The response of Intravenous Iron sucrose in children with Iron Deficiency Anaemia unresponsive to Oral Iron Therapy.

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ABSTRACT:
Objective: To evaluates the efficacy and safety of intravenous iron sucrose in paediatric patients with IDA who have not responded to or tolerated oral iron therapy.
Methodology: This observational study was conducted at Department of Paediatrics, Pakistan aeronautical complex (PAC) Hospital Kamra, from October 2023 to April 2024. Iron sucrose (Venofer®) was administered at a dose of 0.35 ml/kg, providing 100 to 200 mg of elemental iron per dose, on alternate days for three doses. Haemoglobin (Hb) and serum ferritin levels were measured 4 weeks post-treatment to evaluate response.
Results: Among the participants, 70 (70%) were male and 30 (30%) were female, with a mean age of 34.23 ±19.54 months. Results showed a significant increase in mean Hb from 7.92 ± 0.74 g/dl before treatment to 10.46 ± 0.94 g/dl after treatment (p = 0.001)
Conclusion: Clinicians should consider intravenous iron therapy to enhance patient outcomes, improve quality of life, and potentially reduce healthcare costs.

Keywords: Iron Deficiency Anaemia (IDA), Anaemia, Haemoglobin (Hb), Oral Iron, Intravenous Iron.

Introduction:

Anaemia constitutes 8.8% of all global diseases and poses a significant public health challenge.[1-4] Iron deficiency anaemia (IDA) is the most common type of nutritional anaemia in children, affecting 17% of those under the age of 5 in developed countries.[5] Factors contributing to IDA in children include insufficient dietary iron, excessive cow's milk consumption, impaired iron absorption, and blood loss due to conditions such as worm infestations. Chronic IDA in children can lead to behavioural issues, cognitive impairment, and fatigue.[6] Early diagnosis and appropriate treatment are crucial to prevent these complications.[7-10]
Oral iron supplements are commonly used due to their low cost, but they are often poorly tolerated, causing side effects such as metallic taste, nausea, stomach discomfort, diarrhoea, or constipation.[11] Additionally, adherence to oral iron therapy is necessary over several weeks.[12] For some patients, intravenous (IV) iron therapy becomes necessary due to severe IDA, poor adherence, malabsorption, or intolerance to oral iron.[6] Various IV iron formulations are available[13], and while oral supplements typically raise blood iron levels by 70-150 mg/100 ml and increase red blood cell production by 4-5 times, intravenous iron therapy can elevate serum iron by more than 200 mg/100 ml and boost red blood cell production by 4.5-7.8 times.[11]
Iron sucrose (Venofer), a commonly used IV iron preparation for adults, has been extensively studied and approved by the FDA in 2000.[13] It is associated with rare and dose-dependent adverse effects.[14] Malik et al.[15] found that administering IV iron sucrose to 142 children with IDA increased their average haemoglobin (Hb) from 7.85 ± 0.78 g/dl to 10.29 ± 0.89 g/dl after three months of therapy.

Rationale:

While IV iron sucrose has been well-documented for adults, but limited research exists on IV iron sucrose in children, especially in Pakistan. Moreover, studying patients who haven't responded to conventional treatment provides valuable insights. This study aims to evaluate the effectiveness of IV iron sucrose in paediatric patients with IDA.

Methodology:

This Prospective observational study was conducted from October 1, 2023, to April 1, 2024, at the Paediatric Department of Pakistan Aeronautical Complex Kamra after approval from ethical board of hospital. A sample size of 100 was determined using a 95% confidence interval and a 5% margin of error.[16] The study included children aged 2 to 12 years of both genders who had haemoglobin levels below 11 g/dl and serum ferritin levels below 12 ng/ml, and who had previously received at least three months of oral iron therapy without improvement. Samples were collected by non-probability convenience sampling.
Exclusion criteria encompassed refusal to consent, inadequate oral iron therapy, and chronic conditions such as infections, chronic kidney disease, congenital heart disease, celiac disease, Thalassemia, inflammatory bowel disease, bleeding disorders, and chronic lung disease. Non-probability consecutive sampling was employed.
Informed consent was obtained from parents. Demographic information, along with pre-treatment haemoglobin and serum ferritin levels, was recorded. Failure of oral iron therapy was defined as a lack of improvement in haemoglobin and serum ferritin levels after a minimum of three months of treatment.
Iron sucrose (Venofer) was administered at a dose of 0.35 ml/kg, providing 100-200 mg of elemental iron per dose, on alternate days for three doses. Following a test dose, the intravenous iron was given according to protocol, with oral iron therapy continuing thereafter. Haemoglobin and serum ferritin levels were assessed four weeks post-treatment.

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The primary outcome was the mean increase in haemoglobin levels following intravenous iron therapy.

Data analysis was performed using SPSS version 20. Quantitative variables, such as age, haemoglobin concentration, and serum ferritin levels, were described using means and standard deviations. Qualitative variables, including gender, residence, maternal education, and socioeconomic status, were presented as frequencies and percentages. A paired t-test was used to evaluate the statistical significance of changes in haemoglobin and serum ferritin levels pre- and post-treatment. Chi-square tests were used to examine associations between age, gender, and response to iron sucrose therapy, with statistical significance set at $p \leq 0.05$.

Results:

The study included 100 patients with IDA. Of these, 70 (70%) were male and 30 (30%) were female. The mean age of the patients was 34.23 ± 19.54 months, with ages ranging from 24 to 98 months. Most patients (81%) were under 5 years old. Among the participants, 55 (55%) were from rural areas and 45 (45%) from urban areas. Socioeconomic status was poor in 52% of cases, while 48% were from middle-income families. Additionally, 46% of mothers were uneducated and 54% were educated. Family history of IDA was noted in 12% of cases, and dietary iron deficiency was observed in 47%. The mean pre-treatment haemoglobin level was 7.92 ± 0.74 g/dl, which increased to 10.46 ± 0.94 g/dl post-treatment ($p = 0.001$) as shown in table no 1. Treatment response was observed in 89 (89%) of the cases. Response rates were analysed by age, gender, residence, socioeconomic status, maternal literacy, and family history as shown in table.

Table No 1: Demographic and study variables

Age	**Frequency**	**Percentage**
Upto 5 years	81	81%
More than 5 years	19	19%
Total	100	100%
Overall response to treatment	**Frequency**	**Percentage**
Yes	89	89%
No	11	11%
Total	100	100%
Hb% (g/dl)	**Mean**	**±SD**
Pre treatment	7.92 g/dl	±0.74
Post treatment	10.46 g/dl	±0.94
P Value	0.001	
Response to therapy according to age		
	Yes n=89)	No (n=11)
Up to 5 years (n=81)	70	11
More than 5 years (n=19)	19	0
Total	100	
p-value	0.118	

Discussion:

Very recently a phase 2, non-randomized, multicentre study trial conducted to evaluate the safety and efficacy of compound ferric carboxymaltose for the management of iron deficiency anaemia.[16] Results showed that the compound is very well tolerated and only side effect observed was urticaria. However, it will take much time to be available across the world. Currently IV iron therapy is considered gold standard to compare it with oral iron. Although in most cases oral iron is very well tolerated and it has been shown that response in most patient is satisfactory.[17-19] However, in a few children having inadequate response to oral iron, IV Iron therapy should be an option. Benefits of intravenous iron therapy include a rapid repletion of iron stores along with resolution of anaemia, few GITS side effects with a rapid relief for patients and families struggling with long term oral iron therapy. Indications for first-line therapy with intravenous iron in children with chronic conditions have also increased. Four intravenous iron formulations have approved indications in paediatric.[20-22]

Iron deficiency anaemia is the most prevalent nutritional deficiency and important public health issue throughout the globe.[23-24] According to World Health Organization record, 30% of youth aged between 5-14 years are anaemic. Countrywide, the frequency of iron deficiency anaemia has been reported to range in 25.3%-62.5% among children.[25,26]

Iron deficiency anaemia develops in a course of steps starting with the reduction of iron stores, is identified by decreased serum ferritin, low mean corpuscular volume (MCV), and low mean corpuscular haemoglobin (MCH) (26). When iron stores are depleted, it presents as decreased haemoglobin. Thereupon, worsening of this condition and development of anaemia is defined as iron deficiency anaemia (IDA)

We studied 100 patients with Iron deficiency anaemia (IDA). Of these, 70 (70%) were male and 30 (30%) were female. The mean age of the patients was 34.23 ± 19.54 months, with ages ranging from 24 to 98 months. Most patients (81%) were under 5 years old. Among the participants, 55 (55%) were from rural areas and 45 (45%) from urban areas. Socioeconomic status was poor in 52% of cases, while 48% were from middle-income families. Additionally, 46% of mothers were uneducated and 54% were educated. Family history of IDA was noted in 12% of cases, and dietary iron deficiency was observed in 47%. The mean pre-treatment haemoglobin level was 7.92 ± 0.74 g/dl, which increased to 10.46 ± 0.94 g/dl post-treatment. Treatment response was observed in 89 (89%) of the cases.

Gender predominance found during current study is agreement with the reported gender distribution by Malik et al.[9] They studied 142 children; 87 (61%) were males and 55 (39%) were females. Mean Haemoglobin before treatment was 7.85±0.78gm/dl and post treatment it was 10.29±0.89gm/dl.

In a study by Boucher et al. [23] it was suggested that low molecular weight iron dextran was well tolerated by children with most having iron replenishment after a single infusion. They included a total of 191 patients (0.7 to 20 years). Among these 75% of the estimated iron was replaced among 76% of patients. The mean rise in Hb and ferritin were 2.1g/dl and 100ng/ml respectively. Iron Infusion related side-effects occurred only in 4.7% of cases, each rapidly resolved without long term squeal. There was no side effect noted among children below 10 years of age.

The mean age of our patients aligns closely with studies conducted in various regions, indicating a similar demographic distribution. The significant increase in mean haemoglobin levels observed in our study corroborates findings from other research on IV iron sucrose therapy, under-

scoring its efficacy and safety.

In our study the most notable factors leading to iron deficiency anaemia were increase milk consumption, poor dietary habits and lack of awareness in mothers. A study conducted in Canada[27] to identify the modifiable risk factors to reduce iron deficiency anaemia in children also had close results. They documented that there are three potentially modifiable risk factors associated with IDA. It included decreasing cow milk consumption to <500ml/ day, decreasing daytime bottle feeding in >12months of age and decreasing bottle use in bed.

It was also found that children with iron deficiency anaemia had several other associated issues like aggressive behaviour, irritability, insomnia, constipation, cognitive decline and repeated infections due to low immunity.[28] A Canadian study was carried out to determine the outcomes of severe iron deficiency anaemia in children. It revealed that majority of cases with severe IDA were infants, who experienced morbidity issues like developmental delay, cerebral thrombosis and heart failure. These children had health care utilization with 42% hospitalization rate, which was a significant number.[27]

On one had iron deficiency anaemia is a notable problem of our country, on the other hand it easily treatable by simple measures like iron supplementation, food fortification, maternal awareness programs. A study conducted in Pakistan[15] revealed that the prevalence of IDA in Pakistani children represent a moderate burden on country economy. The affected children were more often to belong to mother with IDA and lives in areas where food security is undermined. It requires both vertical and horizontal programs like iron supplementation and food fortification to alleviate the burden.

Iron fortification and supplementation are key strategies for preventing and treating IDA. High-risk groups, such as children and pregnant women, benefit significantly from these interventions. While IV iron preparations offer rapid treatment with fewer side effects, careful dosing is necessary to avoid iron overload. Treatment should be tailored to resolve anaemia and replenish iron stores, with therapy continuing only until normal haematocrit and ferritin levels are achieved.

Conclusion:

IV iron sucrose proved to be an effective and well-tolerated treatment for paediatric patients with IDA who did not respond to oral iron therapy. The significant improvement in haemoglobin levels and minimal adverse reactions support its use as a viable alternative. Clinicians should consider IV iron therapy to achieve optimal clinical outcomes and reduce associated morbidities, enhancing patient quality of life and minimizing additional healthcare costs.

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