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Original Article

Paediatrics Section

Comparative Clinical Outcome Based on Direct Antiglobulin Test Status in Neonates with ABO Incompatibility: A Prospective Cohort Study

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ABSTRACT

Introduction: ABO Haemolytic Disease of the Newborn (ABOHDN) is a significant but often under-recognised cause of neonatal haemolysis. A positive Direct Antiglobulin Test (DAT) is observed in 20-40% of ABO incompatible cases.

Aim: To compare clinical outcomes between DAT-positive and DAT-negative neonates and evaluate the predictive value of DAT in ABO incompatible newborns.

Materials and Methods: This prospective cohort study was conducted at Chettinad Hospital and Research Institute, Kelambakkam, Chennai, Tamil Nadu, Southern India, from February 2024 to March 2025. A total of 288 neonates born to mothers with blood group O who underwent cord blood DAT testing were included. Based on DAT results, neonates were categorized as DAT-positive or DAT-negative. The primary outcome was the need for phototherapy. Secondary outcomes included the timing of hyperbilirubinemia, peak bilirubin levels, duration of phototherapy, haemoglobin levels, and readmission rates. Data were statistically analysed using Student's t-test or the Wilcoxon rank-sum test for continuous variables and the Chi-square or Fisher's exact test for categorical variables.

Results: Among 288 neonates, 60 (20.8%) were DAT-positive and 228 (79.2%) were DAT-negative. Phototherapy was needed in 62% of DAT-positive neonates versus 28% in DAT-negative (RR: 2.98, 95% CI: 1.88-4.72; p<0.001). DAT-positive neonates required phototherapy earlier, by a mean of 28.7 hours (p<0.001). No significant differences were noted in peak bilirubin, phototherapy duration, or haemoglobin levels. Readmission for phototherapy was higher in DAT-positive neonates (RR: 2.34; p=0.047). DAT positivity and gestational age independently predicted phototherapy need. DAT showed moderate specificity of 0.88 (95% CI: 0.83-0.92) but low sensitivity of 0.37 (95% CI: 0.27–0.45), with an AUC of 0.621 (95% CI: 0.569-0.674).

Conclusion: Cord blood DAT performed in neonates born to O-positive mothers can independently predict the need for phototherapy. However, its limited sensitivity restricts its utility as a sole screening tool in ABOHDN.

Keywords: Blood group incompatibility, Coombs test, Erythroblastosis, Hyperbilirubinemia, Immunohaemolytic anaemia

INTRODUCTION

The ABOHDN is a significant yet often under-recognised cause of neonatal haemolysis. ABO incompatibility arises when a mother with type O blood has a foetus with blood group A, B, or AB, leading to the formation of maternal IgG antibodies against foetal ABO blood group antigens. These antibodies can cross the placenta, targeting the foetal red blood cells, causing haemolysis, jaundice, and in severe cases anaemia [1]. Although ABO incompatibility occurs in approximately 15-20% of pregnancies, only a small fraction (1-4%) of affected neonates develop clinically significant haemolytic disease that requires medical intervention, such as phototherapy, exchange transfusion, or other treatments [1,2].

The incidence of ABOHDN varies globally, with reported incidence in Indian neonates ranging from 3% to 10% [3]. However, clinical manifestations can differ, with some neonates showing mild jaundice that resolves without intervention, while others may require more intensive care [4]. Outcomes in affected neonates depend heavily on early diagnosis, timely management, and the severity of the haemolysis. Diagnostic tools like the DAT are used to confirm haemolysis in these neonates, and the rate of DAT positivity in ABO incompatibility cases has been reported to range from 30% to 60% [4-6].

A meta-analysis has shown that maternal IgG (anti A/B) titres are associated with risk of ABOHDN [7]. The AAP recommends routine maternal antibody screening when the mother's blood group is O or Rh negative; if this is not done, DAT testing should be performed on cord blood or peripheral blood of these neonates [8]. However, testing for antibody titres (anti A and anti B IgG) routinely for all O blood group mothers will be challenging in resource limited settings. Selective cord DAT testing in such settings has been done in previous studies and is feasible [9,10].

Given the varied clinical presentation, this study was conducted to compare the clinical outcomes between DAT-positive and DAT-negative neonates and the predictive accuracy of DAT as a screening tool in ABO incompatibility.

MATERIALS AND METHODS

This prospective cohort study was conducted at Chettinad Hospital and Research Institute, a tertiary care centre in Chennai, Southern India, over a one year period from February 2024 to March 2025. The study protocol was reviewed and approved by the Institutional Ethics Committee (IHEC/-I/2198/24).

Inclusion criteria: The study included all neonates with blood group A, B, or AB born to mothers with blood group O, in whom cord-blood DAT testing had been performed.

Exclusion criteria: Neonates were excluded if the maternal blood group was O Rh negative (since the manifestation of Rh and ABO incompatibility is altered by the interplay between anti ABO and anti Rh antibodies), if they were preterm infants born at less than 34 weeks of gestation, or if they had major congenital anomalies. Additionally, neonates admitted to the Neonatal Intensive Care Unit (NICU) for unrelated significant illnesses, those with incomplete records, or those whose blood group was also O (indicating no ABO incompatibility) were excluded.

Sample size calculation: Although the study enrolled all eligible neonates during the designated period, a formal sample size calculation was also considered. Based on findings from a previous study [7] that reported phototherapy requirements in 71% of DAT-positive neonates compared to 35% in DAT-negative neonates, the estimated sample size required to detect a statistically significant difference between groups with 80% power and a 5% level of significance was 92. Accounting for a potential 15% rate of missing data, the minimum required sample size was calculated to be 106. However, the final analysis included all neonates meeting the inclusion criteria with complete data available during the study period.

Study Procedure

Data collection: The primary outcome of interest was the requirement for phototherapy to manage neonatal hyperbilirubinemia. Relevant maternal and neonatal clinical information was collected after informed consent. No interventions were performed in the clinical management for the purpose of the study.

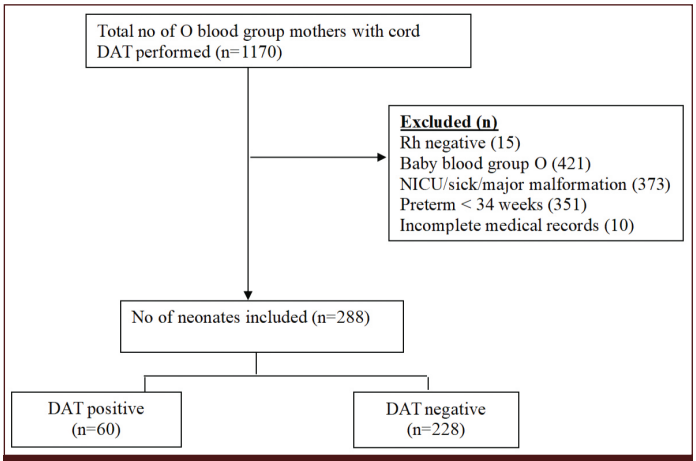
As per unit protocol, a DAT was routinely performed on cord-blood samples of all neonates born to O-positive mothers. The DAT was carried out using the semi-automated gel agglutination method (Bio-Rad Laboratories India Pvt., Ltd., Gurugram, India), and results were recorded on a graded scale (e.g., 1+, 2+, 3+, 4+) [11]. Serum bilirubin measurements were performed either routinely at 48-72 hours of life or earlier in the presence of clinically evident jaundice. Bilirubin levels were measured by spectrophotometry. For neonates with a positive DAT, additional investigations including a complete blood count (CBC), peripheral blood smear, and reticulocyte count were undertaken to evaluate for haemolysis. In the present study, phototherapy was initiated in accordance with the guidelines outlined by the American Academy of Paediatrics (AAP) for the management of neonatal hyperbilirubinemia [8].

STATISTICAL ANALYSIS

Statistical analysis was conducted using Stata version 17 (StataCorp LLC, College Station, TX). Continuous variables were assessed for normality using the Shapiro-Wilk test. Depending on the distribution, they were summarized as either mean and standard deviation or median and interquartile range. Categorical variables were expressed as counts and percentages. Comparisons between the two groups were made using Student's t-test or the Wilcoxon rank-sum test for continuous variables and the Chi-square or Fisher's exact test for categorical variables. Multivariate logistic regression analysis was performed to identify independent predictors of phototherapy requirement, with inclusion of relevant maternal and neonatal variables. Additionally, Receiver Operating Characteristic (ROC) curve analysis was performed to assess the predictive value of a positive DAT for the need for phototherapy. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 288 neonates were included in the study, of whom 60 (20.8%) were DAT-positive and 228 (79.2%) were DAT-negative [Table/Fig-1]. The overall median (IQR) gestational age was 38 (37-39) weeks, and the median birth weight was 2920 (2625-3187) grams. Males comprised 58% of the study population. Late preterm births (34-36 weeks) accounted for 16% of the cohort. Maternal characteristics were also comparable between the groups. Among cases of ABO incompatibility, 38% were OA-type and 62% OB-type.



[Table/Fig-1]: Study flow.

Baseline characteristics were largely comparable between the DAT-positive and DAT-negative groups, with two exceptions: the proportion of male neonates was significantly higher in the DAT-negative group (p=0.012), while OA incompatibility was significantly more common in the DAT-positive group (p=0.002) [Table/Fig-2]. The need for phototherapy was significantly higher among DAT-positive neonates compared to DAT-negative neonates (62% vs 28%; RR: 2.98, 95% CI: 1.88-4.72; p <0.001). Furthermore, the onset of hyperbilirubinemia requiring phototherapy occurred earlier in the DAT-positive group (median: 38 hours vs 52 hours; mean difference: -29 hours, 95% CI: -41 to -16; p <0.001). Readmission rates for phototherapy were also significantly higher in DAT-positive neonates (RR: 2.34, 95% CI: 1.33-4.15; p=0.047) [Table/Fig-3]. Among the DAT-positive neonates, 62% were DAT 1+ and 38% were DAT 2+. The need for phototherapy was not different between DAT 1+ (54%) and DAT 2+ (74%) groups (RR 0.73 [0.49, 1.07], p=0.124).

Variables	Total (n=288)	DAT-negative (n=228)	DAT-positive (n=60)	p-value
Gestation (wk)[b]	38 (37,39)	38 (37, 39)	38 (37, 39)	0.617
Preterma	46 (16)	36 (16)	10 (16)	0.869
Birth weight (g)	2920 (2625, 3187)	2900 (2630, 3195)	2965 (2480, 3170)	0.88
Growth[a]				
AGA	228 (79)	178 (78)	50 (83)	0.275
SGA	51 (18)	41 (18)	10 (16)	
LGA	9 (3)	9 (3)	0	
Gender[a]				
Male	166 (58)	140 (61)	26 (43)	0.012
Female	122 (42)	88 (39)	34 (57)	
Baby blood group[a]				
A	109 (38)	76 (33)	33 (55)	0.002
B	179 (62)	152 (67)	27 (45)	
Mode of delivery[a]				

Vaginal	126 (44)	102 (45)	24 (40)	0.510
LSCS	162 (56)	126 (55)	36 (60)	
Maternal age[b]	27 (24, 29)	27 (24, 29)	26 (24, 29)	0.507
Maternal Hb[b]	10.4 (10.1, 11)	10.4 (10.1, 11)	10.3 (10.1, 11)	0.957
Primigravida[a]	141 (49)	118 (52)	23 (38)	0.064
Maternal diabetes[a]	77 (27)	62 (27)	15 (25)	0.733
Maternal hypertension[a]	24 (8)	17 (7)	7 (12)	0.294
Maternal anaemia[a]	45 (16)	33 (14)	12 (20)	0.294
Maternal hypothyroid[a]	51 (18)	43 (19)	8 (13)	0.318
DCC[a]	252 (88)	208 (91)	54 (89)	0.768
Need for resuscitation[a]	24 (8)	17 (7)	7 (11)	0.294

[Table/Fig-2]: Baseline and clinical characteristics.
a= n(%); b =Median (IQR)

Variables	Total (n=288)	DAT-positive (n=60)	DAT-negative (n=228)	OR/RR/MD 95% CI	p-value
Need for PT[a]	101 (35)	37 (62)	64 (28)	OR: 4.1 (2.27, 7.47) RR: 2.98 (1.88, 4.72)	<0.001
Age of starting PT in hours[c]	48 (42,64)	38 (26, 48)	52 (48, 83)	MD -28.7 (-16.1, -41.2)	<0.001
Peak Serum Bilirubin in mg/dL[c]	11.5 (9.8, 15.1)	11.6 (10.16, 15.4)	11.5 (9.6, 15)	MD 0.34 (-1.1, 1.8)	0.442
Direct fraction[c]	0.31 (0.24, 0.39)	0.27 (0.23, 0.35)	0.31 (0.25, 0.40)	MD: -0.03 (0.01, -0.06)	0.021
Duration of PT in hours[b] (n=101)	26 (±17)	29 (±17)	24.6 (±17)	MD 4.4 (-2.6, 11.5)	0.213
>1 Episode of phototherapy[a]	18 (18)	4 (7)	14 (6)	RR 1.07 (0.44, 2.62) OR: 1.09 (0.35, 3.44)	0.850
Readmission for Phototherapy[a]	2 (2)	2 (5)	0 (0)	RR: 2.34 (1.33, 4.15) OR: 9.1 (0.4, 194.5)	0.047
Hb in g/dL[b] (n=83)	17.8 (±2.3)	17.4 (±2.5)	18.1 (±2.2)	MD: -0.5 (0.4, -1.6)	0.272
Reticulocyte count (%)[b]	5.2±(2)	5.9(±1.8)	3.8±(1.8)	MD: 2.1(1.1, 3.2)	<0.001
Duration of hospital stay in days[c]	5 (4,6)	5 (4,6)	5 (4,5)	MD: 0.10 (0.28, -0.5)	0.877

[Table/Fig-3]: Neonatal hyperbilirubinemia related outcomes between the two groups.
a= n (%); b= Mean (±SD); c= Median (IQR)

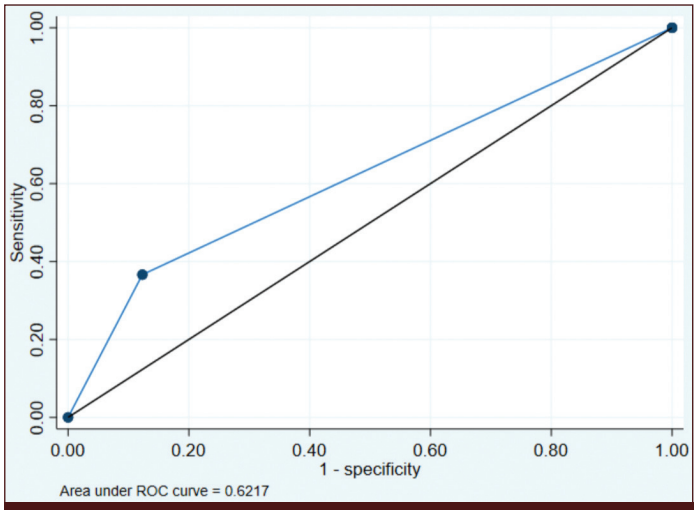
A multivariate logistic regression analysis identified independent predictors of the need for phototherapy. DAT positivity (adjusted OR: 4.84, 95% CI: 2.51-9.34; p <0.001) and lower gestational age (adjusted OR: 0.68, 95% CI: 0.56-0.82; p <0.001) emerged as independent predictors of phototherapy requirement [Table/Fig-4]. The ROC curve analysis evaluated the predictive ability of cord blood DAT for identifying neonates at risk for requiring phototherapy. The test demonstrated modest discriminative ability, with an AUC of 0.621 (95% CI: 0.569-0.674). Sensitivity was 0.37 (95% CI: 0.27–0.45), and specificity was 0.88 (95% CI: 0.83-0.92). The positive likelihood ratio (LR+) was 2.97, while the negative likelihood ratio (LR–) was 0.72 [Table/Fig-5,6].

S. no	Variables	Adjusted OR	95% CI	p-value
1	DAT-positive	4.84	(2.51,9.34)	<0.001
2	Male gender	0.66	(0.37,1.16)	0.155
3	Gestation	0.68	(0.56, 0.82)	<0.001
4	Baby blood group A	0.83	(0.47,1.44)	0.511
5	DCC	0.31	(0.08, 1.19)	0.081
6	Maternal diabetes	1.01	(0.55, 1.85)	0.976
7	Need for resuscitation	0.9	(0.22, 3.51)	0.869

[Table/Fig-4]: Multivariate logistic regression showing predictors of need for phototherapy.

Diagnostic accuracy parameter	Results
Sensitivity (95% CI)	0.37 (0.27, 0.45)
Specificity (95% CI)	0.88 (0.83, 0.92)
LR+	2.97
LR-	0.72
PPV	0.62
NPV	0.72
AUC (95% CI)	0.621 (0.568, 0.674)

[Table/Fig-5]: Predictive ability of DAT-positive for need for phototherapy.



[Table/Fig-6]: ROC curve showing predictive ability of DAT for need for phototherapy.

DISCUSSION

This study evaluated the clinical implications of DAT positivity in neonates with ABO incompatibility. Our findings demonstrate that DAT status serves as an independent predictor of the need for phototherapy, with poor sensitivity (37%) and high specificity (88%).

Approximately two-thirds of DAT-positive neonates required phototherapy, consistent with previous studies suggesting a greater haemolytic burden in this group, predisposing them to earlier onset and more severe hyperbilirubinaemia [10,12]. Additionally, phototherapy was initiated significantly earlier in DAT-positive neonates, indicating more rapid bilirubin accumulation and emphasising the clinical relevance of DAT in early identification of neonates at risk for significant jaundice.

Importantly, despite laboratory evidence of haemolysis, none of the DAT-positive neonates required Intravenous Immunoglobulin (IVIG) or exchange transfusion, reflecting the typically mild to moderate nature of haemolysis associated with ABO incompatibility. This observation is in line with previous studies [9,10]. Interestingly,

although there were significant differences in phototherapy initiation and rates between groups, peak serum bilirubin levels and duration of phototherapy did not significantly differ. This likely reflects the efficacy of standardised treatment protocols, ensuring effective bilirubin control once therapy is initiated. Similarly, mean haemoglobin levels did not show a significant difference between DAT-positive and DAT-negative groups, which may be attributed to the less severe haemolysis in ABO incompatibility compared to conditions such as Rh isoimmunisation.

While demographic differences were noted-namely, a higher proportion of males in the DAT-negative group and increased OA-type incompatibility in the DAT-positive group-multivariate analysis confirmed DAT positivity as an independent predictor of phototherapy requirement, after adjusting for these and other potential confounders. Additionally, lower gestational age emerged as an independent risk factor, consistent with the known susceptibility of late preterm and early term neonates to hyperbilirubinaemia due to immature hepatic conjugation pathways and reduced bilirubin clearance. Despite its association with the need for phototherapy, the diagnostic performance of DAT was modest. The area under the ROC curve (AUC) was 0.621, indicating limited discriminative ability. Although the high specificity (88%) implies that DAT-positive neonates are more likely to require phototherapy, the low sensitivity (37%) suggests that many at-risk neonates would be missed if DAT is used in isolation. The positive likelihood ratio (2.97) modestly improves post-test probability, but the negative likelihood ratio (0.72) limits its utility in ruling out the need for treatment. These findings mirror those reported in previous studies and a recent meta-analysis [9,10,13-19].

To illustrate the modest diagnostic performance of DAT, consider a hypothetical cohort of 100 neonates with ABO incompatibility. Based on our study findings, if 40 of these neonates ultimately required phototherapy, a DAT test with 37% sensitivity and 88% specificity would correctly identify only 15 of them (true positives), while missing 25 neonates who needed treatment (false negatives). Among the 60 neonates who did not require phototherapy, 53 would be correctly classified as true negatives, but 7 would be incorrectly labeled as DAT-positive (false positives).

Collectively, these results reiterate that DAT alone is insufficient as a universal screening tool for clinically significant hyperbilirubinaemia in the context of ABO incompatibility, in line with previous studies [20,21]. Given its low sensitivity, reliance solely on DAT status could delay the recognition and treatment of at-risk neonates. A more comprehensive risk assessment model, incorporating gestational age, clinical findings, and early bilirubin trends, may enhance predictive accuracy and clinical decision-making.

The strengths of this study lie in its prospective nature, well-defined cohort, and the application of multivariate analysis to adjust for potential confounders.

Limitation(s)

The study has several limitations. The single-centre setting may limit generalisability. Additionally, the absence of transcutaneous bilirubin measurement and the lack of follow-up data on long-term outcomes such as anaemia in infancy (due to persistent low-grade haemolysis) restrict the ability to assess the full clinical impact of DAT positivity.

CONCLUSION(S)

Cord-blood DAT positivity is associated with an increased and earlier need for phototherapy, as well as a higher risk of readmission among neonates with ABO incompatibility. Although specificity is moderate, the low sensitivity restricts its usefulness as a standalone screening test. These findings support a more comprehensive risk assessment that includes DAT status, gestational age, clinical risk factors, and early bilirubin monitoring. The routine use of cord-blood DAT, particularly for O-positive mothers, warrants further evaluation of cost-effectiveness given its modest predictive value.

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