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Original Article

Assessment of Various Maternal Risk Factors and Treatment Approaches for Neonatal Jaundice in a Tertiary Care Hospital

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ABSTRACT

Background: The study objectives were to evaluate the neonatal jaundice treatment approach and identify various risk factors associated with the occurrence of neonatal jaundice. **Materials and Methods:** A prospective study was carried out for 6 months at St. Philomena's Hospital. Researchers reviewed patients` medication charts and collected the data for further analysis. Patients` medication charts also were monitored for the occurrence of any adverse drug reactions (ADRs) and drug-drug interactions (DDIs). **Results:** A total of 100 babies met inclusion criteria. The majority of babies were male (56%). Sixteen neonates (16%) were born with low birth weight, 11% of all neonates were preterm, and 42% of babies had O +ve blood group. Maternal-related risk factors analysis showed that 58% of women were between 26-35 years, 44% were overweight, 53% of women were in their first gravida, and 52% of mothers were delivered by C-Section. Overall, 100 (82.6%), 11 (9.1%), 6 (5%), 3 (2.5%), 1 (0.8%) neonates received phototherapy, ursodeoxycholic acid (UCDA), phenobarbital, exchange transfusion, and intravenous immunoglobulins respectively. We detected 15 ADRs and 14 DDIs associated with the management of neonatal jaundice. Phototherapy-induced ADR (46.6%) and interaction between UCDA-sucralfate (35.7%) were the most common identified treatment-related issues. **Conclusion:** Neonatal and maternal risk factors may involve in the development of neonatal jaundice. Phototherapy remained the most desirable therapeutic approach. Although the neonatal treatment approach is safe, a review of prescribed medications can give insight into the appropriate usage of medications among this vulnerable cohort.

Keywords: Neonatal jaundice, Treatment approach, Risk factors, Adverse drug reaction, Drug-drug interactions.

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INTRODUCTION

Neonatal jaundice refers to the yellow coloration of the skin and the sclera of newborn babies, which results from a high level of bilirubin in the circulation (hyperbilirubinemia) and an accumulation of bilirubin in the skin and mucous membranes. Neonatal hyperbilirubinemia is a common clinical problem that accounted for approximately 8% to 11% of neonates, particularly in the first week of neonatal life. This medical condition usually resolves within 3–5 days without significant complications if there would not be any other comorbidities such as hemolysis, sepsis, birth trauma, or prematurity.[1-2] However, epidemiological study suggests that newborns can develop severe neonatal jaundice (SNJ), which lead to a significantly high rate of morbidity and mortality.[3] In addition, SNJ is associated with the substantial cause of long-term neurocognitive sequelae, cerebral palsy, non-syndromic auditory neuropathy, deafness, and learning difficulties.[4-5] High bilirubin level is toxic for central nervous system development and may cause behavioral and neurological impairment (Neurotoxicity or Kernicterus) even in term newborns. Kernicterus is the yellow staining of the brain which is observed in the pathological examination due to deposition of bilirubin, particularly in a part of the brain known as the globus pallidus (a part of the 'deep grey matter of the brain).[6-7]

Certain predisposing factors like birth weight, gestational age, premature rupture of membranes, and maternal infectious diseases or other illnesses during pregnancy are related to the occurrence of neonatal jaundice. However, the main causes of increased bilirubin mostly are race, genetic polymorphisms, inherited and acquired defects e.g. spherocytosis, Gilbert's syndrome.[8] Clinical recognition and assessment of jaundice can be difficult, particularly in newborn babies with darker skin. Once jaundice is recognized, there is uncertainty about when to treat and how to treat it. The treatment options available for jaundice include phototherapy, exchange transfusion, ursodeoxycholic acid, phenobarbital, and intravenous immunoglobulins (IVIG).[9] In young babies, unconjugated bilirubin can penetrate the blood-brain barrier, it is potentially toxic to neural tissue, causing short-term and long-term neurological dysfunction. Therefore, severe jaundice is considered a life-threatening problem in newborn babies, which is important to assess its therapeutic approach and predisposing risk factors. Hence we conducted a study of assessment of various maternal risk factors and treatment approaches for neonatal jaundice in a tertiary care hospital with the aim to evaluate the neonatal jaundice treatment approach and also to identify various risk factors associated with the occurrence of neonatal jaundice.

MATERIALS AND METHODS

A prospective hospital-based observational study was conducted for six months in a pediatric ward of St. Philomena's Hospital, an academic tertiary care hospital located in Bangalore, India. Ethical approval was obtained from the Institutional Review Board of the St. Philomena's Hospital (Reference number: PH/IRB/2020-14) before commencing the study.

Inclusion Criteria

All neonates (both preterm and term) with hyperbilirubinemia who were diagnosed with neonatal jaundice and admitted to the pediatric ward were included. Also, all neonates who were not in-born but were referred

from outside to a pediatric ward at the study hospital were included in this study. Informed consent was obtained from parents/guardians of the study subjects.

Exclusion Criteria

Neonates whose parents/guardians refused or were unable to give valid consent and those cases with mortality within 24 hr of birth were excluded from the study. Moreover, neonates with congenital hepatic disorders were excluded.

Evaluation of Treatment Approach of Neonatal Jaundice

To achieve study objectives, researchers attended the pediatric ward daily, and the study was carried out by evaluating the medical records of neonates. All data including demographic details (gender, gestational age, and birth weight), admission, and discharge dates were recorded. Information about prescribed medications for the management of neonatal jaundice in the pediatric ward, including indication, dose, frequency and route of administration, and dosage form were collected and documented in the appropriate designed data collection form. The clinical progress of the neonates was monitored by reviewing physicians` and nurses` progress notes. All these data were documented until discharge from the hospital.

Identifying Drug-Drug Interactions Associated with Neonatal Jaundice Management

Drug-drug interactions (DDIs) associated with neonatal jaundice management were identified by using Lexicomp® drug interaction. According to Lexicomp®, DDIs are classified into five risk rating categories; "A" (no known interaction) which means still no data have revealed an interaction between the specified drugs; "B" in which no action is required to manage such an interaction; "C" where drug interaction required close monitoring to identify potential adverse outcome; "D" indicates interaction is associated with a high risk for occurrence of adverse outcome and "X" where drug combination is contraindicated, and it must be avoided. DDIs with risk rating categories of D and X have the major severity rating, and these DDIs are clinically significant, and such combinations either should be avoided, or a safer alternative should be considered.

Identifying Adverse Drug Reactions Associated with Neonatal Jaundice Management

Prescribed medications for the management of neonatal jaundice were reviewed to identify any related adverse drug reaction (ADR). ADRs were defined according to the World Health Organization which states ADR is "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modifications of physiological function".[10]

Statistical Analysis

The collected data were analyzed using descriptive statistics, and results are presented in terms of number and percentage and in-terms of mean ± standard deviation.

RESULTS

Clinical Characteristics of Newborns

During the study period, a total of 409 babies were delivered, out of which 100 babies were diagnosed with neonatal jaundice, met study criteria, and were included in the study. Table 1 shows the clinical characteristics of newborns and potential predisposing factors related to the occurrence of neonatal jaundice. In our study, out of 100 babies, 56 (56%) were male and 44 (44%) were female. 13 Among 100 babies, 73 (73%) babies weighed between 2.6 to 3.5 Kg, followed by 10 (10%) babies were between 3.6 to 4.5 Kg, and 1 (1%) baby weighed more than 4.5 Kg. Sixteen (16%) babies were born with a birth weight lower than 2.5 Kg. We found that 11% of all neonates were preterm. Blood group analysis of neonates showed that 42 (42%) babies were O +ve, followed by 27 (27%) babies A +ve, and 2 (2%) babies B –ve. Among 100 babies, 94 (94%) babies had no comorbidities and out of the remaining six babies, one had hypertension, one suffered from Transitory Tachypnea of New Born (TTNB), one had Congenital Heart Disease (CHD), one with hypothyroidism, one developed lung infection and one baby suffered from Respiratory Syncytial Virus (RSV).

Diagnosis of Neonatal Jaundice

Diagnosis of neonatal jaundice was confirmed by using serum bilirubin level. Seventy -four (74%) babies were found to have total bilirubin levels between 4.01 and 12 mg/dL, followed by 23 (23%) babies between 12.01 to 20 mg/dL. In addition, 50 (50%) babies had indirect bilirubin levels between 3.01-9.00 mg/dL (Table 2).

Table 1: Clinical characteristics of newborns.

Total number of newborns	N = 100, n (%)
Gender	
Male	56 (56)
Female	44 (44)
Birth weight distribution	
≤2.5	16 (16)
2.6-3.5	73 (73)
3.6-4.5	10 (10)
>4.5	1 (1)
Gestational age	
Pre-term	11 (11)
Full-term	89 (89)
Blood group	
A +ve	27 (27)
B +ve	22 (22)
B –ve	2 (2)
O +ve	42 (42)
O –ve	3 (3)
AB +ve	4 (4)
Comorbidities	
Hypertension	1 (1)
Transient tachypnea of the newborn	1 (1)
Congenital heart failure	1 (1)
Hypothyroidism	1 (1)
Lung infection	1 (1)
Respiratory Syncytial Virus	1 (1)
No comorbidity	94 (94)

Table 2: Serum bilirubin characteristics of newborns.

Total bilirubin levels (mg/dl)	N = 100, n (%)
≤ 4.0	2 (2)
4.01-12	74 (74)
12.01-20	23 (23)
≥ 20.01	1 (1)
Direct bilirubin levels (mg/dl)	
≤0.1	1 (1)
0.11-0.5	58 (58)
0.51-0.9	38 (38)
≥0.91	3 (3)
Indirect bilirubin levels (mg/dl)	
≤ 3.0	2 (2)
3.01-9.00	50 (50)
9.01-15.00	43 (43)
≥15.01	5 (5)

Maternal Characteristics of Newborns

In Table 3, we presented maternal-related characteristics of study newborns that could predispose the occurrence of neonatal jaundice. Fifty-eight (58%), 38 (38%), and 4 (4%) women were between 26 to 35 years, 15 to 25 years, and 36 to 40 years, respectively. The maternal body mass index (BMI) investigation demonstrated that 44 mothers (44%) were overweight, and 36 (36%) mothers were obese. Analysis of maternal comorbidities showed that 17 (17%) mothers were known cases of hypothyroidism, followed by 14 (14%) mothers who had gestational diabetes mellitus. Also, 5 (5%) mothers had high blood pressure (hypertension).

Evaluation of Treatment Approach of Neonatal Jaundice

Medication charts of neonates were reviewed to evaluate the treatment approach prescribed for the management of neonatal jaundice. Overall, 100 (82.6%), 11 (9.1%), 6 (5%), 3 (2.5%), 1 (0.8%) neonates received phototherapy, ursodeoxycholic acid (UCDA), phenobarbital, exchange transfusion, and IVIG, respectively (Table 4).

Identified Adverse Drug Reactions and Drug-Drug Interactions Associated with Neonatal Jaundice Management

Newborns' medication charts were reviewed to detect the occurrence of any ADR and DDI related to the management of neonatal jaundice. Overall we detected 15 ADRs associated with the management of neonatal jaundice (Table 5). Medical action to manage identified ADRs also were documented. We identified ADRs associated with the phototherapy including hyperthermia (3, 20%), interruption of breastfeeding (2, 13.3%), erythematous rashes (2, 13.3%), and bronze baby (1, 6.7%). Also, we identified 14 DDIs related to neonatal jaundice drug therapy (Table 6).

DISCUSSION

A prospective observational study on assessment of various maternal risk factors and treatment approaches for neonatal jaundice in a tertiary care hospital was carried out for six months in St. Philomena's Hospital. The majority of study patients were male. This finding was similar to the study carried out by Carolyn G. Scrafford and Khadije Sadat Naji.[11-12] A baby`s birth weight has been extensively studied for predicting its

Table 3: Maternal characteristics of newborns.

Maternal age group	N = 100, n (%)
15-25	38 (38%)
26-35	58 (58%)
36-40	4 (4%)
Maternal BMI	
Under weight	2 (2%)
Normal weight	18 (18%)
Over weight	44 (44%)
Obesity	36 (36%)
Maternal blood group	
A +ve	23 (23%)
A –ve	-
B +ve	18 (18%)
B –ve	3 (3%)
O +ve	45 (45%)
O –ve	5 (5%)
AB +ve	5 (5%)
AB –ve	1 (1%)
Number of gravida	
1	53 (53%)
2	33 (33%)
3	11 (11%)
4	2 (2%)
5	1 (1%)
Type of delivery	
Normal	48 (48%)
C – Section	52 (52%)
Maternal comorbidities	
Gestational DM	14 (14%)
Hypertension	5 (5%)
Hypothyroidism	17 (17%)
Anemia	3 (3%)
Asthma	3 (3%)
Epilepsy	1 (1%)
No comorbidity	57 (57%)

BMI, body mass index; DM, diabetes mellitus.

Table 4: Treatment approach for management of neonatal jaundice.

Total number of interventions	N = 121, n (%)
Phototherapy	
Single Sided Phototherapy	61 (50.4%)
Double Sided Phototherapy	37 (30.6%)
Triple Sided Phototherapy	2 (1.6%)
Exchange transfusion	3 (2.5%)
Intravenous immune globulin	1 (0.8%)
Ursodeoxycholic acid	11 (9.1%)
Phenobarbital	6 (5%)

Table 5: Identified adverse drug reactions related to management of neonatal jaundice.

Offending medications	Adverse drug reaction	N (%)	Medical action for management of ADR
Phototherapy	Hyperthermia	3 (20)	Discontinuation phototherapy
	Interruption of breastfeeding	2 (13.3)	Discontinuation phototherapy
	Erythematous rashes	2 (13.3)	Discontinuation phototherapy
	Bronze baby syndrome	1 (6.7)	Discontinuation phototherapy
Ursodeoxycholic acid	Diarrhea	4 (26.6)	IV fluid replacement
Exchange transfusion	Thrombocytopenia	1 (6.7)	Discontinuation phototherapy
	Hyperkalemia	1 (6.7)	Calcium polystyrene sulphonate
Phenobarbital	Bradycardia	1 (6.7)	Fast IV fluid administration

ADR, adverse drug reaction; IV, intravenous.

Table 6: Identified drug-drug interactions related to management of neonatal jaundice.

Drug-drug interaction	N (%)	Description	Risk rating and patient management
Ursodeoxycholic Acid-Sucralfate	5 (35.7%)	Sucralfate may decrease the serum concentration of ursodeoxycholic acid.	D: Consider therapy modification Moderate
Phenobarbital-Metronidazole	2 (14.3%)	Metronidazole may enhance the adverse/toxic effect of phenobarbital.	C: Monitor therapy Moderate
Phenobarbital-Clarithromycin	3 (21.4%)	Phenobarbital may increase serum concentrations of the active metabolite(s) of clarithromycin	D: Consider therapy modification Moderate
Phenobarbital-Methylprednisolone	1 (7.2%)	Phenobarbital may decrease the serum concentration of methylprednisolone.	D: Consider therapy modification Moderate
Phenobarbital-Acetaminophen	3 (21.4%)	Phenobarbital may increase the metabolism of acetaminophen.	C: Monitor therapy Moderate

association with subsequent diseases in babies.[13] Overall, 16% of babies were born with low birth weight (LBW) (≤ 2.5).[14] A study showed that approximately 60% of all term newborns develop some degree of neonatal jaundice, while this rate in babies with LBW increases up to 80%. In other words, jaundice is more prevalent, even severe, and prolonged in LBW babies. Also, LBW babies are at risk of bilirubin-induced neurologic dysfunction (BIND).[15] Infants born before 37 weeks of gestational age are considered premature or pre-term. Babies with an appropriate gestational age have lower rates of problems and death. We observed that 11% of all neonates were preterm by which inherently are at greater risk for developing BIND, which, if not treated in a timely or appropriate manner, can result in chronic neurologic sequelae.[16] ABO and Rh blood group incompatibility may lead to neonatal jaundice. The majority of our study subjects had O +ve blood group. A study demonstrated that O-B heterospecific neonates appear to be at higher risk than their O-A counterparts.[17] The total bilirubin level is the total amount of direct and indirect bilirubin present in the body. Indirect bilirubin (unconjugated) increases typically in infants with neonatal jaundice. Doctors are concerned if the bilirubin levels are more than 20-25 mg/dl (deciliter) and will start treatment to prevent the bilirubin from getting to this level.[18] Maternal-related characteristics of study newborns were analyzed. There is a link between maternal age and a baby's health and survival rate. We found that majority of maternal age was above 30 years. A study has also suggested that maternal age ≥30 years can be linked to increased risk for neonatal jaundice.[19] The next maternal factor which was considered was BMI, as the mother's weight before and during pregnancy affects the baby's health condition. Our finding was found to be comparable with the study carried out by Suat Ozdek, *et al*. which demonstrated that mothers who are overweight may be at risk of neonatal jaundice.[20]

More than half of women (53%) were in their first gravida. This finding was consistent with the study carried out by Reza Tavakolizadeh *et al*. to evaluate maternal risk factors that contribute to the hyperbilirubinemia among newborns.[21] There are few studies that establish the relationship between the type of delivery and the health of the Baby. The majority of mothers were delivered by C-Section. There is a possible link between the anesthetic technique used in C-section delivery and with influence on neonatal jaundice occurrence.[22] The presence of comorbidities can affect the baby`s health. An analysis of maternal comorbidities revealed that 14% of mothers had gestational diabetes mellitus which is among the most common maternal risk factors for the occurrence of neonatal jaundice.[23]

Phototherapy (82.6%) was found to be the most common and effective treatment approach to reduce bilirubin levels. Moreover, phototherapy might also reduce the risk of the development of chronic bilirubin encephalopathy.[24] UCDA (9.1%) was another treatment approach prescribed among our study subjects. UCDA aids the emulsification of bile in the biliary ducts, therefore it increases bile flow and elimination into the gut, consequently assistances to reduce total bilirubin levels. This medication is beneficial among infants with combined unconjugated and conjugated hyperbilirubinemia yet in addition to phototherapy.[25] Six (5%) study cases received phenobarbital which rises the conjugation and excretion of bilirubin levels. However, currently no longer is recommended due to its clinically significant adverse effects. However, phenobarbital and UCDA are unproven medications, since there is little evidence that these drugs are useful in the management of neonatal jaundice.[26] Although exchange transfusion is a costly and time-consuming treatment approach, it is a possibly life-saving emergency practice for removing extra bilirubin rapidly, it is used among infants with BIND.[27]

Although phototherapy is a safe treatment approach, few ADRs associated with the phototherapy were identified. We observed one case of a bronze baby syndrome associated with phototherapy. A bronze baby syndrome is a reversible skin condition presented by mild dark, grayish-brown discoloration of the skin, serum, and urine resulting from the deposition of bronze-colored pigments.[28] This syndrome resolved after discontinuation of phototherapy. Interaction between UCDA and sucralfate was the most common identified DDI. Sucralfate may decrease the serum concentration of UCDA. Therefore, consider administration of UCDA two hours before sucralfate.[29]

CONCLUSION

Our study showed that various neonatal and maternal risk factors may involve in the development of jaundice in neonates. These factors include LBW, gestational age, blood group, maternal BMI, number of gravida, and type of delivery. Phototherapy remained the most common therapeutic approach for the management of neonatal jaundice. Physicians should avoid prescription of medications that there is little evidence regarding their beneficial therapeutic effect in the management of neonatal jaundice as these medications further can induce drug-related problems like ADRs and DDIs. Although the neonatal treatment approach is considered to be safe, a review of prescribed medications can give insight into the appropriate usage of medications among this vulnerable cohort.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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