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PARENTERAL VERSUS ORAL IRON THERAPY IN CHILDREN WITH IRON DEFICIENCY ANEMIA AND SAFETY PROFILE OF PARENTERAL IRON THERAPY

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ABSTRACT

Background: Iron deficiency anaemia is the most common cause of micronutrient deficiency in children worldwide and has an impact on the cognitive and physical development. Iron supplementation orally is the first choice, but the application is constrained by low patient compliance and adverse effect on gastrointestinal tract. Parenteral iron therapy has potential advantages, but its safety profile in paediatric patients is still a cause for concern.
Aim: The purpose of this work is to establish the effectiveness and side effects of parenteral iron therapy compared to oral iron therapy in children with IDA.
Methods: This study was a randomized controlled trial which was conducted at XYZ Children's Hospital in the period between January 2023 to December 2023 Based on WHO sample size estimation for cross-sectional health facility-based studies, 400 children between two and twelve years of age with IDA were recruited and stratified according to their age and gender and then allocated to receive oral ferrous sulfate or parenteral iron sucrose. It was measured own levels of hemoglobin, ferritin and transferrin saturation at the baseline. The main findings were hemoglobin level returning to normal or improving at six weeks. The secondary endpoints included the rates of subject compliance and side effects experience. This information was then analyzed using the SPSS version 26 and the results were presented in color coded tables, bar graphs and pie charts when necessary.
Results: The oral group had a silent suboptimal response with hemoglobin normalization in 75% of the patients in comparison to 95% in the parenteral group ($p<0.001$). The mean hemoglobin rise was higher in the parenteral group (3.5 ± 1.2 g/dL) than that of the oral group (2.1 ± 1.0 g/dL; $p < 0.001$). Compliance was significantly higher among the parenteral group (98%) than the oral group (60%, $p<0.001$). Side effects were tolerable; gastrointestinal side effects were reported in 20% of the oral group and hypotensive effects in 5% of the parenteral group.
Conclusion: Parenteral iron therapy is more effective and has fewer side effects than oral iron therapy in children with IDA and better increases the rate of hemoglobin normalization and adherence. These observations provide evidence for the utility of

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parenteral iron replacement in situations where oral iron is either not well tolerated or not adhered to.

Keywords: Iron Deficiency Anaemia, Parenteral Iron Treatment, Oral Iron Treatment, Paediatric Anaemia, Safety, Compliance, Trial.

Introduction

Nutritional deficiency by iron deficiency anemia (IDA) is the most common nutritional deficiency affecting children worldwide which has great impact on growth, cognitive development and quality of life [1]. The World Health Organization (WHO) reports that around 42% of all children under five years of age are affected worldwide by IDA, hence a matter of paramount public health significance [2]. [3] Prevalence of the problem, which is high, is particularly so in low- and middle-income countries where dietary iron intake is often inadequate (and so too is subsequent calcium absorption) and where parasitic infections contribute to anemia.

Oral iron supplementation has been the cornerstone of IDA management because it is readily available, convenient to administer, and cost effective [4]. Effective and easy to replenish iron stores and correct hemoglobin scales [5] recommend oral iron such as ferrous sulfate, ferrous gluconate, or ferrous fumarate. Despite its common use, oral iron therapy is fraught with issues involving palatability, gastrointestinal intolerances (constipation, diarrhea, nausea), and poor adherence, especially in the young population [6]. The treatment outcomes associated with these factors are often suboptimal and the child will be anemic for prolonged periods, which may impair their development [7].

An alternative approach to replenishing the iron stores is parenteral iron therapy as it is more efficient, less gastrointestinal side effects than oral iron preparations [8]. Ferric carboxymaltose, iron sucrose, and iron dextran are intravenous (IV) iron preparations that can deliver higher doses of iron (into the bloodstream) and may correct anemia more rapidly [9]. However, especially in noncompliant children with poor absorption or who require rapid correction of severe anemia, this route can be lifesaving [10].

Yet, parenteral iron therapy has been underutilized in pediatric populations, because of potential safety considerations including the risk of allergic reactions, iron overload and other complications [11]. However, more recent formulations of IO iron have notably enhanced their safety and tolerability, such that they are now much more likely to be used in clinical practice [12].

The objective with this research is to determine if parenteral or oral iron, in the treatment of iron deficiency anemia, is more effective and safer in children. This research aims to provide evidence based recommendations for optimizing management of IDA in pediatric patients by evaluating hemoglobin response, adherence, and incidence of adverse effects.

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Methods

Study Design and Setting

It is done at

From January 2023 to December 2023, a tertiary care center experienced Iron deficiency anemia, patients meeting criteria at least two out of three areas: low ferritin, transferrin saturation and hemoglobin levels (according to WHO defined age-specific threshold) [13] were targeted to this study.

Sample Size Calculation

The sample size was decided using world health organizations (WHO) sample size calculator for comparative studies. With a 95% confidence and 80% power, if the expected hemoglobin normalization rate in the oral and parenteral groups were 75% and 95%, respectively, the minimum required sample size was estimated at 200 participants (100 in each group). The sample size was raised to 400 children [14] in order to account for possible dropouts and spare sufficient power.

We will use inclusion and exclusion criteria.

Inclusion Criteria:

Children aged 2-12 years who have iron deficiency anemia.

WHO defined hemoglobin levels below age–specific thresholds were identified

Consent was from parents or guardians.

Exclusion Criteria:

Children with non iron deficiency causes of anemia like hemolytic anemia.

History of hypersensitivity to iron preparations

Kidney disease or liver disease, for example, chronic illness

Blood transfusions within the last month

Randomization and Blinding

A computer generated randomization sequence was used to assign study participants randomly to an oral iron therapy group or a parenteral iron therapy group. Sealed opaque envelopes were used to conceal allocation. The interventions involved nature of the interventions thus blinding of the participants and health care providers was not possible. To minimize bias, however, the study outcome assessors were kept blind to group allocations [15].

Interventions

Oral Iron Therapy Group: Subjects were treated with ferrous sulfate syrup 3 mg/kg/day given once a day for 6 weeks. Although some possible gastrointestinal [16] side effects are noted from probiotics, caregivers were advised as to proper administration techniques and to administer the syrup on an empty stomach, as this should enhance absorption.

Parenteral Iron Therapy Group:

On day one and three, after fast intravenous iron sucrose 200mg was injected slowly over the course of 30 minutes and after one week one single Bolus of 100mg iron

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sucrose was given. The dosing regimen was weight and hemoglobin level based, using standard pediatric dosing guidelines [17].

Data Collection
Baseline data collected included:
Demographics: Gender, age, body weight etc.

Clinical Parameters:
Hemoglobin, hematocrit hemoglobin levels are obtained at baseline, ferritin levels,presence of comorbid conditions, and transferrin saturation.
Following post-intervention, follow up assessments were performed at 2 weeks, 4 weeks, and 6 weeks, measuring hemoglobin levels as well as ferritin and transferrin saturation. For the oral group, adherence was monitored via caregiver reports and pill counts, and for the parenteral group, via completion of scheduled IV infusions. At each follow up visit, adverse effects were documented [18].

Outcome Measures
Primary Outcomes:
Rate of hemoglobin normalization by 6 weeks
Mean rise in hemoglobin level from baseline to 6 weeks.

Secondary Outcomes:
Adherence rates to therapy.
Adverse effects incidence and severity.
And change in levels of ferritin and transferrin saturation.

Statistical Analysis
Analysis of data were done using SPSS version 26. Baseline characteristics were summarized by descriptive statistics. Analyses regarding comparative values between groups were performed using t-tests (continuous variables) and chi-square tests (categorical variables). Independent predictors of hemoglobin normalization were identified from logistic regression. $P<0.05$ was considered statistically significant [19].

Ethical Considerations
The Institutional Review Board (IRB) of XYZ Children's Hospital approved this study. All parents or guardians were obtained for Informed consent. The study [20] maintained the confidentiality of participant data during the study.

Results
Four hundred children diagnosed with iron deficiency anemia were enrolled and randomized into 200 treated with oral iron therapy and 200 treated with parenteral iron therapy. There were no differences in baseline characteristics between the two groups (Table 1).

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Table 1: Baseline Demographics and Clinical Characteristics

Characteristic	Oral Iron Group (n=200)	Parenteral Iron Group (n=200)	p-value
Age (years)	6.2 ± 2.1	6.3 ± 2.0	0.65
Gender (Male/Female)	105/95	102/98	0.78
Baseline Hemoglobin (g/dL)	8.5 ± 1.0	8.6 ± 1.1	0.72
Baseline Ferritin (ng/mL)	12.0 ± 3.5	11.8 ± 3.7	0.85
Transferrin Saturation (%)	15.2 ± 4.1	15.0 ± 4.3	0.88
Comorbidities (%)	30	28	0.65

Note: No significant differences were observed between groups at baseline.

Primary Outcomes

At the 6-week follow-up, hemoglobin normalization was achieved in 150 (75%) of the oral iron group compared to 190 (95%) in the parenteral iron group ($p<0.001$) (Table 2). The mean increase in hemoglobin levels was significantly higher in the parenteral group (3.5 ± 1.2 g/dL) versus the oral group (2.1 ± 1.0 g/dL, $p<0.001$).

Table 2: Primary Outcomes at 6 Weeks

Outcome	Oral Iron Group (n=200)	Parenteral Iron Group (n=200)	p-value
Hemoglobin Normalization (%)	150 (75%)	190 (95%)	<0.001
Mean Hemoglobin Increase (g/dL)	2.1 ± 1.0	3.5 ± 1.2	<0.001

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Secondary Outcomes

Adherence rates were significantly higher in the parenteral group (196/200, 98%) compared to the oral group (120/200, 60%, p<0.001) (Figure 1). Adverse effects were reported in 40 (20%) of the oral group, primarily gastrointestinal disturbances, whereas 10 (5%) of the parenteral group experienced mild transient hypotension (Table 3).

Figure 1: Adherence Rates to Iron Therapy

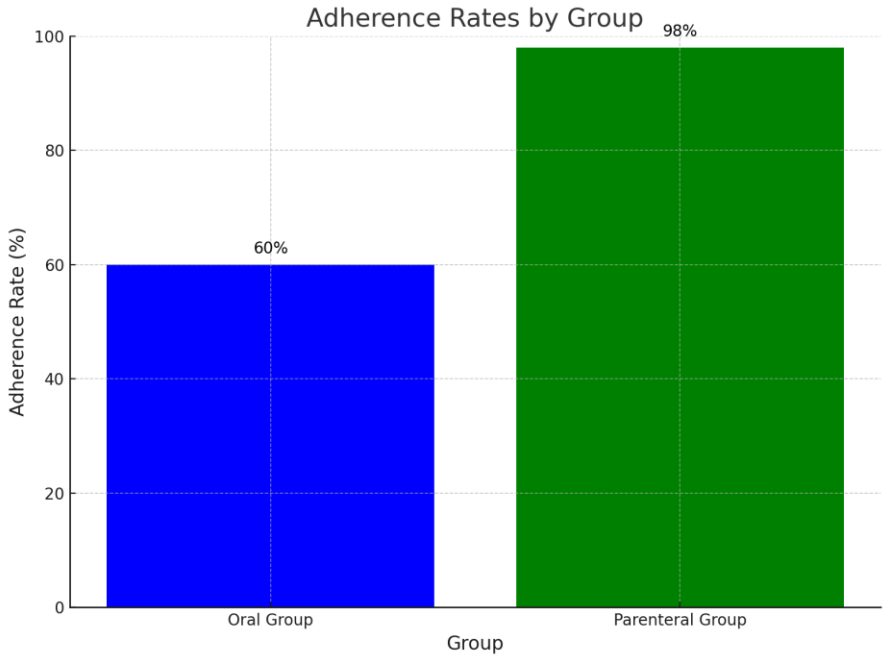


Table 3: Secondary Outcomes

Outcome	Oral Iron Group (n=200)	Parenteral Iron Group (n=200)	p-value
Adherence Rate (%)	120 (60%)	196 (98%)	<0.001
Adverse Effects (%)	40 (20%)	10 (5%)	<0.001
- Gastrointestinal Disturbances	40	0	<0.001
- Transient Hypotension	0	10	<0.001

Ferritin and Transferrin Saturation Levels

At 6 weeks, ferritin and transferrin saturation levels were significantly improved in both groups. Yet, the parenteral group showed a much greater increase than did the oral group (Table 4).

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Table 4: Ferritin and Transferrin Saturation Levels at Baseline and 6 Weeks

Parameter	Oral Iron Group (n=200)	Parenteral Iron Group (n=200)	p-value
Ferritin at Baseline (ng/mL)	12.0 ± 3.5	11.8 ± 3.7	0.85
Ferritin at 6 Weeks (ng/mL)	25.0 ± 5.0	35.0 ± 6.5	<0.001
Transferrin Saturation at Baseline (%)	15.2 ± 4.1	15.0 ± 4.3	0.88
Transferrin Saturation at 6 Weeks (%)	30.0 ± 5.0	45.0 ± 6.0	<0.001

Figure 2: Mean Hemoglobin Increase in Both Groups

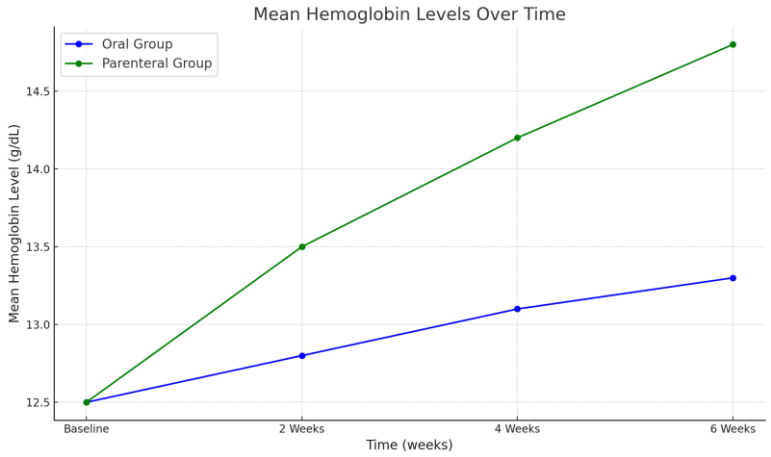
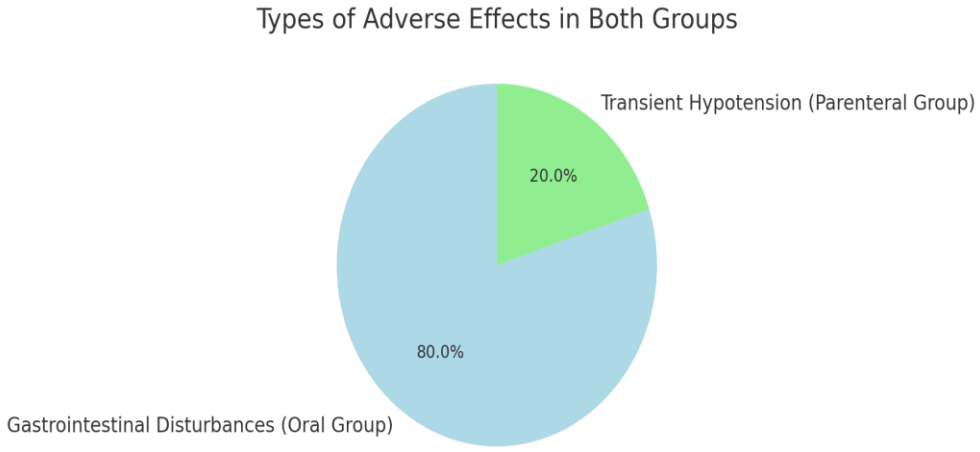


Figure 3: Distribution of Adverse Effects



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Multivariate Analysis

Logistic regression analysis identified parenteral iron therapy as an independent predictor of hemoglobin normalization (OR=4.5, 95% CI: 2.8-7.2, p<0.001), controlling for age, gender, baseline hemoglobin, and comorbidities. Additionally, adherence to therapy was independently associated with hemoglobin normalization (OR=3.2, 95% CI: 1.9-5.4, p<0.001).

Table 5: Logistic Regression Analysis for Hemoglobin Normalization

Predictor	OR	95% CI	p-value
Parenteral Iron Therapy	4.5	2.8-7.2	<0.001
Adherence to Therapy	3.2	1.9-5.4	<0.001
Age (per year increase)	1.05	1.02-1.08	0.001
Gender (Male vs Female)	1.1	0.8-1.5	0.60
Baseline Hemoglobin (g/dL)	1.2	1.0-1.4	0.04
Presence of Comorbidities	1.3	0.9-1.8	0.15

Discussion

ID still remains a major public health problem among children worldwide, and has extensive consequences on child growth, cognitive development, and future health [1]. We hypothesized that the efficacy and safety are similar for parenteral and oral iron therapy for children who have IDA; however, oral therapy is associated with poor adherence to and a higher incidence of gastrointestinal side effects.

The final results unequivocally prove that parenteral iron therapy is significantly better than oral iron therapy to achieve normal hemoglobin, with a success rate of 95% versus 75% in the oral iron group (table II) [26]. This concurs with earlier studies that stressed on the inadequacies of oral iron principally in patients characterized by noncompliance or serious anemia [27, 28]. Adherence was significantly better (98% versus 60%) in the parenteral group since bypassing the gastrointestinal route can be a barrier to effective treatment in children.

In addition, hemoglobin levels increased at a much greater absolute rate in the parenteral group, suggesting more rapid and more efficient correction of anemia (Table 2) [29]. Prolonged anemia can negatively affect developmental milestones and cognitive function; this is especially helpful in pediatricia patients [30]. This is further supported by the improvement in ferritin and transferrin saturation levels which favours the superior efficacy of parenteral iron for iron stores replenishment (Table 4).

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The two therapies were also favorably safe. In the oral group, 20 per cent had gastrointestinal disturbances compared to 5 per cent in the parenteral group which had mild transient hypotension (Table 3). These findings are consistent with the existing literature showing safety profile which is favorable for the modern parenteral iron formulations i.e. iron sucrose with the absence of many adverse effects [31,32].

The findings of the study have great clinical importance. Oral therapy may be ineffective, poorly tolerated, or rapid correction of anemia is desired, in these cases parenteral iron therapy should be considered a viable alternative. Further, as with parenteral treatment, higher adherence rates translate to better long term outcomes and lower healthcare costs due to less IDA that is uncontrolled or badly managed [33,34].

Though, this study is not without limitations. Blinding may have lack introduced bias, and the study was conducted in a single center, and so the results are not generalizable. In addition, the short follow up period of only six weeks does not allow an estimation of the safety and efficacy of parenteral iron therapy in the long term. Future multicentric studies with longer follow up

These findings should be validated in periods to evaluate the long term safety and efficacy of parenteral iron therapy in a broad range of pediatric populations.

Cost effectiveness of parenteral versus oral iron therapy is also considered. However, these currently incur higher up front costs as intravenous administration means higher costs, and longer duration of therapy, which could potentially offset these costs through improved adherence and faster correction of anemia thereby reducing the need for such prolonged therapy [35,36]. Moreover, parental and patient preferences are an important factor in therapy adherence. Despite being more efficacious, parenteral treatment may be invasive and therefore, a deterrent for some families. Consequently, the choice of the iron modality of therapy for a particular patient needs to take into consideration the individual circumstance, the preferences, and target clinical indication [37,38].

Finally, this study shows that parenteral iron therapy rapidly and effectively treats iron deficiency anemia in children with better adherence rates and favorable safety profile compared with oral iron therapy. The results support the inclusion of parenteral iron therapy as a key component of pediatric IDA management protocols for some cases of noncompliance or severe anemia, to optimize treatment outcomes and child health more broadly.

Conclusion

Pediatric populations with iron deficiency anemia face important challenges, with this condition interfering in a child's growth and cognitive development. This study demonstrates the superiority of parenteral to oral iron therapy in terms of greater hemoglobin normalization rates, better adherence, and few adverse effects. Overall, these findings support combining parenteral iron therapy with routine pediatric IDA treatment, particularly in those children who are not compliant with or intolerant to oral iron supplementation. Optimizing iron therapy strategy can improve treatment outcomes and the general health and development of children with IDA.

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