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ORIGINAL ARTICLE

Risk Factors and Outcome of Neonatal Hyperbilirubinemia: A Case Control Study in a Tertiary Level Paediatric Hospital

Sharmin Afroze[1], Ruma Parvin[2], Kamrunnahar[3], Razia Sultana[4], Shyla Rahman[5], Erfan Ahmed[6], Sheikh Farjana Sonia[7], Azmeri Sultana[8], Nobo Krishna Ghosh[9], Nargis Ara Begum[10], MA Mannan[11]

Abstract

Introduction: *Neonatal jaundice is one of the most common morbidities observed during the neonatal period. Several risk factors are responsible for this condition.*

Objective: *This study was aimed to determine the possible risk factors and immediate outcome for jaundice in newborns.*

Methods: *This case control study was performed over a period of 18 months (March 2019 -August 2020) in the Special Care Newborn Unit (SCANU) of Dr. M R Khan Shishu Hospital & Institute of Child Health (ICH). Risk factors for jaundice were evaluated by comparing cases with jaundice and controls having no jaundice.*

Results: *A total of 230 neonates with jaundice and 250 neonates having no jaundice were enrolled. Maternal age between 31-40 years, less than 4 antenatal visits, primi, presence of maternal diabetes, babies born via caesarian section, small for gestational age, prematurity and intra-uterine growth restriction were significantly associated with jaundice in neonates (p value < 0.05). Multi-variate analysis revealed, babies with mothers having <4 antenatal visits were found to have 13 times more risk of developing jaundice than their matched controls (p= 0.00, CI= 0.78-14.9). Mean duration of phototherapy was longer for babies having jaundice due to blood group incompatibilities (4.82 ± 1.94). Most of the patients (91%) were discharged to home.*

Conclusion: *Less than four antenatal visit is a significant risk factor for neonates to develop significant jaundice requiring treatment. Babies with blood group incompatibilities tend to require longer duration of phototherapy wherever most of the babies discharged to home with good recovery.*

Keywords: *Neonatal jaundice; risk factors; case-control, Bangladesh.*

1. Assistant Professor, Neonatology Unit, Dr. M R Khan Shishu Hospital & ICH.
2. Associate Professor, Neonatology Unit, Dr. M R Khan Shishu Hospital & ICH.
3. Assistant Registrar, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH.
4. Ex- Assistant Registrar, Neonatology Unit, Dr. M R Khan Shishu Hospital & ICH.
5. Ex-Registrar, Neonatology Unit, Dr. M R Khan Shishu Hospital & ICH.
6. Ex-Assistant Director, Dr. M R Khan Shishu Hospital & ICH.
7. Assistant Professor, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH.
8. Associate Professor, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH.
9. Professor & Head, Department of Paediatrics, Dr. M R Khan Shishu Hospital & ICH.
10. Senior Consultant, Department of Paediatrics & Neonatology, United Hospital Limited.
11. Professor, Department of Neonatology, Bangabandhu Sheikh Mujib Medical University.

Correspondence to: Dr Sharmin Afroze, Assistant Professor of Neonatology, Dr. MR Khan Shishu Hospital & Institute of Child Health, Dhaka, Bangladesh. Cell: +8801715579709, E-mail:mumu.sharmin8@gmail.com

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Introduction

Jaundice is one of the commonest clinical conditions in newborns.[1] It is the yellow discoloration of skin, sclera and mucous membrane which occurs due to accumulation of unconjugated, lipid soluble bilirubin pigment in the skin encountered during the neonatal period, especially in the first week of life.[2-3] The global incidence of neonatal jaundice varies with ethnicity and geography. Incidence is higher in East Asians and American Indians and lower in Africans.[4] The overall incidence of neonatal jaundice in our country is about 33% and reported by various Indian workers varies from 4.6% to 77%.[5]

About 60% of term and 80% of preterm infants develop jaundice during 1st week of life. In neonates it is due to increased break down of fetal erythrocytes which has shortened life span. Hepatic excretory capacity is also low in newborns. These occur more in premature babies than term infants.[6]

There are various causes of neonatal jaundice under the broad umbrella of physiological and pathological types. Physiological jaundice is the most abundant type of newborn hyperbilirubinemia and has no serious consequences.[7] It appears on 2nd/3rd day of life and peaks on 3^{rd}- 4^{th} day of life in term, 5^{th} -6^{th} days in preterm. Gradually disappears spontaneously. Baby is otherwise healthy. Sometimes exaggerated physiologic jaundice can occur where higher bilirubin levels occur earlier and last longer. Prematurity, severe weight loss, maternal diabetes and bruising in infants are the factors behind this condition.[8-9]

Neonates developing jaundice within first 24 hours is always pathological and commonest causes are: Rh incompatibility, ABO incompatibility and Hereditary spherocytosis. Indirect hyper-bilirubinemia which develops after 2 weeks are mostly due to infection, breast milk factors and hypothyroidism. Breast milk jaundice is found in 66% of breastfed babies from 3rd week of life and may persist up to 3 months. Another similar term is breast feeding jaundice that develops in the 1st week of life.[1]

Jaundice is mostly a benign condition. But in 10-15% it may cause significant jaundice and then interventions like phototherapy or exchange transfusion are required. Sometimes different drugs like phenobarbitone, intravenous immunoglobulins (IVIG), metalloporphyrins are also used. High bilirubin levels can be toxic for central nervous system development and may cause behavioral and neurological impairment (Neurotoxicity or Kernicterus) even in term newborns.[10-13]

Neonatal jaundice is an important cause of neonatal morbidity but if remain unaddressed, can lead to mortality and serious long-term sequel. Identification of risk factors is crucial in this regard for early intervention if required. There are several risk factors such as maternal age, weight, BMI, WBC, Hb, PLT, birth in the first pregnancy, numbers of pregnancies and prolonged delivery etc.[14] which are evident in many studies. But these are limited in number, especially in South East Asian countries. So, this study was planned to determine the possible risk factors for jaundice and its immediate outcome in newborns in a pediatric hospital of Asian region.

Materials and Methods

This case control study was performed over a period of 18 months from 1^{st} March 2019 to 31^{st} August 2020 in the Special Care Newborn Unit (SCANU) of Dr. M R Khan Shishu Hospital & Institute of Child Health (ICH), one of the largest Pediatric teaching hospitals of Dhaka city after taking approval from the Ethical Review Committee. All neonates admitted with jaundice and or those who developed jaundice during hospital stay; requiring treatment according to bilirubin nomogram by AAP guideline (American Academy of Pediatrics)[3] were enrolled as case. Gestational age matched neonates without jaundice were taken as controls. Cases, whose parents did not give consent were excluded from the study.

After taking consent from the parents, medical records were observed as well as maternal interview was taken to find out the risk factors. Neonates were examined for detecting visible risk factors such as signs of growth restriction, cephalhematoma, polycythemia etc. Maternal variables including age, occupation, parity, number of antenatal visits, Gestational diabetes mellitus (GDM), hypertension in pregnancy, maternal infection was evaluated in the study. Mode and place of delivery were also observed in both groups. Neonatal variables included gender, gestational age category (appropriate for gestation, small for gestation, large for gestation, intrauterine growth restriction), polycythemia, cephalhematoma, blood group incompatibilities.

Patients were investigated and managed according to departmental protocol. During treatment with

phototherapy or exchange transfusion; AAP guidelines for hyperbilirubinemia in newborn was used thoroughly.[3] Patients were followed up to hospital stay. Outcome of jaundiced neonates were observed with duration of phototherapy and duration of hospital stay according to significant causes of jaundice.

All data were recorded in a data collection form and then analyzed by using SPSS software version 21. Comparison of maternal and neonatal variables was done with univariate and multivariate logistic regression models. Frequency was calculated for qualitative variables, while the mean and standard deviation were calculated for quantitative variables. Chi-square test was used to examine qualitative data, and t-test for non-dependent samples was used to study quantitative data. P-value of < 0.05 was considered significant.

Results

A total of 230 cases and 250 controls were included during the study period. Cases were matched with their controls in terms of gestational age and birth weight (Table I). Mean maternal age was 26.78 ± 4.05 years among cases, which was slightly higher than controls. Other significant variables among case group were maternal age 31-40 years, primi, less than 4 antenatal visits, hospital delivery, born by caesarian section, infant of diabetic mothers (p value <0.05) as shown in Table II.

Table I
Baseline characteristics of neonates with and without jaundice

Variable	Case: Neonates with Jaundice n=230	Control: Neonates without Jaundice n=250	p value
Mean Gestational age (weeks)	36.96±2.55	37.02±2.34	0.81
Mean Birth weight (g)	2696.09±491.57	2656.48±474.85	0.37

Independent sample 't' test

Table II
Distribution of maternal and delivery variables among cases and controls

Variable	Neonates with Jaundice n=230 (%)	Neonates without Jaundice n=250 (%)	p value
Maternal age (years)			
Mean maternal age	26.78±4.05	25.64±3.48	0.004
<20	11(4.8)	46(18.4)	NS
21-30	180(78.2)	183(73.2)	0.03
31-40	39(17)	21(8.4)	0.03
>40	0	0	NS
Housewife	168(73)	158(63.2)	0.00
ANC <4	146(63.4)	116(46.4)	0.00
Primi mothers	140(61)	88(35.2)	0.00
Maternal diabetes	59(26)	25(10)	0.00
Maternal hypertension	4(1.7)	15(6)	NS
Maternal infection	7(3)	15(6)	NS
Mode of delivery			
NVD	53(23)	84(34)	NS
Assisted VD	9(4)	15(6)	NS
LSCS	168(73)	153(61)	0.004
Place of delivery			
Home	30(13)	61(24)	
Hospital	200(87)	189(76)	0.001

Independent sample 't' test and Chi square test

In Table III, neonatal variables were compared between case and control groups which revealed that small for gestational age (p=0.046) and IUGR (p=0.044) neonates developed jaundice more than their matched controls. After adjusting the confounders by multivariate logistic regression, it was found that neonates whose mothers had less than 4 antenatal visits, were at 13 times more risk of developing jaundice (p=0.00; CI=0.78-14.9) as shown in (Table IV).

Table III

Distribution of Neonatal variables with jaundice and their matched controls

Variable	Neonates with Jaundice n=230 (%)	Neonates without Jaundice n=250 (%)	p value
Gestational age category			
AGA	168 (73)	205 (82)	NS
SGA	33 (14.3)	18 (7)	0.046
LGA	6 (3)	15 (6)	NS
IUGR	23 (10)	12 (5)	0.044
Sex			
Male	152 (66)	164 (66)	NS
Female	78 (34)	86 (34.4)	
Polycythemia	3 (1.3)	0	
Cephalhematoma	4 (2)	0	
Sepsis	56 (24)	72 (29)	
Blood group incompatibility	23 (10)	0	NS

Chi square test

Table IV

Multivariate binary logistic regression analysis of risk factors for neonatal jaundice

Variable	β	OR	CI	p value
Maternal age 31-40 years	0.36	1.89	0.55-8.6	NS
Housewife mothers	0.01	3.37	0.00-4.21	
Primi	0.25	1.82	0.00-2.26	
ANC <4	1.89	13.2	0.78-14.9	0.00
LSCS	1.11	3.12	3.12-3.45	NS
Hospital delivery	0.02	1.82	0.00-2.36	
IDM	0.29	0.95	0.59-9.2	
SGA	3.05	4.11	0.00-5.12	
IUGR	0.73	1.22	0.003-1.31	

Regarding the different causes of neonatal jaundice among the admitted cases, exaggerated physiological jaundice was most common cause (33%) followed by infant of diabetic mothers (26%), sepsis (24%) and others as revealed in Fig.-1.

Mean serum bilirubin level was 16.66±4.6 mg/dl. Mean duration of phototherapy was 3.91±1.49 days. Exchange transfusion was required in 7 patients (3%).

In Table V outcome of the jaundiced neonates were observed according to their causes. Babies with blood group incompatibility required longer duration of phototherapy (4.82±1.94 days) and premature babies had longer hospital stay (6.64±1.56 days). Most of the babies were discharged to home (91%) and 9% left hospital against medical advice.

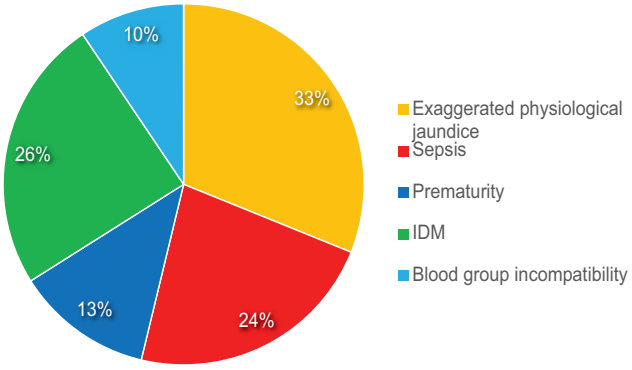

Fig.-1: *Causes of Jaundice among admitted cases*

Table V
Analysis of outcome among cases

Causes of Neonatal jaundice	Mean duration of phototherapy (days)	Mean duration of hospital stay (days)
Exaggerated Physiological Jaundice	3.66±1.00	5.03±1.45
Infant of diabetic mother	3.96±1.44	5.88±2.16
Sepsis	4.18±1.61	6.35±2.47
Prematurity	4.32±1.51	6.64±1.56
Blood group incompatibility	4.82±1.94	6.23±1.74

Discussion

In our study, different maternal, delivery and neonatal variables were compared among neonates with jaundice and no jaundice group. Mean maternal age was found 26.78±4.05 years. It co-relates with the study done by Zhang B et al. where they found peak maternal age 26 years was associated with neonatal jaundice.[15]

The study also observed that maternal age ranging between 31-40 years is a risk factor for developing jaundice. This finding matches with the results of Fetriyah UH et al. where they found mother aged between 20-35 years had neonates with jaundice but not pathological jaundice. Whereas maternal age either <20 or >35 years were at risk of developing pathological jaundice in newborns.[16] In our study, we found jaundice both in 21-30 years and 31-40 years group.

Neonates who were first born child of their parents and who were delivered by caesarian section, they developed jaundice more and this result is similar with other study findings.[14]It has also been reported in previous studies that, mode of delivery is related to jaundice and its severity.

Antenatal visits are planned in such a way so that pregnant women get an idea of caring about her and her upcoming child. Their medical conditions are addressed and treated accordingly so that it cannot affect their health. It is also important to inform mother about the important issues which may develop after birth of her baby. Neonatal jaundice is such a condition which parents need to know from antenatal period. Previous studies on NNJ in Nigeria reported a poor knowledge about its causes, management and complications among pregnant women.[17-22]Interestingly in our study, we found less than four antenatal visits as a significant risk factor for neonates to become jaundiced. The risk is 13 times more among cases which indicate the indirect impact of less visits and parental awareness which eventually lead to delay in admission for phototherapy.

Maternal diabetes is a well-known risk factor for neonatal jaundice and our study finding is also accordant with that (p= 0.00). In some studies, they have described that the incidence of neonatal jaundice in diabetic mothers is three times higher than that in the control group.[23] The increased risk in these babies is well explained and the possible factors evidenced are polycythemia, ineffective erythropoiesis with increased red blood cell turn over, immaturity of hepatic bilirubin conjugation and excretion.

Our study also revealed that, small for gestational age (p=0.046) and intrauterine growth restricted babies (p=0.044) develop jaundice more frequently than appropriate for gestational age and normal birth weight babies. This finding is also consistent with other research works.[24]

Causes of neonatal jaundice usually varies with race and ethnicity. In Asian countries like India and Bangladesh, blood group incompatibilities, breast feeding jaundice, jaundice due to prematurity and sepsis, G-6 PD deficiency are common causes. Although we got patients mostly due to exaggerated physiological jaundice, other causes are not negligible.[25-26]

Regarding the outcome, we found that babies with blood group incompatibilities required longer duration of phototherapy. Study done by Bhat YR also concluded from their study that neonates with hemolysis required phototherapy significantly earlier and for longer than neonates without hemolysis (P<0.001).[27]

Despite a good number of cases with significant results, this study has some limitations. Mothers having hypothyroidism were not included in the study, which is an important risk factor for developing jaundice in newborn. Moreover, in premature babies with jaundice, it was found that they stayed hospital for a longer period. It may be due to completion of treatment or resolution of their complications related to prematurity. These confounders were not excluded and were not analyzed as well.

Conclusion

Less than four antenatal visit is a significant risk factor for developing neonatal jaundice. Babies with blood group incompatibilities tend to require longer duration of phototherapy wherever most of the babies discharged to home with good recovery.

Recommendations

- Early identification and timely screening of neonates having risk factors is essential to decrease the burden as well as severity of jaundice in newborn.
- Attention to be given to improve the rate of antenatal visit of pregnant mothers as indirectly it is delaying the admission of jaundiced babies due to parental ignorance.
- Counseling strategy can be improved in jaundiced neonates as those having blood group incompatibilities and who are premature, tend to require longer duration of phototherapy and hospitalization respectively. This will increase parental understanding of the condition.

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