Original Research Article

Etiological study of jaundice in neonates

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ABSTRACT

Background: Jaundice is the commonest abnormal finding with an incidence of about 60% in term babies and 80% in preterm babies. It is the commonest cause of admission to hospitals in the newborn period. In preterm babies, the percentage is exceedingly high due to their physiological handicaps and other hazards of prematurity like Asphyxia, septicemia, respiratory and circulatory Insufficiency. Non-physiological or pathological jaundice is also known to occur in (8-9)% of newborns. Its timely detection and optimal management are crucial to prevent brain damage and subsequent neuro-motor retardation. Aims of this study to find out the etiology of jaundice in neonates, admitted in neonates unit attached to SMS medical college Jaipur.

Method: This Observational study was conducted in Neonatal Intensive Care Unit (NICU) and Post Natal Ward attached to SMS medical college Jaipur, after approval from the hospital ethical committee, over a period of 12 months (October 2011 to September 2012). Study was carried on 500 neonates presenting clinically with neonatal hyperbilirubinemia.

Result: The onset of jaundice was seen maximum between live hour 24-72 hours (n=290, 58% cases), followed by live hour 72 hours-14 days (n=160, 32%). At more than 2 weeks there was only 3 case (0.6%). The etiological factors in the causation of jaundice in the decreasing order of frequency were exaggerated physiological jaundice accounts for (28%), ABO-incompatibility (24.4%), Rh-incompatibility (13.8%), Idiopathic (10.4%), cephalhematoma (10.2%), septicemia (6%), intrauterine infections (4%), BMJ (1.8%), Galactocemia (0.8%) and G6PD Deficiency (0.6%) respectively.

Conclusion: Hyperbilirubinemia is more severe in newborns, therefore precautionary measure should be adopted by both parents, and clinicians to diagnose and treat the diseases properly.

Keyword: ABO incompatibility, Exaggerated physiological jaundice, Kernicterus, Neonatal jaundice, Prematurity, Rh-incompatibility

INTRODUCTION

Jaundice refers to the yellowish discoloration of the skin and sclera of newborn babies that result from accumulation of bilirubin in the skin and mucus membranes. Clinically it becomes apparent when the serum bilirubin exceeds 7 mg/dl in neonates and >2 mg/dl in adults (PORTER AND DENNIS, 2002).1

Jaundice is an important problem in the first week of life. It is a cause of concern for the physician and a source of anxiety for the parents. In most cases, it is benign and no intervention is required. Prolonged jaundice and jaundice in the first 24 hours merit investigation as they increase the likelihood of an underlying pathological cause.
Approximately 5-10 % of them have clinically significant hyperbilirubinemia mandating the use of phototherapy. The percentage is quite high in preterm babies, due to their physiological abnormalities and other hazards of prematurity like asphyxia, sepsis, respiratory and circulatory insufficiency. Non physiological or pathological jaundice is also known to occur in 8-9% of newborns with approximately 4% after 72 hours of age. The pathological factors which aggravate physiological jaundice by adding to the bilirubin load and risk of bilirubin encephalopathy are maternal factors such as Rh incompatibility or ABO incompatibility, and neonatal factors such as prematurity, birth trauma or infection, polycythemia, hypothyroidism, galactosemia, breast milk jaundice, and genetic syndromes such as Crigler-Najjar and Gilbert's syndrome and administration of drugs such as cephalosporins. Its timely detection and optimal management are crucial to prevent brain damage and subsequent neuro-motor retardation such as hearing loss, athetosis and rarely intellectual deficits.

Dermal staining with bilirubin (Cephalo-caudal progression), first reported by Kramer et al. in 1969 has been widely used to visually assess the severity of neonatal jaundice in clinical practice. However, Moyer et al. in 2000 have reported marked discrepancies between visual assessment by health worker and actual bilirubin levels.

“Kernicterus” refers to the neurologic consequences of the deposition of unconjugated bilirubin in brain tissue. Subsequent damage and scarring of the basal ganglia and brainstem nuclei may occur.

Risk is high in developing country like India where most of the deliveries occur at home.

However, no etiological factors are detected despite a battery of investigations. These are labelled as idiopathic”. The number of such cases however would differ from Centre to centre depending on the work up and the prevalence of known genetic factor such as G6PD deficiency, Rh and ABO incompatibility etc.

This study is being conducted to ascertain the various etiologies of Neonatal jaundice in our establishment and the need for early therapeutic interventions.

METHODS

This Observational study was conducted in Neonatal Intensive Care Unit (NICU) and Post Natal Ward in department of Pediatric Neonatal units of SPMCHI, Mahila and Gangour Hospital, SMS Medical College The, Jaipur, Rajasthan. Duration of study (October 2011 to September 2012). 500 neonates with clinically identified Neonatal jaundice will be included in this study. Children more More than 28 days of age and Neonates admitted in paediatric surgical unit and parents who refused to sign the consent were excluded from the study.

Jaundice was ascertained by clinical methods and confirmed by biochemical methods. Pre-test proforma was filled to record detailed history, clinical findings and investigations in each baby with hyperbilirubinemia. Each baby delivered at hospital has been carefully observed from birth onwards in day light, for appearance of jaundice and in the babies with dark complexion, digital pressure over forehead has been used to detect the icterus. In addition, babies coming from peripheries have been examined thoroughly clinically and detailed investigations have been done to detect the cause of jaundice. Other investigations have been done depending upon the clinical presentation and the report of initial investigations.

Collected data has been analysed statistically. Median were calculated for continuous variables, frequencies and proportions for categorical variables.

RESULTS

Age and sex distribution

According to the gestational age, Pre-term babies contributes to 255 cases (51%) and Term babies constitutes 245 cases (49%) (Figure1). There was not much difference between the preterm and the term babies.

There was male sex preponderance in the study with 260 cases (52%) of male and 240 cases (48%) (Figure2), which is consistent with various other studies.

![Figure 1: Gestational age.](image)

**Table 1: Day of onset of jaundice.**

| Day of onset       | No. of patients | Percentage |
|--------------------|-----------------|------------|
| (<24 hrs.)         | 47              | 9.40%      |
| (24-72 hrs.)       | 290             | 58%        |
| (72hrs-14 days)    | 160             | 32%        |
| (>2 weeks)         | 3               | 0.6%       |
| Total              | 500             | 100%       |
From the Table 1, the day of onset of jaundice was maximum at between (24 - 72 hours) postnatal age which consists of 290 cases (58 %) followed by (72 hours to 14 days) (n=160, 32%) and gradually tapering off with the increasing age. In this study, all the different etiologies were much higher in the preterm delivered babies except in physiological jaundice.

Preterm babies contribute to 51% of the cases and in term babies 49% cases. ABO, Rh incompatibility and septicemia were more common in the preterm babies.

Table 3: weight wise distribution of etiological factors of neonatal jaundice.

| Cause                                | Weight (Kgs.) |
|--------------------------------------|---------------|
| Exaggerated Physiological Jaundice   | <1.5          |
| (28%)                                | 1.5 - 2.49    |
| Rh incompatibility (24.4%)            | 2.5 - 3.49    |
| ABO incompatibility (13.8%)           | >3.5 Total    |
| Galactosemia (0.8%)                   | 35            |
| Idiopathic (10.4%)                    | 32            |
| Cephalhematoma (10.2%)                | 40            |
| Septicemia (6%)                       | 19            |
| Intrauterine infection (4%)           | 4             |
| BMJ (1.8%)                            | 0             |
| Galactosemia (0.8%)                   | 1             |
| GpPD (0.6%)                           | 0             |
| Hypothyroidism (0%)                   | 14            |
| Total                                | 150           |

Table 4: Etiology of hemolytic jaundice.

| ABO Incompatibility | Preterm babies | Term babies |
|---------------------|----------------|-------------|
| MBG (O+), BBG (A+/B+) | 67            | 73          |
| OA Combination      | 45             |             |
| OB Combination      | 77             |             |
| Total               | 122            |             |
| Rh incompatibility  | 69             |             |
| GpPD                | 3              |             |
| Grand total         | 194            |             |

There was much difference in the different age groups in which Low Birth Weight Babies (LBW) contributes to (27%), and VLBW babies contributes to (24%) of the total cases. Rh and ABO incompatibility contributes to highest percentage in the preterm babies.

The Table 4 shows the various causes of hemolytic jaundice, ABO incompatibility consists of 122 cases, Rh

Table 2: Distribution of patients with different etiologies according to gestational age.

| Cause                        | Preterm babies | Term babies |
|------------------------------|----------------|-------------|
| Exaggerated physiological jaundice (28%) | 67     | 73          |
| ABO incompatibility (24.4%)   | 70            | 52          |
| Rh incompatibility (13.8%)    | 49            | 20          |
| Idiopathic (10.4%)            | 24            | 28          |
| Cephalhematoma (10.2%)        | 18            | 33          |
| Septicemia (6%)               | 20            | 10          |
| Intrauterine infection (4%)   | 4             | 16          |
| BMJ (1.8%)                    | 1             | 8           |
| Galactosemia (0.8%)           | 1             | 3           |
| GpPD (0.6%)                   | 1             | 2           |
| Hypothyroidism (0%)           | 0             | 0           |
| Total                        | 255(51%)      | 245(49%)    |

Figure 2: Sex distribution.

Figure 3: Day wise occurrence of jaundice.

| Day of onset | No. of Patients |
|--------------|-----------------|
| (< 24 hrs.)  | 47              |
| (24 – 72 hrs.) | 290            |
| (72 hrs – 14 days) | 160           |
| (>2 weeks)   | 3              |
incompatibility of 69 cases and G,PD of 3 cases. Out of total 194 cases, 47 cases develop jaundice in the first 24 hours. Acute bilirubin Encephalopathy (ABE), as evident from the table was seen in 19 cases, of which maximum cases were in babies with ABO incompatibility (12 cases total) in which 5 had associated with septicemia. Rh isoimmunization was 7 cases, out of which 3 had associated septicemia.

![Figure 4: Distribution of patients according to gestational age of different etiologies.](image)

| Etiology                  | No.  |
|---------------------------|------|
| ABO Incompatibility       | 7    |
| ABO + Septicemia          | 5    |
| Rh Incompatibility        | 4    |
| Rh + Septicemia           | 3    |
| Total                     | 19   |

**Table 5: Etiology of Acute Bilirubin Encephalopathy (ABE).**

From the above table, it was found of that in preterm babies’ peak serum bilirubin levels causing Acute Bilirubin Encephalopathy (ABE) was 18.2mg/dl with standard deviation of 2.5. In full term babies it was 24.2mg/dl with standard deviation of 4.5. Conjugated hyperbilirubinemia was seen in 10% of cases (n=50). The mean age of presentation was 10 days postnatal age. Out of 50 cases, 10 cases were idiopathic.

| Hyperbilirubinemia | No. of cases |
|--------------------|--------------|
| Unconjugated       | 450(90%)     |
| Conjugated         | 50(10%)      |
| Total              | 500          |

**Table 6: Distribution according age and sex.**

| Sex     | Gestational of Age |
|---------|---------------------|
|         | Pre Term | Term |
| Male    | 12        | 8    |
| Female  | 7         | 11   |
| Total   | 19        | 19   |

| Gestation | Serum total bilirubin (SBR) | Standard deviation (SD) |
|-----------|-----------------------------|-------------------------|
| PreTerm   | 18.2                        | 2.5 (15.7-20.7)         |
| Term      | 24.2                        | 4.5 (19.7-28.7)         |

**Table 7: Peak bilirubin levels in causing Acute Bilirubin Encephalopathy (ABE).**

Thus, from the above table it was found that septicemia was a potentiating factor in causing severe neonatal hyperbilirubinemia in patients with blood group incompatibility. There was a male preponderance and majority of the patients were preterm babies (n=11) and full term (n=8).

DISCUSSION

The study comprises of 500 newborns less than 28 days of life in which 260 were Males (52%) and 240 were Females (48%) (Figure 1).

This is Comparable to study done by Effiong et al, Nigeria, 1972, Narang et al, 1996 India and Korejo et al, 2007 Karachi. A probable explanation may be due to social bias, males being more cared for, and promptly brought to medical attention. In our study (Figure 2), as per gestational age 255 (51%) were preterm and 245 (49%) were term delivered babies. Bhutani et al in their study found out that prematurity was a significant risk factor for hyperbilirubinemia and is known to be a basis
for increased biologic vulnerability to risk of bilirubin induced neurotoxicity. Bajpai et al, Indian Journal of pediatrics, had shown an incidence of 14% as physiologic jaundice with prematurity. Onyearugha et al, prematurity was the second leading cause of NNJ both in inborn and outborn babies. Singhal et al, had given an incidence of 16.7% (Prematurity) as a cause of neonatal jaundice probably more because of physiological handicaps in premature, LBW babies. Hussain et al, Karachi, too had shown that prematurity and LBW was an important risk factor for development of severe hyperbiliru-binemia. Preterm newborns are prone to developing jaundice due to immaturity of their bilirubin conjugating system, higher rate of hemolysis, increased enterohepatic circulation and decreased caloric intake.

In the present study (table 1 and figure 3), jaundice was detected maximum on Live hour (24-72) which consist of 290 cases (58%) followed by 72 hours to 14 days which contributes to 160 cases (32%). The onset of jaundice during live hour 24 was 47 cases (9.4%) which is always an indicative of pathological jaundice. After 2 weeks of post-natal age, the number of cases decreased significantly to 3 case (0.6%). All three case was cholestatic jaundice. The results in our study are similar to work done by Anand et al, where the highest incidence of jaundice was on 3rd (45%) post-natal day followed by 4th day (35.5%). This may be because of increased bilirubin production due to increased RBC volume per kilogram and decreased RBC survival, increase ineffective erythropoiesis and increased turnover of nonhemoglobin heme proteins.

In this study (Table 2), all the different etiologies were much higher in the preterm delivered babies except in physiological jaundice. Preterm babies contribute to 51% of the cases and in term babies 49% cases. ABO, Rh incompatibility and septicemia were more common in the preterm babies. There was much difference in the different age groups (Table 3) in which Low Birth Weight Babies (LBW) contributes to (27%), and VLBW babies contribute to (24%) of the total cases. Rh incompatibility and ABO incompatibility contributes to highest percentage in the LBW and VLBW babies. Similar study done Narang et al, the incidence of significant NNJ was 82.9% at gestational age <28 weeks reduced where to 56.9% at gestational age of 35-36 weeks. The incidence was 75.3%, 78.5% and 76.3% birth weight group of 750-799 gm, 1000-1249 gm and 1250-1499gm respectively.

In this study (Table 2), it was observed that exaggerated physiological jaundice was highest which accounts for 140 cases (28%). Table 9 and 10 shows the comparison of our study with the other Indian studies and foreign studies with respect to various etiological agents. In the study by Bahl et al, had shown that physiological jaundice contributed to highest 63.8% incidence. It was comparatively higher as compared to our study. Singhal et al, (16.7%) and Merchant et al, (25.3%) too had reported highest incidence of physiological jaundice in their studies. The study by Bedowra et al, Bangladesh (n=60), physiological jaundice contributes to 53.3% as the most common cause in their study. It was comparatively higher too as compared to our study. These higher incidence of physiologic jaundice may be due to increased enterohepatic circulation, decreased intestinal bacteria and decreased gut motility with poor evacuation of bilirubin-laden meconium, defective uptake of bilirubin from plasma caused by decreased ligandin and binding of ligandin by other anions and defective conjugation due to decreased UGT activity and decreased hepatic excretion of bilirubin.

In our study (Table 2) it was observed that ABO incompatibility was 24.4%. In the study conducted by Shao-wen et al, ABO incompatibility was 18.3% and Rh incompatibility was 2.4% G6PD 20% which is higher. Farhad et al and Joshi et al in their studies found that ABO was 38.1% and 28.8% respectively, in which the incidences were similar to our study. In the study conducted by Sgro M et al concluded that ABO incompatibility 51.6% was the most common cause, which was much higher than in our studies.

### Table 9: Etiologies of neonatal jaundice in different studies in India.

| Worker (India) | Physiological | ABO Incomp | Rh Incompat | G6PD | Idiopathic | Cephal | Septicemia | IU | BMJ | Galactosemia | Hypothyroidism | Others |
|---------------|---------------|------------|-------------|------|------------|--------|-------------|---|-----|-------------|---------------|--------|
| Present Study, SMS Medical College (n=500) | 28% | 24.4% | 13.8% | 8.6% | 10.4% | 10.2% | 6% | 4% | 1.8% | 0.8% | - | 4% |
| Narang et al, PGI Chandigarh, India (n=512) | - | 1.95% | 0.39% | 12.1% | 73.3% | 2.93% | 4.49% | - | - | - | - | 2.34% |
| Singhal et al, AIIMS (n=454) | 16.7% | 14.3% | 8.1% | 5.1 | 34.4% | 2.9% | 5.7% | 1.3% | 0 | 0.2% | 0.7% | - |
| Bahl et al, Shimla (n=105) | 63.8% | 4.7% | 1.9% | 2.9% | 11.4% | 1.9% | 10.5% | - | 2.9% | - | - | - |
| Narang, Geeta et al, PGI (n=551) | - | 5.6% | 9.2% | 17.2% | 35.4% | 1.4% | 24.4% | - | - | - | - | 7% |
Table 10: Etiologies of neonatal jaundice in different studies in other countries.

| Other countries or worker | Etiology (%) | Physiological | ABO Incom pat | Rh Incom pat | G6PD | Idiopathic | Cephal | Septicemia | IUI | BMJ | Galactocoea | Hypothyroidism | Others |
|--------------------------|--------------|---------------|----------------|--------------|------|------------|--------|------------|-----|-----|-------------|----------------|--------|
| Present Study, SMS Medical College (n=500) | 28% | 24.4% | 13.8% | 8.6% | 10.4% | 10.2% | 6% | 4% | 1.8% | 0.8% | - | 4% |
| Bedowara et al, Bangladesh, (n=60) | 53.3% | 33.3% | 3.3% | 1.7% | 1.7% | - | 26.7% | - | - | - | - | - |
| Shao-WEN et al, Taiwan (n=485) | - | 18.3% | 2.4% | 20% | 12.9% | 5.5% | 1.8% | - | 32.5% | 0.2% | 0.2% | 5.4% |
| Farhad et al, Iran, (n=118) | - | 38.1% | 16.1% | 3.4% | 25.4% | 3.4% | 8.5% | - | - | - | - | 3.4% |

Hemolytic jaundice due to isoimmunization in the mother and baby was seen in (Table 2) 38% of cases which on splitting up was (24.4%) due to ABO and due to Rh isoimmunization (13.8%). Hemolytic jaundice due to G6PD deficiency was seen in (0.6%) of the cases. In our study, ABO incompatibility was found to be the most common cause, followed by Rh incompatibility and G6PD. The results are consistent with Sgro M et al, in which ABO (51.6%) incompatibility was the most common cause followed by G6PD (21.5%) and other antibody incompatibility (12%). Farhad et al, too had consistent results with ABO (38.1%), Rh (16.1%) and G6PD (3.4%).

In this study (Table 2), it was observed that exaggerated physiological jaundice was highest which accounts for (n=140, 28%) cases followed by ABO (24.4%) and Rh incompatibility (13.8%). Lalita et al, 1994,similar results were also seen in which physiological jaundice (63.8%) incidence was the highest followed by sepsis (10.5%) and ABO incompatibility (4.7%). Septicemia accounts for 6% of the cases. G6PD deficiency accounted for 3 cases (0.6%) causing hyperbilirubinemia in our study.

The incidence is very low as compared to that of ABO and Rh incompatibility due to limited laboratory diagnostic facilities and earlier discharge of the newborns and lack of proper follow up. In our study, only one case were followed up with the enzyme assay results. Galactosemia contributes to (n=4, 0.8% cases) in the study. Cephalhematoma (enclosed hemorrhage) is a benign condition of the newborn. The incidence is about 1-2% of deliveries and 3.9-4.3% following vacuum and forceps deliveries. Herman W. Hyatt et al, too had mentioned about risk of hyperbilirubinemia in the newborn probably related to cephalhematoma. In our study, it was (n=51,10.2%),in which the onset of jaundice was maximum after the 3rd post-natal age. It was more in full term delivered, AGA babies (33%), and 18% in preterm babies in the study. Anil Narang et al, too had shown 4% incidence in their study.

As given in Table 5, Acute Bilirubin Encephalopathy (ABE), was seen in 19 cases, of which maximum cases were in babies with ABO incompatibility (n=12) in which 5 had associated with septicemia. Rh isoimmunisation was 7 cases, out of which 3 had associated septicemia. Thus, it was found that septicemia was a potentiating factor in causing severe neonatal hyperbilirubinemia in patients with blood group incompatibility.

CONCLUSION

Neonatal jaundice is an important aspect of neonatal morbidity. There are well-developed system to identify, investigate and manage the problem in developed health care systems, but much research and development is still needed to address the problem in resource-poor setting.

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