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The Effect of Intravenous Immunoglobulin in Newborns with Hemolytic Disease Due to ABO Incompatibility

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Abstract

Objective: To determine the efficacy of intravenous immunoglobulin (IVIG) in reducing the need for exchange transfusion (ET) in neonates with ABO hemolytic disease of the newborn (HDN).
Methodology: This prospective cohort study was conducted at Neonatal ICU of Bahawal Victoria Hospital, Bahawalpur, from January 2023 to July 2023. Term neonates with significant hyperbilirubinemia due to ABO incompatibility and a positive direct Coombs test were enrolled. Eligible infants were allocated into two groups: Group A received intensive phototherapy plus IVIG (1 g/kg), while Group B received intensive phototherapy alone. Baseline demographic and clinical parameters, serum bilirubin levels, need for ET, and immediate adverse effects were recorded. Data were analyzed using chi-square and t-tests, with $p < 0.05$ considered statistically significant.
Results: A total of 30 neonates were included, 15 in each group. The need for ET was significantly lower in the IVIG group (26.7%) compared to the phototherapy-only group (66.7%) ($p = 0.028$). No significant differences were observed in baseline characteristics between groups. No immediate adverse effects related to IVIG were noted.
Conclusion: Administration of IVIG in addition to phototherapy significantly reduces the need for ET in term neonates with ABO hemolytic disease, without immediate complications. These results support its role as an effective adjunctive therapy in managing severe hyperbilirubinemia.
Keywords: ABO hemolytic disease, exchange transfusion, hyperbilirubinemia, intravenous immunoglobulin, neonates.

Introduction

Hemolytic disease of the newborn (HDN) arises from immune-mediated destruction of red blood cells (RBCs) by maternal antibodies.[1] This process may lead to rapid hemolysis, anemia, and severe unconjugated hyperbilirubinemia, placing affected neonates at risk for bilirubin encephalopathy and kernicterus[2]. Among the various types of alloimmune hemolysis, ABO incompatibility is the most common cause encountered in the neonatal period and represents a significant contributor to early neonatal jaundice worldwide.[1,2] While ABO incompatibility occurs in approximately 25% of all pregnancies, less than 1% of these cases lead to HDN.[3]

Phototherapy remains the standard of care for neonatal hyperbilirubinemia, offering a safe and effective means of lowering bilirubin concentrations in most cases[4]. However, when bilirubin levels rise close to ET thresholds, escalation of therapy becomes necessary. ET has historically been used as a definitive treatment to rapidly reduce bilirubin and remove sensitized red cells.[5] Despite its efficacy, ET is invasive and carries considerable risks of cardiovascular, biochemical, or hematological complications and mortality rates vary from 0.5 to 3.3%.[6] These concerns highlight the need for adjunctive strategies that can reduce ET requirements in infants with severe hemolysis.

Intravenous immunoglobulin (IVIG) has been increasingly explored as a therapeutic option in alloimmune HDN[1]. IVIG is believed to reduce the need for ET by blocking antibody-coated RBCs from being destroyed in the reticuloendothelial system.[1,7] Clinical reports suggest that IVIG may shorten the duration of phototherapy and hospitalization and decrease the need for ET. However, evidence remains conflicting. A recent multicenter registry analysis found that a single dose of IVIG in ABO HDN did

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not reduce ET rates and was associated with higher readmission rates[1]. Similarly, a large retrospective series of 579 neonates showed no reduction in ET requirements among IVIG recipients[8]. Conversely, other studies have suggested potential benefits: Mohan et al[4] reported a low ET rate (3.4%) and no major adverse effects in IVIG-treated neonates, while Jalali et al.[9] observed lower bilirubin-to-hemoglobin ratios and no ET requirement among infants treated with IVIG

The inconsistency in findings underscores the lack of consensus regarding IVIG use in ABO-mediated HDN. Recent guidelines recommend selective use only in direct antiglobulin test (DAT)-positive infants near escalation thresholds or when ET is not immediately feasible[4]. In many regions, including our own, robust data on IVIG effectiveness in ABO incompatibility are limited. Therefore, this study is designed to evaluate the role of IVIG in neonates with ABO HDN, focusing on its impact on ET rates, duration of phototherapy, and short-term outcomes. The results may provide evidence to guide policy and inform clinical practice for the optimal management of this common condition.

Methodology

This randomized controlled trial was conducted in Pediatrics Unit-II, Bahawal Victoria Hospital, Bahawalpur, from January 2023 to July 2023, after approval from the hospital Ethical Review Board (ERB). Informed consent was obtained from parents/caregivers prior to enrolment.

The sample size was calculated using data from El Habashy, et al[10], who reported that 12.5% of newborns receiving IVIG plus phototherapy required ET compared to 62.5% of those treated with phototherapy alone. Using an 80% power, a 95% confidence interval (two-sided), and a 1:1 allocation ratio, the required sample size was calculated with the OpenEpi online calculator and found to be 15 neonates in each group.

Non-probability consecutive sampling was applied for participant recruitment. Neonates less than 7 days of age, of either gender, weighing more than 2.5 kg, with a gestational age of 38 weeks or more, and diagnosed with HDN due to ABO incompatibility were included. Exclusion criteria were the presence of neonatal sepsis, refusal of consent by parents or caregivers, hemolytic disease due to Rhesus incompatibility, or clinical signs of acute bilirubin encephalopathy, including somnolence, hypotonia, or loss of neonatal reflexes.

Eligible neonates were randomly assigned into two groups (group A and B) using a computer-generated randomization list with sealed opaque envelopes to ensure allocation concealment. The intervention group (group A) received IVIG at a dose of 1 g/kg, diluted in normal saline and administered over 2 hours, in addition to conventional intensive phototherapy. The control group (group B) received conventional intensive phototherapy alone. All infants were managed according to unit protocols for fluid, feeding, and monitoring of bilirubin levels. Serum bilirubin levels were measured at baseline and at regular intervals as per the department policy. Escalation of care, including the need for ET, was determined according to the American Academy of Pediatrics (AAP) guidelines. The primary outcome was the requirement for ET. Secondary outcomes included duration of phototherapy, rate of rise of serum bilirubin, length of hospital stay, and short-term complications such as anemia, necrotizing enterocolitis, or IVIG-related adverse effects.

Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 20. The mean and standard deviation were calculated for quantitative variables such as age, weight, serum bilirubin levels, duration of phototherapy, and length of hospital stay, while categorical variables including the need for ET and adverse outcomes were presented as frequencies and percentages. The efficacy of treatment, defined as avoidance of ET, was calculated for each group and compared using the chi-square test to assess whether IVIG plus conventional phototherapy was more effective than conventional phototherapy alone. Stratification was performed to control for potential effect modifiers including age (0–3 days and 4–6 days), gender, and weight categories (2.5–3.0 kg, 3.1–3.5 kg, 3.6–4.0 kg, and >4.1 kg). The chi-square test or Fisher's exact test, where appropriate, was applied to compare categorical data, while the independent-samples t-test was used for continuous data. A p-value of ≤0.05 was considered statistically significant.

Results

The baseline demographic and clinical characteristics of both groups were comparable, with no statistically significant differences in mean age, weight, gestational age, or baseline serum bilirubin levels (Table I). The

distribution of age, weight, and gender across both groups was also similar (Table II).

Table I: Baseline characteristics of study groups.

Variables	Group A (n=15)	Group B (n=15)	p-value
Age (days)	2.86±1.55	3.53±1.88	0.299
Weight (kg)	3.23±0.54	3.33±0.59	0.621
Gestational age (weeks)	39.76±1.34	39.25±1.25	0.288
Baseline serum bilirubin (mg/dl)	15.01±2.39	17.07±3.81	0.086

Table II: Distribution of demographic and clinical variables.

Variables		Group A (n=15)	Group B (n=15)	p-value
Age (days)	0-3days	9(60.0%)	9(60.0%)	1.000
	4-6days	6(40.0%)	6(40.0%)	
Weight (kg)	2.5-3kg	6(40.0%)	6(40.0%)	0.958
	3.1-3.5kg	5(33.3%)	4(26.6%)	
	3.6-4kg	2(13.3%)	3(20.0%)	
	>4kg	2(13.3%)	2(13.3%)	
Gender	Male	8(53.3%)	6(40.0%)	0.464
	Female	7(46.7%)	9(60.0%)	

Stratified analyses showed that the requirement for ET did not differ significantly by age group, gender, or body weight within either treatment group ($p>0.05$ for all comparisons).

ET was required in 4 patients (26.7%) in Group A (IVIG plus phototherapy) compared to 10 patients (66.7%) in Group B (phototherapy alone), and this difference was statistically significant. ($p=0.028$) (Table III)

Table III: Requirement of exchange transfusion between study groups.

Variable		Group A (n=15)	Group B (n=15)	p-value
Exchange transfusion	Required	4(26.7%)	10 (66.7%)	0.028
	Not required	11 (73.3%)	5(33.3%)	

Discussion

Our study demonstrates a significant reduction in the requirement for ET among neonates with ABO hemolytic disease treated with IVIG plus phototherapy (26.7%) compared with phototherapy alone (66.7%) ($p = 0.028$). Baseline demographic and clinical parameters were comparable between groups, minimizing confounding by age, weight, gestational age, or initial bilirubin level. These findings suggest that adjunctive IVIG may reduce the need for invasive ET in term neonates with ABO HDN when added to intensive phototherapy.

Our results are in line with the recommendation of the APP and many other international studies to give IVIG in ABO isoimmune hemolytic disease.[10-15] HabashySA et al and Miqdad AM et al. found that giving IVIG to newborns with significant hyperbilirubinemia from ABO hemolytic disease and a positive direct Coombs test can lower the need for ET, without causing immediate side effects, supporting our findings.[10,12] Similarly, El Fekey SW et al. reported that adding IVIG in the treatment of HDN significantly reduced bilirubin levels, duration of phototherapy, need for ET, and length of hospital stay[13]; however, their study included newborns with HDN due to both ABO and Rhesus (Rh) incompatibility. Nasseri F, et al. also reported that IVIG was effective in reducing bilirubin-to-hemoglobin ratios in neonates with HDN and helped to avoid ET without major side effects[14]. In addition, a recent report by Mohole J et al also demonstrate that rapid identification and adjuvant therapy with IVIG successfully avoids ET in a case of severe immune-mediated HDN.[15]

In contrast, larger registry and multi-institutional datasets failed to demonstrate a clear ET-sparing effect. For example, Daunov et al. reported no reduction in exchange or red blood cells transfusions with IVIG in a cohort of 579 neonates with ABO incompatibility[8]. Similarly, Okulu et al. found that one dose of IVIG did not reduce the need for ET and was associated with higher readmission in term infants.[1] A Cochrane review also found insufficient evidence to recommend the use of IVIG in alloimmune HDN[14].Some International guidelines, generally do not recommend routine use of IVIG for ABO-mediated HDN, citing very low certainty of evidence, limited benefit, and potential risks.[17] Similarly, broad registry data point to wide variability in practices and highlight the importance of gestational age in determining ET rates but stop short of endorsing routine IVIG.[18]

Why the mixed results across studies? There are several likely reasons. Studies differ in who got IVIG (DAT status, how close bilirubin is to ET threshold), the timing and dose of IVIG, and the phototherapy technology/intensity used[12,19]. Some reports describe multi-dose strategies, which may produce different results from single-dose regimens; for example, Zheng et al. recently described three-to-four-dose approaches with promising bilirubin

declines in selected infants.[20] Reviews and narrative analyses also stress that heterogeneity in protocols and selection make comparisons difficult.[21] In addition, cohort analyses show that DAT positivity and bilirubin kinetics strongly affect outcomes and therefore who benefits most from IVIG.[22]

Our study has a few limitations like the trial had a small sample size and was single-center. Follow-up was short and limited to early outcomes; we did not assess long-term neurodevelopment or late hematologic effects. The study included only term infants (≥38 weeks), so results may not apply to preterm babies. Although we observed no IVIG-related adverse events in our cohort, the sample was too small to detect rare harms.

Recommendations: Based on our results and the mixed international evidence, IVIG may be considered selectively for DAT-positive term neonates with ABO HDN who are approaching ET thresholds or when ET is not immediately available. Larger, multicenter randomized trials are needed. Those trials should predefine DAT status, IVIG dose and timing, phototherapy intensity, and ET criteria, and should include cost and safety monitoring.

Conclusion

Our study demonstrates that IVIG given alongside intensive phototherapy significantly lowers the need for ET in term neonates with ABO hemolytic disease. No immediate adverse effects were observed, supporting its safety in this setting. These findings suggest IVIG may serve as a useful adjunct in managing severe hyperbilirubinemia due to ABO incompatibility, though larger multicenter studies are needed to confirm these results and guide routine clinical use.

References

1. Okulu E, Erdeve O, Kilic I, Olukman O, Calkavur S, Buyukkale G, et al. Turkish Neonatal Society IVIG Study Group. Intravenous Immunoglobulin Use in Hemolytic Disease Due to ABO Incompatibility to Prevent Exchange Transfusion. Front Pediatr. 2022;10:864609. doi: 10.3389/fped.2022.864609.
2. Kemper AR, Newman TB, Slaughter JL, Maisels MJ, Watchko JF, Downs SM, et al. Clinical Practice Guideline Revision: Management of Hyperbilirubinemia in the Newborn Infant 35 or More Weeks of Gestation. Pediatrics. 2022;150(3):e2022058859. doi: 10.1542/peds.2022-058859.
3. Hall V, Vadakekut ES, Avulakunta ID. Hemolytic disease of the fetus and newborn [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan– [updated 2025 Jan 22; cited 2025 Sep 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK557423/
4. Mohan DR, Lu H, McClary J, Marasch J, Nock ML, Ryan RM. Evaluation of Intravenous Immunoglobulin Administration for Hyperbilirubinemia in Newborn Infants with Hemolytic Disease. Children (Basel). 2023;10(3):496. doi: 10.3390/children10030496.
5. Hall CP, Lightfoot JK. Exchange transfusion [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan– [updated 2025 Mar 28; cited 2025 Sep 7]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK563179/
6. Sabzehei M K, Basiri B, Shokouhi M, Torabian S. Complications of Exchange Transfusion in Hospitalized Neonates in Two Neonatal Centers in Hamadan, A Five-Year Experience.JCompr Ped.2015;6(2):e20587.https://doi.org/10.17795/compreped-20587.
7. Rasiah S, Jegathesan T, Campbell DM, Shah PS, Sgro MD. Intravenous immunoglobulin G therapy for neonatal hyperbilirubinemia. Pediatr Res. 2023;94(6):2092-2097. doi: 10.1038/s41390-023-02712-0.
8. Daunov M, Schlosser A, Malay S, Adams J, Clark R, Ferrerosa L, et al. A Description of IVIG Use in Term Neonates with ABO Incompatibility. Am J Perinatol. 2024;41(13):1761-1766. doi: 10.1055/a-2255-8772.
9. Jalali SZ, Mahdipour S, Asgarzad R, Saadat F. Effect of intravenous immunoglobulin on the management of Rh- and ABO-mediated hemolytic disease of the newborn. HematolTransfus Cell Ther. 2024;46 Suppl 5(Suppl 5):S57-S64. doi: 10.1016/j.htct.2024.03.002.
10. HabashySA,Toaima DN, GadGI,ElNazerMG. High doseintravenous immunoglobulin in Rh and ABO hemolytic disease of Egyptian neonates. Egypt J Pediatr Allergy Immunol 2014;12(1):21-26.
11. American Academy of Pediatrics. Frequently asked questions about the 2022 AAP guideline on the management of hyperbilirubinemia [Internet]. Itasca (IL): American Academy of Pediatrics; 2025 Jul 17 [cited 2025 Sep 07]. Available from: https://www.aap.org/en/patient-care/hyperbilirubinemia/frequently-asked-questions-about-the-2022-aap-guideline-on-the-management-of-hyperbilirubinemia/
12. Miqdad AM, Abdelbasit OB, Shaheed MM, Seidahmed MZ, Abomelha AM, Arcala OP. Intravenous immunoglobulin G (IVIG) therapy for significant hyperbilirubinemia in ABO hemolytic disease of the newborn. J Matern Fetal Neonatal Med. 2004;16(3):163-166. doi: 10.1080/14767050400009873.
13. El Fekey, S. W. I., El-Sharkawy, H. M., Ahmed, A. A. E., Nassar, M. A., Elgendy, M. M. Effect of Intravenous Immunoglobulin in Reducing Bilirubin Levels in Hemolytic Disease of Newborn. Egypt JHosp Med. 2019;74(5): 957-968. doi: 10.21608/ejhm.2019.25779
14. Nasseri F, Mamouri GA, Babaei H. Intravenous immunoglobulin in ABO and Rh hemolytic diseases of newborn. Saudi Med J. 2006;27(12):1827-1830.
15. Mohole J, Beyder M, Sharma Y. Guiding Light: How the Updated AAP Clinical Guidelines for Hyperbilirubinemia Impacted Management of a Case of Severe and Persistent Hemolytic Disease of the Newborn. Pediatr Ann. 2025;54(4):e125-e129. doi: 10.3928/19382359-20250206-01.
16. Zwiers C, Scheffer-Rath ME, Lopriore E, de Haas M, Liley HG. Immunoglobulin for alloimmune hemolytic disease in neonates. Cochrane Database Syst Rev. 2018 Mar 18;3(3):CD003313. doi: 10.1002/14651858.CD003313.pub2.
17. Lieberman L, Lopriore E, Baker JM, Bercovitz RS, Christensen RD, Crighton G, et al. International Collaboration for Transfusion Medicine Guidelines (ICTMG). International guidelines regarding the role of IVIG in the management of Rh- and ABO-mediated haemolytic disease of the newborn. Br J Haematol. 2022;198(1):183-195. doi: 10.1111/bjh.18170.
18. de Winter DP, Verweij EJTJ, Debeer A, Devlieger R, Lewi L, Verbeeck S, et al. Worldwide Collaboration for Hemolytic Disease of the Fetus and Newborn (DIONYSUS) Investigators. Variations and Opportunities in Postnatal Management of Hemolytic Disease of the Fetus and Newborn. JAMA Netw Open. 2025;8(1):e2454330. doi: 10.1001/jamanetworkopen.2024.54330.
19. Demirel G, Akar M, Celik IH, Erdeve O, Uras N, Oguz SS, et al. Single versus multiple dose intravenous immunoglobulin in combination with LED phototherapy in the treatment of ABO hemolytic disease in neonates. Int J Hematol. 2011;93(6):700-703. doi: 10.1007/s12185-011-0853-4.
20. Zheng Y, Almeyda-Alejo Y, Tumin D, Redpath NSJ, Guillen-Hernandez

J. Three or four doses of intravenous immunoglobulin G treatment for isoimmune hemolytic disease: A case series and literature review. J Neonatal Perinatal Med. 2024;17(1):153-158. doi: 10.3233/NPM-230070.
21. Vardar G, Okan MA, Karadag N, Topcuoglu S, Ozalkaya E, Karatepe HO, et al. Intravenous immunoglobulin in hemolytic disease of the newborn: A moving target in time. Niger J Clin Pract. 2022;25(8):1262-1268. doi: 10.4103/njcp.njcp_1_22.
22. Wu H, Li R, Wei H, Zhu W, Xing Y. Clinical Characteristics and Prognosis of Hemolytic Disease of the Newborn Caused by Irregular Antibodies: A 13-Year Retrospective Analysis. Children (Basel). 2024;11(12):1409. doi: 10.3390/children11121409.