ORIGINAL ARTICLE

Parental Iron Therapy to Treat Iron Deficiency Anemia in Malnourished Children

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ABSTRACT

Objective: To evaluate the safety and efficacy of parental iron therapy to treat iron deficiency anemia in malnourished children.

Study Design: Quasi experimental design.

Place and Duration of Study: Stabilization Centre, Children Hospital and the Institute of Child Health, Multan from 1st December 2014 to 31st December 2020.

Materials and Methods: A total of 250 malnourished children with iron deficiency were included in the study. The laboratory parameters i.e., Hemoglobin, Hematocrit, Red Blood Cells Count, mean corpuscular hemoglobin, mean corpuscular volume, and Serum ferritin of all patients were done. Using the iron deficit formula, all participants were given the measured iron sucrose complex. The iron sucrose complex was diluted with 0.9% normal saline and administered steadily for 3-4 hours. After 6 weeks of therapy, hemoglobin, RBC count , ferritin was measured. Comparison of mean ±SD of baseline laboratory parameters and after 6 weeks of iron supplementation was analyzed by using t-test.

Results: A total of 250 participants were registered, male patients (57.2%) were more than female patients (42.8 %). Most of the 92(36.8%) participants were 12-24 months old. The key cause of anemia among 102(40.8%) admitted patients was inadequate diet or excessive milk consumption. The mean ±SD value of the Hb level at admission was 7.5±1.9 and it increased to 11±1.15g/dL after 6 weeks of active supplementation which is statistically significant (P-value < 0.05). Six weeks after giving intravenous iron therapy mean serum Ferritin increased from 11.5ml to 21.61 ng/ml.

Conclusion: Current study concluded that controlled administration of IV iron sucrose for treatment of iron deficiency anemia among inpatients is efficacious and safe. IV iron sucrose should be considered for patient with severe IDA, those who are not compliant with oral formulations, and patients with malabsorption.

Key Words: *Hemoglobin, Intravenous Iron Sucrose, Iron Deficiency Anemia, Red Blood Cells, Severe Acute Malnutrition, Serum Ferritin.*

Introduction

Protein energy malnutrition is a prime concern of developing countries, and it is often linked with iron deficiency anemia (IDA) among children. Iron deficiency anemia is prevalent in children up to 63% in Pakistan. According to Pakistan National Nutritional Survey 2018, 17% children were wasted, 24% children were stunted and 31% were underweight.[1]

Anemia is interpreted as a low red blood cell concentration along with low hemoglobin, or hematocrit, in a routine blood test. The main causes of iron deficiency anemia are poor Infant and Young Child Feeding Practices (IYCF) practices, poor diet, and consumption of over diluted milk and worm infections. Poor serum iron concentration in blood can lead to growth failure, developmental delay, behavioral and cognitive issues, learning disabilities and immune dysfunction.[2-5]

Oral iron therapy is the global standard for the management of anemia.[6] It is mostly well tolerated by well-nourished children but in under-nourished children particularly Severe Acute Malnutrition (SAM) children body undergoes reductive

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adaptations, Gut absorptive abilities also compromised.[7,8] Previous studies suggested that iron supplementation by malnourished children mostly presents with complications of diarrhea and vomiting that leads to poor compliance of iron in children with severe acute malnutrition which may be especially due to GIT dysfunction.[6,8] Moreover, young children are non-compliant with the oral iron supplements, therefore, other alternatives such as the parenteral route of iron administration must be sought.

For decades parenteral iron has been used to treat iron deficiency unresponsive to oral iron therapy. Iron preparations, including low molecular weight (LMW) iron dextran, iron sucrose, ferric gluconate, and the newest formulation, ferumoxytol, have generally replaced HMW iron dextran for use in both adults and children with chronic kidney disease due to their more favorable safety profiles.[7] Intravenous (IV) iron sucrose was approved by the FDA in 2000 for patients. Iron sucrose has been reported to be safe and effective in adults with iron deficiency due various non-renal causes, including pregnancy or inflammatory bowel disease.[9] Blood transfusions is not a solution to overcome this problem in children particularly with mild and moderate anemia with low iron residues.[9] Previous studies documented that IV iron sucrose therapy can help in improving Hb level to a variable extent. Previous international as well as national studies documented that intravenous (IV) iron therapy is safe for the management of anemia in children.[10-14] A study conducted at Ben-Gurion University of the Negev, Israel showed Hemoglobin (Hb) rise to 9.27±1.23g/dl with intravenous (IV) iron sucrose therapy in children with Iron deficiency anemia IDA. Unfortunately, some adverse effects have limited its use in children.[15]

To this date, only a few studies from Pakistan have emerged evaluating the safety and efficacy of parental iron therapy in malnourished children. Hence, the current study will have significant clinical implications enhancing our understanding and our capability to tackle the malnourished children with iron deficiency anemia. So current study was planned to evaluate the safety and efficacy of parental iron therapy to treat iron deficiency anemia in malnourished children. This study will help establish the usefulness of intravenous iron sucrose in malnourished children with anemia in resource-constrained countries like Pakistan.

Materials and Methods

This was a quasi-experimental study conducted in preventive Pediatrics Department Children Hospital and the Institute of Child Health, Multan from 1st January 2014 to 31st December 2020. Registration of patients was started after taking approval from Institutional Ethical Committee (Ref. no. 794, dated: 16.12.2013). Simple convenient sampling technique was used. Informed consent was taken from parents and guardians after explaining risk and benefits of IV iron therapy. A total of 250 participants were registered in current study by fulfilling inclusion criteria i.e., all the children were included with age group 1 year to 5 years with primary Severe Acute Malnutrition (SAM) with Wt/Ht Z-score <-3SD or MUAC 11.5cm or presence of any bilateral pedal edema and/or primary Moderate acute Malnutrition (MAM) children Wt/Ht Z-score <-2SD or MUAC 11.5-12.5 cm with anemia categorized as: Serum Hb levels 6-10g/dl was classified as anemic, 6-8g/dl was classified as moderate anemic, 8-10g/dl was classified as mild anemic and <6g/dl was categorized as severely malnourished and Serum ferritin levels <20ng/ml.

Exclusion criteria was defined as critically ill children with anemia less than 6g/dl and any previous iron therapy during last 3 months, hemolytic anemia, those who refused consent, children with chronic illnesses or secondary malnutrition.

A planned questionnaire was designed by trained medical staff and required variables were noted. The laboratory parameters i.e., Hemoglobin, Hematocrit, Red Blood Cells Count, Serum ferritin, mean corpuscular hemoglobin, mean corpuscular volume of all patients were done once at admission and again 6 weeks after the intervention.

Injectable iron is available in 5ml ampule that contains 100mg of iron in it. Dose of IV iron was calculated by using following standard formula[10]

$$\frac{\text{Normal Hb levels for age-Initial Hb levels}}{100} \times \text{Body blood volume} \times 3.4 \times 1.5$$

Here:3.4 is converting factor for Hb in mg of iron,1.5 is constant to replenish iron stores and 80ml/kg blood volume.

Derived dose from formula was injected 2ml/day for

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consecutive two days but not more than 3ml/day was given. After proper available aseptic measures calculated dose diluted in 100ml normal saline in peds chamber with precautions and cannot co-mixed with other medications and TPN. Unlike other forms of injectable iron viable of anaphylactic reaction are minimum with iron sucrose but were not overloaded. So, test doze was given initially over 15 minutes for any reaction. Required calculated dose added to 100 ml normal saline with the help of infusion pump. 100 ml fluid was adjusted over 4 hours. After 15 minutes infusion stopped and assessed for any reaction for 30 minutes. If no anaphylactic reaction occurs in 15 minutes infusion was started again. Hypotension, anaphylaxis, nausea, vomiting, diarrhea, abdominal pain, headache, edema, muscle cramps, fatigue and dizziness were common side effects of IV iron that were monitored throughout the infusion. Post and parental iron sucrose therapy was started and changes in ferritin levels were accurately measured within 48 hours even. Data shows 18-68% IV iron dose incorporated into erythrocytes within 2 weeks.[2] After completion of initial dose over two consecutive days, MMS (multi micronutrient sachet) with iron content one per day was started. After 15 days repeat samples of CBC and Serum Ferritin was sent and compared with initial baseline levels. All the patients turned up for follow up and no lapse was noted. Comparison of mean ±SD of baseline laboratory parameters and after 6 weeks of iron supplementation was analyzed by using t-test.

After completion of study duration, this data was entered in SPSS version 21.0 for analysis. Frequency distribution of qualitative variables was done. Descriptive statistics was applied to analyze the significance of study. Mean comparison of quantitative variables was analyzed by using t-test and p-value less than 0.05 was considered as statistically significant.

Results

A total of 250 malnourished patients were enrolled in present study, from which 150(60%) patients were severely malnourished and 100(40%) were moderately malnourished. Male/female was 1.3:1. Male participants (57.2%) were more than female participants (42.8%). The majority of 92(36.8%) participants belonged to 12-24 months, followed by 72(28.8%) from age group 36-48 months and 47(18.8%) were from age group 36-48 months respectively (Table II).

Table I: Gender, Age and Nutritional Status Distribution of all Participants (N= 250)

Characteristics	Frequency	Percentage (%)
Gender		
Male	143	57.2
Female	107	42.8
Age(months)		
12-24	72	28.8
24-36	92	36.8
36-48	47	18.8
48-60	39	15.6
Nutritional stats		
MAM	100	40
SAM	150	60

MAM: Moderate Acute Malnutrition, SAM: Severe Acute Malnutrition

The feeding history and diagnosis of admitted patients was noted in Table II. Most of the participants were on mother feed along with formula feed after birth (39.2%) and only 23.2% admitted patients were exclusively on breast milk and 37.6% were on formula milk only. Poor diet or excessive milk intake was the major cause of anemia among 102(40.8%) admitted patients and another reason behind anemia was mal absorption in 58(23.2%).

Table II :Feeding history and Diagnosis at the time of admission

Variables	Frequency	Percentage (%)
Feeding history		
Exclusive B.F	58	23.2
B.F + Formula Feed	98	39.2
Only Formula Feeding	94	37.6
Etiology of IDA in SAM		
Excessive milk	89	35.6
Poor IYCF	102	40.8
Celiac disease	37	14.8
Worm infections	22	8.8

IYCF: Infant and young child feeding practices

Severe acute malnutrition with edema was present in 13.3% enrolled subjects and without edema was observed in 86.67% enrolled subjects. Anemic status (moderate and severe anemia) compared to nutritional status of admitted patients was statistically significant as P-values was <0.05 analyzed (Table III).

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Table III: Distribution of anemia according to nutritional status (n=250)

Anemic status	MAM N=100	Edematous SAM N=20	Non-Edematous SAM N=130	*P*-value
Mild Anemia (8-10 g/dl)	29	02	35	0.09
Moderate Anemia (6-8g/dl)	45	09	73	0.022

Mean ±SD value of Hb level was 7.5±1.9 at admission and it improved up to 11±1.15g/dL after successful supplementation of 6 weeks. Mean levels of Hb, RBCs count, MCH and ferritin levels was significantly correlated (Table IV).

Table IV: Comparison of Base line and after 6 weeks laboratory parameters (n=250)

Baseline	At admission		After 6 weeks		*P*-value
	SAM N=150	MAM N=100	SAM N=150	MAM N=100	
Mean Hb	7.5 ± 7.9	8.0 ± 0.05	10.03 ± 1.15	10.5±1.10	0.02
HCT	20.17 ± 6.13	20.13 ± 5.14	25.5 ± 1.55	26 ± 1.13	0.13
RBC count 10^{12}/L	3.928 ± 1.77	4.0 ± 1.5	4.2 ± 1.8	4.1 ± 1.5	0.04
MCV	42.7 ± 3.0	45.7 ±5.0	75.55 ± 3.55	72.35 ± 2.03	0.051
MCH	15.50 ± 1.50	15.30 ± 1.00	23 ± 5.00	22 ± 4.00	0.047
Ferritin	10 ± 3.37	12 ± 4.01	22 ± 3.00	21 ± 2.00	0.01

Common side effects were analyzed of all studied participants; fever was highly prevalent in 25(10%) patients (Table V)

Table V: Common Side Effects Observed in Studied Subjects

Side effects	Frequency	Percentage
Fever	25	10
Anaphylaxis	6	2.4
Nausea	2	0.8
Vomiting	2	0.8

Discussion

Iron deficiency anemia has a significant impact on health and survival of children under five years of age. It is the leading cause of global burden of disease.[1] According to UNICEF report 2020, over 149 million children less than 5 years of age in developing countries have significantly impaired growth.[11] Therefore, it is imperative that iron deficiency anemia should be treated promptly and effectively, more so in malnourished children. Some children with severe acute malnutrition may be intolerant, non-complaint or non-responsive to oral iron therapy. As blood transfusion carries some hazards, parenteral iron therapy was assessed for its safety as well as efficacy in malnourished iron deficient children. Current study reported that IV iron sucrose in pediatric patients with IDA leads to clinical meaningful and statistically significant increases in hemoglobin, RBCs, MCH, and serum ferritin. We carried out this study in malnourished children who were having iron deficiency anemia Current study reported children were 60% severely malnourished and 40% were moderately malnourished. Similar trends were also observed in another study, where 79% children were severely malnourished and were intolerant, non-compliant or unresponsive to oral iron therapy.[11] All these patients were treated for malnutrition according to WHO guidelines in addition to intravenous iron therapy.[13] Male were prominent participants of our study. Another study also shares the same results where male outnumbered than females.[12]

The significant cause of anemia among 40% admitted patients was poor IYCF practices, excessive milk intake 35.6% and celiac disease 14.8%. While similar findings suggested that most of the participants were on mother feed along with formula feed after birth (39.2%) and only 23.2% admitted patients were feeding exclusively mother milk and 37.6% were feeding only formula milk.[16]

This study revealed that serum Hb levels improved up to 11±1.15g/dL by intravenous iron sucrose therapy. Another national study documented that parenteral iron sucrose therapy improved mean Hb level from 6.65±0.65g/dl to 10.35±1.17g/dl in malnourished children with IDA.[14] A Pakistani study reported Hb rise to 9.21±1.13g/dl with IV iron sucrose therapy.[10] These findings were lower than current study however they also concluded that IV iron sucrose therapy in malnourished children with IDA is safe and efficient.[6,17] An international study conducted at Ben-Gurion University of the Negev, Israel showed Hemoglobin (Hb) rise to 9.27±1.23g/dl with intravenous (IV) iron sucrose therapy in children with IDA.[15] Current study reported that IV

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iron sucrose in pediatric patients with IDA leads to clinical meaningful and statistically significant increases in hemoglobin, RBCs, MCH, and serum ferritin. Similar findings were also reported by Kaneva et al., 2017 where significant association with hemoglobin, ferritin and iron therapy was documented.[16] A rise in posttreatment hemoglobin levels implies that erythropoietic recovery is achieved with intravenous iron sucrose which also strengthens the findings of our study.[16,18]

The most common side effect in our study is fever 10% whereas the study by Mantadakis et al. reported the most common adverse effect of parental iron to be injection site extravasation followed by a transient alteration in taste.[19] Papadopoulos et al. found that rash following infusion and the urticarial rash was a common adverse effect following therapy.[20] No side effects were noted in children during follow up and the objective of follow up was to analyze hematocrit profile only.

Iron sucrose complex therapy appears to be highly and rapidly effective without major side effects.[21] This makes it convenient and cost effective in iron deficient, malnourished children.

We followed-up patients till 6weeks for study purpose but we recommend further trials with prolonged follow-ups to rectify the IDA completely and achieve normal hemoglobin level. It should be emphasized that iron deficiency even without anemia should be prevented before its development. In other words, to treat patients when they become anemic is too late.

Conclusion

Current study concluded that controlled administration of IV iron sucrose for treatment of iron deficiency anemia among inpatients is efficacious and safe. IV iron sucrose should be considered for patient with severe IDA, those who are not compliant with oral formulations, and patients with malabsorption.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

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