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Mean Rise in Hemoglobin After Intravenous Iron Therapy in Children with Iron Deficiency Anemia

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ABSTRACT

Introduction: Iron deficiency anemia (IDA) is a significant public health issue in Pakistan, affecting up to 63% of children, as revealed by the Pakistan National Nutritional Survey 2018. While oral iron remains the primary choice, challenges in compliance have led to the consideration of intravenous (IV) iron therapy, particularly iron sucrose. The study discusses the safety and efficacy of IV iron therapy in Pakistani children and aims to broaden our understanding of treating IDA in resource-constrained regions.

Aims & Objectives: To determine the average hemoglobin (Hb) increase in iron-deficient-anemic children aged 01 to 12 years after treatment with intravenous iron sucrose.

Place and Duration of Study: A quasi-experimental study was undertaken at Fauji Foundation Hospital in Rawalpindi, spanning from September 2021 to September 2022.

Material & Methods: The study focused on a cohort of pediatric patients aged between 1 and 12 years, all of whom were diagnosed with iron deficiency anemia and had previously encountered ineffective outcomes with oral iron therapy. In this investigation, the patients received treatment involving intravenous iron sucrose. Subsequently, their progress was diligently monitored after a period of 8 weeks. Improvement in hemoglobin level was assessed at the end of treatment to evaluate its efficacy.Data processing and statistical analysis were carried out using SPSS version 23,p-value of <0.05 indicated statistical significance.

Results: Out of 150 study cases, 96 (64.0 %) were male, while 54 (36.0 %) were female. The mean age of our study cases was 05 ± 2.3 years of these 150 study cases, 74 (49.3 %) belonged to rural areas, and 76 (50.7 %) belonged to urban areas. Poor socioeconomic status was noted in 97 (64.7 %), and 53 (35.3%) were middle-income. A family history of iron deficiency anaemia was recorded in 16 (10.7%). Iron deficiency due to dietary iron insufficiency was reported in 67 (44.7%), Total Parentral Nutrition (TPN) dependencywas seen in 61 (40.7%) and 22 (14.7%) had chronic gastritis. The mean baseline (pretreatment) haemoglobin level was 7.71 ± 0.63 g/dl, while the mean post-treatment haemoglobin level was 10.68 ± 0.60 g / dl (p = 0.001).

Conclusion: After intravenous iron sucrose, we noted a significant rise in paediatric patients' hemoglobin levels, emphasizing its effectiveness and safety. Statistically, we found correlations with age, family history, and causes. Healthcare practitioners should consider injectable iron treatments for better results and reduced health issues in this group.

Keywords: Iron Deficiency Anemia, Hemoglobin, Intravenous iron.

INTRODUCTION

Iron deficiency anemia (IDA) among children, remains a significant concern in developing nations Pakistan, in particular, grapples with an alarming prevalence of IDA amongst its young population with up to 63% of children affected, as highlighted by the Pakistan National Nutritional Survey 2018[1]. This unsettling statistic underscores the urgency of addressing this pressing public health concern. Iron deficiency anemia, characterized by reduced red blood cell count and diminished hemoglobin levels (Hb), continues to affect the health and development of Pakistani children. The gravity of the situation becomes even more apparent when considering additional findings from the same survey, which reveal that 17% of children are classified as wasted, 24% as stunted, and 31% as underweight, painting a comprehensive picture of the nutritional challenges faced by the country's youth[1]. The roots of this

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anemia epidemic are multifaceted and include factors such as suboptimal infant feeding practices, inadequate dietary intake, consumption of diluted milk, and susceptibility to worm infections. These elements collectively contribute to insufficient serum iron concentration in children's bloodstreams, leading to a range of adverse consequences, including stunted growth, developmental delays, behavioral and cognitive impairments, and compromised immune function[2,3].

Oral iron remains the primary treatment for pediatric IDA due to its affordability and efficacy. It presents challenges like taste aversion, gastrointestinal side effects, and the need for extended daily dosing thus making the compliance of young children with oral iron supplements a substantial challenge, necessitating exploration of alternative avenues for iron administration. This quest has led to the recognition of parenteral iron therapy as a viable alternative. Over the years, parenteral iron preparations, including low molecular weight (LMW) iron dextran, iron sucrose, ferric gluconate, and the latest entrant, ferumoxytol, have garnered favor due to their enhanced safety profiles. While commonly utilized in adults, IV iron treatment in children is typically reserved for those with particular conditions like chronic gastrointestinal ailments or renal failure[4-8].

The approval of intravenous (IV) iron sucrose by the FDA in 2000 marked a significant milestone in iron deficiency treatment. This particular formulation has proven its safety and efficacy, not only in adults but also in individuals facing iron deficiency stemming from diverse non-renal causes, such as pregnancy and inflammatory bowel disease. It is important to note that blood transfusions are not a practical solution for addressing mild and moderate anemia with low iron reserves in children, as documented by previous studies[9].

Both international and national research endeavors have lent credence to the safety and efficacy of intravenous (IV) iron therapy in children. A notable study conducted at Ben-Gurion University of the Negev in Israel revealed a substantial increase in Hb to 9.27±1.23g/dl with IV iron sucrose therapy among children with Iron Deficiency Anemia (IDA)[10]. Nonetheless, it is essential to acknowledge that the utilization of IV iron therapy in children is not without challenges, as certain adverse effects have been reported, underscoring the need for a comprehensive evaluation.

Our study in Pakistan sets itself apart from most others. Instead of focusing solely on malnourished children, as many studies have done before[11,12], we are taking a broader approach. We're including children with iron deficiency anemia, no matter their nutritional status. This inclusive approach shows our commitment to addressing the complexities of iron deficiency anemia in a diverse group of Pakistani children.

By looking at children with iron deficiency anemia across the nutritional spectrum, our study aims to improve our understanding of the condition and find better ways to treat it. Our main goal is to show that intravenous iron sucrose can effectively treat anemia in children in resource-limited areas like Pakistan. This work aligns with global efforts to combat childhood anemia and highlights our unique approach in the Pakistani context.

MATERIAL AND METHODS

After the ethical approval from the Institutional Review Board (IRB NO: PED-20150023572), this quasi-experimental study was conducted at the Department of Pediatrics, Fauji Foundation Hospital, Rawalpindi, from 25-09-2020 to 24-09-2021. The sample size was calculated using the WHO calculator with a study power of 80 %. The number of study subjects was increased from the required number of 142 to 150 for the ease of statistical purposes. Through non-probability consecutive sampling, children between the ages 01-12 years of either gender, non-responsive or non-compliant to oral iron therapy or who developed gastrointestinal adverse effects with oral iron therapy were included in the present study. Children allergic to iron, systemic diseases, and acute infections were excluded from the study. Written informed consent was acquired from the parents of the children who participated in the study.

The study's primary outcome was the mean rise in Hb concentration at eight weeks after administration of IV iron sucrose. An increase of 2.5 g/dl in Hb after eight weeks of treatment was considered an effective response to treatment.

The following method was used to determine the **Total Iron Dose:**

Iron deficiency (in mg) = weight in kg x (gm/dl of desired Hb- the actual Hb) x 2.4 +depot iron (mg).

We used a depot iron dose of 15 mg/kg of body weight and a target Hb of 13 mg/dL.

An intravenous dose of iron sucrose to be given in **ml = Total iron deficit/20 mg.**

For the intravenous administration of iron sucrose, an initial test dose of 0.5-1ml, diluted in 10ml of saline, was given over a span of 10 minutes. Following this, patients were monitored for half an hour to assess potential adverse reactions. A

cardiopulmonary resuscitation (CPR) setup was readily available at the treatment site to ensure safety. A solitary maximum dose of 7 mg/kg/day was diluted within 100 ml of saline solution and subsequently administered as a gradual infusion spanning a period of 6 hours. This cumulative dosage was administered in segmented portions, with intervals of one dose every third day. Continuous patient monitoring was maintained throughout the infusion duration. A thorough history and clinical assessment were conducted for each child. We meticulously documented demographic information and recorded the hemoglobin before and after the transfusion. Data processing and statistical analysis were carried out using SPSS version 23. Numerical variables, such as children's age and levels of serum hemoglobin were described using mean ± standard deviation. Categorical variables like gender were presented as frequencies and percentages. The Paired Sample "t" test was utilized to identify significant differences between hemoglobin levels before and after the treatment, with a p-value of <0.05 indicating statistical significance. We accounted for potential effect modifiers, including gender, age, residential and socioeconomic status, family medical history, and underlying etiology through stratification. A stratified t-test was employed to determine their influence on the outcomes. A p-value of 0.05 or lower was deemed statistically significant.

RESULTS

A total of 150 children were recruited for the present study. The demographic details and clinical parameters of the study subjects are displayed in Table-1. After therapy, the average patient's hemoglobin level increased from 7.71 g/dl (pretreatment) to 10.68 g/dl (p 0.001), as shown in Table-2. None of the children experienced any serious adverse reaction with the treatment, although 29 children out of 150 showed mild side effects that included abdominal pain (n=16), pruritis at the site of infusion (n=7), fever (n=4), and headache(n=2).Poststratification analysis of post-transfusion HB regarding gender, age, residential status, socioeconomic status, maternal literacy, family history and etiology is represented in Table-3.

Parameters	n (%) (n=150)
Gender	
Male	96 (64%)
Female	54 (36%)
Age	
Up to 5 years	132 (88%)
More than 5 Years	18 (12%)
Residence	
Rural	**74 (49.3%)**
Urban	**76 (50.7%)**
Socioeconomic status	
Poor	**97 (64.7%)**
Middle class	**53 (35.3%)**
Maternal Literacy	
Illiterate	**85 (56.7%)**
Literate	**65 (43.3%)**
Family History	
Yes	**16 (10.7%)**
No	**134 (89.3%)**
Aetiology	
Dietary Iron Insufficiency	**67(44.7%)**
TPN Deficiency	**61 (40.7%)**
Chronic gastritis	**22 (14.7%)**

Table-1: Demographic And Clinical Parameters Of The Study Participants.

Haemoglobin (g/dl)	Mean+/-SD	P-Value
Baseline	7.71±0.639	0.001
Post-Treatment	10.68±0.609	

Table-2: Mean Hb Level Before And After Therapy

Parameters	Post Treatment HB level (g/dL) Mean+/- SD	P-Value
Gender		
Male (n=96)	10.67±0.628	0.726
Female (n=54)	10.70±0.570	
Age		
Up to 5 years (n=132)	10.63±0.605	0.004
More than 5 years (n=18)	11.06±0.506	
Residence		
Rural (n=74)	10.59±0.550	0.076
Urban (n=76)	10.77±0.654	
Socioeconomic status		
Poor (n=97)	10.62±0.610	0.135
Middle class (n=53)	10.78±0.601	
Maternal Literacy		
Illiterate	10.65±0.487	0.565
Literate	10.71±0.743	
Family History		
Yes (n=16)	11.03±0.688	0.014
No (n-134)	10.64±0.588	
Etiology		
Dietary Iron Insufficiency (n=67)	10.53±0.645	0.019
TPN Dependency (n-61)	10.83±0.548	
Chronic Gastritis (n=22)	10.72±0.575	

Table-3: Stratification Analysis of Mean HB Post Treatment

DISCUSSION

Iron deficiency anemia casts a profound shadow on the health and survival of children below the age of five. It stands as the foremost contributor to the global burden of disease, a fact underscored by the UNICEF report of 2020, which lamented that over 149 million children in developing countries, aged less than 5 years, suffer from significantly impaired growth[13]. Hence, it becomes paramount that iron deficiency anemia receives swift and effective treatment. However, it's worth noting that some children, particularly those with severe IDA, may prove intolerant, non-compliant, or non-responsive to conventional oral iron therapy. Considering the inherent risks associated with blood transfusions, we sought to assess the safety and efficacy of parenteral iron therapy in iron-deficient children.

Our study findings conclusively report that intravenous (IV) iron sucrose administration in pediatric patients with IDA yields both clinically meaningful and statistically significant increases in hemoglobin levels. In routine clinical practice, primary indications for IV iron therapy in pediatric cases are non-responsiveness to oral iron, mal-absorption issues, the urgent need for rapid correction of anemia, and excessive menstrual bleeding, particularly in adolescent females[11]. Within our cohort, IV iron was prescribed for a range of reasons, with the most prevalent being inadequate dietary iron intake, followed by children reliant on Total Parenteral Nutrition (TPN). It's worth noting that a separate study identified inadequate diet or excessive milk consumption as the cause of anemia among 102 (40.8%) admitted patients[11]. A study from Turkey revealed that 58% of people were recommended IV iron treatment to counter insufficient dietary iron intake, while another 24% to rectify iron deficit due to oral malabsorption[9].

Following the intervention, we observed a notable increase in the average hemoglobin (Hb) level, which soared from 7.71 g/dL to 10.68 g/dL (p 0.001). Remarkably, this aligns with findings from a Greek study by Mantadakis et al., where Hb levels improved from an average of 7.6±2.38 g/dL to 12.4±0.64 g/dL[5]. Similarly, our study outcomes find resonance with a study recently conducted in Multan, reporting a statistically significant increase in mean Hb levels after six weeks of active supplementation[11]. Another national study documented that parenteral iron sucrose therapy improved mean Hb levels in malnourished children with IDA[12]. Meanwhile, another Pakistani study reported Hb levels rising to 9.21±1.13 g/dL with IV iron sucrose therapy[14]. Further substantiating the efficacy of IV iron therapy, an international study conducted at Ben-Gurion University of the Negev in Israel showcased a rise in Hemoglobin (Hb) levels to 9.27±1.23 g/dL among children with IDA who underwent intravenous (IV) iron sucrose therapy[10]. These studies showed a lower rise in mean hemoglobin level as compare to our study which could be explained by the fact that most of these studies focused on malnourished children which had much lower initial Hb as compare to children in our study.

Our study only looked at Hb levels pre and post intervention while the findings of other studies extended beyond hemoglobin levels and also indicated statistically significant increases in red blood cell count (RBCs), mean corpuscular hemoglobin (MCH), and serum ferritin levels. These results align with the fact that effective erythropoietic recovery is achieved through intravenous iron sucrose[14,15].

Of the 150 participants meeting our study criteria, 64 (36.0%) were female, while 96 (64.0%) were male. These demographics are consistent with the findings of Zaman et al, who also reported that out of total patient's male were 35 (64%) and female were 20 (36%)[15].

Moreover, study from Multan corroborates these ratios with a male-to-female ratio of 1.3:1[11].

Notably, a substantial proportion of our participants, accounting for 132 (88.0%), were aged five or younger.

Given the detrimental effects of IDA on neurodevelopment, the prompt and safe restoration of iron levels in affected children becomes paramount. Various studies have illustrated the ability of IV iron formulations to elevate Hb levels by varying degrees, ranging from 1.56 to 4.8 g/dL within a span of one to sixteen weeks[16]. Our study echoes these findings, demonstrating a substantial rise in Hb levels by 2.97±0.6 g/dL eight weeks after IV iron therapy.

While it is acknowledged that IV iron treatment incurs higher initial costs compared to oral iron therapy, the former offers the advantage of faster recovery for patients dealing with severe anemia. This can translate into reduced medical visits, fewer laboratory tests, decreased school absenteeism, a diminished need for red blood cell transfusions, and, ultimately, potential cost savings in the long term. A dependable IV iron option becomes particularly crucial for young patients who may struggle with or avoid oral formulations.

Remarkably, our study noted a conspicuous absence of significant adverse reactions to IV iron therapy

with only 19.3 percent children (29 out of 150) experienced a mild reaction. In our study abdominal pain was the most common mild adverse reaction followed by pruritis at the site of injection. The study conducted in Multan, reported fever as the most common side effect[11]. Contrarily, Mantadakis et al. identified injection site extravasation as the most frequent adverse effect of parenteral iron, followed by a transient alteration in taste[17]. Furthermore, Papadopoulos et al. documented rash following infusion and urticarial rash as common adverse effects[18].

Despite its valuable contributions, our study does have certain limitations. It primarily utilized mean Hb levels as the hematological metric to gauge the efficacy of IV iron therapy, deviating from more comprehensive studies that also incorporated metrics such as mean corpuscular volume (MCV), hematocrit, and serum ferritin. Additionally, our research constitutes a single-center, prospective study. While an increasing body of corroborative evidence highlights the efficacy and tolerability of parenteral iron in pediatric populations, existing literature predominantly comprises retrospective studies, non-randomized uncontrolled prospective studies, or case reports. Consequently, a clear imperative emerges for further research in the form of randomized controlled trials within pediatric settings.

CONCLUSION

Considering the substantial rise in mean hemoglobin levels following treatment with IV iron therapy, our research findings indicate that intravenous iron in juvenile patients is well accepted and has a favorable therapeutic outcome with limited deleterious effects. There were statistically substantial correlations between age, family history, cause, and mean hemoglobin level after therapy. To accomplish the intended therapeutic results and reduce the load of associated morbidities, clinicians managing such patients should always use injectable iron treatment among these patients. It will improve the patient's quality of life and reduce the costs involved with their treatment.

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