 0.003 < 0.05 significant).*

Early identification of at risk newborn for significant hyperbilirubinemia by using simple predictors can help to prevent possible bilirubin induced neurological damage.

Abbrevations

AABR an automated auditory brainstem response
ASAT Aspartate aminotransferase
CBBil cord blood bilirubin
CBC Complete blood count
CS Caesarian section
DAT Direct antiglobulin test
ETCO End-tidal carbon monoxide
GGT γ-glutamyltransferase
Hb Hemoglobin

HDN hemolytic disease of newborn

HIDA hepatoiminodiacetic acid

IgG Immunoglobulin G

IVIG intravenous immune globulin

NPV negative predictive value

NPV negative predictive value

NVD Normal vaginal delivery

RBCs Red blood cells

SGOT Alanine aminotransferase

TSB Total serum bilirubin level

UCS umbilical cord serum

UDPGT uridine diphosphoglucuronyl transferase enzyme

AAP American Academy Of Pediatrics

Introduction

Jaundice is the most common condition that requires medical attention in newborns (1) Neonatal hyperbilirubinemia results from a predisposition to the production of bilirubin in newborn infants and their limited ability to excrete it. Infants, especially preterm infants, have higher rates of bilirubin production than adults, because they have red cells with a higher turnover and a shorter life span.(2)

In newborn infants, unconjugated bilirubin is not readily excreted, and the ability to conjugate bilirubin is limited. Together, these limitations lead to physiologic jaundice— that is, high serum bilirubin concentrations in the first days of life in full-term infants (and up to the first week in preterm infants), followed by a decline during the next several weeks to the values commonly found in adults. The average full-term newborn infant has a peak serum bilirubin concentration of 5 to 6 mg per deciliter (86 to 103 μmol per liter). Exaggerated physiologic jaundice occurs at values above this threshold (7 to 17 mg per deciliter [104 to 291 μmol per liter]). Serum bilirubin concentrations higher than 17 mg per deciliter in full-term infants are no longer considered physiologic, and a cause of pathologic jaundice can usually be identified in such infants.(2)

The predominant source of bilirubin is the breakdown of hemoglobin in senescent or hemolyzed red cells. Heme is degraded by heme oxygenase, resulting in the release of iron and the formation of carbon monoxide and biliverdin (Metabolic Pathway of the Degradation of Heme and the Formation of Bilirubin.). Biliverdin is further reduced to bilirubin by biliverdin reductase. Bilirubin then enters the liver and is modified to an

excretable conjugated form that enters the intestinal lumen but can be deconjugated by bacteria so that the bilirubin is reabsorbed into the circulation.

Increased production of bilirubin, deficiency of hepatic uptake, impaired conjugation of bilirubin, and increased enterohepatic circulation of bilirubin account for most cases of pathologic jaundice in newborn infants.(2)

Increased production of bilirubin occurs in infants of various racial groups, as well as in infants with blood-group incompatibilities, erythrocyte-enzyme deficiencies (2)

or structural defects of the erythrocyte .The propensity toward hyperbilirubinemia in certain racial groups is not well understood. (2)

Another reason for pathologic hyperbilirubinemia is deficient hepatic uptake of bilirubin, as occurs in patients with Gilbert's syndrome. (2)

Deficiency of uridine diphosphate glucuronosyltransferase, the enzyme required for the conjugation of bilirubin, is another important cause of neonatal jaundice. Although all newborn infants are relatively deficient in this enzyme, those with Crigler–Najjar syndrome type 1, in whom the deficiency is severe, have bilirubin encephalopathy in the first days or months of life. (2)

In contrast, encephalopathy is rare in infants with Crigler–Najjar syndrome type II, in which serum bilirubin values rarely exceed 20 mg per deciliter (342 μmol per liter). In glucose-6-phosphate dehydrogenase deficiency, there is an increased risk of hemolysis and impaired conjugation of bilirubin. (2)

There is a previous study done on Canada shows severe hyperbilirubinemia is the most common cause of neonatal readmission to hospital in Canada even though, in the majority of cases, risk factors can be identify before discharge. Severe neonatal hyperbilirubinemia and kernicterus continue to be reported worldwide in otherwise healthy term infants. (3)

Statement of problem:

Neontal hyperbilirubinemia resulting in clinical jaundice is a common problem among infants, particularly during the first weeks of life.(3) A study showed that ABO incompatibility is present in about 12% of pregenancies, with evidence of fetal sensitization in 3% live birth. Less than 1% of birth which are ABO incompatible are associated with significant hemolysis.(34)

Justification:

We observed that ABO incompatibility is common among neonates in Omdurman Matetrnal Hospital.An early detection of hyperbilirubinemia can prevent morbility.

I didn't find recent study done in Sudan about correlation of cord bilirubin level in newborns in group O+ve mothers with neonatal hyperbilirubinemia.

Objectives:

General objective:

To find out the correlation of cord bilirubin level in newborn in Group O+ve mother compared with neonatal hyperbilirubinemia.

Specefic objectives:

1- To measure the relationship of cord bilirubin level and the hemolytic disease of the newborn

2- To determine the ferquancy of ABO incompatibility in Omdurman Maternity Hospital.

3- To measure the umbilical cord biliribin level in case of ABO incomaptibility compared with the level in newborns without ABO incompatiblity.

4- To measure the correlation of cord bilirubin with Hb level in newborn with ABO incomatibility

Methodology

study design: Discriptive Hospital Based Comparative Cross sectional study.

study area: Omdurman Maternity Hospital is located in Omdurman city near museum of monsque of Alcaliph and was establised on 1925 which include:

General obesterical and gynecological word, intensive care unit,labour room ,neonatal intensive care unit and private department which provide health care services for all patients from differnt states of the country.

Study duration: Total duration to complete the thesis is 6 months (From Augast\2018 to January2019)

Study population: All neonates with mothers having blood group O+ve.

All deliveries attended in the hospital during the period of study.

Inclusion criteria:

Neonate with blood group A,B or O

Apperant health neonate

Elective CS

Exclusion criteria:

Mothers and neonates with Rh –ve blood group.

Mothers with group A,B,AB.

Sick babies.

Sampling:

Sample Size:

Sample size was calculated from OpenEPI Version 21 open source calculater- SSPropor

The sample size was calculated by using this formula:

Simple randam sample technique,that every individual or item from the target frame has an equal chance of being selected.

$n = [Z^2 \times P(1 – P)] / [e^2]$

Where:

- Z = Value from standard normal distribution corresponding to desired confidence level.

(Z = 1.96 for 95% CI)

- P = P is expected true proportion.
- e = e is desired precision(halfdesired CI width).

In the equation:

P = 0.5 , e = 0.1

n = [(1.96)2 × 0.5 × (1 – 0.5)] ÷ [(0.1)2] = 96.04 = 96.

To estimate the sample size, read across the expected proportion(P) who have the variable of interest and down from the desired total width (W) of the confidence interval. The three numbers represent the sample size required for 90%, 95%, and 99% confidence levels.

Sample technique :

Simple randam sample technique systemic in C.S list or total number of patient./5 if C.S of O+ve mothers

(5 average NO. of C.S per day O+ve mothers)

Data management

Data collection technique: Face to face interview(by myself)

Data collection tools and methods:

Structured questionnaire in form of demographic and history taking from the patiant. Method:(1)cord blood sample (2)amount:10 ml (3)sample type:TSG-BG-Hb level Payment: The investigation done free in the hospital but if not I will pay for this. Cut off point for cord biluribin was taken as 2.0 mg/dl based on previous study in Brazil showed that the most useful cutoff point for unconjugated bilirubin in cord blood was 2.0 mg/100 ml [35].

Study variable:

Independent varibles:

-Gestational age

-Birth weight

-Age of neonate

-Twin

Dependent varibles:

-Blood group

-Cord bilirubin level

-Jaundice

-Hb

Data analysis:

The data was analyzed by computerized programe statistical package for social science (SPSS) version 21. The data was presented in tables and figures and cross tabulation(P-value) was used to test the association (0.05).

Ethical consideration:

The ethical clearance was obtained from sudan medical specialization board and written consent was taken from parents.

Results

Regarding maternal age 53(53%) of the mothers of the studied neonates aged between 20 – 30 years, 32(32%) 31-40 years, 13(13%) less than 20 years and only 2(2%) aged above 40 years (Figure 1).

History of jaundice among the siblings of the studied neonates was reported in 18(18%) (Figure 2), of them (n=18) 11(61.1%) received phototherapy,3(16.7%) conservative at home, 1(5.6%) exchange transfusion and 1(5.6%) immunoglubin 1(5.6%) and 2(11.1%) their mothers not remember if the neonate received treatment or not (Figure 3).

Male neonates were 53(53%) and females were 47(47%). Male to female ratio was 1.13:1 (Figure 4).

The majority of the studies neonates 75(75%) their birth weight was 2.5-3.5 kg, 15(15%) between 3.6 – 4.5 kg and 10(10%) less than 2.5 kg (Figure 5).

According to Table (1) 53(53%) of the studied neonates their blood group was O, 25(25%) A, 21(21%) B and 1(1%) AB. Compatibility found in 53(53%) of the neonates and incompatible in 47(47%).The Frequency in neonate with ABO incompatibility is 47%

Cord bilirubin ≥ 2 mg/dl reported in 52(52%) of the studied neonates and less than 2 in 48(48%) (Figure 6). It should be noted that cord bilirubin > 2- 3 mg/dl reported in 26(26%),> 3 – 4 mg/dl 17(17%) and > 4 – 5 mg/dl in 5(5%) (Table 2).

During sampling clinically jaundice neonates were 31(31%) and normal 69(69%) (Table 3).

The majority of neonates who were clinically jaundice (n=31) 15(48.4%) received management in terms of observation and follow up, 13(41.9%) phototherapy and 3(9.7%) exchange transfusion (Table 4).

The majority of the studied neonates 84(84%) were not clinically pale, and 16(16%) were clinically jaundice (Table 5).

(Figure 7) shows that Hb >= 12 mg/dl reported in 77(77%) of the studied neonates and < 12 mg/dl in 23(23%).

According to Table (6) sensitivity of cord bilirubin in determination of neonatal jaundice against clinical assessment was 93.75%, specificity 70.59%, positive predictive value was 60%, negative predictive value 96% and accuracy 78% (P value = 0.003 < 0.05 significant).

It is clear from Table (7) cord bilirubin above 3 mg/dl significantly associated with ABO incompatibility(P value < 0.05).

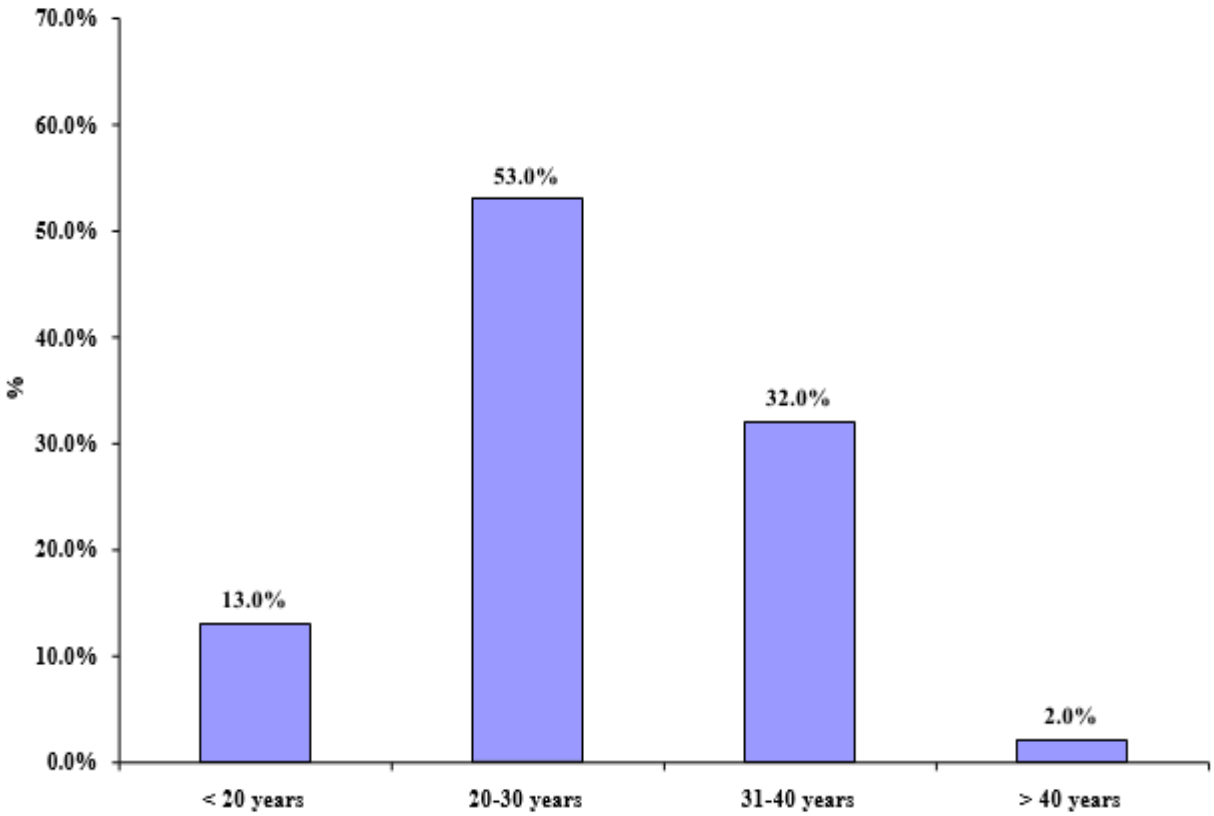

Figure (1) Distribution of the mothers of the studied neonates according to age group

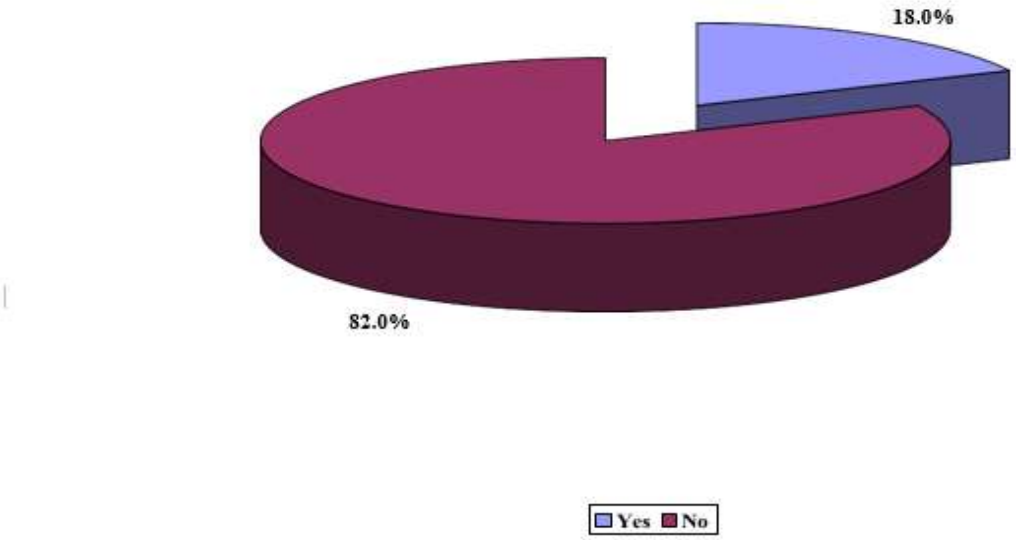

Figure (2) Distribution of the studied neonates according to history of jaundice in siblings

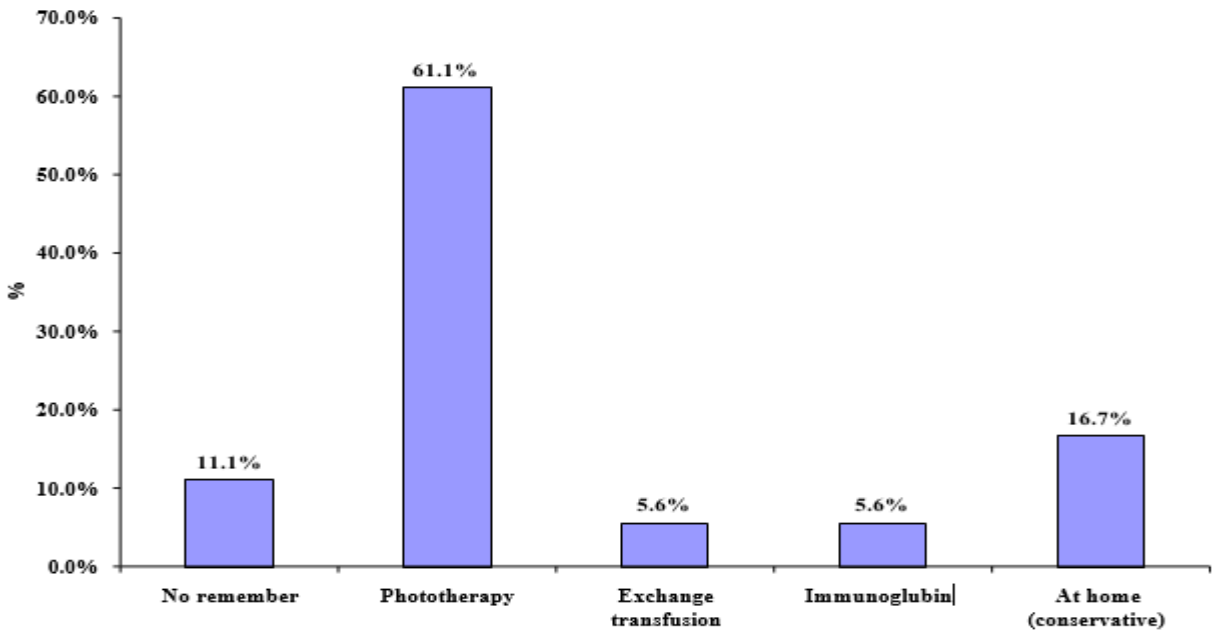

Figure (3) Distribution of the studied neonates according to treatment of jaundice in siblings (n=18)

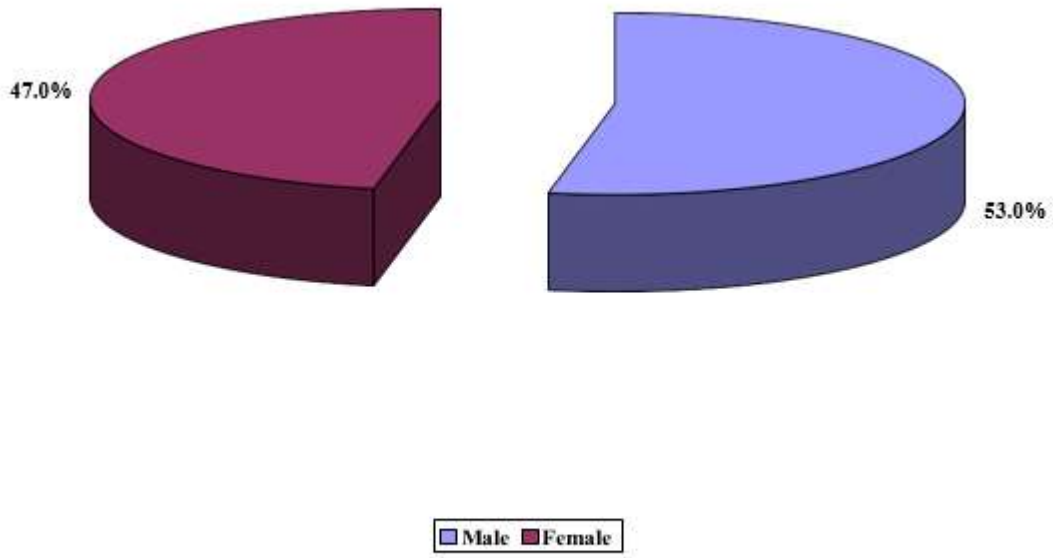

Figure (4) Distribution of the studied neonates according to sex

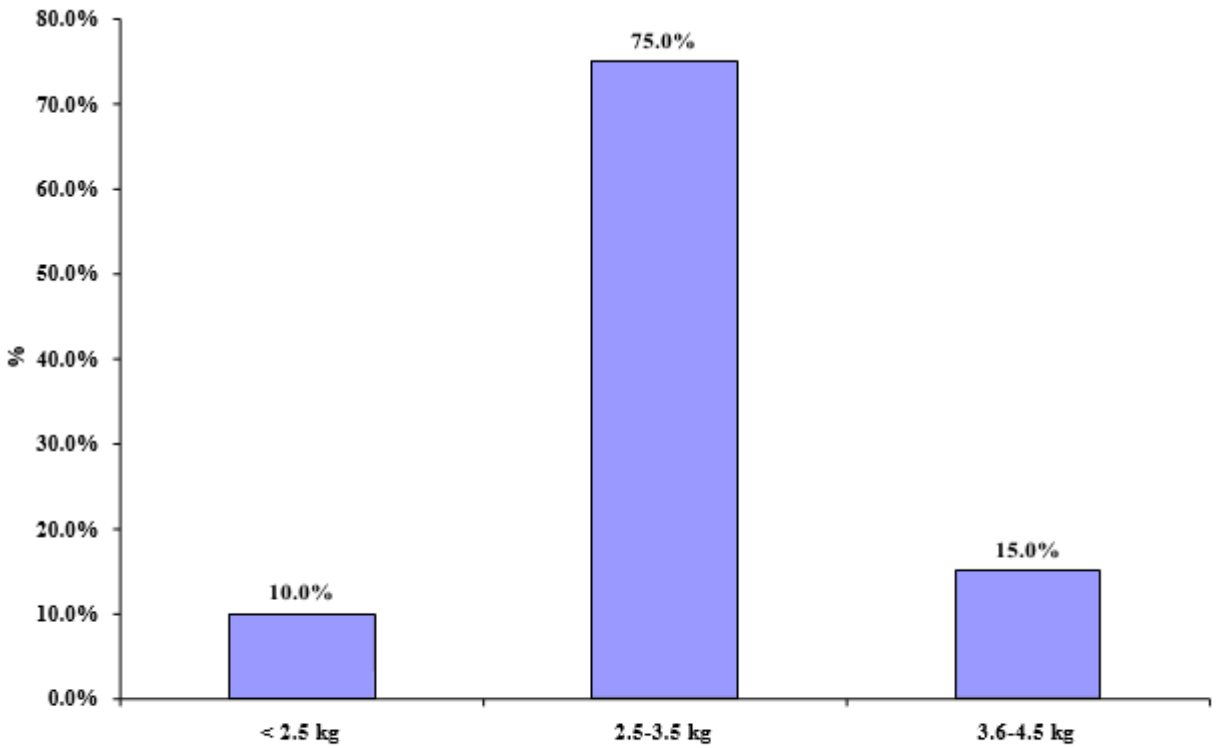

Figure (5) Distribution of the studied neonates according to weight at birth

Table 1: Distribution of the studied neonates according to blood group

Blood group	**N**	**%**
Group A	25	25.0
Group B	21	21.0
Group O	53	53.0
Group AB	1	1.0
Total	100	100.0

Table (2) Distribution of the studied neonates according to range of bilirubin level

Range	**N**	**%**
1-2 mg/dl	52	52.0
>2 - 3 mg/dl	26	26.0
>3-4 mg/dl	17	17.0
>4-5 mg/dl	5	5.0
Total	100	100

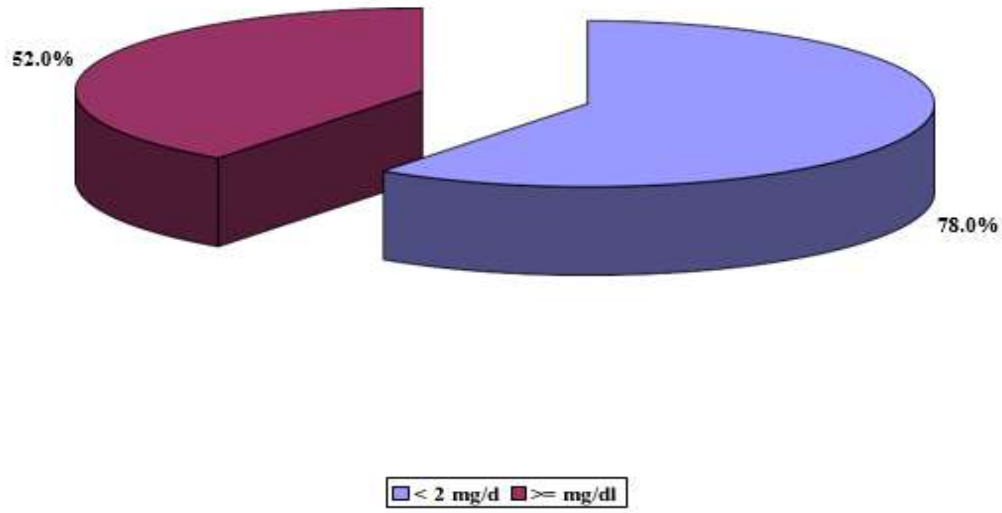

Figure (6) Distribution of the studied neonates according to cord bilirubin level range

Table 3 Distribution of the studied neonates according to clinically jaundice at sampling time:

Clinically jaundice during sampling	**N**	**%**
Clinically jaundice	31	31.0
Not jaundice	69	69.0
Total	100	100.0

Table (4) Distribution of the studied neonates according to treatment in case of clinically jaundice

Treatment	**N**	**%**
Observation and follow up	16	51.6
Phototherapy	14	45.2
Exchange transfusion	1	3.2
Total	31	100.0

Table (5) Distribution of the studied neonates according to pale presentation

Pale clinically	**N**	**%**
Not pale	84	84.0
Clinically pale	16	16.0
Total	100	100.0

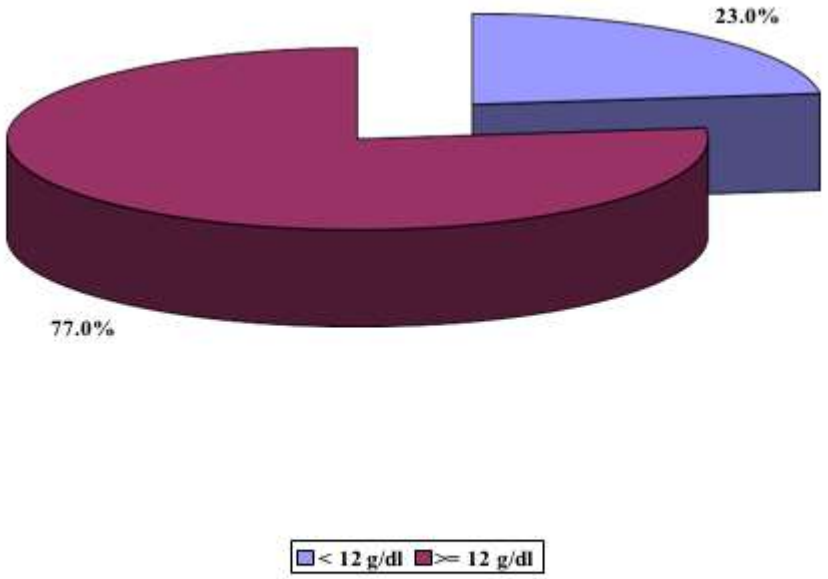

Figure (7) Distribution of the studied neonates according to Hb level

Table (6) Distribution of the studied neonates according to sensitivity and specificity of cord bilirubin in prediction of neonatal jaundice

Statistic	**Value**	**95% CI**
Sensitivity	93.75%	79.19% to 99.23%
Specificity	70.59 %	58.29% to 81.02%
Positive Predictive Value	60.00% (*)	50.66% to 68.66%
Negative Predictive Value	96.00 % (*)	86.15% to 98.93%
Accuracy	78.00% (*)	68.61% to 85.67%

P value = 0.0030

Table (7) Distribution of the studied neonates according to correlation between range of cord bilirubin and blood group compatibility

	Compatibility				
	Compatibility		Incompatibility		
Range	N	%	N	%	
1-2 mg/dl	41	77.4	11	23.4	
>2 - 3 mg/dl	12	22.6	14	29.8	P value 0.017
>3-4 mg/dl	0	0.0	17	36.2	
>4-5 mg/dl	0	0.0	5	10.6	
Total	53	100.0	47	100.0	

Discussion

In this study 100 neonates were selected to find out the correlation of cord bilirubin level in newborn with ABO incomaptibility compared with newborn without ABO incompatiblity. A cut-off value of neonatal hyperbilirubinemia in cord serum cord bilirubin level in this study is 2mg/dl, the number of jaundiced newborns undergoing phototherapy was significantly higher when these levels were higher than 2.0mg/dl.

Higher cord bilirubin levels among neonates who later became jaundiced compared to cord bilirubin levels in neonates without ABO incompatibility indicate that mechanisms of importance for the subsequent jaundice are already active in late fetal life.

In this study Compatibility was found in 53(53%) of the neonates and incompatibility in 47(47%) were cord bilirubin ≥ 2 mg/dl was reported in 52 (52%) of the studied neonates and less than 2 mg in 48 (48%). It should be noted that cord bilirubin > 2- 3 mg/dl was reported in 26 (26%), > 3 – 4 mg/dl in 17(17%) and > 4 – 5 mg/dl in 5 (5%). Our study was similar to a study in USA which showed that serum cord total bilirubin levels can define a subgroup of infants who are at a higher risk for developing significant hyperbilirubinemia and requiring phototherapy. Infants with cord bilirubin levels less than 2.0 mg/dL have only a 4 percent chance of developing hyperbilirubinemia and a 1.4 percent chance of needing phototherapy. However, if serum cord bilirubin levels are more than 2.0 mg/dL, the infant has a 25 percent chance of developing subsequent hyperbilirubinemia. With early discharge from the nursery which is a more common practice, this level can identify at an early age those infants who need closer follow-up. (29)

In our study Hb > = 12 mg/dl was reported in 77 (77%) of the studied neonates and <12 mg/dl in 23 (23%). Comparable to a study from USA which showed that maternal-fetal ABO incompatibility was a common

hematological problem affecting the newborns. In general, hemolysis is minimal and the clinical course is relatively benign (32). Another study in Nigeria showed that antenatal haemolysis in association with ABO incompatibility occurs very rarely. Two cases of hydrops fetalis in black infants caused by anti-B haemolysins are reported. The greater severity of ABO incompatibility in black African peoples may have important implications for antibody screening in this ethnic group. ABO incompatibility is the most common materno-fetal blood group incompatibility which, unlike rhesus disease, is usually a problem of the neonate rather than the fetus. Anemia was rare; the main clinical problem was jaundice. The incidence is about 2% of all births, but severe haemolytic disease occurs in only 0.03% of births (31).

In our study, during sampling, clinically jaundiced neonates were 31 (31%) and normal 69 (69%). Almost half of neonates who were clinically jaundiced (n=31) ie 16 (51.6%) received management in terms of observation and follow up, 14 (45.2%) phototherapy and 1 (3.2%) exchange transfusion. The majority of the studied neonates 84 (84%) were not clinically pale, and 16(16%) were clinically pale. Our study was similar to a study in India aimed to evaluate cord blood bilirubin and hemoglobin analysis in predicting pathological hyperbilirubinemia in newborn at risk of ABO incompatibility. Out of 191 babies, 25 (13%) did not develop any jaundice, 122 (64%) developed physiological jaundice and 44 (23%) had pathological jaundice. The mean cord bilirubin and cord hemoglobin values of newborns who did not develop jaundice were 1.35mg/dl and 15.3g/dl while the values among pathological jaundice were 3.15mg/dl and 14.97g/d4. (24) In USA a study of correlation of cord bilirubin levels with hyperbilirubinaemia in ABO incompatibility was done where 91 offspring of ABO incompatible pregnancies and 30 controls resulting from O-O pregnancies were tested to show whether cord bilirubin levels could use to predict the severity of hyperbilirubinemia in ABO incompatibility. Blood group, direct Coombs's test, and serum bilirubin estimations were carried out in cord blood with bilirubin estimations at 12, 24, 36 and 48 hours of life. All newborns in which the cord bilirubin was greater than 4 mg/100 ml (68 umol /l) developed severe hyperbilirubinemia (level > 16 mg/100ml (273 umol/l) at 12-36 hours) and required exchange transfusion. It was concluded that in ABO incompatibility infants with cord bilirubin level greater than 4 mg/100 ml represent a special 'high risk' category and should be placed in a centre where frequent re-evaluation and appropriate therapy are available. (23)

In our study sensitivity of cord bilirubin in determination of neonatal jaundice against clinical assessment was 93.75%, specificity 70.59%. Positive predictive value was 60%, negative predictive value 96% and accuracy 78% (P value = 0.003 < 0.05 significant). Our study was comparable to a study from Turkey that aimed to investigate the predictive value of umbilical cord blood bilirubin (CBBil) level for significant neonatal hyperbilirubinemia. Phototherapy treatment was needed in 14.7% of 95 patients. For recognition the newborns

at high risk for developing hyperbilirubinemia, using a CBBil cut-off level of 2.60 mg/dl, they found a positive predictive value of 41.18%, negative predictive value of 97.9% and sensitivity of 50%. Newborns with CBBil values below 2.6 mg/dl were at very low risk of developing hyperbilirubinemia and further need of phototherapy. Knowledge of low risk of hyperbilirubinemia in a newborn could encourage the physicians in the decision of early postnatal discharge. (27) A study done in Egypt aimed to study whether umbilical cord serum (UCS) bilirubin values could predict the risk of significant hyperbilirubinemia requiring treatment in newborns. A cut-off value of neonatal hyperbilirubinemia in cord blood was 2 mg/dl and the end point of the study was the need for treatment. The mean value for total bilirubin in cord blood was significantly higher among newborns whose bilirubin values required phototherapy. The specificity reached 94.2% with a negative predictive value (NPV) of 96.32%. At cut-off cord serum bilirubin level > 4 mg/dl, the specificity was 98.92% and the NPV was 99.1%. Cord blood serum bilirubin can be used as a useful screening test for predicting neonatal hyperbilirubinemia and allowing safe postnatal hospital discharge.

(26) Pradhan et al did an study in India aimed to verify whether the cord bilirubin levels predicted the development of pathological hyperbilirubinemia. The incidence of pathological hyperbilirubinemia in their study is 12.87%. The mean gestational age is 38.3 weeks. There was a significant association between cord blood total bilirubin levels and the development of pathological hyperbilirubinemia in newborns with a P-value of 0.000. A critical cord bilirubin level ≥ 2.50 mg/dl had sensitivity of 84.1%, specificity of 88.5%, positive predictive value of 98% and negative predictive value of 45.1% for predicting the risk of developing pathological jaundice .(25)

In our study the frequency of neonate with ABO incompatibility in Omdurman Maternity Hospital was 47% (table 1)

Conclusions

The results of our study confirm that measurement of umbilical cord serum bilirubin (UCS) level can be used as a screening tool for predicting the development of significant hyperbilirubinemia requiring interventional therapy. It could be concluded that 48% of the newborns who had greater than 2mg/dl of (UCS) bilirubin level in term and near term newborns indicated a 76.6 % that need phototherapy.

A 100% Negative Predictive Value in the present study suggests that in healthy term babies (without ABO incompatibility with Cord Blood Bilirubin < 2mg/dl) cord serum bilirubin can help to identify those newborns who are unlikely to require further evaluation and intervention.

Recommendations

• Cord blood serum bilirubin can be used as a useful screening test for predicting neonatal hyperbilirubinemia and allowing safe postnatal Hospital discharge.

• Early identification of at risk newborn for significant hyperbilirubinemia by using simple predictors.

• Babies with Cord Blood Bilirubin level ≥ 3mg/dl should be followed more frequently to reduce morbidity and mortality due to neonatal hyperbilirubinemia.

• More studies are needed in larger group of newborns and in a wider scale.

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