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Original Article

Neonatology Section

# Severe Neonatal Hyperbilirubinaemia in the First 24 Hours of Life: Tertiary Center Experience in Oman

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## ABSTRACT

**Introduction:** Neonatal jaundice is a common condition observed in approximately two-thirds of all newborns in the first postnatal week of life. In most cases it is benign and no treatment is required. However, in severe cases, pathological jaundice can lead to acute bilirubin encephalopathy and kernicterus.

**Aim:** To characterise the main predisposing factors as well as the treatment modalities of babies with significant neonatal jaundice presenting in the first 24 hours of life.

**Materials and Methods:** We conducted a retrospective, observational study of all babies admitted to the neonatal unit at the Royal hospital in Oman in the period between 1st January 2014 and 31st December 2014 and treated for significant hyperbilirubinaemia presenting in the first 24 hours of life. Patients were selected from the Royal Hospital neonatal admission registry. A total of 125 patients records were analysed for the sake of the study.

**Results:** The mean gestational age was 34 weeks and the mean birth weight was 2070 grams. Male to female ratio was 1:1.2. About 30 (45%) of the males and 15 (26%) of the females had Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency. Blood group of the babies was A 42 (33.6%), B 34 (27.2%), AB 4 (3.2%) and O 45 (36%). About 4.8% were Rhesus negative. In all 27 (21.6%) of the babies tested positive for Direct Coombs Test. The maximum Total Serum Bilirubin (TSB) in the first 24 hours of life was 130±65 µmol/L and the maximum TSB anytime during the admission was 215±80 µmol/L. About 88 (70%) of the babies received standard phototherapy and 37 (30%) received intensive phototherapy. Intravenous Immunoglobulin (IVIG) in addition to phototherapy was administered in 21 (17%) of the babies. None of the babies required exchange transfusion.

**Conclusion:** It was observed that the most common predisposing factors for significant neonatal jaundice presenting in the first 24 hours of life were prematurity, G6PD deficiency and isoimmune hemolytic disease. Phototherapy and IVIG was the treatment modalities used.

**Keywords:** Encephalopathy, Glucose 6 phosphate dehydrogenase deficiency, Neonatal jaundice, Rh isoimmunisation

## INTRODUCTION

Neonatal jaundice is a common condition encountered by paediatricians worldwide. It occurs in approximately two-thirds of all newborns in the first postnatal week [1]. It is regarded as physiological and caused by immature liver enzymes, increased breakdown of haeme, increased enterohepatic circulation of bilirubin and inadequate oral intake in the immediate postnatal life. In most cases it is benign and no treatment is required. However, in severe cases, pathological jaundice can lead to acute bilirubin encephalopathy and kernicterus [2,3]. Features of kernicterus include choreoathetotic cerebral palsy, hearing loss, paralysis of upward gaze, dental dysplasia and intellectual deficits [4,5].

If jaundice becomes clinically evident in the first 24 hours of life, it is regarded as pathologic [6-9]. Because of the possible risk of severe hyperbilirubinaemia, serum bilirubin measurement and, if indicated, further evaluation for possible haemolytic disease should be done in this age group [4,10,11]. Risk factors for severe hyperbilirubinaemia and neurotoxicity include prematurity, isoimmune haemolytic anaemia, G6PD deficiency, sepsis, acidosis and perinatal asphyxia [12,13].One of the correctable correlates of kernicterus is the failure to check bilirubin level in an infant with jaundice noted in the first 24 hours of life [14].

The aim of this study was to identify the characteristics as well as the possible risk factors for severe unconjugated hyperbilirubinaemia presenting in the first 24 hours of life.

## MATERIALS AND METHODS

This is a retrospective observational study. All newborn babies

admitted to the Department of Neonatology at the Royal Hospital in Oman in the period between 1st January 2014 and 31st December 2014 and treated for significant unconjugated hyperbilirubinaemia presenting in the first 24 hours of life were included in this study. Babies with congenital anomalies and those who received in-utero blood transfusion were excluded from the study. We expected that the number of patients admitted over one year period with the criteria mentioned above would reasonably represent the characteristics of the population in the study. A total sample of 125 patient's records was analysed for the study purpose.

The Department of Neonatology at the Royal Hospital is a tertiary center with a delivery rate of around 8500 per year. Babies who present with clinical jaundice will have a blood test done for Complete Blood Count (CBC), reticulocyte count, TSB, direct bilirubin, G6PD status and Direct Coomb's Test (DCT).

For treatment of neonatal jaundice, NICE (National Institute for Health and Care Excellence) guidelines and charts on neonatal jaundice management were followed [9]. Standard available treatments for hyperbilirubinaemia include standard and intensive phototherapy, Intravenous Immunoglobulin (IVIG) and exchange transfusion. Intensive phototherapy implies the use of high levels of irradiance in the 430 to 490 nm band delivered to as much of the infant's surface area as possible.

Patients were selected from the Royal Hospital Neonatal Admission Registry. The hospital electronic information system (Al-Shifa 3+) was the source of detailed demographic and clinical data of the babies and their mothers. Institutional Research Ethical Committee approval was obtained for this study. Data collected was not made available to any person or organisation other than the study team and regulatory authorities.

## STATISTICAL ANALYSIS

Data were analysed using SPSS version 20.0 (SPSS Inc., Chicago, USA). Student's 't'-test was used for continuous variables and Chi-square test for categorical variables. To analyse the risk factors for significant unconjugated hyperbilirubinaemia presenting in the first 24 hours of life, multivariate regression was done using clinically significant variables. The p-value <0.05 was considered as statistically significant.

## RESULTS

During the study period, there were 8530 deliveries at the Royal Hospital. A total of 1069 babies were admitted to the neonatal unit with different conditions. Out of these, 127 babies presented with significant unconjugated hyperbilirubinaemia in the first 24 hours of life and required treatment. Two babies were excluded from the study because they received inutero blood transfusion in the antenatal period for Rhesus isoimmunisation and foetal anaemia. A total of 125 patient's records were analysed for the sake of the study.

The demographic data of these babies are shown in [Table/Fig-1]. The mean gestational age was 34 weeks and the mean birth weight was 2070 gm. Total 17 (14%) babies had a family history of neonatal jaundice in a previous sibling. Male to female ratio was 1:1.2.

Total 30 (45%) of the male babies and 15 (26%) of the female babies were G6PD deficient. DCT was positive in 27 (21.6%)

| Characteristics | Value |
|---|---|
| GA in weeks, mean±SD | 34±4 |
| BW in grams, mean±SD | 2070±870 |
| **Sex** | |
| Male, n (%) | 67 (53.6%) |
| Female, n (%) | 58 (46.4%) |
| **Family History of Neonatal Jaundice** | |
| Yes, n (%) | 17 (13.6%) |
| No, n (%) | 108 (86.4%) |

**[Table/Fig-1]:** Demographic data of babies with significant hyperbilirubinaemia presenting in the first 24 hours of life.

| Clinical data | Value | |
|---|---|---|
| G6PD* status, n (%) | Males (n=67) | Females (n=58) |
| Normal | 35 (52) | 43 (74) |
| Deficient | 30 (45) | 15 (26) |
| Unknown | 2(3) | 0 |
| **Newborn Blood Group, n* (%)** | | |
| A | 42 (33.6) | |
| B | 34 (27.2) | |
| AB | 4 (3.2) | |
| O | 45 (36) | |
| **Direct Coomb's Test (DCT), n* (%)** | | |
| Positive | 27 (21.6) | |
| Negative | 98 (78.4) | |
| Maximum TSB in the first 24 hours of life (µmol/L), mean±SD | 130±65 | |
| Maximum TSB‡ anytime during admission (µmol/L), mean±SD | 215±80 | |
| Hemoglobin at admission (g/dL), mean±SD | 16.2±2.7 | |
| Minimum hemoglobin anytime during admission (g/dL), mean±SD | 14.0±3.3 | |
| Reticulocyte percentage, mean±SD | 6.9±4.3 | |
| Urea level at admission (mmol/L), mean±SD | 4.6±2.3 | |
| Creatinine level at admission (µmol/dL), mean±SD | 70.6±15.0 | |
| Serum Sodium level at admission (mmol/L), mean±SD | 137±5 | |

**[Table/Fig-2]:** Clinical data of babies with significant Hyperbilirubinaemia presenting in the first 24 hours of life.
G6PD quantitative assay, deficient is defined as cut off value <2.1U/g Hb
‡TSB: Total Serum Bilirubin; *n=125

| Clinical Data | n* (%) |
|---|---|
| **Maternal Blood Group** | |
| A | 33 (26.4) |
| B | 16 (12.8) |
| AB | 3 (2.4) |
| O | 73 (58.4) |
| **Maternal Rh Status** | |
| Positive | 108 (86.4) |
| Negative | 17 (13.6) |
| **Indirect Coomb's Test (ICT)** | |
| Positive | 7 (5.6) |
| Negative | 117 (93.6) |
| Unknown | 1 (0.8) |

**[Table/Fig-3]:** Maternal clinical data.
*n=125

| Mode of Treatment | n (%) |
|---|---|
| Standard Phototherapy | 88 (70) |
| Intensive Phototherapy | 37 (30) |
| Intravenous Immunoglobulin (IVIG) + Phototherapy | 21 (17) |
| Exchange Transfusions | 0 |

**[Table/Fig-4]:** Mode of treatment for babies with significant Hyperbilirubinaemia presenting in the first 24 hours of life.

babies [Table/Fig-2]. The mean maximum TSB in the first 24 hours of life was 130 µmol/L. The mean maximum TSB anytime later on during the admission was 215 µmol/L. The range of minimum haemoglobin level during admission was 6.5-19.9 g/dL and the range of reticulocyte percentage was 0.5-31.9%.

[Table/Fig-3] shows the maternal clinical data. Total 73 (58.4%) mothers were blood group O and 17 (13.6%) mothers were Rhesus negative. Indirect Coomb's Test (ICT) was positive in 7 (5.6%) mothers during pregnancy.

Total 88 (70%) babies received standard phototherapy and 37 (30%) received intensive phototherapy. IVIG in addition to phototherapy was administered in 21 (17%) babies. None of the babies required exchange transfusion [Table/Fig-4] and none of the babies had any signs of acute bilirubin encephalopathy during the admission period.

## DISCUSSION

Our study showed that prematurity, isoimmune haemolytic disease, and G6PD deficiency were the most common predisposing factors for significant neonatal jaundice in the first 24 hours of life. Left untreated, it can lead to a devastating neurological outcome [15]. To the best of our knowledge, this is the first study from our region investigating the characteristics of these babies in this age group.

We would like to emphasise here that our study group included only the babies presenting with significant jaundice in the first 24 hours of life and that was the aim of the study. Neonatal jaundice observed after the first 24 hours of life might have different characteristics.

All gestational age groups were included in the current study. Prematurity was the main predisposing factor in our patients. Hyperbilirubinaemia in preterm infants is related to increased bilirubin production and/or concurrent delayed bilirubin elimination. A higher risk of mortality, longterm neurologic injury, and risk of Bilirubin Induced Neurologic Dysfunction (BIND) have been more evident in preterm as compared with term neonates [16]. Alizadeh Taheri P et al., in a retrospective study of 94 neonates underwent exchange transfusion for severe hyperbilirubinaemia, found that 63% of them were preterm [17]. Late preterm infants also have greater prevalence, severity and duration of neonatal jaundice [15].

About 58.4% of the mothers were of blood group O and 13.6% were Rhesus negative. It is known that ABO and Rhesus mismatch are major predisposing factors for significant neonatal jaundice in the first 24 hours of life. In a retrospective review of 1,251 pregnant Omani women who attended Sultan Qaboos University Hospital between June 2011 and June 2013, Al-Dughaishi T et al., showed that 52.2% of them were blood group O and the prevalence of Rhesus negative pregnant women was 7.3% [18]. In comparison, the prevalence of maternal blood group O in our study was 58.4%. Moreover, the prevalence of Rhesus negative mothers in our study was 13.6% which is almost double that reported in the above study and 21.6% of the babies tested positive for DCT, indicating that Rhesus incompatibility is a predisposing factor for severe neonatal hyperbilirubinaemia presenting in the first 24 hours of life. In Rhesus negative women who have given birth to a Rhesus positive infant, anti-D, given within 72 hours after child birth, reduces the risk of RhD alloimmunisation [19].

In G6PD deficiency, neonatal jaundice is usually evident by 1-4 days of age and varies widely in their frequency and severity in different populations [20,21]. In our study, 45% of the male babies and 26% of the female babies had G6PD deficiency. It is known that the prevalence of G6PD deficiency is high in Oman. However, our figures outweigh those reported for the prevalence of G6PD deficiency in the general population. Al-Riyami A et al., in a survey of genetic blood disorders among Omani children under five years of age reported that 25% of the males and 10% of the females were G6PD deficient [22]. The higher prevalence of G6PD deficiency in our study indicates that it is a significant predisposing factor for neonatal jaundice in the first 24 hours of life. Neonatal jaundice due to G6PD deficiency might not be severe in the first 24 hours of life. However, if it is unrecognised and untreated especially with early discharge from hospital after birth, can lead to a devastating neurological outcome.

Nair PA et al., in a case series from Oman reported 14 cases of kernicterus (10 males and 4 females) during a time period of six years, 71% of them had G6PD deficiency [23].They presented at 3-15 days of age. None of the babies in our study had any neurological sequelae during the admission. This is partly because the study included only babies with significant jaundice presenting in the first 24 hours of life, hence being investigated and treated promptly before discharge from the hospital.

To standardise the care of jaundiced babies in our unit, NICE (National Institute for Health and Care Excellence) guidelines for diagnosing and treating jaundice in newborn babies are followed [10]. Nearly, 70% of the babies in our study received standard phototherapy and 30% received intensive phototherapy.

IVIG in addition to phototherapy was given to 17% of the babies in our study. In isoimmune hemolytic disease, administration of IVIG (0.5-1 g/kg over 2 hours) is recommended if the serum bilirubin level is rising despite intensive phototherapy or if it is just below the exchange level [4]. IVIG has been shown to reduce the need for exchange transfusions in Rh and ABO haemolytic disease [24].

None of the babies in our study required exchange transfusion and none of them had any signs of acute bilirubin encephalopathy or kernicterus during admission. One of the reasons could be the use of IVIG in those babies with evidence of isoimmune hemolytic disease. In a prospective cohort study, Arun Babu T et al., showed that the occurrence of significant jaundice within two days of life was associated with abnormal developmental quotient at six months of age in term babies [25].

Although, significant neonatal jaundice noticed in the first 24 hours of life is regarded as a major risk factor for severe pathologic jaundice with its potential consequences, we find paucity in the literature addressing and characterising the disease in this particular risky period of brain susceptibility to bilirubin neurotoxicity. Hence, we believe that this study adds a significant understanding of the risk factors as well as the short term outcome of the disease, at least in our population.

## LIMITATION

Being a retrospective chart review study and single centered, it might not reflect the true picture of severe neonatal hyperbilirubinaemia for the whole country. The other limitation is that no control group was used for comparison.

## CONCLUSION

Severe neonatal hyperbilirubinaemia presenting on the first day of life is regarded pathologic and carries a high risk of adverse neurological outcome if not recognized and treated promptly. Prematurity, isoimmune hemolytic disease, and G6PD deficiency were the most common predisposing factors. Phototherapy and IVIG were the main treatment modalities. Further, multicenter studies are recommended in order to understand the burden of the disease and to standardise diagnosis and treatment strategies.

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