

A Comparative Analysis of the Efficacy of Blood Exchange Therapy in Neonatal Hyperbilirubinemia Induced by ABO and Rh Incompatibility

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Background: This study challenges the prevailing view that hemolytic diseases of the newborn (HDN) associated with the Rh blood group system are more severe than those caused by the ABO system. The objective was to assess the effectiveness of exchange transfusion (ET) in managing HDN, with a focus on comparing treatment outcomes between ABO and Rh incompatibility cases.

Methods: A study enrolled 125 neonates diagnosed with hyperbilirubinemia, comprising 66 males and 59 females. The gestational age of the neonates ranged from 33 to 41 weeks, and their birth weights varied between 2.11 to 4.3 kilograms. Based on the etiology of hemolysis, the study categorized 73 cases as ABO group and 52 as Rh group.

Results: Post- ET, there was a significant reduction in serum total bilirubin (STB), serum indirect bilirubin (SIB), and platelet (PLT) counts ($P < 0.001$). Pre- ET, differences in SIB and PLT were noted between neonates with ABO and Rh incompatibilities ($P < 0.05$). There was no statistically significant disparities in the therapeutic effects of ET on STB, SIB, and PLT levels when comparing male and female neonates across both the ABO and Rh incompatibility groups.

Conclusion: Our study demonstrated that ET is efficacious in reducing bilirubin levels and platelet counts in neonates presenting with ABO and Rh blood group incompatibilities. Notably, the effectiveness of ET was found to be independent of the neonates' gender, a finding that underscores the universal applicability of this treatment approach. Our study observation contradicts the prevalent belief that HDN associated with the Rh system is inherently more severe than that linked to the ABO system. This revelation underscores the imperative for the swift implementation of ET in managing cases of severe hyperbilirubinemia.

Keywords: exchange transfusion, hyperbilirubinemia, ABO incompatibility, Rh Incompatibility, neonate

Introduction

Neonatal hyperbilirubinemia is a common condition that can lead to severe consequences if left untreated, including kernicterus and neurodevelopmental disorders.¹ ET is a therapeutic intervention employed to rapidly reduce bilirubin levels in neonates with severe hyperbilirubinemia.^{2,3} The causes of neonatal hyperbilirubinemia are complex and varied, Hemolysis caused by ABO and Rh blood group incompatibilities being prominent contributors.⁴ ABO incompatibility occurs when the mother has antibodies against the infant's blood type, leading to the destruction of red blood cells and subsequent hyperbilirubinemia.⁵ Similarly, Rh incompatibility arises from maternal antibodies attacking the infant's Rh-positive red blood cells.⁶ Both conditions need effective treatment to mitigate the risks associated with severe hyperbilirubinemia.

Preventive measures and early intervention play a important role in both ABO hemolytic disease and Rh hemolytic disease. The significance of these approaches lies in their potential to reduce the severity of the conditions and to prevent complications such as kernicterus and hydrops fetalis. ABO incompatibility is more common due to the high prevalence

of type O blood. Rh incompatibility is less common but can have more severe outcomes. Historically, ABO hemolytic disease has been considered less severe compared to Rh hemolytic disease.⁷ However, comparative analyses between ABO and Rh groups and the stratification by gender are limited.^{8,9}

The objective of our research was to assess the effectiveness of exchange transfusion (ET) in lowering serum bilirubin levels and platelet counts among neonates suffering from hyperbilirubinemia due to ABO and Rh blood group incompatibilities. Our investigation sought to challenge the conventional wisdom that hemolytic diseases of varying etiologies, specifically ABO and Rh, might differ in their response to ET. We hypothesized that ET would exhibit similar efficacy across both groups, regardless of the underlying cause of hemolysis. Additionally, we were intrigued by the potential influence of gender on the treatment outcomes, considering the biological variations that could modulate the response to ET.

Materials and Methods

This study at the Sentinel Hospital in Fuzhou meticulously evaluated the efficacy of ET in treating infants with elevated bilirubin levels. The research targeted a select group of neonates:

1. Hospitalized newborns diagnosed with hyperbilirubinemia who underwent ET.
2. Infants meeting predefined criteria for ET eligibility.
3. Pediatric patients who received medically compatible blood during ET.

Exclusions were based on:

1. Lack of ET treatment for hyperbilirubinemia.
2. Health conditions precluding ET.
3. Incomplete medical records hindering comprehensive analysis.
4. Severe health issues that could bias study outcomes.

In our study, we meticulously gathered and analyzed serum total bilirubin (STB), serum indirect bilirubin (SIB), and platelet (PLT) levels both before and after exchange transfusion (ET). The data were sourced from reliable diagnostic equipment, ensuring that the quality control measures for these instruments were strictly adhered to and remained within the manufacturer's specified parameters.

To deepen our understanding of the treatment effects, we performed subgroup analyses based on gender. This approach allowed us to dissect the changes in these parameters within and between male and female neonates. By doing so, we aimed to provide a more comprehensive and nuanced evaluation of the therapeutic impact of ET on neonates with hyperbilirubinemia.

Patients and Equipments

Our in-depth analysis spanned 125 cases of neonatal hyperbilirubinemia treated with ET from 2011 to 2022. The study's core was assessing ET's impact on key biochemical and hematological indicators.

We employed the Abbott al16200 analyzer, a leading-edge instrument developed by Abbott Laboratories in Chicago, to accurately measure bilirubin levels. This high-performance device is renowned for its precision in clinical diagnostics. For determining platelet counts, we utilized the Sysmex[®] XN-3000 hematology analyzer, a sophisticated piece of technology from Sysmex Corporation in Kobe, Japan, known for its advanced capabilities in blood cell analysis. Additionally, for blood typing and assessing neonatal hemolysis, we depended on the WADiana DG-57, a reliable diagnostic tool offered by Diagnostic Grifols in Barcelona, Spain, which has proven its efficacy in our laboratory settings.

Blood Selection and Dosage

Children with ABO hemolytic disease are treated with O-type red blood cells and AB-type fresh frozen plasma; those with Rh hemolytic disease are treated with red blood cells that are ABO-compatible with the child and Rh-compatible

with the mother. A stringent standard of 160–180 mL/kg body weight guided our meticulous cross-matching process, tailored to the required ET volume and each infant's weight.

ET was conducted with meticulous attention to detail, employing the simultaneous peripheral arteriovenous double tubing technique. This method involved using the scalp vein for the infusion of replacement fluid, while simultaneously withdrawing blood through the radial artery, in accordance with established clinical protocols. We maintained strict control over the total blood exchange volume, targeting a range of 160–180 mL/kg of body weight, with a meticulous balance of 3–5 mL/kg between the volume of blood infused and that withdrawn. The infusion rate was carefully regulated to approximately 5 mL/(kg.min), which allowed for a consistent duration of ET, ranging from 1.5 to 2.0 hours. To address the potential risk of hypocalcemia, a prophylactic measure was taken by administering 1 mL of 10% calcium gluconate for every 100 mL of blood exchanged, ensuring the safety and efficacy of the procedure.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Fujian Maternity and Child Health Hospital College of Clinical Medicine for Obstetrics & Gynecology and Pediatrics, Fujian Medical University (the ethics approval number: 2021KR022). As this retrospective analysis used routinely collected data informed consent was waived. All personal information and medical data of the patients have been anonymized to ensure that no individual identities can be identified. The collection, storage, and analysis of all data during the research process comply with the relevant ethical and privacy protection standards.

Statistical Analysis

We performed all statistical analyses with the robust SPSS Statistics software, version 27.0 (Armonk, NY, USA), developed by IBM Corp., Armonk, NY, USA. Our presentation of measurement data adhered to the standard format of mean $\pm$ standard deviation, represented as $x \pm s$. The paired sample *t*-test was selected for analyzing differences within matched pairs, and the independent sample *t*-test was applied for assessing disparities between distinct groups. For the evaluation of categorical variables, we relied on the chi-squared test. The threshold for statistical significance was set at a *p*-value of less than 0.05.

Results

Our study involved 125 infants who were diagnosed with severe hyperbilirubinemia. The sample consisted of 66 male and 59 female neonates. The gestational age at birth for these infants ranged from 33 to 41 weeks. The timing for the administration of ET occurring at various intervals between 1 to 12 days post-birth, and the neonates' birth weights were distributed between 2.11 and 4.3 kilograms.

In our examination of 125 cases of neonatal hyperbilirubinemia, we observed that ET resulted in a pronounced reduction in STB levels, serum total bilirubin (STB) from 432.50 ± 87.29 to 241.20 ± 58.79 , serum indirect bilirubin (SIB) from 406.72 ± 84.71 to 226.15 ± 58.57 , and platelet (PLT) counts from 243.40 ± 88.43 to 88.79 ± 39.86 (Figure 1).

In our pediatric cohort, we identified two distinct groups based on the etiology of hemolysis. A total of 73 cases were found to be associated with ABO blood group incompatibility, stemming from the presence of ABO blood group antibodies. These cases were categorized as the ABO group. Conversely, 52 cases were attributed to Rh blood group incompatibility, due to the action of Rh blood group antibodies, and were accordingly designated as the Rh group. This classification allowed us to explore the specific impacts of these two types of blood group antibodies on the patients enrolled in our study.

Upon analyzing our pediatric patient data, we found that there were no statistically significant differences in gestational age or the timing of ET post-birth between the ABO and Rh groups. Pre-ET, in the ABO group and Rh group, the STB was 443.87 ± 87.19 and 416.53 ± 85.72 , SIB was 422.49 ± 83.02 and 384.59 ± 82.82 ; PLT was 257.81 ± 89.47 and 223.17 ± 83.66 , the differences in SIB and PLT were statistically significant ($P < 0.05$); Post-ET, in the ABO group and Rh group, the STB was 246.01 ± 60.24 and 234.46 ± 56.58 , SIB was 232.85 ± 60.63 and 216.75 ± 54.73 ; PLT was 89.36 ± 37.57 and 88.00 ± 43.23 , the differences in SIB and PLT were no statistically significant ($P > 0.05$) (Table 1).

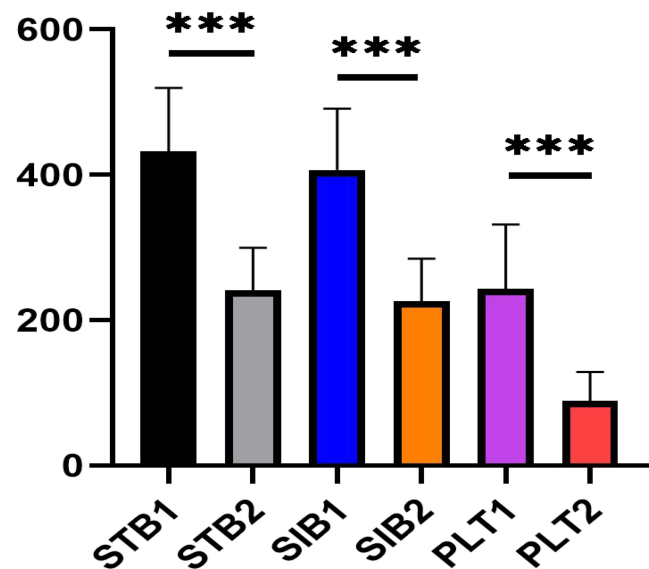


Figure 1 The effect in STB, SIB, PLT, Hb pre- and post-ET.1: Pre-exchange transfusion 2: Post-exchange transfusion.
Notes: ***Indicates a statistically significant difference with a P-value less than 0.001.
Abbreviations: STB, Serum Total Bilirubin (umol/L); SIB, Serum Indirect Bilirubin (umol/L); PLT, Platelet count (10⁹/L); Hb, Hemoglobin (g/L); ET, exchange transfusion.

In our comparative analysis assessing the efficacy of ET, we observed that there was no significant difference in the treatment’s efficiency between the ABO and Rh groups when considering STB, SIB, and PLT levels. For the ABO group, the average reductions were 44.20±10.17, 44.59±10.60, and 62.61±16.86 for ABO, In contrast, the Rh group exhibited average reductions were 42.61±12.49, 42.46±12.95, and 58.14±19.05 (Table 2).

In our gender-stratified analysis within the ABO and Rh groups, we included a total of 66 male and 59 female neonates. The ET efficiencies for STB, SIB and PLT among males were 43.80±12.06, 43.82±12.30 and 61.44±15.49. The ET efficiencies for STB, SIB and PLT among females were 43.25±10.18, 43.57±10.94 and 59.98±20.31 (Table 3).

Upon a more detailed examination of our data, we observed a gender distribution within the ABO group that consisted of 35 males and 38 females, which is in contrast to the Rh group, comprising 31 males and 21 females. The

Table 1 Comparative Analysis of STB, SIB, and PLT Before and After Transfusion

	Pre-ET		P	Post-ET		P
	ABO (73)	Rh (52)		ABO (73)	Rh (52)	
STB	443.87±87.19	416.53±85.72	0.084	246.01±60.24	234.46±56.58	0.281
SIB	422.49±83.02	384.59±82.82	0.013	232.85±60.63	216.75±54.73	0.130
PLT	257.81±89.47	223.17±83.66	0.030	89.36±37.57	88.00±43.23	0.852

Abbreviations: STB, Serum Total Bilirubin (umol/L); SIB, Serum Indirect Bilirubin (umol/L); PLT, Platelet count (10⁹/L); ET, Exchange transfusion.

Table 2 Comparison of Transfusion Efficiency Within the Same Gender for ABO and Rh Groups

ET Efficiency (%)	ABO (73)	Rh (52)	P
STB	44.20±10.17	42.61±12.49	0.437
SIB	44.59±10.60	42.46±12.95	0.316
PLT	62.61±16.86	58.14±19.05	0.169

Abbreviations: STB, Serum Total Bilirubin (umol/L); SIB, Serum Indirect Bilirubin (umol/L); PLT, Platelet count (10⁹/L); ET, Exchange transfusion.

Table 3 Comparative Analysis of ET Efficacy Among the ABO and Rh Groups

ET Efficiency (%)	Male (66)	Female (59)	P
STB	43.80±12.06	43.25±10.18	0.787
SIB	43.82±12.30	43.57±10.94	0.903
PLT	61.44±15.49	59.98±20.31	0.649

Abbreviations: STB, Serum Total Bilirubin (umol/L); SIB, Serum Indirect Bilirubin (umol/L); PLT, Platelet count ($10^9/L$); ET, Exchange transfusion.

Table 4 Comparative of Transfusion Efficiency within the Same Gender for ABO and Rh Groups

ET Efficiency (%)	Male		P	Female		P
	ABO (35)	Rh (31)		ABO (38)	Rh (21)	
STB	44.26±11.08	43.28±13.25	0.745	44.14±9.40	41.64±11.53	0.370
SIB	44.78±11.29	43.82±12.30	0.507	44.41±10.08	42.04±12.47	0.430
PLT	63.33±14.43	59.30±16.58	0.295	61.94±19.00	56.42±22.54	0.322

Abbreviations: STB, Serum Total Bilirubin (umol/L); SIB, Serum Indirect Bilirubin (umol/L); PLT, Platelet count ($10^9/L$); ET, Exchange transfusion.

male participants in our study rates for STB, SIB, and PLT in both ABO and Rh groups showed no significant variation, For the ABO group with figures of 44.26±11.08, 44.78±11.29, 63.33±14.43, and for the Rh group with figures of 43.28±13.25, 43.82±12.30, 59.30±16.58. The female participants for the ABO group with figures of 44.14±9.40, 44.41±10.08, 61.94±19.00, and and for the Rh group with figures of 41.64±11.53, 42.04±12.47, 56.42±22.54 (Table 4).

Discussion

Hemolytic diseases of the newborn, whether due to ABO or Rh blood group incompatibilities, stem from maternal-fetal blood type mismatches that trigger isoimmune hemolysis. Traditionally, it has been believed that ABO-related hemolysis is milder in comparison to Rh-related hemolysis. Contrary to this prevailing view, our study unexpectedly discovered that, before undergoing exchange transfusion (ET), neonates in the ABO group presented with higher serum total bilirubin (STB), serum indirect bilirubin (SIB), and platelet (PLT) counts than those in the Rh group. Notably, the differences in SIB and platelet levels reached statistical significance. These findings emphasize the critical need for vigilant surveillance of ABO hemolysis due to the risk of neurological complications that can arise from increased SIB levels. On the other hand, in cases of Rh hemolysis, there is an urgent requirement to manage coagulation abnormalities that may stem from diminished platelet counts. However, the lack of significant difference in post-ET STB, SIB, and PLT levels between the ABO and Rh groups suggests that the underlying cause of hemolysis does not significantly influence the efficacy of ET in reducing bilirubin levels.^{10,11}

Our research takes a distinct approach compared to previous studies in a few significant ways. Notably, we found that before the ET procedure, neonates with ABO blood group incompatibility had higher levels of STB, SIB, and PLT counts than those with Rh blood group incompatibility. Importantly, the differences in SIB and platelet levels between these two groups were statistically significant, marking a departure from the expectations set by earlier research. This finding contradicts some studies that generally regard hemolytic disease due to ABO incompatibility as relatively mild.¹² Our findings, which highlighted statistically significant differences in serum indirect bilirubin (SIB) and platelet levels, challenge the conventional wisdom that hemolytic disease attributed to ABO incompatibility is generally milder. Contrary to some existing studies, our data suggest that ABO incompatibility could be linked to more severe neurological complications, emphasizing the need for vigilant monitoring. This revelation is particularly important as it shifts our understanding of the severity of ABO-related hemolysis. Moreover, our study revealed no significant differences in STB,

SIB, and PLT levels after ET between the ABO and Rh groups. This indicates that the underlying cause of hemolysis does not substantially affect the efficacy of ET in reducing bilirubin levels, suggesting that the treatment's impact is consistent across different types of blood group incompatibilities. A finding consistent with previous studies that have questioned the impact of blood group incompatibility on the severity of hyperbilirubinemia.¹³

In this study, we conducted an in-depth examination of the effects of ET on neonates grappling with severe hyperbilirubinemia, a condition that demands urgent attention to avert potential long-term neurological consequences. Our results demonstrate a pronounced decrease in STB, SIB, and PLT counts following ET, which is in line with the anticipated therapeutic benefits of this intervention for managing hyperbilirubinemia.^{14–16}

The statistically significant decrease in STB and SIB levels post-ET underscores the effectiveness of this procedure in rapidly lowering bilirubin levels, this rapid decrease is of paramount importance, as it is instrumental in averting the neurologic dysfunction that can arise from elevated bilirubin levels. The reduction in PLT counts, although significant, requires careful consideration, as it may have implications for neonatal hemostasis and the potential for bleeding complications.¹⁷

In our analysis, which was stratified by gender, we observed no significant differences in the efficacy of exchange transfusion (ET) between our male and female neonates with severe hyperbilirubinemia. This suggests that gender may not play a role in how patients respond to ET in the context of severe hyperbilirubinemia. Our findings align with those of previous studies, which also failed to establish gender as a predictive factor for the outcomes of ET.¹⁸

The comparison of ET efficacy between the ABO and Rh groups showed no significant differences. It shows that the type of blood group antibodies causing hemolysis does not significantly affect the response to ET. This finding is in line with research that has questioned the influence of blood group incompatibility on the severity of hyperbilirubinemia.⁷

Our research boasts several advantages that include a well-defined patient population and a clear demonstration of the therapeutic impact of ET. However, limitations include the relatively small sample size and the lack of long-term follow-up data to assess the impact of ET on neurodevelopmental outcomes. Future studies with larger sample sizes may provide further insight into any subtle differences that were not apparent in the current analysis.

Conclusion

Our study confirms the effectiveness of ET in reducing bilirubin levels in neonates with severe hyperbilirubinemia, irrespective of the cause of hemolysis or the patient's gender. While the prevailing belief posits that hemolytic disease in newborns due to the Rh blood group system is more critical than that attributed to the ABO blood group system, our findings challenge this notion.

Highlights and Shortcomings

Our research presents several notable findings: it challenges the prevailing notion that the Rh blood group system is more likely to cause severe hemolytic disease in newborns compared to the ABO system; it affirms the efficacy of exchange transfusion as a treatment for neonatal hyperbilirubinemia; and it examines the influence of various factors associated with ABO and Rh blood group system-induced hemolysis on the efficacy of exchange transfusion. However, our study has a limitation: it does not delve into the underlying mechanisms, an aspect we intend to explore in subsequent research.

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Disclosure

The author(s) report no conflicts of interest in this work.

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