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ORIGINAL ARTICLE

Analysis of the clinical and laboratory outcomes of newborns with ABO incompatibility reactions

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Abstract

Introduction: Although ABO incompatibility presents a high incidence, the occurrence of hemolytic disease of the newborn requiring therapy, such as phototherapy, is low. There are controversies in literature regarding positivity of the immunological tests and their correlation with clinical features of hemolytic disease. **Objectives:** To describe and analyze clinical and laboratory outcomes, as well as treatment strategies for those who presented with a positive eluate testing. **Methods:** A retrospective cohort study conducted during one year in a public hospital in São Paulo, Brazil. **Results:** A total of 360 newborns were included. The majority presented a blood group type A and a negative coombs test (69%). Phototherapy was required for 43.6% of the patients and 25.8% developed HDN. **Conclusion:** The minority of all patients evaluated need treatment with phototherapy, one third was diagnosed with hemolytic disease of the newborn and any severe outcomes.

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INTRODUCTION

Newborns with blood type A or B, born to group O mothers, present ABO incompatibility.¹ Diagnosis is based on detecting erythrocytes sensitized by maternal immunoglobulins. Although the Coombs test identifies maternal antibodies, it does not determine their specificity. The eluate test, more sensitive than the Coombs test, can detect antibodies bound to red cells even at low concentrations.²

Maternal and neonatal blood typing is universally performed in Brazilian hospitals.³ Eluate testing is indicated when the mother is group O and the newborn is A or B, even with a negative Coombs test. Maternal antibodies may persist for weeks, causing increased unconjugated bilirubin due to immature hepatic conjugation and, occasionally, hemolytic anemia.¹

Despite an ABO incompatibility incidence of about 20%,¹ hemolytic disease of the newborn (HDN) occurs in only 0.3–0.8% of Caucasians and up to 5% of Africans and Asians.⁴ Most cases are mild, with 0.02–1.4% developing HDN.^{5–6} This study analyzed clinical and laboratory outcomes of newborns with positive eluate results in a São Paulo public maternity hospital.

METHODS

We conducted a retrospective cohort study at a public hospital in São Paulo, Brazil. The study included all newborns with a gestational age greater than 35 weeks, admitted to rooming-in care, who presented ABO blood group incompatibility confirmed by positive eluate testing, between January and December 2020.

Patients with comorbidities that could affect their clinical or laboratory outcomes during the first days of life were excluded, such as those born to mothers with positive tests for COVID-19 or syphilis. Newborns with incomplete clinical or laboratory data were also excluded.

The project was approved by the Research Ethics Committee of Hospital Israelita Albert Einstein. The Informed Consent Form was obtained digitally from one of the parents or a legal guardian, and telephone contact was used when necessary. Exemption from the consent form was requested when it was not possible to reach the parents through hospital records.

Data were collected from electronic medical records by two trained members of the research team, including a medical student and a physician. Baseline characteristics included gestational age, birth weight, sex, type of delivery (vaginal, cesarean, or forceps), and maternal parity.

Laboratory data included neonatal blood type, direct Coombs and eluate results, maximum bilirubin levels during hospitalization, bilirubin levels at phototherapy initiation and at discharge, hemoglobin, hematocrit, and reticulocyte counts.

Clinical outcomes included the need for phototherapy, age (in hours) at indication, phototherapy duration, need for intravenous immunoglobulin or exchange transfusion, length of

hospital stay, occurrence of hemolytic disease of the newborn (HDN), kernicterus, outpatient follow-up, and rehospitalization. The diagnosis of HDN followed institutional laboratory criteria, based on the presence of positive antibodies and any of the following: reticulocytosis, hemoglobin below reference value, and/or total bilirubin ≥ 10 mg/dL in the first 24 hours of life.

Data analysis

From 423 newborns with positive eluate testing between January and December 2020, 63 were excluded: one with gestational age < 35 weeks, one due to refusal to participate, two who died at birth, forty-seven requiring intensive care, and twelve with incomplete data.

Quantitative variables were described using mean $\pm$ standard deviation (SD), minimum and maximum values, median, and interquartile range (IQR). Qualitative variables were expressed as absolute and relative frequencies.⁷ Comparisons between groups were performed using Fisher's exact or Chi-square tests for qualitative variables, and Student's t-test or Mann–Whitney test for quantitative variables, according to data distribution.

Data normality was assessed with the Shapiro–Wilk test, boxplots, histograms, and quantile–quantile plots.⁷ Associations between variables and phototherapy requirement were analyzed using simple and multiple logistic regression, with results expressed as odds ratios (OR), 95% confidence intervals (CI), and p values.⁸

Analyses were performed using IBM SPSS Statistics, version 26.0, adopting a 5% significance level.⁹

RESULTS

Baseline characteristics

Data were collected from 360 newborn medical records. Analysis showed a predominance of male infants, term neonates (37 to 41 weeks + 6 days), vaginal delivery, and mothers with one or more previous pregnancies (66.7%). Most newborns had a birth weight between 3,000 and 3,499 grams (52.8%). Laboratory results revealed a predominance of blood type A+ (66.9%), consistent with the general population (Figure 1). All patients tested positive for eluate, and the Coombs test was performed in every mother–infant pair.

Phototherapy was required for 157 newborns, with a mean initiation time of 31 hours of life. Data on phototherapy duration were available for 154 patients, with a mean duration of 37 hours. The mean bilirubin level at phototherapy initiation was 10.6 ± 2 mg/dL. All patients had at least one bilirubin measurement during hospitalization, with a mean total value of 8.5 ± 3.4 mg/dL.

The mean hospital stay was 2.8 ± 1.5 days. Nine newborns had prolonged hospitalization for reasons unrelated to jaundice or phototherapy. Two of these required phototherapy—one receiving triple phototherapy—both met

criteria for hemolytic disease of the newborn (HDN) but did not require readmission.

One patient (0.3%) presented with early jaundice and persistent hyperbilirubinemia despite phototherapy, requiring human immunoglobulin (initial bilirubin 14.0 mg/dL, 67 hours of phototherapy). The outcome was favorable, with discharge and no complications. No patient required exchange transfusion, developed kernicterus, hospital-acquired infection, or died.

At discharge, 59 patients (16.4%) were advised to return for jaundice reassessment; 14 (23.3%) attended follow-up, and 3 were readmitted—two for rebound jaundice and one for a surgical condition.

Hemolytic disease of the newborn (HDN).

Hemolytic disease of the newborn (HDN) was evaluated in 155 patients who had complete laboratory data for diagnosis. Among them, 40 (25.6%) met the criteria for HDN.

Sex and neonatal blood type were significantly associated with HDN occurrence (72.5% vs. 46.1%; $p = 0.004$).

Newborns with HDN had a longer median duration of phototherapy (47 h vs. 29.5 h; $p < 0.001$) and higher mean bilirubin levels at the time of phototherapy indication (11.3 vs. 10.2 mg/dL; $p = 0.002$). Their maximum total bilirubin levels were also higher (11.8 vs. 10.4 mg/dL; $p = 0.003$), as was the reticulocyte count, whereas hemoglobin levels were significantly lower compared with those without HDN. Patients with HDN also required a longer hospital stay.

Coombs test.

A significant difference was observed between groups with positive and negative Coombs tests regarding sex ($p = 0.001$), with a higher proportion of female newborns among those with positive results (64% vs. 45.8%). Other demographic variables showed no significant differences between groups.

Table 1 - Sample comparison about presence or not of HDN (Hemolytic disease of the newborn).

	Hemolytic disease of the newborn				<i>p-value</i>
	No (n=115)		Yes (n=40)		
	n	%	n	%	
Sex					0,004 ^a
Male	62	53,9	11	27,5	
Female	53	46,1	29	72,5	
Blood type					0,001 ^b
A	85	73,9	24	60	
B	30	26,1	16	40	
Phototherapy					0,237 ^a
No	17	14,8	3	7,5	
Yes	98	85,2	37	92,5	
Direct Coombs test					0,0093 ^a
Negative	77	67,0	18	45,0	
Positive	38	33,0	22	55,0	
Hours of life at phototherapy indication					0,079 ^c
Mean and standard-deviation	31,3	11,2	27	10	
Minimum and maximum	11	72	12	51	
Median and quartiles	30	24-37	26	20-35	
Time in phototherapy (hours)					<0,001 ^c
Mean and standard-deviation	33	15,9	50	27	
Minimum and maximum	6	89	14	158	
Median and quartiles	29,5	22,5-42,5	47	30-68	
Days of hospitalization					0,035 ^c
Mean and standard-deviation	3,1	1,5	3,5	1,4	
Minimum and maximum	2	16	2	8	
Median and quartiles	3	2-3	3	2,5-4	

^a - Chi-square test

^b - Fisher's exact test

^c - Mann-Whitney test

Phototherapy was more frequent in newborns with positive Coombs tests (57.7% vs. 37.3%; $p < 0.001$), and these infants began treatment earlier (median 25 h vs. 32 h). Although bilirubin levels at the time of phototherapy indication did not differ significantly, newborns with positive Coombs tests required longer treatment (median 42 h vs. 24 h; $p < 0.001$).

The prevalence of hemolytic disease of the newborn (HDN) was also higher among those with positive Coombs results (36.7% vs. 18.9%; $p = 0.014$). In addition, these newborns had higher bilirubin levels at admission (median 9.5 vs. 8.3 mg/dL; $p = 0.003$), increased reticulocyte counts (median 4.2% vs. 3.8%; $p = 0.012$), and longer hospital stays.

Phototherapy

Among the 360 patients analyzed, those requiring phototherapy showed a significantly higher proportion of positive direct Coombs tests compared with those who did

not (40.8% vs. 23.2%; $p < 0.001$). Blood type distribution did not differ significantly between groups (Table 3).

Newborns who required phototherapy had higher bilirubin levels at admission (median 10.8 mg/dL vs. 7.2 mg/dL; $p < 0.001$), longer hospital stays (median 3 vs. 2 days; $p < 0.001$), and a greater proportion of outpatient returns (30.6% vs. 5.4%; $p < 0.001$).

Multiple logistic regression was performed to identify factors associated with phototherapy requirement among newborns with positive eluate testing. Variables that showed significant associations in univariate analyses included birth weight < 3000 g, greater in-hospital weight loss, positive Coombs test, maximum bilirubin values at admission and discharge, length of hospitalization, and need for outpatient follow-up (Table 4).

In the multivariate model, percentage of weight loss and maximum bilirubin level during hospitalization remained independently associated with an increased likelihood of requiring phototherapy.

Table 2: Sample comparison about direct Coombs test (n=360).

	Direct Coombs Test				<i>p-value</i>
	Negative (n=249)		Positive (n=111)		
	n	%	n	%	
Sex					0,001 ^a
Male	135	54,2	40	36,0	
Female	114	45,8	71	64,0	
Blood type					0,051 ^b
A	163	65,5	88	79,3	
B	86	34,5	23	20,7	
Phototherapy					<0,001 ^a
No	156	62,7	47	42,3	
Yes	93	37,3	64	57,7	
Hemolytic disease of the newborn					0,014 ^a
No	77	81,1	38	63,3	
Yes	18	18,9	22	36,7	
Hours of life at phototherapy indication					<0,001 ^c
Mean and standard-deviation	34	12	26	9	
Minimum and maximum	11	72	12	57	
Median and quartiles	32	26-39	25	19,5-33	
Time in phototherapy (hours)					<0,001 ^c
Mean and standard-deviation	32	16	44	24	
Minimum and maximum	6	74	12	158	
Median and quartiles	24	20-41	42	24-51	
Days of hospitalization					0,049 ^d
Mean and standard-deviation	2,7	1,4	3,1	1,7	
Minimum and maximum	2	16	2	13	
Median and quartiles	2	2-3	3	2-3	

^a - Chi-square test

^b - Fisher's exact test

^c - Mann-Whitney test

Table 3 - Sample comparison about phototherapy need (n=360).

	Phototherapy				<i>p-value</i>
	No (n=203)		Yes (n=157)		
	n	%	n	%	
Sex					0,946 ^a
Male	99	48,8	76	48,4	
Female	104	51,2	81	51,6	
Blood type					0,592 ^b
A	140	69,0	93	59,2	
B	63	31,0	64	40,8	
Direct Coombs test					<0,001 ^a
Negative	156	76,8	93	59,2	
Positive	47	23,2	64	40,8	
Hemolytic disease of the newborn					<0,001 ^d
No	17	85,0	98	72,6	
Yes	3	15,0	37	27,4	
Days of hospitalization					<0,001 ^c
Mean and standard-deviation	2,5	1,3	3,3	1,6	
Minimum and maximum	2	13	2	16	
Median and quartiles	2	2-3	3	2-4	

^a - Chi-square test^b - Fisher's exact test^c - Mann-Whitney test**Table 4:** Need for phototherapy models.

	Simple Model		Multiple model	
	Odds ratio (OR)	P-value	Odds ratio (OR)	P-value
	(95% CI)		(95% CI)	
Birth weight (grams)				
Bellow 3000g	2.71 (1.43 - 5.12)	0,002	1.82 (0.61 - 5.45)	0,284
3000g to 3499g	2,32 (1,34 - 4,03)	0,003	1,89 (0,76 - 4,70)	0,170
Above 3500g	Reference	-	Reference	-
Weight loss during hospitalization (%)	1.29 (1.17 - 1.42)	<0,001	1.25 (1.07 - 1.47)	0,006
Direct Coombs Test				
Positive	2.28 (1.45 - 3.60)	<0,001	1.65 (0.75 - 3.63)	0,212
Negative	Reference	-	Reference	-
Maximum bilirubin value at admission (mg/dl)	3.02 (2.37 - 3.84)	<0,001	6,08 (3,71 - 9,95)	<0,001
Bilirubin value at hospital discharge (mg/dl)	1.85 (1.60 - 2.13)	<0,001	0.42 (0.28 - 0.62)	<0,001
Days of hospitalization	1,98 (1,51 - 2,60)	<0,001	1.06 (0.73 - 1.55)	0,764
Outpatient return				
Yes	7.69 (3.83 - 15.42)	<0,001	2.53 (0.96 - 6.70)	0,061
No	Reference	-	Reference	-

DISCUSSION

ABO incompatibility is the leading cause of neonatal jaundice related to blood group incompatibility, affecting about 20% of newborns, yet it usually has a benign course.^{4,10} The correlation between positive immunologic tests and clinical

severity remains uncertain. Although HDN is more frequent in infants with blood type A, severe cases may also occur in those with type B.¹¹

Unlike Rh incompatibility, ABO hemolytic disease does not require prior maternal sensitization.¹¹ Antibodies may form during the first pregnancy and recur in up to 87% of

subsequent ones.¹¹ In our cohort, 66.7% of newborns were from multiparous mothers, compared with 51.5% reported among live births in São Paulo from 2013 to 2017.¹²

Eluate Test

In clinical practice, a positive eluate test in asymptomatic newborns often prompts additional tests and interventions motivated mainly by concern over potential hyperbilirubinemia. However, most newborns with a positive eluate result do not develop significant hyperbilirubinemia.¹³ In our cohort, only 43.6% of these patients required phototherapy, indicating that the majority experienced an uncomplicated clinical course.

A Dutch cohort study reported a case of neonatal jaundice in an infant with ABO incompatibility and a negative direct Coombs test. Because of strong clinical suspicion of hemolytic disease, an eluate test was performed, confirming anti-A antibodies.¹³ This illustrates the rational use of the eluate test guided by clinical context rather than routine screening.

The eluate test remains useful to identify antibodies involved in hemolysis and to guide monitoring for hyperbilirubinemia requiring phototherapy.

Coombs Direct Test

The direct Coombs test screens for antibodies attached to neonatal red blood cells. In cases of ABO incompatibility, approximately 33% of newborns show a positive result,¹⁴ while the eluate test demonstrates greater sensitivity for detecting anti-erythrocyte antibodies.¹⁵

Although widely used in clinical practice, the direct Coombs test has a low positive predictive value (12–53%) for identifying hemolytic disease of the newborn (HDN) or predicting the need for phototherapy.¹⁶ In our cohort, most newborns with a positive Coombs result required phototherapy, whereas only a minority of those with negative results did. Thus, the test alone is unreliable for identifying infants at risk but may indicate increased attention to potential hyperbilirubinemia.

Currently, bilirubin measurement remains the only reliable indicator for initiating phototherapy, despite other tests suggesting possible risk for pathological hyperbilirubinemia. A positive Coombs test does not necessarily correlate with jaundice severity.^{16,17}

Newborns with both positive eluate and Coombs tests had an earlier phototherapy indication and required longer treatment compared with those with positive eluate but negative Coombs results, confirming that dual antibody positivity increases the likelihood of phototherapy need.

Bilirubin dosage

The Brazilian Society of Pediatrics recommends active screening for hyperbilirubinemia risk factors in all newborns older than 35 gestational weeks.¹⁷ A useful early predictor of hyperbilirubinemia due to ABO incompatibility is a total bilirubin level of 4–6 mg/dL at six hours of life.¹⁸

Most newborns, regardless of blood group incompatibility, develop physiological jaundice within the first week of life, characterized by a mild bilirubin rise around the third or fourth day and spontaneous resolution by the second week.¹⁹ In our sample, most cases of hyperbilirubinemia occurred after 24 hours of life, often without medical intervention. In our institution, phototherapy is indicated based on postnatal age and bilirubin levels according to the Bhutani nomogram. Thus, some newborns with ABO incompatibility may present physiological jaundice that resolves naturally within the first weeks of life.

Newborns who required phototherapy had higher bilirubin levels, with a 508% increased likelihood of treatment for each 1 mg/dL increase in total bilirubin.

A Turkish cohort of 136 newborns with ABO incompatibility measured bilirubin at six hours and performed serial testing during the first five days. Reticulocyte count, positive direct Coombs test, and sibling history of jaundice were significant predictors of hyperbilirubinemia development.¹⁸

Phototherapy

Phototherapy is the first-line treatment for neonatal jaundice. It is safe, effective, and prevents the need for invasive procedures. Indications are based on total bilirubin levels, postnatal age, and gestational age.¹⁷ In our study, less than half of the newborns required phototherapy. Similarly, an Indian prospective cohort reported that 30.4% of infants with ABO incompatibility required treatment.¹⁰

In univariate analysis, birth weight <3000 g, greater in-hospital weight loss, positive Coombs test, higher maximum bilirubin levels (at admission and discharge), longer hospital stay, and need for follow-up were all associated with phototherapy in newborns with positive eluate results.

When evaluated together, only the greatest weight loss and maximum bilirubin value remained independently associated with phototherapy need, consistent with current guidelines emphasizing bilirubin-based thresholds. Specific antibody tests did not influence phototherapy indication.

Each 1% increase in weight loss raised the likelihood of requiring phototherapy by 25.3%. Significant weight loss is therefore a key risk factor for clinically relevant hyperbilirubinemia.¹⁷ Although the etiology of hyperbilirubinemia in newborns with ABO incompatibility and marked weight loss is multifactorial, these findings highlight the importance of careful monitoring in such cases.

Newborns with both positive eluate and Coombs tests had twice the likelihood of requiring phototherapy compared with those with a positive eluate but negative Coombs result. A retrospective cohort from New Zealand reported that 23% of newborns with a positive Coombs test developed hyperbilirubinemia requiring phototherapy.²⁰

Hemolytic disease of newborn

Hemolytic disease of the newborn (HDN) should be considered in infants with early-onset or severe

hyperbilirubinemia, positive maternal antibody tests, severe anemia, fetal hydrops, hemolysis, or prolonged jaundice.¹⁶ HDN accounts for approximately 20% of all jaundice cases, with ABO and Rh incompatibility responsible for two-thirds of diagnoses.²¹ Predicting which newborns with ABO incompatibility will develop HDN during hospitalization remains a clinical challenge.

In our cohort, 155 patients had sufficient data for HDN evaluation. Of these, one-quarter were diagnosed with HDN, corresponding to 1.1% of all births in our hospital. Reported incidences of HDN in ABO incompatibility range from 1:150 to 1:3,000.¹¹

Most infants with HDN required phototherapy and remained under treatment longer than those without hemolysis. Literature indicates that 4–6 hours of phototherapy can reduce bilirubin to non-treatment levels.¹⁶ In an Indian prospective cohort, 54.3% of infants requiring phototherapy showed laboratory evidence of hemolysis.¹⁰ In our sample, 27.4% of those treated with phototherapy had confirmed HDN.

Current guidelines recommend early initiation of phototherapy in newborns at high risk or diagnosed with HDN to prevent the need for immunoglobulin, exchange transfusion, or adverse neurological outcomes.²²

Most cases of HDN due to ABO incompatibility are characterized by bilirubin levels above 17.5 mg/dL, often observed during readmission, but without significant anemia.¹⁶ In our study, none of the readmitted infants were diagnosed with HDN.

Hospital Stays

The National Breastfeeding Incentive Program of the Brazilian Ministry of Health recommends rooming-in for the mother–newborn dyad for at least 48 hours, recognizing hospitals as safe, educational environments for detecting early neonatal conditions.²³

In our sample, the average hospital stay was 60 hours, increasing to 134.4 hours among patients with HDN. Newborns with positive Coombs tests or those receiving phototherapy had a mean hospital stay of 72 hours. Previous studies have shown that infants undergoing phototherapy remain hospitalized longer than those who do not (79 vs. 50 hours).²⁴

Prolonged hospitalization impacts healthcare costs, infection risk, and family well-being. At our institution, the average daily cost of rooming-in care is approximately R\$800. Patients with ABO incompatibility incur an average total cost of R\$2,000, which increases by 20% when phototherapy is required and by 123% when HDN is diagnosed.

The Pan American Health Organization defines healthcare-associated infections in newborns as those acquired during the neonatal period, excluding transplacental transmission. Infections occurring after 48 hours of life are typically due to exposure to hospital flora, transmitted by contact with colonized individuals (health professionals' hands or contaminated instruments).²³ Newborns with ABO incompatibility, especially those receiving phototherapy,

undergo multiple venipunctures that disrupt skin integrity and increase susceptibility to infection from hospital or endogenous microorganisms.

The social impact of prolonged hospitalization includes maternal distress, unmet expectations, and economic strain, as families may lose income during the newborn's hospital stay.

Weaknesses

This was a historical cohort study conducted in a single hospital, with data manually extracted from medical records that were sometimes incomplete or inconsistently documented. Additional information loss occurred due to the absence of standardized record-keeping and the lack of clearly defined criteria for discontinuing phototherapy.

CONCLUSION

The results demonstrate that newborns with ABO blood group incompatibility and a positive eluate test present several clinical and laboratory findings during the first days of life. Phototherapy indication remains based exclusively on bilirubin levels, as no other test currently predicts the need for treatment.

Although the Coombs and eluate tests confirm the presence of antibodies, they do not predict the risk of developing HDN or the need for phototherapy. Their positivity should instead serve as a warning for possible bilirubin elevation and hemolysis, given their potential neurological implications.

While the eluate test helps elucidate the etiology of jaundice, its routine use in ABO incompatibility cases does not appear clinically justified. Understanding these associations may guide more rational diagnostic testing, optimize therapeutic decisions, reduce hospitalization time, and promote safer, more cost-effective neonatal care.

Future studies should further investigate the influence of these variables by comparing newborns with positive and negative eluate results.

ADDITIONAL INFORMATION

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