

COMPARISON OF EFFICACY AND TOLERABILITY OF FERROUS SULPHATE AND IRON POLYMALTOSE COMPLEX IN TREATMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN AGE BETWEEN 6-12 YEARS

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ABSTRACT

Objective : Comparing iron polymaltose complex with ferrous sulphate in terms of the mean change in haemoglobin and the incidence of adverse effects during the course of therapy of iron deficiency anaemia (IDA) in children is the aim of this study.

Method: This one-year randomised controlled experiment was conducted at the Outpatient Department of The Children's Hospital Lahore from March 2021 to March 2022. As per the operational criteria, the study comprised 106 patients who had iron deficiency anaemia. The patients were stratified into two groups, each consisting of 53 patients, by a balloting procedure. The research proforma included information on the medication's tolerability as well as any gastrointestinal side effects that occurred while the patient was receiving therapy. SPSS 25 was used for the data analysis.

Results: The study population's mean age was 6.842 ± 3.541 years. There was an dominant male representation in the study population, with 62%(66/106) of the male population and 38%(40/106) of research participants being female. In both treatments groups, haemoglobin levels at months 1 and 3 of treatment significantly improved from baseline. After 3 months post-treatment, both treatment groups had an increase in hemoglobin of more than 2 g/dL. (FS: 2.9 ± 2.7 g/dL; IPC 2.03 ± 1.6 g/dL; both $P = 0.01$ from baseline values). After three months of therapy, there was a statistically significant increase in the serum iron level in both groups. After 3 month therapy, serum iron in group A it was 71.3 ± 54.5 μ g/dL and in group B it was 71.6 ± 31.8 μ g/dL (p-value:0.01). Serum ferritin levels also increased significantly, from 9.7 ± 6.5 mcg/dL to 31.3 ± 22.6 mcg/dL in group A and from 6.8 ± 5.6 to 32.3 ± 22.3 mcg/dL in the group B.

Conclusion: the outcomes of this study show that IPC is equally as effective as ferrous sulphate when used as an oral iron supplementation therapy for paediatric patients with iron deficiency anaemia. However, IPC has fewer side effects than ferrous sulphate, which might enhance compliance and tolerance.

KEYWORDS: IPC, ferrous sulphate, tolerance, iron deficiency anaemia, gastrointestinal side effects

INTRODUCTION

Iron deficiency is the most frequent type of malnutrition worldwide affecting nearly one-third of the world's population. This is responsible for 62.6% of all cases of anemia reported worldwide, and the population with the highest prevalence of anemia is children under the age of 10 years [1]. It is quite common in developing countries such as Pakistan, where it is found that approximately 47 % of children are affected by it. According to reports, in Pakistan, 69% of children under the age of two and 40-50% of preschoolers are suffering from iron deficiency anemia [2]. Anemia gets diagnosed when the amount of hemoglobin in the blood drops below a certain threshold level. According to WHO, children are considered to have iron deficiency anemia if they have a hemoglobin level that is lower than 11 g/dL and an adjusted ferritin concentration that is lower than 12 ug/L. RBCs' oxygen-carrying ability is negatively impacted when their Hb levels fall below a defined threshold value [3]. The resulting tissue hypoxia causes fatigue and impairment of functional capacity, which harms both physical and cognitive development in children and is strongly linked to impaired cellular and humoral immunity. Growth retardation, fatigue, poor cognitive inhibitory control, poor work performance, and low-quality life are reported in infants and children with iron deficiency anemia [4]. They attain very fewer scores on motor and mental development tests compared to children with normal iron status [5,6]. The systemic neurological and developmental problems that can occur as a result of iron deficiency anemia (IDA) in children and adolescents can be significantly prevented by appropriate iron supplements, ideally before the development of anemia [7].

Examining the red cells indices of full blood counts is another effective method for diagnosing anemia. Due to an iron deficit, mean cells volume (MCV) and mean cells hemoglobin (MCH) decrease, leading to microcytic and hypochromic type of anemia. This test has moderate to good sensitivity levels, although this blood picture is only seen in children with chronic IDA [8]. Several test indicators may be used to establish iron - deficiency anemia as the main root cause of anemia. Serum levels of ferritin has the best specificity (98%) in the absence of acute inflammation or infection and corresponds proportionally with total body iron stores. Iron deficiency is diagnosed when the quantity of iron in the blood is less than 15 g/L for individuals over the age of five, and less than 12 g/L in kids under five. Serum ferritin, on the other hand, is ineffective in identifying IDA in inflammatory illnesses, malignancies, and liver disease. In these cases, it is easier to evaluate transferrin saturation by evaluating the iron concentration and total iron-binding capacity [9]. Clinicians must distinguish between isolated IDA and iron deficiency caused by a chronic condition like malaria, cancer, TB, as well as HIV. This is because many distinct factors may lead to IDA [10]. Isolated iron deficiency anemia, also known as uncomplicated IDA, can occur in otherwise healthy individuals who have high iron metabolism demand. This can happen, for instance, when children go through growth spurts, and it can also happen in pregnant women because the fetus has a greater demand for iron than the mother does. Iron deficiency with chronic illness, on the other hand, occurs as a result of a reduction in iron transport to the plasma caused by inflammatory responses to the underlying chronic illnesses [11,12].

OBJECTIVE:

“To compare the efficacy and tolerability of ferrous sulphate and iron polymaltose complex in the treatment of iron deficiency anemia in children.”

MATERIAL AND METHODS:

This Randomized Control Trial was conducted in the Outpatient Department of The Children's Hospital Lahore from March 2021 to March 2022. The study population consisted of children with iron deficiency anemia presenting to the pediatric outpatient department. The study duration was 12 months following approval of the synopsis. The sample size was calculated using the WHO Sample Size Determination in Health Studies calculator (version 2.0.21) for comparison of two mean values. The calculation was based on an anticipated mean hemoglobin level of 10.6 g/dL in the ferrous sulphate group and 11.2 g/dL in the iron polymaltose complex group, with standard deviations of 1.0 and 0.9 g/dL, respectively. With 90% study power and a 5% level of significance, the minimum required sample size was 53 patients in each group. Therefore, a total of 106 children were enrolled, with 53 patients in each treatment group. Eligible participants were recruited using non-probability consecutive sampling. After enrollment, patients were randomized into two equal groups using the balloting method. Group A received ferrous sulphate, while Group B received iron polymaltose complex. Children aged 6–12 years with hemoglobin levels below 11.5 g/dL and serum ferritin levels below 7 ng/mL were included. Written informed consent was obtained from the parents or guardians before enrollment. Children with systemic infections, severe anemia with hemoglobin level of 4 g/dL, anemic heart failure, diarrheal illness, critical illness, or whose parents or guardians did not provide consent were excluded.

Data Collection Procedure

After obtaining informed consent, demographic and clinical information was recorded using a predesigned proforma. Baseline hematological and iron-profile parameters were obtained before initiation of therapy. Five milliliters of venous blood were collected aseptically, preferably from the median cubital vein. For complete blood count, blood was collected in an EDTA tube and analyzed using the MEK 9100-5 hematology analyzer by flow cytometry. Hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count were recorded. For iron studies, blood was collected in serum-separating tubes. After clot formation, samples were centrifuged at 3000 rpm for 10 minutes. The separated serum was transferred into appropriately labeled sterile Eppendorf tubes and stored until biochemical analysis. Serum ferritin, serum iron, and total iron-binding capacity were measured using the Immulite 2000 system. Patients in Group A received oral ferrous sulphate syrup once daily at a dose equivalent to 6 mg/kg/day of elemental iron. Patients in Group B received oral iron polymaltose complex once daily at the same elemental iron dose of 6 mg/kg/day. Parents were advised regarding the prescribed dose and administration of the medication. Compliance was assessed during follow-up visits by questioning parents and reviewing used medication bottles. Gastrointestinal adverse effects, including nausea, vomiting, abdominal discomfort, diarrhea, and constipation, were recorded on the study proforma. Patients were followed for three months. The first follow-up was performed on day 7 to assess treatment compliance and early adverse effects. Subsequent follow-up visits were conducted at one month, two months, and three months. Complete blood count and iron studies were repeated at one, two, and three months to assess hematological response and restoration of iron stores. Post-treatment hemoglobin, hematological indices, serum ferritin, serum iron, and total iron-binding capacity were compared with baseline measurements. Treatment success at three months was assessed on the basis of improvement in hemoglobin concentration and restoration of serum ferritin levels according to the predefined study criteria.

Data Analysis

Data were entered and analyzed using SPSS version 25.0. Quantitative variables including age, baseline hemoglobin concentration, follow-up hemoglobin levels, and change in hemoglobin concentration were expressed

as mean $\pm$ standard deviation. Categorical variables including gender and gastrointestinal adverse effects such as nausea, vomiting, diarrhea, constipation, and abdominal discomfort were presented as frequencies and percentages. The independent-samples t-test was used to compare mean hemoglobin changes between the two treatment groups. The chi-square test was used to compare the frequency of adverse effects between the groups. A p-value <0.05 was considered statistically significant.

RESULTS

The patients were stratified into two groups, each consisting of 53 patients, by a balloting procedure. Ferrous sulphate, administered orally once daily in syrup form, at a dose of 6 mg/kg/d was given to the children in Group A. Iron Polymaltose Complex was administered orally to Group B patients once a day at a dosage of 6 mg/kg/d. The research proforma included information on the medication's tolerability as well as any gastrointestinal side effects (such as nausea, vomiting, stomach discomfort, diarrhoea, and constipation) that occurred while the patient was receiving therapy. The study population's mean age was 6.842 ± 3.541 . In Group A mean age was 6.954 ± 3.325 years, while in Group B the mean age was 6.790 ± 4.595 years. The p-value of 0.352 indicates that there was no difference in age distribution between the two groups.

Table 1: showing distribution of patients in terms of age

Study Group	Mean	Std. Deviation	p-value
Group A (ferrous sulphate)	6.954	3.325	0.352
Group B (Iron Polymaltose complex)	6.790	4.595	
Total	6.842	3.541	

At the start of the treatment, the haemoglobin level were nearly comparable in both groups (8.4 ± 1.6 vs 8.5 ± 1.20). In both treatments groups, haemoglobin levels at months 1 and 3 of treatment significantly improved from baseline (Table 3). Around month 1, there was a noticeable improvement in Hb among the ferrous sulphate group (10.2 ± 0.9 , $P = 0.01$) and the IPC group (9.6 ± 1.10 , $P = 0.01$). After 3 months post-treatment, both treatment groups had an increase in hemoglobin of more than 2 g/dL. (FS: 2.9 ± 2.7 g/dL; IPC 2.03 ± 1.6 g/dL; both $P = 0.01$ from baseline values). When the two groups were compared, a P-value of 0.23 indicated that there was no statistical difference between the both groups

Table 2: Changes in hemoglobin levels during treatment

	Group A (Ferrous sulphate)			Group B (IPC)			
Hb (g/dL)	Baseline Hb	Change of Hb from Baseline	P-value	Baseline Hb	Change of Hb from baseline	p-value	P-value (FS vs IPC)
Before treatment	8.4 ± 1.6	—	—	8.5 ± 1.20	—	—	—
1 month	10.2 ± 0.9	1.8 ± 1.7	0.01	9.9 ± 1.10	1.5 ± 0.9	0.01	0.06
3 months	11.4 ± 1.0	2.9 ± 2.7	0.01	10.9 ± 0.8	2.4 ± 1.6	0.01	0.23

Both MCH and MCHC values increased statistically significantly from baseline after 3 months of both types of treatment, Nonetheless, there was no noticeable difference between the two therapy groups in all parameters (Table 4).

Table 3: Changes in red cell indices after three months of treatment

	GROUP A (FERROUS SULPHATE)			GROUP B (IPC)			
Hb (g/dL)	Baseline values	Changes values from baseline	P-value	Baseline values	Changes values from baseline	P-value	P-value (FS vs IPC)
MCV (fL)							
Baseline	67.7 ± 6.9	—	—	67.4 ± 7.1	—	—	0.843
3 months	75.31 ± 4.3	6.5 ± 5.7	0.001	78.5 ± 4.8	10.1 ± 7.2	0.001	0.06
MCH (pg)							
Baseline	21.4 ± 2.6	—	—	20.8 ± 2.6	—	—	0.55

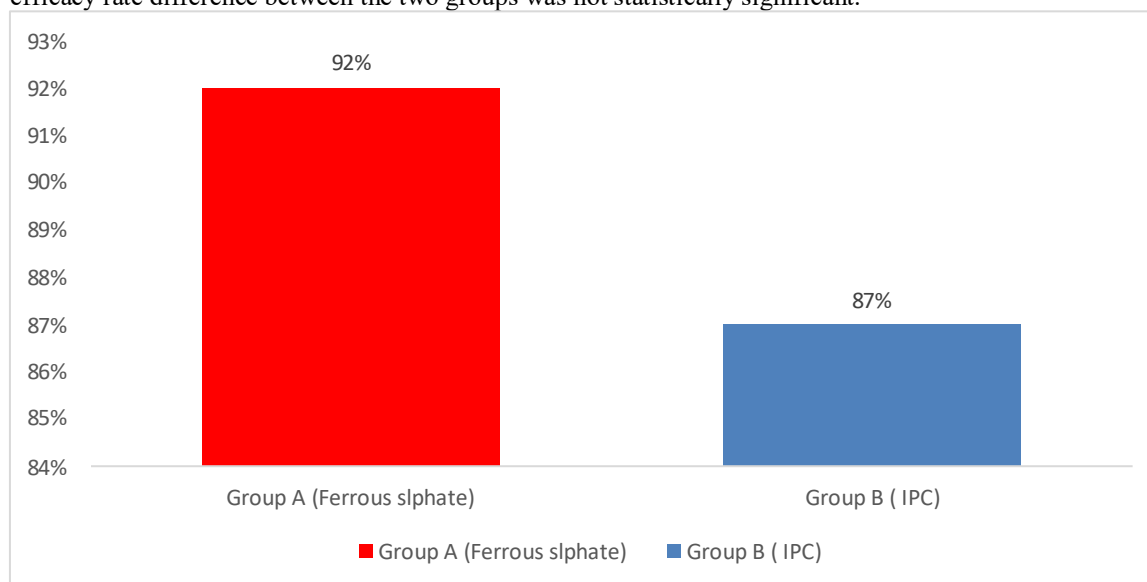
3 months	24.3 ± 1.3	2.6 ± 2.4	0.001	24.1 ± 2.4	3.2 ± 2.7	0.001	0.15
MCHC (%)							
Baseline	30.6 ± 2.7	—	—	31.6 ± 2.4	—	—	0.45
3 months	32.5 ± 0.9	1.9 ± 1.6	0.001	32.2 ± 1.4	1.6 ± 1.4	0.001	0.139

Ferritin and serum iron levels both considerably rose in the treated groups. At the beginning of the trial, the FS group had blood iron levels of 22.2 ± 11.4 mcg/dL while the IPC group had blood iron levels of 23.2 ± 13.9 mcg/dL. After three months of therapy, there was a statistically significant increase in the serum iron level in both groups. After 3 month therapy, serum iron in group A it was 71.3 ± 54.5 μ g/dL and in group B it was 71.6 ± 31.8 μ g/dL (p-value:0.01). Serum ferritin levels also increased significantly, from 9.7 ± 6.5 mcg/dL to 31.3 ± 22.6 mcg/dL in group A and from 6.8 ± 5.6 to 32.3 ± 22.3 mcg/dL in the group B.(table 5)

Table 4: Changes in serum iron and ferritin after three months

	GROUP A (FERROUS SULPHATE)			GROUP B (IPC)			
	Intial Value	Values At 3 months	P value	Value	Change from Baseline	P value	
Serum iron (μg/dL)							
	22.2 ± 11.4	71.3 ± 54.5	0.001	23.2 ± 13.9	71.6 ± 31.8	0.001	
Serum ferritin (μg/dl)							
Baseline	9.7 ± 6.5	31.3 ± 22.6	0.001	6.8 ± 5.6	32.3 ± 22.3	0.001	

The FS group had 92% effectiveness, whereas the IPC group had 84.7% efficacy. With a p-value of 0.23, the efficacy rate difference between the two groups was not statistically significant.



Both groups experienced gastrointestinal adverse effects that are typical of oral iron supplementation, with the IPC group experiencing significantly fewer incidents 33.9% (18/53). In comparison to this, in ferrous sulphate group, 67.9 % of children experienced GI side effects . The p value of 0.013 between groups indicated that IPC had a substantial advantage over FS in terms of gastrointestinal side effects.

Table 5: Gastrointestinal adverse effects in the two treatment groups

Complications	Group-A (n = 53)	Group-B (n = 53)	P value
	%	%	
Nausea	6	4	

Vomiting	7	3	0.013
Diarrhea	10	4	
Constipation	11	5	
Abdominal pain	4	2	
Total	36/53 (67.9%)	18/53 (33.9%)	

DISCUSSION:

The world still worries about iron deficiency and iron deficiency anaemia (IDA), especially among young people. Children in developing nations are particularly impacted by iron deficiencies, making it the most common nutritional shortfall. Children in developed nations still frequently have IDA as the cause of their anaemia, even though the condition is obviously becoming less common. But evidence that iron deficiency, even in the absence of IDA, may also have detrimental long-term effects on children's neurodevelopment and behavior—some of which may be permanent—makes iron shortage even more relevant than anaemia [13]. The incidence of iron deficiency anemia in Pakistan is very high and affects as much as 65 percent of the general population, which includes both children and adults. This places a significant load on health care providers. The world Health Organization (WHO) estimates that 43 % of children throughout the world and 29 % of children in Pakistan suffer from iron deficiency [14]. The two groups in our study were similar to one another with regard to demographics (age, weight, gender, etc.). In our study, males outnumbered females in the study population, with 62% of participants being male. This gender split is consistent with other research on this topic.

The current study found a statistically significant increase in haemoglobin levels in both groups at three months of follow-up. (FS: 11.4 ± 1.0 ; IPC: 0.9 ± 0.8 , p-value: 0.001). When the groups were compared, the increase in mean haemoglobin was greater in the Ferrous sulphate group, but it was not statistically significant when compared to the IPC group (2.9 vs 2.4 change from baseline values). Similar results were seen in trials conducted by Sozmen et al. and Sheikh et al., in which both formulations were shown to produce a significant increase in haemoglobin levels with no significant difference between the both groups [15,16]. Oral iron therapy is a proven strategy of treating iron deficiency anemia in individuals of all ages [17]. Nevertheless, inadequate compliance and prolonged treatment period are stumbling blocks in the efficient management of this critical condition. A collaborative UNICEF and USAID forum suggested iron supplements such as ferrous sulphate (FS) or iron polymaltose complex for usage in young children [18]. A delayed release of iron from the stabilised IPC complex is thought to be the cause of the variations in safe characteristics between the two preparations. Localised gastrointestinal responses and symptoms including dyspepsia and vomiting are caused by the fast release of iron from ferrous sulphate inside the gastric lumen. Iron from the intestine is absorbed directly into the circulation when the active uptake mechanism is overloaded, which results in passive absorption through the intercellular pathway and an increase in nontransferrin bound iron (NTBI) [19]. It is well established that NTBI iron can produce oxidative stress, which can lead to systemic side effects including nausea. The size of the hydroxide complex prevents almost all passive diffusion, and the slow release of iron prevents overloading the active transport mechanism, so the increase in NTBI following IPC dosing is negligible. Therefore, whereas IPC administration is not linked to elevated NTBI levels or enhanced oxidative stress, ferrous sulphate is [20]. Due to the short time span of examination, this study is a single-center study with a small sample size. Future multicenter research should incorporate the study's lacking components. Furthermore, the issue of compliance wasn't investigated in this study, which has a substantial effect on the success of any therapy for iron deficiency.

CONCLUSION

In conclusion, this study's findings demonstrate that, when administered as an oral iron supplementation treatment for paediatric patients with iron deficient anaemia, IPC is just as effective as ferrous sulphate. However, IPC has fewer adverse effects than ferrous sulphate, which may improve compliance and tolerance.

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