References:

1. Özcan M, Sevinç S., Erkan V et.al. (2017). Hyperbilirubinemia due to minor blood group (anti- E) incompatibility in a newborn: a case report. **Turkish Archives of Pediatrics/ Türk Pediatri Arşivi**. 52 (3): 162- 164.
2. Zwiers C., Scheffer- Rath M, Lopriore E. et.al. (2018). **Immunoglobulin for alloimmune Effect of Intravenous Immunoglobulin in Reducing Bilirubin Levels in Hemolytic Disease of Newborn 968 hemolytic disease in neonates**.
3. Dalakas MC. (2002). Blockade of blocking antibodies in Guillain-Barré syndromes: "Unblocking" the mystery of action of intravenous immunoglobulin. **Ann Neurol**. Jun; 51 (6): 667- 9.
4. Kazatchkine MD, Kaversi SV. (2001). Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. **N. Engl. Med**. Sep 6; 345 (10): 747- 55.
5. Ree I., Smits- Wintjens V., Van der B. et.al. (2017). Neonatal management and outcome in alloimmune hemolytic disease. **Expert review of hematology**, 10 (7): 607- 616.
6. Kushwah S., Kumar A., George N. et.al. (2017). A case of coombs-positive severe late anemia without hyperbilirubinemia, refractory to blood transfusion, improved with immunoglobulin. **Chrismed Journal of Health and Research**, 4 (3): 212- 213.
7. Cant AJ; Gibb DM; Davies EG; et.al. (2003). **Replacement therapy in immune deficiency in ForFar and Arneil's textbook of pediatrics 6th edition, edited by Niel Mclntosh**, Peter Halms, Rosalind S, P 1293, Churchill Livingstone.
8. Erdeve O., Okulu E, Olukman O. et.al. (2018). The Turkish Neonatal Jaundice Online Registry: A national root cause analysis. **PloS one**, 13 (2): e0193108.
9. Van Dijk R., Aronson S, Dirk R. et.al. (2017). Biliverdin Reductase inhibitors did not improve severe unconjugated hyperbilirubinemia in vivo. **Scientific reports**, 7 (1): 1646- 1649.
10. Shaimaa Waheed Ibrahim ElFekey, Hamed Mohammed ElSharkawy, Aisha Abd- Ellatif Elsaied Ahmed, Mohammed AbdEllatif Nassar and Marwa Mohamed Elgendy. **Effect of Intravenous Immunoglobulin in Reducing Bilirubin Levels in Hemolytic Disease of Newborn Departments of Pediatric Medicine and Clinical Pathology**, Faculty of Medicine, Tanta University, Egypt. (January 2019) Vol. 74 (4), P957- 968.
11. El Habashy S., Toaima D., Gad G. et.al. (2014). High dose intravenous immunoglobulin in Rh and ABO hemolytic disease of Egyptian neonates. **Egyptian Journal of Pediatric Allergy and Immunology**, 12 (1), 21- 26.

	Group	Mean± SD	P1	P2	P3
48 Hrs	Control	13.72± 1.71	<0.0001	<0.0001	0.16
	IIa	11.17± 2.12			
	IIb	10.36± 1.07			
72 Hrs	Control	11.84± 1.17	0.19	0.77	-
	IIa	12.58± 1.42			
	IIb	11.5			
96 Hrs	Control	10.56± 0.67	0.003	-	-
	IIa	12.15± 0.49			
	IIb	-			

P1 comparison between group IIa and control group, P2 comparison between group IIb and control group
P3 comparison between group IIa and IIb. Group IIa only 2 cases were measured after 96 hours.

This table showed that there was a statistical significant difference between group IIa, and control and between group IIb and control as regards the initial measure of bilirubin and after 24 and 48 hours, P< 0.0001, but there was no statistical difference after 72 hours P> 0.05. There was no statistical significant difference between group IIa and group IIb as regards the initial measure of bilirubin (P= 0.94), after 24 hours (P= 0.38), and after 48 hours (P= 0.16).

Table (2) Comparison between the three studied groups regarding duration of hospital stay (days) showed that there was significant statistically difference between the three group regarding duration of hospital stay (P<0.0001)

Group	Mean ± SD	F	P	Sig.
Control	4.72± 0.78	43.55	<0.0001	HS**
IIa	3.36± 0.86			
IIb	3.07± 0.26			

P>0.05 (NS), P<0.05 (S)*, P<0.001 (HS**) F= ANOVA test

Table (3) Comparison between the three studied groups regarding frequency of exchange transfusion

Group		Exchange Transfusion				
		- Ve	+ Ve	X^2	p	Sig.
Control	No.	39	11	5.68	0.06	NS
	%	78.00%	22.00%			
IIa	No.	23	2			
	%	92.00%	8.00%			
IIb	No.	15	0			
	%	100%	0%			

Discussion:

The majority of newborns develop neonatal jaundice, which is the most common cause of hospital admission or rehospitalization in the first week of life.[8][9]

The beneficial effect of IVIG therapy on the severity and course of Rh hemolytic diseases of newborn was evident in our study. By comparing the 3 groups regarding initial bilirubin level, it was high in the intervention groups in comparison to control group with a mean of 12.72mg/ dl for the control group, and 14.24mg/ dl for both intervention groups.

The rate of drop in bilirubin level was significant comparing the intervention groups with the control group especially at 24.48 and 96 hours (P< 0.0001 for all), peak builirubin level was 15.4mg/ dl for control group reached at 24 hours, while for both intervention groups was 14.2 mg/dl initially which indicates that IVIG ameliorates the rise of bilirubin level when it is administrated.

The duration of phototherapy in terms of hours was significantly shorter in the intervention groups than in the conventional group (p< 0.0001), in the intervention groups the mean duration of phototherapy was 50 hours, while in conventional group was 84 hours (P< 0.0001). No difference was noticed comparing both intervention groups to each other P= 0.2.

Shaimaa et.al. in their study found that the rate of decline in total serum bilirubin after 24 hours was significantly higher among those who received IVIG.[10] This was in agreement with ElHabashy et.al.[11] who reported also more decline in total serum bilirubin in IVIG group with mean± SD equaled 12.9± 5.2, but mean± SD in cases with phototherapy only equaled 17.4± 3.3 after 24 hours. They also found that low Effect of Intravenous Immunoglobulin in reducing Bilirubin Levels in Hemolytic Disease of Newborn dose of IVIG (500mg/kg) reduce duration of phototherapy and hospital stay like high dose (1000 mg/kg), but less effective in avoiding exchange transfusion in Rh hemolytic disease of newborn.

Duration of hospital stay was significantly shorter in the intervention groups with a mean of 3 days, when compared to control group with a mean of 5 days (P< 0.0001), with no difference between the two intervention groups (P= 0.32). This signifies the importance of IVIG in decreasing the hospital stay hazards hence decreasing nosocomial infections.

After the treatment had commenced, in the form of single infusion of IVIG, 11 patients (22%) in the conventional group required exchange transfusions, whereas 2 (8%) exchange transfusions were performed in group IIa, and none (0%) in group IIb, though the difference was not statistically significant (P= 0.2). Also there was no statistical significant difference comparing the two intervention groups (P= 0.52). Concerning the need for exchange transfusion Shaimaa et al., found that there was a highly Significant decrease in the number of cases who needed exchange transfusion in the group treated with IVIG (20 patients), where only one of them (5%) required exchange transfusion in view of 7 cases (35%) of the other group (20 patients) who were in need for exchange transfusion with p value equals 0.044.[10]

Conclusion:

The use of IVIG is effective in treatment of cases of hemolytic jaundice due to Rh incompatibility, whereas the use of low dose IVIG (0.5gm/kg) is as effective as HDIVIG (1gm/kg) in reducing the phototherapy duration, hospital stay duration and frequency of exchange transfusion.

Introduction:

Hemolytic disease of the newborn is an autoimmune haemolytic disease and occurs due to hemolysis and shortening of the life span of the newborn's erythrocytes. This occurs because of antibodies crossing from the mother by the placenta. Hemolysis of erythrocytes in the fetus and newborn is mostly caused by antibodies produced due to Rh and ABO incompatibilities.[1] Exchange transfusion and phototherapy have been used traditionally to treat jaundice and avoid the associated neurological complications. Because of the side effects of exchange transfusion, intravenous immunoglobulin (IVIG) has been used as an alternative therapy for alloimmune hemolytic disease of the newborn (HDN) to reduce the need for exchange transfusion.[2]

Intravenous immunoglobulins (IVIGs) are sterile, purified immunoglobulin G (IgG) products manufactured from pooled human plasma and typically contain more than 95% unmodified IgG, which has intact FC- dependent effector functions and only trace amounts of immunoglobulin A (IgA) or immunoglobulin M (IgM). IVIG is an immunomodulating agent that has multiple activities.[3] IVIG contains cytokines, antibodies of unclear clinical significance, perhaps neutralizing; interestingly, antibodies against granulocyte macrophage colony-stimulating factor, interferon, interleukin-1, and interleukin-6 in immune globulin have biologic activity in vivo. IVIG contains natural antibodies, accounting for some of its effects.[4] Administration of intravenous immunoglobulin (0.5-1 gm/ kg) is currently recommended by the American Academy of Pediatrics (AAP) if the total serum bilirubin rising despite intensive phototherapy or the bilirubin level is within (2- 3) mg/dl (34- 51 µmol/L) of the exchange level.[5] The current recommendations of the American Academy of Pediatrics and the National Advisory Committee on Blood and Blood Products of Canada and Canadian Blood Services advice the use of IVIG for the treatment of haemolytic disease of newborn with established jaundice.[6]

Undesirable effects from IVIG occur in less than 5% of patients as include headache, flushing, chills, myalgia, wheezing, tachycardia, lower back pain, nausea, and hypotension. If this happens during an infusion, the infusion should be slowed or stopped.[7] IVIG can induce reactions in patients with IgA deficiency. This occurs in I in 500- 1000 patients. Serous anaphylactoid reactions occur soon after the administration of IVIG.[4]

Aim of the study:

To assess the efficacy of intravenous immunoglobulins in neonates with Rh and/or ABO incompatibility in reducing the time of phototherapy and the need for exchange transfusion and subsequent hospital stay.

Subjects& Methods:

This prospective interventional case control study was conducted on 90 neonates with isoimmune- hemolytic jaundice admitted in the neonatal intensive care unit in El Galaa Hospital over a period of 10 months from March 2019 to January 2020. Patients were randomly assigned equally into two groups the conventional and intervention groups. However, 5 parents of the intervention group did not consent using IVIG so they were treated eventually by conventional method. Of the 40 infants in the intervention group; 25 infants received IVIG once in a dose of (0.5gm/ kg) while the remaining 15 infants received IVIG once in a dose of (1gm/ kg) due to limited finances, so patients' groups are:

- Group I: Control group (n= 50): neonates presented with isoimmune-hemolytic jaundice due to Rh, ABO incomaptibility treated by phototherapy alone.
- Group IIa: Treatment group a (n= 25): neonates presented with isoimmune hemolytic jaundice due to Rh, ABO incompatibility treated by conventional phototherapy plus intravenous immunoglobulin infusion (0.5gm/ kg) as a single dose.
- Group IIb: Treatment group b (n= 15): neonates presented with isoimmune hemolytic jaundice due to Rh, ABO incomaptibility treated by phototherapy plus single dose of intravenous immunoglobulin infusion (1gm/ kg).

Verbal consent from the parents was obtained before randomization.

Comparison between the 3 groups according to: Rate of drop of total serum bilirubin. Duration of phototherapy and hospital stay. Number of babies required exchange transfusion.

Intravenous Immunoglobulin: The neonates were treated by single dose of I. V. Globulin S® (Heat- treated Immune Serum Globulin, Green Cross company, Korea) at the time of admission and soon the diagnosis of the case took place through IV infusion over 4 hours of 0.5 gm/kg (for group IIa). And a dose of 1 gm/ kg single infusion dose over 4 hours of 1 gm/ kg (for group IIb). Estimation of total serum bilirubin was done after 4 hours from termination of infusion and then every 24 hours.

Laboratory Investigations: Total serum bilirubin, Direct Coombs' test, Reticulocytic count, Complete blood count (CBC).

Statistical analysis:

All statistical analysis were performed using the SPSS 10th version of Windows (Statistical Package for the Social Sciences).

Results:

Table (1) Pair wise comparison between the three studied groups regarding total serum bilirubin level (mg/dl) on admission (in a mean of 10 hours after birth), after 24, 48, 72 and 96 hours of treatment

	Group	Mean± SD	P1	P2	P3
On Admission	Control	12.72± 1.21	<0.0001	<0.0001	0.94
	IIa	14.24± 1.59			
	IIb	14.21± 1.18			
24 Hrs	Control	15.14± 1.72	<0.0001	<0.0001	0.38
	IIa	13± 2.48			
	IIb	12.45± 1.46			

Effect of Intravenous Immunoglobulin in Neonatal Isoimmune Hemolytic Anemia

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Summary

Background: Neonatal jaundice secondary to isoimmune hemolytic anemia (Rh, ABO incompatibility) is a cause of high serum bilirubin level due to hemolysis of RBCs secondary to transplacental passage of antibodies. To avoid the associated neurological complications; exchange transfusion and phototherapy have been traditionally used.

Aim: Was to assess the effect of intravenous immunoglobulins in neonates with Rh and/or ABO incompatibility in reducing the duration of phototherapy and the need for exchange transfusion and hospital stay.

Methodology: This is an interventional study in the first phase followed by case control in the second phase was conducted on 90 neonates with isoimmune- hemolytic jaundice admitted in the neonatal intensive care unit in El Galaa Hospital over a period of 10 months from March 2019 to January 2020. The neonates under study were divided into three groups: Infants received IVIG once in a dose of (0.5gm/ kg) while the remaining infants received IVIG once in a dose of (1gm/ kg) and a control group of neonates presented with isoimmune-hemolytic jaundice due to Rh incomaptibility treated by phototherapy alone.

Results: In the current study, the rise of bilirubin level was attenuated by intravenous immunoglobulin (IVIG); the rate of drop in bilirubin level was significant especially at 24, 48 and 96 hours. The duration of phototherapy was significantly shorter in the treatment group than in the conventional group (p = 0.05).

Conclusion: The use of IVIG is effective in treatment of cases of hemolytic jaundice due to Rh incompatibility, whereas the use of low dose IVIG (0.5 gm/ kg) is as effective as HDIVIG (1 gm/ kg) in reducing the phototherapy duration, hospital stay duration and frequency of exchange transfusion.

KeyWords: Hemolytic Disease of Newborn, Bilirubin, Intravenous Immunoglobulin.

أثر استخدام الأميونوجلوبيولين فى علاج مرض الأنيميا التكسيرية فى الأطفال حديثى الولادة

الخلفية: الأنيميا التكسيرية عند الأطفال حديثى الولادة تنتج من عبور الأميونوجلوبيولين خلال المشيمة أثناء الحمل مما ينتج عنه تكسر كرات الدم الحمراء عند الجنين وأنيميا شديدة تكسر كرات الدم الحمراء عند الجنين بعد الولادة ينتج عنه زيادة فى نسبة الصفراء خلال ٢٤ ساعة بعد الولادة. من أسباب الأنيميا التكسيرية عند الأطفال حديثى الولادة هو تكسر كرات الدم الحمراء نتيجة لعامل ريسس الموجب فى الدم ويكون عند الأطفال المولودين لأمهات سالبة لعامل ريسس فى الدم. حقن الأميونوجلوبيولين بالوريد أثبت حالياً أنه عامل مهم فى علاج حالات الصفراء والأنيميا الحادة عند الأطفال حديثى الولادة نتيجة لعامل ريسس فى الدم مما أدى إلى تقليل الحاجة إلى علاج الصفراء بنقل الدم.

الهدف: الحقن الوريدى للأميونوجلوبيولين للأطفال حديثى الولادة ٣٥ أسبوع أو أكثر والموجبة لعامل ريسس المولودين لأم سالبة عامل ريسس سبق لها الإنجاب لطفل موجب، وتأثيره فى تقليل الحاجة إلى علاج الصفراء بتغيير الدم وفترة العلاج الضوئى. جرى البحث على تسعين طفل حديثى الولادة الذين تم تشخيص حالتهم بمرض الأنيميا التكسيرية نتيجة عامل ريسس فى الدم. وتم اختيارهم من وحدة العناية بالأطفال حديثى الولادة مستشفى الجلاء التعليمى. وتم تقسيمهم إلى مجموعتين: المجموعة الأولى: تكونت من خمسون طفلاً لم يتم إعطاؤهم العقار. المجموعة الثانية: تكونت من خمسين طفلاً وتم إعطاؤهم العقار بجرعات مختلفة وتم تقسيم هذه المجموعة إلى مجموعتين طبقاً للجرعة إلى: مجموعة اولى (أ): تكونت من خمسة وعشرون طفلاً تلقوا العقار بجرعة ١جم/ كجم. مجموعة ثانية (ب) تكونت من خمسة عشر طفلاً تلقوا العقار بجرعة ٠,٥ جم/ كجم.

النتائج: كانت النتائج كالآتى: استخدام عقار الأمينوجلوبيولين فى الأطفال المصابين بالصفراء نتيجة عامل ريسس يقلل من حاجتنا إلى العلاج بتغيير الدم أو العلاج الضوئى وفترة البقاء فى المستشفى.

التوصيات: سرعة تشخيص مرضى الصفراء الناتج من عدم توافق عامل ريسس يجنب الطفل من حدوث مضاعفات. سرعة استخدام عقار الأمينوجلوبين يقلل من فرصة استخدام العلاج بتغيير الدم والعلاج الضوئى وفترة البقاء فى المستشفى. استخدام جرعة العقار (٥٠٠ مجم/ كجم) بدلاً من (١جم/ كجم) لقلة تكاليفه ونفس نتائجه الطبية.

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