Original Research Article

Hemolytic disease of the new-born due to ABO incompatibility

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ABSTRACT

Background: Better understanding of the clinical characteristics of HDN due to ABO incompatibility helps to optimise care. The objective of this study was to investigate the clinical manifestations and outcome of treatment modalities.

Methods: This study was a hospital based cross sectional study conducted in the neonatal unit of Cheluvamba hospital attached to Mysore Medical College and Research Institute. A total of 50 neonates with blood group A or B born to mothers with blood group O; with jaundice and or anemia were enrolled during the period from January 2015 to December 2015. The various maternal and neonatal parameter and their association with development of jaundice and or anemia was studied. The outcome of treatment modalities was studied.

Results: Out of 50 ABO Incompatible neonates 24 (48%) were male and 26 (52%) were female. The percentage of O–A and O–B incompatible neonates were 38% (19) and 72% (31), respectively. Jaundice was detected within the first 24 hours in 6% and 18% neonates had anemia. The mean age of presentation was 2.9±0.89 days. The various maternal and neonatal factors had no significant association with development of jaundice and or anemia due to ABO Incompatibility. The mean initial Indirect Bilirubin was 21.26±3.97, initial hemoglobin was 14.3±2.31 and the mean Reticulocyte count was 16.6±5.3. Total 22 (44%) neonates had laboratory evidence of hemolysis (microspherocytosis). DCT was positive in 4 (8%) neonates. The main clinical manifestation was jaundice and was treated with phototherapy in 49 (98%) of the cases. The mean duration of phototherapy was 53.84±9.82 hours. Only one infant required exchange transfusion and on follow up had no neurological sequelae. The mean total duration of stay was 3.6±1.2 days. There was no significant difference in the HDN due to either O–A or O–B incompatibility.

Conclusions: Early identification of high risk neonates with ABO Incompatibility, diagnosis and early intervention can reduce morbidity and mortality.

Keywords: Direct coombs test, Hemolytic disease of the new-born, Phototherapy

INTRODUCTION

Hemolytic disease of the new-born due to ABO Incompatibility occurs exclusively in newborns of blood group A or B having mothers of group O. Even though hemolytic disease of the newborn has been reported in a baby whose mother was group A with a high titres of anti B. Jaundice in hemolytic disease of the newborn is more frequent and severe in ABO incompatible black than white newborns and, furthermore, jaundice due to any other cause, is more likely to be more severe in ABO incompatible babies than compatible ones.2

The etiology of haemolytic disease of the newborn due to ABO incompatibility is complex because anti-A and anti-B antibodies are composed mainly of Immunoglobulin M. Since only Immunoglobulin G antibodies cross the placenta, those pregnant women with high levels of
Immunoglobulin G anti-A or B with an ABO incompatible fetus will be the ones to give birth to a newborn with ABO hemolytic disease of the newborn.³ Although hemolytic disease of the newborn as a result of ABO incompatibility is clinically milder than Rhesus incompatibility, severe hemolysis occasionally occurs, such that some cases require exchange transfusion.⁴

It has been noted that hemolytic disease of the newborn due to ABO incompatibility frequently occurs during the first pregnancy, and about 50% of infants are affected unlike Rhesus hemolytic disease of the newborn in which the first born babies are usually spared or free of the disease and subsequent babies are the ones that are affected. ABO incompatibility is present in about 12% of pregnancies, with evidence of fetal sensitization in 3% live births. Less than 1% of births which are ABO incompatible are associated with significant haemolysis.⁵ ⁶ In general 15-20% of all maternal/fetal pairs are ABO incompatible, but hemolytic disease of the newborn due to ABO incompatibility is confined to approximately 1% of group O mothers who have high titres of Immunoglobulin G anti A/B antibodies.⁶ Hemolysis due to anti A is more common (1 in 150) than that due to anti-B.

The diagnosis of Hemolytic disease of the newborn due to ABO incompatibility cannot be made serologically using one single test; however, several tests together make the diagnosis more probable. In contrast to Rhesus haemolytic disease, the immunological findings in hemolytic disease of the newborn due to ABO incompatibility do not correlate well with the severity of the clinical course.⁷ Sometimes it is impossible to differentiate between hemolytic disease of the newborn due to ABO incompatibility and non-antibody mediated hyperbilirubinemia.⁸

Hemolytic findings due to maternal-fetal ABO blood group incompatibility were defined as the presence of at least two of the followings:

- Jaundice and or anemia of varying degree,
- Circulating nucleated red blood cells,
- Microspherocytosis, or
- Polychromasia on peripheral blood smear.⁹

Hemolytic disease of the newborn due to Rhesus incompatibility is preventable and preventable measures are in place in many countries. In contrast there are currently no preventable measures for Hemolytic disease of the newborn due to ABO incompatibility.⁹ ABO incompatibility hence is now the single most common cause of neonatal jaundice.¹⁰

Hemolytic disease of the newborn can be managed by using any of the following modalities: phototherapy, exchange transfusion or intravenous immunoglobulins. Early application of any of these methods in the treatment of hemolytic disease of the newborn prevents bilirubin encephalopathy and Kernicterus with subsequent development of severe neurological sequelae or death. Nearly 50% of babies with hemolytic disease of the newborn due to ABO incompatibility do not require treatment. Of the remaining 50%, half of them become extremely jaundiced and without treatment, 90% of them will die and 10% become severely affected by Kernicterus. The other half are severely affected in utero and become hydroyic.¹¹ ¹²

Hence, this study titled “Hemolytic disease of the newborn due to ABO incompatibility” considering its clinical manifestations and outcome of treatment modalities was conducted at NICU, Cheluvamba hospital attached to Mysore Medical college and Research Institute.

**METHODS**

It was a cross sectional hospital based study. Primary source of information was by observational method on a sample size of 50 term neonates admitted to NICU with Neonatal jaundice and or anemia due to ABO Incompatibility by purposive method.

**Inclusion criteria**

Term babies admitted to NICU with Neonatal jaundice and or Anemia due to ABO Incompatibility.

**Exclusion criteria**

- The neonates with history of Birth asphyxia, Sepsis.
- The neonate with congenital anomalies.
- Neonate with other known causes of jaundice and hemolysis.

A pre drawn proforma was explained to the mother or the caregiver. Informed consent regarding participation in the study was obtained in the regional language

Data was collected as per the proforma. Questionnaire method, maternal case file and examination of the newborn were used to obtain the required data.

Maternal variables like history of jaundice, first trimester bleeding, gestational hypertension, mode of delivery and use of drugs during pregnancy were collected. Medication during labour, details of delivery, APGAR score and maternal blood group were collected from the maternal file.

Babies were clinically assessed for age, sex, gestational age, birth weight, previous history of jaundice in the family, day of onset of jaundice, pattern of feeding, fever and other neurological symptoms. Thorough clinical examination of the baby was done to identify: Pallor, temperature, icterus, hepatosplenomegaly, extravasation of blood (cephalhematoma/subgaleal bleed), excessive bruising, neurological signs like opisthotonus.
Thus, all term neonates admitted to NICU with neonatal jaundice and or Anemia were subjected to thorough clinical examination. The following investigations were done.

- Blood Grouping and Rh typing of mother and baby: The blood grouping was done by using known antisera with slide and tube methods. Complete blood count of baby including hemoglobin, total count, differential count, band cells, peripheral smear examination and reticulocyte count.
- Estimation of hemoglobin was done by cyanmethemoglobin method.
- Peripheral smear was stained by Leishman stain.
- Reticulocyte count was done by supravital stain using Brilliant cresyl blue.
- Direct Coombs Test (DCT)

Other relevant investigations required for the management of the case were carried out as per the clinical indication.

Standard treatment by using any of the following modalities; phototherapy, exchange transfusion or intravenous immunoglobulins was given for each case and the outcome of treatment modalities were studied and compared with other studies.

The maternal factors like parity, gestational hypertension, mode of delivery, medication with oxytocin and initiation of breast feeding within 30 minutes and neonatal factors like sex, weight, blood group were considered. The association between these parameters and development of jaundice and or anemia in ABO Incompatibility were studied and the results were compared with other studies.

Statistical analysis

The descriptive statistics, chi-square test, contingency table analysis, one sample ‘t’ test all statistical techniques were carried out using SPSS for window (version 16.0).

RESULTS

In this cross sectional hospital based study of 50 newborns with HDN due to ABO incompatibility, the following observations were made. The study results were analyzed using appropriate statistical methods.

In the present study, there was uniform sex wise distribution and no significant difference in the number of male and female babies. 42 (84%) of newborns were AGA and 8 (16%) were SGA. The mean birth weight was 2.80±0.37 kilograms. 29 babies were born through vaginal delivery and 21 were born through LSCS due to various indications like previous LSCS, Deep Transverse arrest, cephalo pelvic disproportion and failed induction.

Table 1: Association between neonatal jaundice in ABO Incompatibility and maternal and neonatal variables with p value.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Cases</th>
<th>Percent</th>
<th>P value</th>
<th>Association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24</td>
<td>48</td>
<td>0.457</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>26</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AGA</td>
<td>46</td>
<td>92</td>
<td>0.74</td>
<td>NS</td>
</tr>
<tr>
<td>SGA</td>
<td>4</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode of delivery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTND</td>
<td>29</td>
<td>58</td>
<td>0.36</td>
<td>NS</td>
</tr>
<tr>
<td>LSCS</td>
<td>21</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primi</td>
<td>36</td>
<td>72</td>
<td>0.97</td>
<td>NS</td>
</tr>
<tr>
<td>Multi</td>
<td>14</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal gestational hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>29</td>
<td>58</td>
<td>0.49</td>
<td>NS</td>
</tr>
<tr>
<td>No</td>
<td>21</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With oxytocin</td>
<td>11</td>
<td>22</td>
<td>0.04</td>
<td>NS</td>
</tr>
<tr>
<td>Without oxytocin</td>
<td>39</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timing of initiation of breast feeding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 min</td>
<td>37</td>
<td>74</td>
<td>0.51</td>
<td>NS</td>
</tr>
<tr>
<td>&gt;30 min</td>
<td>13</td>
<td>26</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Comparison of demographic and clinical characteristics of newborn with blood group A or B.

<table>
<thead>
<tr>
<th></th>
<th>Blood group A (n=19)</th>
<th>Blood group B (n=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight (g)</td>
<td>2.9±0.39</td>
<td>2.75±0.4</td>
<td>0.42</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>10/9</td>
<td>14/17</td>
<td></td>
</tr>
<tr>
<td>Day of hospitalization (day)</td>
<td>3.06±1.07</td>
<td>2.8±0.7</td>
<td>0.42</td>
</tr>
<tr>
<td>Initial hemoglobin (g/dl)</td>
<td>13.7±2.18</td>
<td>14.66±2.36</td>
<td></td>
</tr>
<tr>
<td>Initial indirect bilirubin (mg/dl)</td>
<td>20.4±4.2</td>
<td>21.79±3.7</td>
<td>0.23</td>
</tr>
<tr>
<td>Positive direct coombs test, n (%)</td>
<td>2/7</td>
<td>2/29</td>
<td>0.9</td>
</tr>
<tr>
<td>Anemia (Hb &lt;13 g/dl), n (%)</td>
<td>5</td>
<td>4</td>
<td>0.65</td>
</tr>
<tr>
<td>Presence of hemolysis, n (%)</td>
<td>9/10</td>
<td>13/18</td>
<td>1</td>
</tr>
<tr>
<td>Jaundice in the first 24 hours, n (%)</td>
<td>2</td>
<td>1</td>
<td>0.27</td>
</tr>
<tr>
<td>Duration of phototherapy (hr)</td>
<td>52.7±9.21</td>
<td>54.5±10.27</td>
<td>0.97</td>
</tr>
<tr>
<td>Number of exchange transfusion, n (%)</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Need for IVIG therapy, n (%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
Primiparous mothers were more than the multiparous mother. 29 (58%) cases had history of gestational hypertension, 11 (22%) cases had history of induction of labor with oxytocin and 37 (74%) neonates were breastfed within 30 minutes. Thus, there was no significant association between the maternal and neonatal factors with the serum bilirubin level. O-A and O-B Incompatibility were 19 (38%) and 31 (62%) respectively.

Figure 1: Maternal and neonatal risk factors.

Three (6%) neonates developed jaundice within first 24 hours of life followed by 13 (26%) on second day, 19 (38%) on third day followed by 15 (30%) on fourth day. Majority of neonates presented with jaundice on third day (38%) followed by fourth day (30%), followed by second day (26%) followed by first day (6%). Mean age of presentation with jaundice was 2.9±0.89 with the range from 0 to 4 days. The mean initial Indirect Bilirubin was 21.26±3.97 with the range from 12.3 to 31 mg/dl.

Mean age of clinical presentation was 2.9±0.89 days. The main clinical manifestation was jaundice and was treated with phototherapy in 98% of the cases. The duration of phototherapy was 53.84±9.82 hours. Only one neonate required exchange transfusion and on follow up had no neurological sequelae. The mean total duration of stay was 3.6±1.2 days.

DISCUSSION

In this present study, various parameters and their association with the clinical manifestation of ABO Incompatibility were analysed. Neonatal jaundice was the main clinical feature in majority of the cases and mild anemia in few cases.

Maternal factors like parity, gestational hypertension, mode of delivery, medication with oxytocin and initiation of breast feeding within 30 minutes and neonatal factors like sex, weight, blood group were considered. The association between these parameters and development of jaundice and or anemia in ABO Incompatibility was studied and the results were compared with other studies.
In the present study, there was no significant correlation between the serum bilirubin levels and the sex of the newborn and observation was comparable with that of studies by Kumar A et al, Akgul S, Shah A and Preethi et al.13-16 Male newborns had more risk of jaundice, in studies by Mantani et al, Sharma et al and Maisal et al.17. The serum bilirubin levels and weight of the newborn had no correlation but in the studies by Nepal D et al (19.2%) and Chaudhary et al (42%) observed significance with weight of the newborn (SGA).20,21

The serum bilirubin was independent of the parity of the mother (p value 0.97) as similar to that of in studies by Shah A et al and Kalakheti et al.22,23 In the study, 11 cases had history of induction of labor with oxytocin and had no significant correlation with the development of jaundice and or anemia as in studies by Taksande A et al (p 0.245) and Knudsen et al and there was significant correlation observed in, Rostami et al, Oral E et al and Awasthi et al (p 0.004) studies.24-28

In the study, serum bilirubin level was independent of mode of delivery as observed in studies by Amar Taksande et al, Rudyn Satrya and Knudsen et al.

In the study, 37(74%) neonates were breastfed within 30 minutes of birth and serum bilirubin level was independent of time of initiation of breast feeding as similar in Awasthi et al study with p value 0.9.

Thus, in the present study, maternal factors like parity, gestational Hypertension, mode of delivery, medication with oxytocin and initiation of breast feeding within 30 minutes and neonatal factors like sex, weight, blood group had no significant association with development of jaundice and or anemia due to ABO incompatibility, which were the main clinical manifestations. These observations were similar to that of in studies by Kumar A et al, Akgul S et al and Kalakheti et al.

In present study there was no significant difference in severity and outcome in both O-A and O-B incompatibility, although O-B incompatibility was more. Similar observation was made by Kumar A et al, Ella E et al, Akgul S and Bhat YR et al.25 But McDonell et al and Stiller et al concluded that ABO Incompatibility might cause more fetal anemia in patient with type B blood group.26,27 Adewuyi et al observed that anti-B antibodies showed greater hemolytic activity than anti-A antibodies.28 Akgu S et al, concluded that blood type had no effect on the severity of the hemolytic jaundice due to ABO incompatibility.

In the present study, mean age of presentation with jaundice was 2.92±0.89 (0-4) days. Mean initial IB was 21.26±3.97 with the range from 12.3 to 31 mg/dl. Three neonates (6%) developed jaundice in the first 24 hours of life. Mean initial hemoglobin was 14.3±2.31 (9.10-23.20) g/dl. Nine (18%) developed anemia.

In a study by Akgul, Mean age on the day of admission to hospital was 4.4±2.4 (0-9) days. Mean initial IB was 19.9±5.7 (7.1-41.3) mg/dl. Fifteen neonates (9.0%) developed jaundice in the first 24 hours of life and 17 neonates (10.2%) had anemia in the first complete blood count examination. Mean initial hemoglobin was 15.6±2.3 (8.2-20.8) g/dl. Twenty-four neonates (14.5%) had hemolytic findings on peripheral blood smear. In study by Bhat YR, hemolysis was present in 25 (54.3%), with the range of indirect bilirubin from 11.9 to 25.6 mg/dl, 47.8% babies presented with jaundice in 24 hours. In study by Shah A, mean age of presentation was 2.97±1.2 days, mean bilirubin level, 15-19-9 mg/dl (52.4%). In a study by Thakkar B et al, lowest hemoglobin (9.0mg/dl), highest reticulocyte count (10%) and maximum rise in serum bilirubin (30.0mg/dl) were seen in cases of ABO compatibility.33

In the present study DCT was positive in 4 (8%) neonates, 17 (10.2%) in Akgul et al, 60% in Beena Thakkar et al, 1.9% in Bhat YR et al, and 6% in Ella et al.34 The direct antiglobulin test should be at least weakly positive for anti-A or anti-B; however, because of the sparse distribution of antigenic sites on a newborn's RBCs, HDN due to ABO incompatibility may be present even without a positive result on the direct antiglobulin test. A positive Coombs test in ABO incompatible infants does not necessarily indicate disease.

Kumar A et al observed p-value of <0.001 and a high predictive value of Antiglobulin test for occurrence of disease but for neonates affected by disease, p-value was >0.1 and was statistically insignificant. Thus, Direct Antiglobulin test was nonspecific in predicting severity of disease. Thakkar B et al, observed that DCT and ICT were positive in 100% of cases of Rh incompatibility and 60% cases of ABO incompatibility. The reason for this difference might be that 'A' and 'B' antigens are weaker antigens and the distance between A/B antigenic sites on the foetal red cells as compared to adult red cell is more.

The hallmark of HDN due to ABO incompatibility is the presence of microspherocytes on the peripheral blood smear. In present study 22 (44%) neonates had microspherocytes in peripheral blood smear. 14.5% of neonates in Akgul S et al study, 54.3% of neonates in Bhat YR et al study 76% of neonates in Kalakheti study.

In present study mean leukocyte count was 23972±11620 and neutrophilia was present in 14 infants. Differential Count for Monocytes, Lymphocytes, Neutrophils, Basophils, Eosinophils was within normal range. Ella et al observed mean count for lymphocyte (37.6±7.2), neutrophil (41±4.9), monocytes (10.8±20), eosinophil, (9.6±2.7), basophils (1.2±0.83) and inferred that elevated level of neutrophil and basophils were present in incompatible cases and Baker et al inferred that total and differential count were useful indices in detecting cases of bacterial infections.35
The mean age of presentation in the study was 2.9±0.89 days. The main clinical manifestation was jaundice and was treated with phototherapy in 98% of the cases.

The required phototherapy duration was 53.8±49.82 hours. Only one neonate required exchange transfusion and on follow up had no neurological sequelae. The total duration of stay was 3.6±1.2 days. In Bhat YR et al study, phototherapy was required in 46% of the cases and none required exchange transfusion. In Akgul et al study, 10.8% required exchange transfusion and 10.8% required IV Ig therapy. In Sharma et al study, neonates with serum bilirubin in the range of 22.4-26.4 mg/dl required exchange transfusion.96

The present study infers that early identification of high risk neonates with ABO incompatibility might reduce the morbidity and mortality due to jaundice and or anemia. All babies born to O positive mother with A or B or AB father should be evaluated for blood group as soon as possible to identify the high risk neonates developing jaundice and or anemia due to ABO incompatibility.

Present study was limited to only symptomatic ABO Incompatibility. Small sized study population was another limitation of this study.

CONCLUSION

In present study, maternal factors like parity, gestational hypertension, mode of delivery, medication with oxytocin and initiation of breast feeding within 30 minutes and neonatal factors like sex, weight, blood group had no significant association with development of jaundice and or anemia due to ABO Incompatibility. Thus, the present study concludes early identification of ABO incompatibility reduced the mortality and morbidity due to jaundice and or anemia. All babies born to O positive mother with A or B or AB father should be evaluated for blood group as soon as possible to identify the high risk neonates developing jaundice due to ABO Incompatibility. Early identification, diagnosis and intervention can reduce morbidity and mortality due to HDN due to ABO Incompatibility.

Recommendations

Inclusion of both symptomatic and asymptomatic ABO Incompatible newborn to know the prevalence.

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