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ORIGINAL ARTICLE

Etiology of Unconjugated Hyperbilirubinemia in Admitted Term Neonates

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ABSTRACT

Objective: To find the frequency of different causes of unconjugated hyperbilirubinemia in admitted term neonates**.**

Study Design: Cross-sectional study.

Place and Duration of Study: The study was conducted at the neonatal ward of the Children's Hospital and the Institute of Child Health, Lahore from 20 August 2018 to 19 February 2019.

Material and Methods: The criteria of inclusion was neonates from birth to twenty eight days of life having unconjugated hyperbilirubinemia. Consent was taken and all the data was written on pre designed proforma.

Results: A total of 200 patients were enrolled. There were 140 (70%) male and 60 (30%) female neonates in the study group. The mean serum bilirubin was 9.96 ± 2.47 mg/dl. Seventy seven (38.5%) neonates had hemolytic jaundice, 26% had ABO incompatibility while 12.5% had Rh incompatibility. Twenty four (12%) had non-hemolytic jaundice due to breast feeding while breast milk jaundice was diagnosed in 99 (49.5%) neonates.

Conclusion: Most common cause was hemolytic jaundice among neonates. By identifying different causes of neonatal hyperbilirubinemia, we can reduce disease burden in our community by formulating measures for their early detection, prevention and management of severe neonatal jaundice.

Key Words: *Unconjugated hyperbilirubinemia, Hemolytic jaundice, Non-Hemolytic jaundice*

INTRODUCTION

Accumulation of unconjugated bilirubin in the skin and mucous membrane of neonate leads to yellow discoloration of skin and sclera, resulting in neonatal jaundice. In this disease, the level of bilirubin in the circulation is raised, a condition known as hyperbilirubinaemia,[1] which is defined as a total serum bilirubin level above 5 mg/dl. Bilirubin is the by product of heme degradation. At physiologic pH, bilirubin is insoluble in plasma and requires protein binding, and after conjugation in the liver it is excreted in bile. Unconjugated bilirubin is fat soluble and is potentially neurotoxic. Reticuloendothelial system breaks down the heme leading to production of bilirubin and when bilirubin production is more than its elimination, hyperbilirubinemia develops, primarily by conjugation. Equilibrium between the processes of production of bilirubin and elimination is affected by the various genetic, racial and environmental factors.[2] In the first week of life, approximately

60% of term and 80% of preterm babies develop jaundice[2] and about 10% of breastfed babies are still jaundiced at 1 month of age. There is no underlying disease in most babies with jaundice termed 'physiological jaundice'. However, in neonates, there are also pathological causes of jaundice. Such pathological jaundice may co-exist with physiological jaundice.[1] A local study showed that in neonates, neonatal jaundice was among the third cause of requiring admissions and accounted for 13.5%.[3] Another study revealed the overall detected rate of hyperbilirubinemia (bilirubin >5 mg/dl) among 1690 newborns of 39.7/1000 live births (95% CI 29.3–47.6). The minimum detected incidence of pathological hyperbilirubinemia (>15 mg/dl) in this study was 16.5 per 1000 live births.[4] A study in UK and Ireland showed an incidence of severe hyperbilirubinemia of 7.1 per 100,000 live births (95% CI 5.8 to 8.6)[5]. In preterm infants, hyperbilirubinemia is more prevalent and severe, and its course is more protracted than in full term neonates.[6] The etiological and contributory factors to neonatal jaundice vary according to ethnic and geographical differences. In developing countries, social practices and negative traditions have a contributory role in causing jaundice. Severe neonatal jaundice can therefore be said to have modifiable risk factors.[7-9] In neonatal jaundice, etiology include: a) – Rh incompatibility b) - ABO incompatibility. In one study out of 200 neonates presented with jaundice, prevalence of ABO-incompatibility was found to be 22.5% followed by Rh-incompatibility 12.5%.[9] c) - Breast feeding jaundice[8,10] and d) Breast milk jaundice. The incidence of breastfeeding jaundice was 13% and that of breast milk jaundice was 2% in one study[10]. All healthy newborns are at potential risk, if their jaundice is unmonitored or managed inappropriately. Early detection and treatment of neonatal hyperbilirubinemia is important in the prevention of bilirubin-induced encephalopathy.[11] Because of the risk for serious neurological complications related to the toxicity of bilirubin, management of hyperbilirubinemia remains a challenge for neonatal medicine.[12,13] This study sets out to determine the frequency of different causes of unconjugated hyperbilirubinemia in term neonates admitted in a tertiary care hospital. Regarding frequency of different causes of unconjugated hyperbilirubinemia Western literature is available and our data on this topic is scanty. So by identifying different causes of neonatal hyperbilirubinemia, we can reduce disease burden in our community by formulating measures for their early detection, prevention and management of severe neonatal jaundice.

MATERIAL AND METHODS

It was a cross-sectional study held at the neonatal unit of the Children's Hospital and the Institute of Child Health, Lahore from 20 August 2018 to 19 February 2019. The criteria of inclusion was neonates of both gender from birth to twenty eight days of life and all term neonates having unconjugated hyperbilirubinemia (as per operational definition). Neonates initially having unconjugated hyperbilirubinemia, during stay but developed conjugated hyperbilirubinemia (direct bilirubin >2 mg/dl) and patients who left against medical advice or expired during data collection procedure were excluded. Total 200 patients fulfilling inclusion criteria admitted through neonatal emergency and outpatient department were enrolled. Consent was taken.After history, physical examination and relevant lab investigations (complete blood count (CBC), total and direct serum bilirubin, reticulocytes count (RC),urine and blood culture, direct combs' test, c-reactive protein (CRP), blood group & Rh type of neonate and mother to define cause of hyperbilirubinemia), data was collected on a proforma. Outcome variables such as Rh incompatibility, ABO incompatibility, and breast feeding jaundice were recorded as per operational definitions. All the data was written on pre designed proforma and entered into SPSS version 20. Numerical variables; age, weight and bilirubin level have been presented by mean ±SD. Frequencies and percentages have been used for categorical variables i-e gender, cause of jaundice i.e Rh incompatibility, ABO incompatibility and breast feeding jaundice. For age, weight, gender, and bilirubin level to address effect modifiers, data has been stratified. Post-stratification chi-square test has been applied taking p value ≤0.05 as significant.

Operational Definitions

1. **Term Neonates:** Neonates having gestational age between 37 to 42 weeks according to dating scan.

2. **Unconjugated Hyperbilirubinemia:** Neonates having yellowish discoloration of skin and sclera with serum total bilirubin above 5mg/dl and direct fraction within normal limits (0.1-0.4 mg/dl). It was assessed at the time of inclusion into study.
3. **Causes of Jaundice:**
    a. **Hemolytic jaundice:** jaundiced neonates having positive direct coomb's test (qualitative test. clumping of antibody bound red cells give positive result).
        i. **Rh Incompatibility:** mother having Rh^{-ve} and baby Rh^{+ve} blood group determined by agglutination method using anti D serum. If clotting seen at 5 minutes then it was Rh positive.
        ii. **ABO Incompatibility:** mother having O blood group and neonate either A or B (agglutination method using anti A and anti B sera). Clumping with A or B antisera is group A and B respectively. Group O shows no clumping at 5 minutes.
    b. **Non Hemolytic Jaundice:** Jaundiced neonates having negative direct coomb's test (qualitative test. no clumping of red cells give negative result)
        i. Breast Milk Jaundice: It is a type of neonatal jaundice associated with breastfeeding that is characterized by indirect hyperbilirubinemia in an otherwise healthy breastfed newborn that develops after the first 4-7 days of life, persists longer than physiologic jaundice, and has no other identifiable cause.
        ii. Breast Feeding Jaundice: It manifests in the first 3 days of life, peaks by 5-15 days of life, disappears by week 3 of life, and is caused by insufficient production or intake of breast milk.

RESULTS

The age ranged from 1 day to 28 days with a mean of 4.17 ± 3.10 days. There were 140 (70%) male and 60 (30%) female neonates in the study group as shown in fig:1. The weight of the neonates ranged from 2.10 kg to 2.95 kg with a mean of 2.59 ±.19 Kg. Bilirubin ranged from 6.65 mg/dl to 15.42 mg/dl with a mean of 9.96 ± 2.47 mg/dl. Seventy seven (38.5%) neonates had hemolytic jaundice, 26% had ABO incompatibility while 12.5% had Rh incompatibility. Twenty four (12%) had non-hemolytic jaundice due to breast feeding while breast milk jaundice was diagnosed in 99 (49.5%) neonates as shown in fig:2.When the data was stratified, the frequency of Rh (15.0% vs. 6.5% vs. 0.0%; p=0.190), ABO (32.0% vs. 10.9% vs. 0.0%; p=0.005) incompatibility and breast feeding jaundice (16.3% vs. 0.0% vs. 0.0%; p=0.007) were highest between days 1-5 of life while the frequency of breast milk jaundice was highest between 11-20 days of life followed by 6-10 days and 1-5 days of life (36.7% vs. 82.6% vs. 100%; p=0.000) as shown in fig:3.Rh incompatibility was associated with higher serum bilirubin level in the range of 12.51-15.42 mg/dl (30.8%; p=0.001) while ABO incompatibility was associated with moderate levels of serum bilirubin in the range of 9.51-12.50 mg/dl (38.1%; p=0.021). Breast feeding jaundice was associated with mildly raised serum bilirubin level in the range of 6.65-9.50 mg/dl (22.4%; p=0.000).

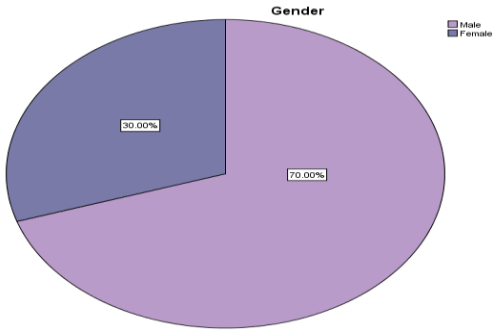

Fig 1: Gender Distribution

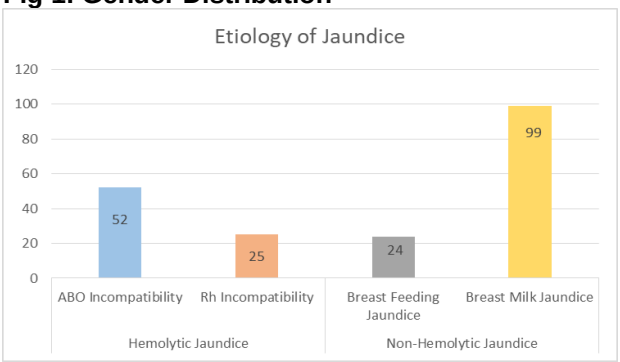

Fig 2: Etiology of Jaundice

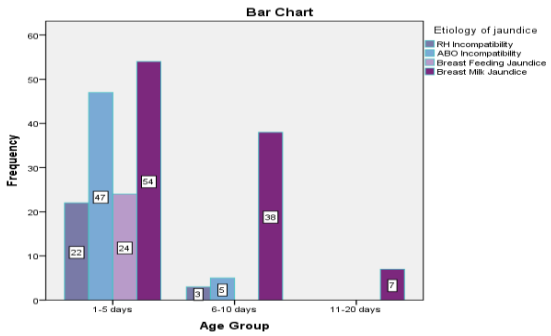

Fig 3: Age Groups and Etiology of Jaundice (n=200)

DISCUSSION

In neonates, jaundice which is one of the most common conditions, medical attention is required. In developing countries, where the vast majority of births occur at home, information about the incidence of neonatal jaundice is not available. Most of the data is from tertiary care intensive care unit with no population denominator. Regarding frequency of different causes of unconjugated hyperbilirubinemia Western literature is available and our data on this topic is scanty.[7-9] In this study, mean age of the patients was 4.17 ± 3.10 days. A similar mean age of 4.5 ± 2.3 days was reported by Rasul at el. (2009) at Bangladesh among neonates with hyperbilirubinemia.[14] Irshad et al. (2011) observed the mean age to be 3.56 ± 2.56 days in neonates presenting with jaundice at Lady Reading Hospital, Peshawar Pakistan.[9] There were 140 (70%) male and 60 (30%) female neonates in the study group. A similar male predominance (70% vs. 30%) was also reported by Irshad et al. in 2011.[9] A somewhat lower male predominance has been reported by Taheri et al. in 2014 (56.4% vs. 43.6%), Najib et al. in 2013 (58.2% vs. 41.8%), Heydarian et al. in 2010 (63.6% vs. 36.4%) in Irani population and Bulbul et al. in 2014 (57.6% vs. 42.6%) in Turkish Population.[15-18] The mean weight was 2.59 ±.19 kg in the present study while mean weight of 3.3 ± 0.4 Kg has been reported in Korean Population by Yoon et al. in 2007.[10] Taheri et al. (2014) reported much lower mean weight of 1950 ± 40 g among Irani neonates with hyperbilirubinemia.[15] Mean serum bilirubin was 9.96 ± 2.47 mg/dl in the present study. A similar mean serum bilirubin level of 9.91 ± 1.90 mg/dl has been reported in Turkish population by Eroglu et al. in 2015.[19] Heydarian et al. in 2010 (28.7 ± 9.2 mg/dl), Bulbul et al. in 2014 (19.26 ± 4.80 mg/dl) reported a much higher mean serum bilirubin level.[17,18] Seventy seven (38.5%) neonates had hemolytic jaundice. 26% had ABO incompatibility while 12.5% had Rh incompatibility. A similar frequency of hemolytic jaundice (35%) has been reported previously by Irshad et al. in 2011. They also observed similar frequency of ABO incompatibility (22.5%) and Rh incompatibility (12.5%) in neonates with hyperbilirubinemia.[9] Somewhat similar frequency of ABO incompatibility (24.5%) and Rh incompatibility (8.5%) has also been reported by Taheri et al. in 2014.[15] A similar frequency of Rh incompatibility (16.1%) has also been reported by Heydarian et al. in 2010. However, they observed much higher frequency of 38.1% for ABO incompatibility.[17] Bulbul et al. in Turkey observed quite different frequencies of ABO incompatibility (21.9%) and Rh incompatibility (5.3%) among neonates with hyperbilirubinemia.[18] Much lower frequencies of 11.3% and 5.4% were reported by Rasul et al. in Bangladesh for ABO and Rh incompatibility respectively.[14] Twenty four (12%) neonates had non-hemolytic jaundice due to breastfeeding. Our results are in accordance with Yoon et al. where frequency of breastfeeding jaundice is reported to be 13%,[10] while in another study it was 35%.[15] When the data is stratified, the frequency of Rh (15.0% vs. 6.5% vs. 0.0%; p=0.190), ABO (32.0% vs. 10.9% vs. 0.0%; p=0.005) incompatibility and breast feeding jaundice (16.3% vs. 0.0% vs. 0.0%; p=0.007) were highest between days 1-5 of life while the frequency of breast milk jaundice was highest between 11-20 days of life followed by 6-10 days and 1-5 days of life (36.7% vs. 82.6% vs. 100%; p=0.000). Our results are in line with the previously published local study by Irshad et al. who also observed similar age difference in the frequency of ABO and Rh incompatibility.[9] Thus in the present study majority of neonates had hemolytic jaundice with most of patients had ABO incompatibility. So in future practice special attention should be given to anticipate, timely recognize and treat these causes to decrease the morbidity and mortality associated with neonatal hyperbilirubinemia. A very important observation made in the present study was association of

different types of jaundice with different neonatal age and serum bilirubin level which can further help in the clinical and laboratory diagnosis.

CONCLUSION

Most common cause was hemolytic jaundice among neonates. By identifying different causes of neonatal hyperbilirubinemia, we can reduce disease burden in our community by formulating measures for their early detection, prevention and management of severe neonatal jaundice

Conflict of interest: Nil

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