ORIGINAL ARTICLE

# Effectiveness and Safety of Intravenous Iron Sucrose Therapy in Children with Iron Deficiency Anemia

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## Abstract

**Background:** Iron deficiency anemia is linked with growth retardation, cognition impairment, reduced interest in daily activities and has been shown to contribute to infant mortality.

**Objectives:** To evaluate the effectiveness and safety of intravenous iron sucrose treatment in children with iron deficiency anemia.

**Methodology:** A quasi-experimental study was conducted at the Lady Reading Hospital, Peshawar from November 2020 to April 2021. Patients younger than 18 years with iron deficiency anemia who were refractory to conventional therapy were included and patients who were non-compliant with the oral iron therapy prescribed before the study were excluded. Patients were administered iron sucrose complex intravenously as per standard protocol. Patients' demographics, hemoglobin, ferritin levels, and other related variables were recorded.

**Results:** A total of 152 patients were enrolled in the study with a mean age of 4.26 ± 3.21 years. At baseline, the mean hemoglobin was 7.01 ± 0.69 g/dL which increased to 12.35 ± 0.71 g/dL ($p<0.001$). The mean corpuscular volume (MCV) before treatment was 66.35 ± 3.56 fL which was raised significantly to 88.42 ± 6.87 fL by day 30 ($p<0.001$). The greatest pre-and post-treatment difference was observed in ferritin levels (6.95 ± 4.37 µg/L versus 49.67 ± 4.82 µg/L, $p<0.001$).

**Conclusion:** The current study revealed that iron sucrose therapy is very effective and considered safe for children between the ages of 1 and 17 years with no serious adverse effects.

**Keywords:** *Iron sucrose therapy, iron deficiency anemia, anemia, ferritin levels, hemoglobin.*

## INTRODUCTION

According to the World Health Organization (WHO), the approximated occurrence of anemia is 39 percent in children < 5 years of age and 48 percent in the pediatric population between 5-14 years of age [1]. In Pakistan, the occurrence of iron deficiency anemia among children of age 5 or less fluctuates between 40 to 70% [2, 3]. Iron deficiency anemia is linked with growth retardation, cognition impairment, reduced interest in daily activities and has been shown to contribute to infant mortality [4]. The causes of iron insufficiency are multifactorial; however, some individuals are unable to absorb iron due to intake of drugs including proton pump inhibitors or disorders like short bowel syndrome. In such patients' oral iron treatment is not beneficial. 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. Evidence suggests that intravenous iron is effective in treating the patients who are refractory to oral iron treatment regime and those with renal failure who are hemodialysis dependent. One such treatment is the administration of iron dextran, however, anaphylactic shock and other adverse reactions have been associated with the treatment, so its use as an iron supplement in the pediatric population has been limited [5].

In the year 2000, Food Drug Administration (FDA) approved the intravenous (IV) iron sucrose was approved by FDA 2000 for patients with non-dialysis dependent patients receiving or not receiving erythropoietin therapy and for dialysis-dependent chronic kidney disease receiving erythropoietin. Iron sucrose has been reported to be safe and effective in adults with iron deficiency due to various non-renal causes, including pregnancy or inflammatory bowel disease [6, 7]. However, the use of IV iron sucrose in children without any kidney disease is extremely limited [7].

In a local study conducted in 2016, it was found that intravenous sucrose treatment was safe and efficacious for the treatment of iron deficiency anemia in children. They reported that the mean hemoglobin level prior to the intravenous iron sucrose treatment was 7.85 ± 0.78 gm/dl which increased to 10.29 ± 0.89 gm/dl ($p<0.001$)

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after three months of treatment [7]. However, the study failed to acknowledge the efficacy of iron sucrose in patients resistant to oral iron treatment.

To this date, only a few studies from Pakistan have emerged evaluating the alternatives of oral and intramuscular iron supplements for the treatment of resistant iron deficiency anemia [7-10]. Hence, the current study will have significant clinical implications enhancing our understanding and our capability to tackle the pediatric population with iron deficiency anemia which is resistant to the traditional treatment regimes. The present study evaluated the effectiveness and safety of intravenous iron sucrose treatment in children with iron deficiency anemia. This study will help establish the usefulness of intravenous iron sucrose in children with anemia in resource-constrained countries like Pakistan.

## MATERIALS AND METHODS

A quasi-experimental study was conducted at the Lady Reading Hospital, Peshawar from November 2020 to April 2021. A non-probability consecutive sampling technique was used to recruit the participants. Ethical approval was obtained before study initiation by the institutional review board (Ref#2533). We assume to detect a medium effect size of 0.5 at a power of 90% and 5% level of significance. A sample of 44 patients is required using G-power 3.1.9.4. All patients younger than 18 years with iron deficiency who were refractory to conventional therapy were included in the study. Patients who were non-compliant with the oral iron therapy prescribed before the study were excluded.

After obtaining the informed verbal and written consent from the patients, the demographic data was collected. The patient's demographics, hemoglobin, ferritin levels, and other related variables were recorded before and after the initiation of treatment.

Patients were administered iron sucrose complex intravenously as per standard protocol. The total amount of iron administered was calculated according to the child's body weight and hemoglobin level using the following formula [8]:

(Normal hemoglobin for age-initial hemoglobin) / 100 X blood volume (ml) × 3.4 × 1.5. Doses were rounded up to multiples of 100 mg. The product used was SANGOBION INJ by Merck Private Limited, 20mg per ml ampoules for injection and was diluted to normal saline by the trained nursing staff before the infusion to a final concentration of 1 mg/mL. The duration of infusion was about two hours. Multiple infusions in the same patient were administered on alternate days, up to 3 times in 7 days.

The determination of iron deficiency anemia was made when all three conditions were met:

1. hemoglobin level > 2 SD below the normal 15.5% blood level corrected for age
2. a ferritin level > 16 µg/L
3. red blood cell distribution width > 15%

Hemoglobin levels (g/dL), mean corpuscular value (MCV) (in fL), mean corpuscular hemoglobin (MCH) ( in pg), and red blood cell count (x106 cells/$mm^3$), and ferritin levels (µg/L) were determined at day zero and day - 30 after the first iron sucrose dose. Side effects (if any) were also documented. Statistical Package for the Social Sciences (SPSS) version 24 was utilized for information mining and examination. Categorical variables were presented as frequency and percentages. All continuous variables including mean age of all patients, mean hemoglobin level, MCH, MCV, RBC count, and PCV were presented as mean and standard deviation after assessing the assumption of normality with the Shapiro-Wilk test. Paired t-tests were used to compare the changes in red blood cell indices and iron levels before and after the completion of iron sucrose therapy. A p-value of ≤ 0.05 was the cut-off value for statistical significance.

## RESULTS

A total of 152 patients were enrolled in the study. Mean age of 4.26 ± 3.21 years was noted. The most common age group was 1-5 years old with a frequency of 61 (40.1%). There were more male patients as compared to female children. Table **1** shows the demographics of participants.

**Table 1:** Demographics of the study participants (n=152).

| Demographics | Frequency (n) | Percentage (%) |
|---|---|---|
| **Age Groups** | | |
| 1-5 years | 61 | 40.1 |
| 6-10 years | 40 | 26.3 |
| 11-15 years | 27 | 17.8 |
| 16-17 years | 24 | 15.8 |
| **Gender:** | | |
| Female | 70 | 46.1 |
| Male | 82 | 53.9 |
| **Siblings** | | |
| No Siblings | 55 | 36.2 |
| 1-3 Siblings | 76 | 50 |
| ≥4 siblings | 21 | 13.8 |
| **Education of Mother** | | |
| No Formal Education | 86 | 56.6 |
| Primary | 36 | 23.7 |
| Secondary | 30 | 19.7 |
| **Employment Status of Father:** | | |
| Employed | 126 | 82.9 |
| Unemployed | 19 | 12.5 |
| Recently terminated/resigned | 7 | 4.6 |

Table **2** illustrates the comparison of iron indices at baseline and day 30. On day zero of treatment, the mean hemoglobin was 7.01 ± 0.69 mg/dl which increased to 12.35 ± 0.71 mg/dl (p<0.001). Mean corpuscular hemoglobin concentration at day zero was 23.92 ± 2.7 pg which elevated to 36.12 ± 6.81 pg in 30 days

**Table 2:** Follow-up for iron indices among participants during iron sucrose treatment.

| Parameters | Day - 0 | Day - 30 | p-value |
|---|---|---|---|
| Hb (g/dL) | 7.01 ± 0.69 | 12.35 ± 0.71 | **<0.001 |
| MCV (fL) | 66.35 ± 3.56 | 88.42 ± 6.87 | **<0.001 |
| MCH (pg) | 23.92 ± 2.7 | 36.12 ± 6.81 | **<0.001 |
| Ferritin (µg/L) | 6.95 ± 4.37 | 49.67 ± 4.82 | **<0.001 |
| RBC (x106 cells.mm3) | 3.53 ± 0.38 | 5.61 ± 0.43 | **<0.001 |
| PCV (%) | 21.26 ± 2.29 | 37.46 ± 2.51 | **<0.001 |

Hb: hemoglobin, MCH: Mean corpuscular of Hb, MCV: Mean corpuscular value, PCV: Packed cell volume, RBC: Red blood cell count. **Statistically significant at p<0.01

of treatment (p<0.001). The mean corpuscular volume (MCV) before treatment was 66.35 ± 3.56 fL which was raised significantly to 88.42 ± 6.87 fL by day 30 (p<0.001). Similarly, the mean red blood cell count initially was 3.53 ± 0.38 x 106 cells/mm$^3$ which at day 30 was 5.61 ± 0.43 x 106 cells/mm$^3$(p<0.001).

The greatest pre- and post-treatment difference was observed in ferritin levels (6.95 ± 4.37 versus 49.67 ± 4.82, p<0.001). Only mild side effects were noted as demonstrated in **Fig. (1)**.

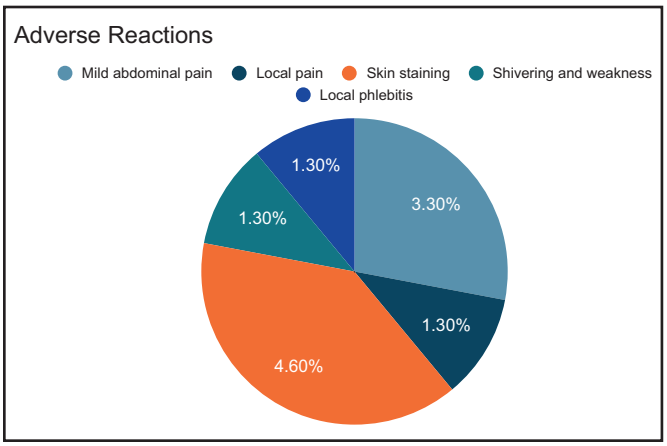


**Fig. (1):** Frequency of Adverse Reactions in the Study.

## DISCUSSION

Iron deficiency commonly affects physical and neurocognitive functions, which must be identified and managed in early childhood [11, 12]. Numerous parenteral iron therapies have been introduced, which have a strong safety profile with very limited adverse effects [13, 14].

Our study evaluated the safety and effectiveness of intravenous iron sucrose for the management of iron deficiency anemia in children who do not respond to traditional/oral treatment. It was found that intravenous iron sucrose administration resulted in a significant rise in hemoglobin, MCV, MCH, RBC, and PCV. The results of our study were consistent with the findings of a study conducted by Pinks *et al.* who noted that following treatment, the levels of hemoglobin rose from 7.43 g/dl at the time of treatment to 9.27 g/dl on day 14 and 12.4 g/dl after 6 months of therapy [11]. Though the baseline hemoglobin levels before treatment (7.43 g/dL) were a little higher than that of our study (7.01 ± 0.69 g/dL), the association between therapy and a rise in hemoglobin was found in the study. A rise in post-treatment hemoglobin levels implies that erythropoietic recovery is achieved with intravenous iron sucrose.

A similar study by Kazanci *et al.* compared hemoglobin and MCV levels before and after treatment. The baseline hemoglobin level was 7.72 ± 1.21 g/dl which rose to 11.44 g/dl ± 0.68 g/dl following six months of treatment. Similarly, the value of MCV increased from 63.2 ± 7.12 fL to 76.6 ± 3.81 fL. The effectiveness of iron sucrose treatment in study participants as iron indices significantly improved from day zero to day 30 of treatment. The study implied that using IV iron sucrose can result in a rapid symptomatic recovery of a child and improve the symptoms of iron deficiency anemia.

Similar results were also obtained by Kaneva *et al.* and Nazir *et al.*, both of those studies concluded that the use of IV iron sucrose in children suffering from iron deficiency is safe and resulted in an increase in hemoglobin with improved iron profiles [15, 16].

Though skin staining and abdominal pain was the most reported side effect in our study, the study by Mantadakis *et al.* reported the most common adverse effect to be injection site extravasation followed by a transient alteration in taste [17]. Papadopoulos *et al.* found that rash following infusion and the urticarial rash was a common adverse effect following therapy [18]. Hussain *et al.* revealed that intramuscular iron therapy is another efficacious route of administration of sorbitol among the pediatric population [19]. Iqbal *et al.* previously revealed that intravenously administered iron sucrose was also very beneficial and replenished iron stores among iron-deficient children [20]. Our study revealed that intravenous iron administration improved the red blood cell indices, which resulted in improvement in the symptoms of iron deficiency anemia among children.

However, our study was limited due to the small sample size. Research on a larger population must be conducted to better understand the safety and efficacy of intravenous iron sucrose therapy in the pediatric population.

## CONCLUSION

The current study revealed that iron sucrose therapy is very effective and considered safe for children between the ages of 1 and 17 years with no serious adverse effects.

## ETHICS APPROVAL

Ethical approval was obtained before study initiation by the institutional review board (Ref#2533). All procedures performed in studies involving human participants were in accordance with the ethical standards of the Helsinki declaration.

## CONSENT FOR PUBLICATION

Informed verbal and written consent was obtained from the patients.

## AVAILABILITY OF DATA

Data sets generated or analyzed during the current study are not made public because authors are concerned about the confidentiality of the patients. Data sets can be released upon request to the corresponding author.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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None.

## AUTHOR'S CONTRIBUTION

MSK designed the study and came up with the concept. AK and UH contributed to data acquisition and statistical analysis. AK and MT contributed to draft writing.

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