

## CLINICAL PROFILE OF MATERNAL ANTIBODY-MEDIATED ABO HAEMOLYTIC DISEASE OF FOETUS AND NEWBORN

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### ABSTRACT

#### BACKGROUND

ABO incompatibility can cause neonatal jaundice and haemolytic disease of foetus and newborn (HDFN). The aim of this study is to describe the clinical profile of ABO HDFN in a tertiary care centre.

Settings and Design- This was a descriptive study conducted in neonates suffering from ABO HDFN. Setting for the research was Dept. of Transfusion Medicine and Neonatology, Division of Sree Avittom Thirunal Hospital for women and children attached to Govt. Medical College, Trivandrum.

#### MATERIALS AND METHODS

Neonates who fulfilled the inclusion criteria were enrolled in this study. Demographic details, maternal history, birth details, neonatal blood group, haemoglobin, reticulocyte count, peripheral smear, bilirubin levels, mode of treatment, duration of treatment, ICU stay and followup status, etc. were recorded. Risk of jaundice, severity of disease and intensity of treatment was assessed. Statistical Analysis- All statistical data were analysed using SPSS software version 16.

#### RESULTS

The mean bilirubin levels in neonates on Day 1, 2, 3, 4 and 5 were 5.16, 9.55, 11.95, 13.42 and 13.8 mg% respectively. Among 110 neonates with ABO HDFN 51 (46.4%) belonged to low risk, 22 (20%) to low intermediate risk, 19 (17.3%) to high intermediate risk and 18 (16.4%) to high risk categories. Among infants no anaemia was detected in 58 (52.7%), mild anaemia was detected in 40 (36.4%), moderate anaemia in 8 (7.3%) and severe anaemia in 4 (3.6%). Spherocytes were seen in peripheral smears of 94 (85.5%) infants, whereas it was absent in the rest 16 (14.5%) of cases. Disease was mild, moderate and severe among 101 (91.8%), 7 (6.4%) and 2 (1.8%) infants respectively; 74 (67.3%) infants required no treatment. Phototherapy alone was the modality of treatment in 21 (19.1%) infants. IVIG was given along with phototherapy in 13 (11.8%) infants; 2 (1.8%) of infants required exchange transfusion along with IVIG and phototherapy. Regarding transfusion 7 (6.4%) received packed red cells, 3 (2.7%) received platelet concentrate and 1 (0.9%) received fresh frozen plasma. Intensity of treatment was as follows- 74 (67.3%) belonged to grade-0, 21 (19.1%) belonged to grade-1, 13 (11.8%) to grade-2 and 2 (1.8%) to grade-3 category of treatment.

#### CONCLUSION

Majority of infants had mild hyperbilirubinaemia and no or minimal anaemia. Disease was mild in majority of infants with ABO HDFN, thereby requiring no interventions.

#### KEYWORDS

Haemolytic Disease of Foetus and Newborn, Hyperbilirubinaemia, Antibody, ABO, Phototherapy, IVIG, Exchange Transfusion.

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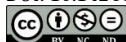
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#### BACKGROUND

ABO incompatibility is a leading cause of neonatal jaundice and haemolytic disease of foetus and newborn (HDFN) in countries with high human development index.<sup>1</sup> ABO HDFN had a worldwide incidence of 54.4 per 1,000 births.<sup>2</sup> Assessing the magnitude of disease by observing their clinical profile was quite an essential tool for effective planning and implementation of better management protocols. Thus, aim of this study was to describe the clinical profile of ABO HDFN in a tertiary care centre.

## MATERIALS AND METHODS

This was a descriptive study conducted in 110 neonates who were suffering from ABO HDFN. Setting for the research was Dept. of Transfusion Medicine and Neonatology division of Sree Avittom Thirunal hospital for women and children attached to Govt. Medical College, Trivandrum.

According to institutional policy, all neonates with hyperbilirubinaemia were admitted in newborn nursery. Those neonates who fulfilled the inclusion criteria were enrolled in this study. Study was accomplished for a period of 18 months from 01-03-2012 to 30-08-2013.

### Inclusion Criteria for ABO HDFN

1. High bilirubin levels during first 24 hours after birth.
2. Incompatibility between mother and baby ABO blood groups.
3. Same neonatal and maternal Rh-D type.
4. Negative antibody screen results in mother.
5. IgG titre of anti-A or anti-B  $\geq 32$  in maternal serum.
6. Neonatal DAT along with elution positive/ elution alone is positive/ IAT positive for maternal antibodies in cord blood serum.
7. No other aetiology factors for hyperbilirubinaemia.

### Exclusion Criteria

HDFN concomitantly present with twin-to-twin transfusion, cardiac failure, infections, haemoglobinopathies, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, extravascular blood loss, cephalhaematoma, hypothyroidism, Dubin-Johnson syndrome, cystic fibrosis, biliary atresia, cholestasis, total parenteral nutrition and antibiotic treatment.

Demographic details such as name, age, IP no., bed no. and addresses were noted. Relevant maternal history such as age, blood group, parity, history of transfusion, abortion, IUD, ectopic pregnancy, amniocentesis, neonatal jaundice in previous delivery, IVIG administration, chronic disease, chronic infection and intrauterine transfusion were noticed. Mode of delivery and other birth details such as birth weight, maturity, gender, APGAR score and feeding pattern were recorded.

For classifying hyperbilirubinaemia, chart provided by American Academy of Pediatricians (AAP) was followed. Further investigations such as neonatal blood group, haemoglobin, reticulocyte count, peripheral smear and bilirubin levels were recorded. Anaemia was graded as described in Wintrobe's Haematology<sup>3</sup> (No- Hb  $\geq 17$  g%, Mild-Hb 14 – 17 g%, Moderate- Hb 12 – 14 g%, Severe- Hb  $< 12$  g%).

Risk related to peak bilirubin values was documented as given in AAP chart. The disease was graded as mild, moderate, severe and very severe according to grading proposed by Andrew et al.<sup>4</sup> (Mild- Grade 0: Hb  $> 12.5$  g/dL, no transfusions, Moderate- Grade 1: Hb  $> 12.5$  g/dL + top-up or exchange transfusion, Severe- Grade 2: Hb  $< 12.5$  g/dL + exchange transfusion, Very Severe- Grade 3: Intrauterine transfusions and/or Hb  $< 10.0$  g/dL  $\pm$  exchange transfusions or foetal death).

Mode of treatment namely phototherapy, IVIG, exchange transfusion and top-up transfusion with blood components were observed. Treatment was graded based on the

description given in Wintrobe's Haematology.<sup>5</sup> (Grade 0- no treatment, Grade 1- phototherapy alone, Grade 2- phototherapy and IVIG, Grade 3- phototherapy, IVIG and single exchange transfusion, Grade 4- phototherapy, IVIG and multiple exchange transfusions).

Duration of treatment, ICU stay and survival status of the neonate were noted during followup. Haemoglobin and serum bilirubin levels of neonates were done on 14<sup>th</sup> day in review clinic.

### Ethics

Study was approved by Human Ethical Committee and Review Board of Institution. Counselling was done for parents of all neonates included in the study and a written consent was obtained from them.

### Statistical Analysis

Data were analysed statistically by SPSS software version 16. Mean  $\pm$  standard deviation was the mode for expression of continuous variables, while qualitative data was expressed as frequencies and percentages. Categorical variables were compared using chi-square test. All p values were two tailed and values of p  $< 0.05$  were considered statistically significant. Correlation between variables was done using Spearman correlation test.

## RESULTS

Among the mothers of infants with ABO HDFN 27 (24.5%) belonged to 18 - 22 years, 53 (48.2%) belonged to 23 - 27 years, 19 (17.30%) belonged to 28 - 32 years and 11 (10%) belonged to 33 - 37 years. Mean maternal age was  $25.74 \pm 4.76$ . The minimum and maximum age of mothers was 18 and 37 years respectively.

While analysing the parity of mothers 71 (64.6%) belonged to primi gravida, 33 (30%) to second gravida, 4 (3.6%) to third gravida and 2 (1.8%) to fourth gravida. All mothers of infants with ABO HDFN were invariably group O; 1 case of previous blood transfusion (0.9%), 5 abortions (4.5%), 19 neonatal jaundiced babies (17.3%), 2 intrauterine deaths (1.8%), 1 neonatal death (0.9%), 2 cases of diabetes mellitus (1.8%), 2 cases of pregnancy-induced hypertension (1.8%), 2 cases of tuberculosis (1.8%) and 1 case of hepatitis (0.9%) were observed on reviewing the obstetric history of mothers.

Regarding mode of delivery there were 75 (68.2%) vaginal deliveries, 15 (13.6%) induced vaginal deliveries and 20 (18.2%) caesarean sections; 53 (48.2%) infants belonged to male gender and 57 (51.8%) to female gender. Among infants 97 (88.2%) were with birth weight of 2500 g or more and 13 (11.8%) with birth weight less than 2500 g; 108 (98.2%) were term babies and 2 (1.8%) were preterm babies; 103 (93.6%) had APGAR score 7 - 10 and 7 (6.4%) had APGAR score 4 - 6; 67 (60.9%) neonates were fed with breast milk, 25 (22.7%) with both breast milk and formula feed and 18 (16.4%) with formula feed alone.

The mean bilirubin levels in neonates on Day 1, 2, 3, 4 and 5 were 5.16, 9.55, 11.95, 13.42 and 13.8 mg% respectively. Among 110 neonates with ABO HDFN 51 (46.4%) belonged to low risk, 22 (20%) to low intermediate risk, 19 (17.3%) to high intermediate risk and 18 (16.4%) to high-risk categories. The mean cord blood bilirubin level was  $5.157 \pm 1.906$ . Minimum and maximum bilirubin levels were 3 and 10.6 mg% respectively.

Grading of Hyperbilirubinaemia	Frequency	Percentage
Low risk	51	46.4
Low intermediate risk	22	20.0
High intermediate risk	19	17.3
High risk	18	16.3
<b>Total</b>	<b>110</b>	<b>100.0</b>

**Table 1. Risk related to Peak Bilirubin Levels**

Among infants no anaemia was detected in 58 (52.7%), mild anaemia was detected in 40 (36.4%), moderate anaemia in 8 (7.3%) and severe anaemia in 4 (3.6%). The mean cord blood haemoglobin value was  $14.470 \pm 1.975$ . Minimum and maximum haemoglobin values were 9.8g% and 17.7g% respectively.

Grading of Anaemia	Frequency	Percentage
No anaemia	58	52.7
Mild	40	36.4
Moderate	8	7.3
Severe	4	3.6
<b>Total</b>	<b>110</b>	<b>100.0</b>

**Table 2. Grading of Anaemia in Infants with HDFN**

Those with reticulocyte count  $\geq 4.6$  were 88 (80%) and those with  $< 4.6$  were 22 (20%). Spherocytes were seen in peripheral smear 94 (85.5%) of infants, whereas it was absent in the rest 16 (14.5%) of cases.

Disease was mild, moderate and severe among 101 (91.8%), 7 (6.4%) and 2 (1.8%) infants respectively. 74 (67.3%) infants required no treatment. Phototherapy alone was the modality of treatment in 21 (19.1%) infants. IVIG was given along with phototherapy in 13 (11.8%) infants; 2 (1.8%) of the infants required exchange transfusion along with IVIG and phototherapy.

Grade	Frequency	Percentage
Mild	101	91.8
Moderate	7	6.4
Severe	2	1.8
Very Severe	0	0.0
<b>Total</b>	<b>110</b>	<b>100.0</b>

**Table 3. Severity of HDFN**

Treatment Modalities	Frequency	Percentage
No treatment	74	67.3
Phototherapy alone	21	19.1
Phototherapy and IVIG	13	11.8
Exchange transfusion, IVIG and phototherapy	2	1.8
<b>Total</b>	<b>110</b>	<b>100.0</b>

**Table 4. Treatment Modalities in Infants with HDFN**

Regarding transfusion, 7 (6.4%) received packed red cells, 3 (2.7%) received platelet concentrate and 1 (0.9%) received fresh frozen plasma. Intensity of treatment was as follows: 74 (67.3%) belonged to grade-0, 21 (19.1%) belonged to grade-1, 13 (11.8%) to grade-2 and 2 (1.8%) to grade-3 category of treatment.

In infants with ABO HDFN 53 (48.2%), 4 (3.6%), 10 (9.1%), 11 (10%), 12 (10.9%), 4 (3.6%), 8 (7.3%), 7 (6.4%) and 1 (0.9%) had undergone 0, 3, 4, 5, 6, 7, 8, 9 and 10 days of treatment respectively. In infants with ABO HDFN 55 (50%), 6 (5.5%), 13 (11.8%), 10 (9.1%), 3 (2.7%), 5 (4.5%), 2 (1.8%), 3 (2.7%), 6 (5.5%) and 7 (6.4%) had stayed in ICU for 5, 6, 7, 8, 9, 10, 11, 12, 13 and 14 days respectively. Mean treatment duration was  $3.13 \pm 3.32$  days. Median and maximum treatment duration was 3 and 10 days respectively. Mean duration of stay in ICU was  $7.21 \pm 2.96$  days. All neonates were observed in ICU for a minimum of 5 days and a maximum of 14 days.

During follow-up after two weeks, hyperbilirubinaemia was detected in 1 (0.9%) infant. Eleven neonates did not attend follow-up clinic. One infant was readmitted for treatment.

Association between neonatal jaundice in siblings and high bilirubin levels in infants with ABO HDFN was assessed using chi-square test. Those coming under high risk and high intermediate risk categories in AAP grading were considered as high bilirubin group and those coming under low intermediate risk and low risk categories were considered as low bilirubin group. P value was 0.001, which was significant. History of neonatal jaundice in sibling was associated with 3.3 times higher risk for hyperbilirubinaemia in neonates affected with ABO HDFN. Odds ratio was 3.332 and confidence interval was 2.226 - 4.987.

Parameters	High Bilirubin	Low Bilirubin	Total	P value	Risk Estimate	95% Confidence Interval
H/O NNJ in sibling	16	3	19	0.001	3.332	2.226 - 4.987
No H/O NNJ in sibling	23	68	91			
<b>Total</b>	<b>39</b>	<b>71</b>	<b>110</b>			

**Table 5. History of Neonatal Jaundice (NNJ) in Siblings and High Bilirubin Levels in Infants with ABO HDFN**

Association between moderate and severe disease and high bilirubin levels was assessed using chi-square test. P value was 0.001, which was significant. Moderate and severe diseases had 2.9 times higher risk for high bilirubin levels in neonates affected with ABO HDFN. Odds ratio was 2.896 and confidence interval was 1.994 - 4.206.

Parameters	High Bilirubin	Low Bilirubin	Total	P value	Risk Estimate	95% Confidence Interval
Moderate and severe disease	8	1	9	0.001	2.896	1.994 - 4.206
Mild disease	31	70	101			
<b>Total</b>	<b>39</b>	<b>71</b>	<b>110</b>			

**Table 6. Severity of Disease and High Bilirubin Levels in Infants with ABO HDFN**

Association between high bilirubin levels and anaemia was assessed using chi-square test; p value was 0.001, which was significant. High bilirubin levels were associated with 4.5 times higher risk for anaemia in neonates affected with ABO HDFN. Odds ratio was 4.491 and confidence interval was 2.848 - 7.080.

Parameters	Anaemia	No Anaemia	Total	P value	Risk Estimate	95% Confidence Interval
High bilirubin	37	2	39	0.001	4.491	2.848 - 7.080
Low bilirubin	15	56	71			
<b>Total</b>	<b>52</b>	<b>58</b>	<b>110</b>			

**Table 7. High Bilirubin Levels and Anaemia in Infants with ABO HDFN**

Association between anaemia and ICU stay for more than one week was assessed using chi-square test; p value was 0.001, which was significant; 19 times higher risk of ICU stay for more than one week was noted in anaemic neonates affected with ABO HDFN. Odds ratio was 18.962 and confidence interval was 4.789 - 75.076.

Parameters	ICU Stay > 1 Week	ICU Stay ≤ 1 Week	Total	P value	Risk Estimate	95% Confidence Interval
Anaemia	34	18	52	0.001	18.962	4.789 - 75.076
No anaemia	2	56	58			
<b>Total</b>	<b>36</b>	<b>74</b>	<b>110</b>			

**Table 8. Anaemia and Duration of Stay of Infants with ABO HDFN in ICU**

In ABO-HDFN, cord blood haemoglobin was negatively correlated with intensity of treatment and severity of disease with a significant p value of 0.001. Correlation was significant at the 0.01 level.

Variable (n-110)	Correlation Coefficient	P value	Interpretation
Intensity of treatment	-.738	.001	Significant Negative Correlation
Severity of disease	-.710	.001	Significant Negative Correlation

**Table 9. Correlation of Cord Blood Haemoglobin in Infants with ABO HDFN**

**DISCUSSION**

This was a research conducted in the Dept. of Transfusion Medicine and Neonatology division in the Dept. of Paediatrics, Govt. Medical College, Thiruvananthapuram from 2012 March to 2013 August; 110 neonates admitted in newborn nursery with ABO HDFN were included in the study.

Mothers of infants with ABO HDFN were mainly primipara (64.6%). ABO incompatible infants of first pregnancy were at risk of significant haemolysis, because ABO antibodies were naturally occurring. Harvey Klein and David Anstee described that in about 50% of cases of ABO HDFN, first ABO incompatible infant was affected. They added that a severe ABO haemolytic disease in first born infant could be followed by a similar severe disease in subsequent infants.<sup>6</sup> Our research yielded similar results.

Mode of delivery was mainly vaginal (68.2%) among mothers of infants with ABO HDFN; 48.2% of infants were males. An analysis by Chan Shu et al had narrated that there was no significant difference in the sex distribution of affected infants in ABO HDFN.<sup>7</sup> Slight female preponderance in ABO HDFN in the present study might be a reflection of population statistics in Kerala, the female-male ratio being 1084:1000.<sup>8</sup>

AAP chart was used to stratify the risk related to bilirubin levels. Among 110 neonates with ABO HDFN 51 (46.4%) belonged to low risk, 22 (20%) to low intermediate risk, 19 (17.3%) to high intermediate risk and 18 (16.4%) to high risk categories. Gilja BK and Shah VP observed that in ABO incompatible infants, minor degrees of red cell destruction

frequently raised neonatal bilirubin levels and slightly dropped haemoglobin concentration.<sup>9</sup> Halbrecht found out that one in 70 - 180 ABO incompatible infants developed jaundice within 24 hours of birth.<sup>10</sup> In a study by Valentine, one in 70 - 180 ABO incompatible infants developed jaundice within 24 hours of birth.<sup>11</sup> Sherer et al observed that in ethnic groups expressing strong, numerous and branched A or B antigen sites, high bilirubin levels, severe anaemia, nucleated red cells and even hydrops fetalis was witnessed.<sup>12</sup> Schellong G had opined that premature infants were protected from ABO HDFN due to fewer A and B sites on erythrocytes.<sup>13</sup> In a research carried out by David and Levine, cord blood bilirubin was not diagnostic of haemolytic disease but was moderately predictive of peak bilirubin levels in ABO HDFN.<sup>14</sup> Whyte J and Graham observed that the cord blood bilirubin was not diagnostic of haemolytic disease, but it correctly predicted on peak bilirubin levels.<sup>15</sup>

In our study, among 110 infants with ABO HDFN, 66.4% had low (risk) bilirubin levels and 33.6% had high (risk) bilirubin levels. History of neonatal jaundice in siblings and severity of disease in ABO HDFN were significantly associated with a higher risk of high bilirubin levels. As found out in our research, Gilja et al and Sherer et al postulated that severe disease was likely to be followed by a similar severe disease in subsequent siblings of the same blood group.<sup>9,12</sup> In our study, during followup after two weeks one infant with ABO HDFN was readmitted for treatment of hyperbilirubinaemia.

In present research among infants with ABO HDFN, majority had no anaemia. Quite accordingly, Shah and Gilja observed that minor degrees of red cell destruction resulted only in slight lowering of haemoglobin concentration in infants with ABO HDFN.<sup>9</sup> In this research mild anaemia was detected in 40 (36.4%), moderate anaemia in 8 (7.3%) and severe anaemia in 4 (3.6%). Mollison and Cutbush observed that in moderately severe ABO haemolytic disease, the cord blood haemoglobin concentration was below normal limits. But it was short lived and anaemia was unusual after first two weeks of life.<sup>16</sup> Murray postulated that severe anaemia was observed in ethnic groups expressing strong, numerous and branched A

and B antigen sites substantiates our above mentioned finding.<sup>17</sup> As with Cutbush and Mollison, who noticed that anaemia was unusual after first 2 weeks in moderately severe ABO haemolytic disease, was similar in our study too.<sup>16</sup> Dufour D R, Monaghan W P opined that sex, race, gravidity, birth weight, blood type, etc. of the infant had no significant relationship to clinical outcome.<sup>2</sup>

In this study, haemoglobin levels displayed a significant negative correlation with intensity of treatment and severity of disease. Close negative correlation between the haemoglobin concentration in cord blood and the infant's chance of survival was demonstrated by Mollison and Cutbush.<sup>18</sup>

Reticulocyte count was increased in 80% of infants in present study. Crawford et al witnessed that a slight increase in reticulocytes was a common feature in ABO HDFN and in an analysis by Levine et al, reticulocyte count exceeded 15% in 54.5% of neonates.<sup>19,20</sup> In present research, spherocytosis was seen in 85.5% of infants with ABO HDFN. Grumbach summarised that in ABO HDFN microspherocytes were frequently prominent in blood films.<sup>21</sup>

Treatment options of HDFN included phototherapy, IVIG and exchange transfusions with supplementary top-up transfusions. In present study majority of infants with ABO HDFN (67.3%) required no interventions, while a few required phototherapy alone (19.1%). Our results were similar to the observations of Bel et al, who described that 26% DAT positive infants with hyperbilirubinaemia needed phototherapy.<sup>22</sup> Osborn et al opined that phototherapy usually prevented further rise in serum bilirubin levels.<sup>23</sup> Murray et al and Osborn et al explained that even dangerous levels of bilirubin concentration in full-term infants with ABO HDFN could be controlled by modern phototherapy alone.<sup>17</sup> They observed that high dose of IVIG and exchange transfusion might be required in certain ethnic groups who express strong A and B sites.<sup>17</sup>

Vreman HJ too opined that moderate hyperbilirubinaemia and even dangerous levels of bilirubin concentration in full-term infants with ABO HDFN could be controlled by modern phototherapy alone.<sup>24</sup> But M D Eugene Kaplan clearly opined that in severely affected infants a trial period of phototherapy was justified, but would not exclude consideration of an exchange transfusion.<sup>25</sup> Severe ABO HDFN which required exchange transfusion was relatively rare in few analyses; none among 1500 neonates in one study, 3 out of 14,000 consecutive births in another study, 3 out of 8000 births in a third study and 6 out of 5704 infants in fourth one.<sup>26,27,28</sup> Falterman C G and Richardson J has observed that transfusion of adult A or B red cells with more antigenic sites might undergo rapid destruction which could result in severe jaundice, kernicterus, haemoglobinuria and even death.<sup>29</sup>

In a Saudi Arabian research, the value of phototherapy along with IVIG was compared with phototherapy alone in reducing the requirement for exchange transfusion in ABO HDFN. They found out that without any side effects IVIG reduced exchange transfusion rate to one-fourth as compared to control group.<sup>30</sup> An alternative successful regime for exchange transfusion was suggested by Lakatos et al which included oral D-penicillamine, phototherapy, intravenous fluids and recombinant human erythropoietin.<sup>31</sup> In a trial by Romano et al, bilirubin levels became normal in 10 out of 13 infants within 5 - 6 days of treatment with A or B

trisaccharides as compared to the control group who never received trisaccharides.<sup>32</sup>

The research was a cross-sectional descriptive study. So the assessment of risk and correlation between variables was done with a limited data. Long term analytical studies with greater number of samples are needed for assessing correlation or risk in ABO HDFN.

## CONCLUSION

1. Majority of infants had mild hyperbilirubinaemia and no or minimal anaemia.
2. Disease was mild in majority of infants with ABO HDFN, thereby requiring no interventions.
3. There is significant association between neonatal jaundice in siblings and high bilirubin levels in next infants, moderate and severe disease and high bilirubin levels, high bilirubin levels and anaemia and anaemia and ICU stay.
4. Cord blood haemoglobin is negatively correlated with intensity of treatment and severity of disease.

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