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EFFECTS OF INTRAVENOUS IRON VERSUS PACKED RBC TRANSFUSION ON RETICULOCYTE COUNT OF PATIENTS WITH IRON DEFICIENCY ANEMIA

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ABSTRACT

Objective: *To compare effects of intravenous iron and blood transfusion on hemoglobin and retic count in pediatric patients with iron deficiency anemia (IDA)*

Methodology: *This Comparative Cross-Sectional Study was conducted at Department of Pediatric, KRL Hospital, Islamabad, Pakistan, during August 2024 to December 2024. A total of 341 pediatric patients of either gender, aged 5-11 years, diagnosed with iron deficiency anemia with Hb <9 g/dL and failed to improve hemoglobin after 3 months of oral iron therapy with poor tolerance and good compliance and being admitted for parenteral iron therapy were included. Children with Hb 7-9 mg/dL were given IV iron sucrose whereas those with severe iron deficiency anemia Hb<7 g/dL and features of cardiovascular impairment were given packed RBC transfusion. Absolute reticulocyte count, hemoglobin and MCV were checked pre and post-treatment in both groups and difference of increase after treatment were noted and compared in both groups.*

Results: *Out of 341, 252 (73.9%) patients had Hb (7-9 g/dL) who were given IV iron and 89 (26.1%) had Hb < 7 mg/dL meeting the criteria for transfusion. There was no significant difference in the ARC at 72-hours post intervention between the two groups (p=0.249). However, at 14 days post intervention the ARC increased significantly in IV iron therapy as compared to transfusion group (p<0.0001). The change in Hemoglobin (ΔHb) at 14 days had a median value 0.8 (0.3) g/dL in IV iron therapy as compared to 1.6 (0.3) g/dL in the transfusion group (p<0.0001).*

Conclusion: *RBC transfusion acutely and transiently increased hemoglobin and retic count in IDA. However, IV iron therapy, while slower in improving Hb, offers a more sustained effect on red cell production.*

Keywords: *Absolute Reticulocyte count (ARC), Hemoglobin, Iron deficiency Anemia (IDA), RBC Transfusion, iron sucrose*

INTRODUCTION

Reticulocytes, or "Reticulated Erythrocytes" are quite different from early stage, nucleated red blood cells (RBCs) and represent a much later but still premature, enucleated stage of RBC maturation before they become a mature, biconcave RBC.[1] The reticulocyte count in the blood is in direct proportion to the degree of anemia which in turn, is the determinant of erythropoietin release which in fact determines the reticulocyte release into blood.[2] Reticulocyte count in the blood is therefore a marker of anemia whether it is improving or not.

Anemia has been defined for children by the World Health Organization as a hemoglobin concentration of less than 11g/dL. Iron deficiency anemia is a world wide problem for the developing countries where it has been estimated to afflict over 40% of the school going children.[3] The recommended daily allowance of iron for school going children is around 10mg/day.[4] Iron absorption from the intestine is less than 20% of the intake, making repletion of the stores very slow and requiring a prolonged therapy.[5] Treatment of iron deficiency anemia is mainly done by oral iron supplements, available in a variety of formulations, given in a dose of 3-6 mg/kg/day.[6] Intravenous iron therapy is reserved for only those cases where there is an issue with tolerance of oral iron, absorption defects in the gastrointestinal system or there is an urgent need for correction of iron stores. Transfusions of a single unit of packed red blood provides free iron as much as one to two tablets of ferrous sulfate contain. Blood transfusion has no role in the treatment of iron deficiency except in case of severe anemia when hemoglobin is <7 g/dL with symptoms and signs of cardiovascular impairment.[7]

There is much debate in our country about the use of injudicious use of transfusion related products.[8] Despite clear guidelines and evidence-based medicine, iron deficiency anemia is still treated at times with transfusion in our country, especially in the lower hierarchal set ups of our healthcare system, which carries risks of its own.[9] With this background in mind, we conducted a simple study on reticulocyte count in children with iron deficiency anemia who absolutely needed transfusion and those who received parenteral iron therapy to demonstrate if there is any difference in the hematological parameters with either intervention.

Methodology

It was conducted as a Comparative Cross-Sectional Study in the Department of Pediatrics, KRL Hospital, Islamabad, Pakistan, from August 2024 to December 2024 over a period of 5 months following approval of the Ethical committee of KRL Hospital Islamabad. The sample size of 329 was calculated using the WHO sample size calculator taking a confidence interval of 95%, a margin of error of 5%, and a reported prevalence of iron deficiency anemia in children with ages 4-6 years by Akhtar et al as 44%.[10] Consecutive non-probability sampling technique was used. Total 452 patients of IDA reporting in the pediatric OPD during study period were screened, and 380 IDA patients fulfilling inclusion criteria and whose parents given consent were included in the study. Final analysis, however included 341 patients(Figure-1).

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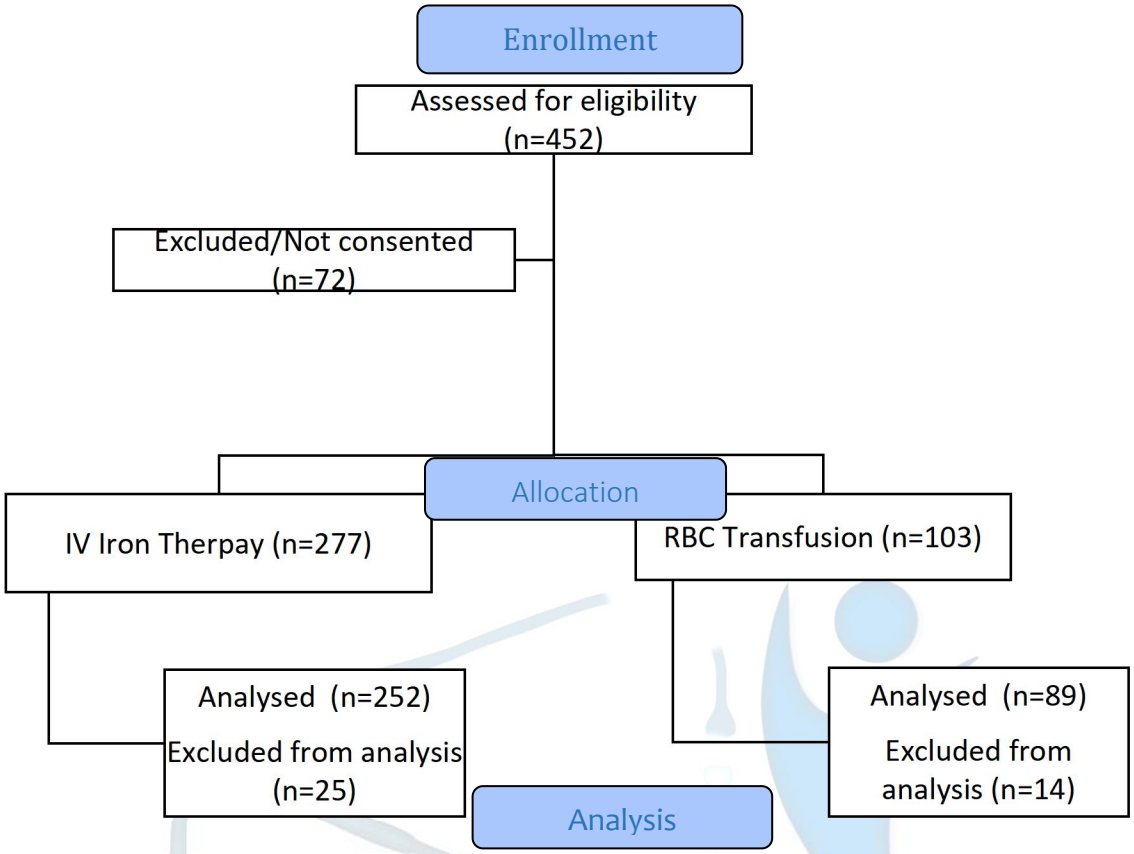

Figure 1: Patient Selection Flow Diagram (n=341)

Inclusion Criteria:

Pediatric patients of either gender, aged 5-11 years, diagnosed with iron deficiency anemia based on serum ferritin assay conducted at the time of diagnosis, having Hb < 9 g/dL and resistant to 3 months of oral iron therapy with poor tolerance and good compliance and being admitted for parenteral iron therapy or packed RBC transfusion were included in the study.

Exclusion Criteria:

Patients with a coexisting hemoglobinopathy, chronic kidney disease, poor compliance to oral iron therapy or hypersensitivity to iron sucrose (Venofer^{R}) were excluded from the study.

All patients were admitted in pediatric wards/HDU depending upon severity and sign/symptoms of anemia. Patients were segregated in two group on the basis of treatment required. Group-A included the patients with Hb of 7-9 g/dL who were advised IV iron (Venofer). Group-B comprised of patients with Hb < 7 g/dL and/or with signs / symptoms suggestive of cardiovascular impairment were planned for packed RBC transfusion.

Baseline data were collected for the patients with regards to age, duration of symptoms, socioeconomic status, hemoglobin, serum ferritin and reticulocyte count and index. The patients were later on followed up after the intervention. The dose of IV iron was calculated using Ganzoni's equation as follows.

Total Iron Deficit(mg) = Weight (kg) x [Target Hb(g/dL) – Actual Hb(g/dL)] x 2.4 + Iron stores(mg)[11]

For children with weight >35 kg, iron stores were taken to be 500mg and for those with weight <35 kg, stores were calculated as 15mg/kg body weight. Maximum dose of Venofer^{R} administered per day was 7 mg/kg.[12] Reticulocyte count and hemoglobin was checked again for both groups at 72 hours and at 2 weeks follow up post iron/transfusion therapy completion. For patients who were to receive multiple doses of Venofer^{R} over next few days, follow up was done after the therapy completion. Acute side effects of either

therapy, were also recorded. The primary outcome of the study was to compare the absolute reticulocyte count (ARC) between the two groups at 72 hours and 14 days post intervention. Secondary outcomes included comparison of changes in Hb, MCV, platelet count and adverse reactions between the two groups. Data were collected using a specially designed proforma and later on entered in to Statistical Package for Social Sciences (SPSS) software version 25. Normality of the data was checked using Kolmogorov Smirnov Test which showed a non-normal distribution. Frequencies were calculated for qualitative variables and compared using Pearson Chi Square test. Median and Interquartile ranges were calculated for quantitative variables and compared using Mann Whitney U test and Friedman test. A p-value of ≤ 0.05 was considered statistically significant.

Results

There were 341 IDA patients included in the final analysis among which 208 (61%) were males and 89 (39%) were females with mean age of 5.81±3.19 years. Total 252 (73.9%) patients had moderate anemia with Hb of 7-9 g/dL who were in the IV iron group while 89 (26.1%) patients had Hb < 7 mg/dL meeting the criteria for transfusion. Patients in the IV iron group had a mean age of 5.92±3.47 years where as those in the transfusion group had a mean age of 5.49±2.22 years (p=0.28). There were no statistically significant difference in Hb and ARC at baseline in both groups. The median reticulocyte counts along with interquartile ranges at baseline, 72 hours post intervention (IV iron or transfusion) and 14 days post intervention has been summarized in the Table-I (p<0.001).

Table-I. Absolute Reticulocyte Count at Baseline, 72 hours and 14 days (n=341)

Variable		Temporal Juncture			p-value
		Baseline	72 hours	14 days	
Absolute Reticulocyte Count (ARC) **Median (IQR) x 10^9 /L**	**IV Iron**	12.00(7.00)	28.00(11.00)	94.00(11.00)	<0.0001
	Transfusion	13.00(4.00)	27.00(10.00)	74.00(17.50)	<0.0001

There was no significant difference in the ARC at 72-hours post intervention between the two groups (p=0.249). However, at 14 days post intervention the ARC increased significantly more in the patients who received IV iron therapy as compared to those who received RBC transfusion (p<0.0001).

Hemoglobin also increased at 14 days post intervention in both groups (p<0.0001). The change in Hemoglobin (ΔHb) at 14 days had a median value 0.8 (0.3) g/dL in the patients who received IV iron therapy which was less as compared to 1.6 (0.3) g/dL in the transfusion group (p<0.0001). The MCV also increased significantly in both groups but the change was more prominent in the transfusion group (p<0.0001).

Table-II. Change in Hemoglobin and MCV at Baseline and 14 days (n=341)

Variable		Temporal Juncture		p-value
		Baseline	14 days	
Hemoglobin **Median (IQR) g/dL**	**IV Iron**	7.60(0.60)	8.50(0.40)	<0.0001
	Transfusion	4.70(1.10)	6.50(1.05)	<0.0001
MCV **Median (IQR) fL**	**IV Iron**	63.00(8.75)	74.00(4.00)	<0.0001
	Transfusion	58.00(0.90)	72.00(3.00)	<0.0001

The side effect profile was observed in both groups has been summarized in Figure-2 as follows.

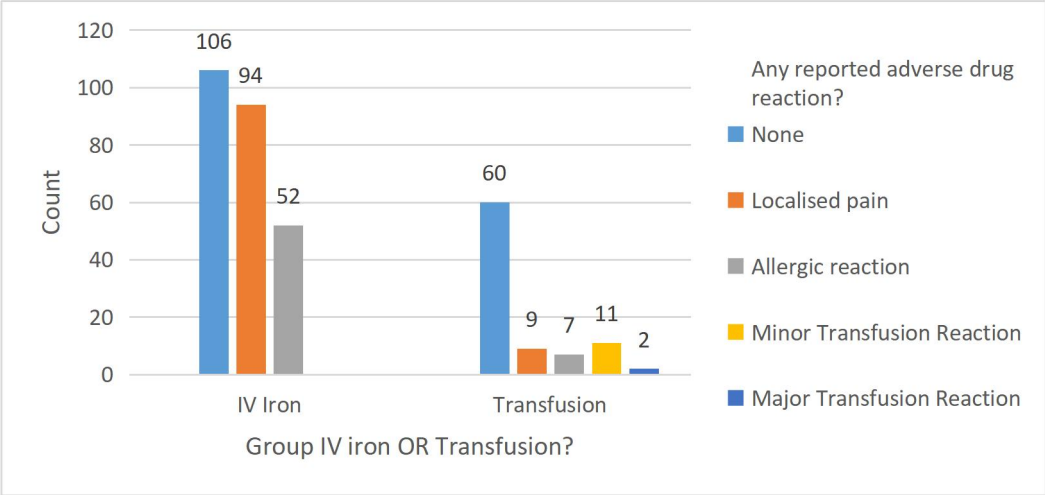

Figure-2: Comparison of Side effect profiles between IV Iron and Transfusion Groups (n=341)

Discussion

Iron deficiency anemia being common entity in pediatric age group requires treatment approach which acutely improve Hb and retic count as well as provide long term persistent maintenance of body Hb and iron stores as well. IV iron therapy and RBC transfusion for correction of IDA were studied which showed significant improvements in ARC, hemoglobin (Hb), and mean corpuscular volume (MCV) over time in both groups. At 14 days, ARC increased more significantly in the IV iron group compared to the transfusion group, reflecting enhanced erythropoietic activity. Choi et al also concluded in his study that IV iron administration was associated with higher hemoglobin at 30-day post administration as compared to RBC transfusion (10.1 ± 1.8 g/dL vs 9.4 ± 1.7 g/dL, p=0.001).[13] Conversely, the transfusion group exhibited a greater immediate increase in Hb and MCV, consistent with the direct replacement of red cells. In this study it was observed that the change in Hemoglobin (ΔHb) at 14 days had a median value 0.8 (0.3) g/dL following IV iron therapy which was less as compared to 1.6 (0.3) g/dL in the transfusion group (p<0.0001). In a study by Shah et al it was observed that iron therapy modestly increase Hb concentration (Mean Difference: 0.31 g/dL, 95% CI: 0.014-0.59, p=0.03) as compared to red cell transfusion.[14]

It may be particularly beneficial for patients requiring long-term correction of iron deficiency without immediate cardiovascular compromise. On the other hand, RBC transfusion remains critical for patients with severe anemia or urgent needs. Boshuizen et al explained in his study that RBC transfusion acutely and transiently increased hemoglobin and ferritin levels in patients with IDA.[15] In a study by Froissart et al concluded that following IV iron and RBC transfusion there was significant changes in hemoglobin, absolute reticulocyte count (ARC) and serum folate levels but 97% patients with IDA who received RBC transfusion still had low serum ferritin and transferrin saturation post transfusion as compared to patients who received IV iron therapy. These findings suggest that IV iron therapy, while slower in improving Hb, offers a more sustained effect on red cell production.[16] However, we were not able to study serum ferritin pre and post intervention due to affordability issues.

The adverse effect chart shows that IV iron therapy was associated with more cases of localized pain and allergic reactions, while transfusions resulted in a greater frequency of minor and major transfusion reactions. However, IV iron therapy is generally safer and associated with minor discomforts like localized pain and fewer severe adverse events. Hung et al concluded that IV iron therapy reduced the risk and requirement of blood transfusion and subsequently reduces the risk of transfusion related complications (RR 0.77, 95% CI:0.65–0.91, *p*=0.002, certainty of evidence: moderate).[17]

As shown by Thomas et al that IV iron therapy in the form of ferric derisomaltose give 1 gm of iron in less time (approximately quarter) of the time required for a blood transfusion, leading to sustained Hb increase. Also, IV iron is cost-effective and reduce risk of transfusion related complication like alloimmunization, allergic reactions and transfusion related lung injury (TRALI) and transfusion-associated circulatory

overload (TACO).[18] Similarly, Nestor et al also concluded that IV iron sucrose is better, preferable and long term cost-effective treatment in pediatric patients and even adolescents with IDA.[19] Similar results were shown in a retrospective cohort study by Barghi et al.[20] Despite all this evidence, the role of transfusion remains critical in emergencies. It does carry a higher risk of significant reactions, necessitating vigilant monitoring.

Conclusion

Iron Deficiency Anemia not responding to 3 months trial of oral iron therapy required parenteral iron or transfusion according to severity of anemia and degree of cardiovascular compromise. The RBC transfusion exhibited a greater immediate increase in Hb, MCV and ARC, which is critical in severe anemia or anemia causing cardiovascular impairment. RBC transfusion acutely and transiently increased hemoglobin and ferritin levels in patients with IDA. However, IV iron therapy, while slower in improving Hb and MCV, offered a more sustained effect on red cell production.

Limitations

Conducting the study at a single center and a limited sample size are amongst the major limitations of the study. The effect of dietary elements, ethnicity, genetics and family history were not taken into account in current study. Also, this study was focused on the ARC, Hb and MCV change while effect of parenteral iron and RBC transfusion on other parameters including serum ferritin levels, TIBC, transferrin saturation and RBC count were not checked in this study. The results therefore cannot be generalized to other demographics or healthcare environments.

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Conflict of Interest None

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Author`s Contribution:

The authors confirm the contribution to the paper as follows:

Dr Hajra Javed: Concept and study design, Data Acquisition, Manuscript writing, Analysis & interpretation.
Dr Sughra Wahid: Concept and study design, Analysis & interpretation, critical review & final approval.
Dr Amber Latif: Data Acquisition, Manuscript writing, critical review & final approval.
Dr Maliha Akhtar: Concept and study design, Analysis & interpretation, critical review.
Dr Mahnoor Amin: Concept and study design, Analysis & interpretation, critical review & final approval
Dr Sarmad: Data Acquisition, Manuscript writing, Analysis & interpretation, critical review.

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