

## **Comparative study of efficacy, tolerability and compliance of oral iron preparations (Iron edetae, iron polymatose complex) and intramuscular Iron sorbitol in iron deficiency anaemia in children**

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### **Abstract**

**Objective:** To compare the efficacy, tolerability and compliance of oral iron preparations (iron edetate and Iron polymaltose complex) with each other and with intramuscular iron sorbitol in iron deficiency anaemia in children.

**Methods:** A Randomized Controlled Trial (RCT) was carried out at the Paediatric Department of Combined Military Hospital (CMH) from January 2006 to December 2007. In total 146 children, up to 12 years age having haemoglobin (Hb%) less than 8 gm% were included. They were randomly distributed into three groups. Group A (64 cases) received oral sodium iron edetate (SIE), Group B (40 cases) received oral iron polymaltose complex (IPC) and group C (42 cases) received intramuscular iron sorbitol (IS) in recommended dosages. Rise in Hb% > 10 gm% was kept as desired target. Maximum duration of treatment planned was 2 weeks for parenteral iron (group C) and 12 weeks for oral iron (groups A and B). Haematological parameters- Hb%, mean corpuscular volum (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC) were measured at induction followed at 2 weeks, 4 weeks, 8 weeks and 12 weeks after start of treatment. Compliance and drop out rates were determined on each visit. Data was analyzed using SPSS version 10. ANOVA was used to analyze difference in rise in Hb% at various intervals.

**Results:** Statistically significant increase in mean Hb%, MCV, MCHC after 02 weeks was observed in group C (IS). Rise in these parameters became significant in group A (SIE) and B (IPC) after 04 weeks. Persistent rise was observed in oral groups at 08 and 12 weeks.

Rise in Hb% was much faster in group C (IS). It took 2 weeks to achieve mean Hb% > 10 gm% and compliance rate was 40.5%, while to achieve same target, duration required was 8 weeks in group A (SIE) and 12 weeks in group B (IPC) and compliance rate was 39% and 30% respectively. Adverse effects were much more common with group A (SIE) as compared to other two groups.

**Conclusion:** Intramuscular iron sorbitol is a reliable and faster alternative modality for treatment of iron deficiency anaemia in children. Short duration of treatment, sure rise in Hb% and minimal adverse effects improve compliance as compared to oral preparations.

Among oral preparations, rise in Hb% is more rapid with iron edetae. While IPC gives relatively slower rise in Hb% but side effects are much less as compared to SIE (JPMA 59:764; 2009).

### **Introduction**

Iron deficiency anaemia (IDA) is a common nutritional disorder worldwide especially in children and pregnant women.<sup>1</sup> In Pakistan prevalence of Iron deficiency anaemia is about 65%.<sup>2,3</sup> It is estimated that about 40% children are anaemic in various under developed countries in both Asia and Africa and IDA is the most common and preventable form among these cases. According to WHO statistics 43% children worldwide and 29% in Pakistan are iron deficient. Iron deficiency is the commonest one among three micronutrient deficiencies (Iron, Vit-A and iodine) in the developing world. IDA is an important component of malnutrition in malnourished children.<sup>4,5</sup> It also further complicates and augments malnutrition due to its consequential effects of

anorexia, apathy, irritability and pica. This further reduces food intake thus multiplying problems of malnutrition.

Iron deficiency anaemia should not be taken as a simple fall in haemoglobin rather it must be considered as a systemic disease affecting various organs and systems of body including central nervous system.<sup>6</sup> Iron is involved in synthesis of dopamine, serotonin, probably GABA (Gamma aminobutyric acid), myelin formation as well as in many other intermediary metabolic and catalytic agents in the body. Various studies have proved association of IDA with poor development, behavioral changes, poor school performance, low intelligence levels and other neurological problems like increased risk of febrile seizures in children.<sup>7-9</sup>

So IDA warrants to be diagnosed early and treated

effectively to avoid all these complications.<sup>10</sup> Oral iron supplementation is well accepted and time tested mode of treatment of IDA in all age groups except very few cases of gastrointestinal intolerance.<sup>11</sup> However, poor compliance and prolonged duration of treatment are limiting factors in effective management of this important problem. Parenteral iron (intravenous) preparations have been used in various studies to overcome these problems but this mode also carries its own hazards and requires hospital admission.<sup>12</sup> Intramuscular iron sorbitol (IS) has been used widely in treating IDA in pregnant women.<sup>13</sup> We have conducted this study to compare efficacy, tolerability and compliance of intramuscular iron sorbitol with oral iron preparations (SIE and IPC) as alternative modality in treatment of IDA. Oral preparations have also been compared with each other with reference to their efficacy, tolerability and compliance.

### Patients and Methods

A randomized controlled trial was carried out in outpatient department of paediatrics at Combined Military Hospital (CMH) Multan from Jan 2006 to Dec 2006. Children presenting with anaemia (Hb <8gm%) from 6 months to 12 years of age were included. Diagnosis of iron deficiency anaemia was confirmed by doing Hb%, MCV, MCHC, MCH, in all cases and in some cases serum Ferritin because facility for serum ferritin was not readily available. Patients excluded were all cases of anaemia other than iron deficiency anaemia, patients with severe anaemia (Hb <5gm%) or those with clinical features of decompensated heart disease, all patients with acute infection, systemic diseases like cardiac, renal, liver diseases and thalassaemia trait or other haemoglobinopathies and patients having prolonged treatment for some other diseases like tuberculosis, epilepsy, and malignancy.

In total 180 patients were screened and 146 patients

were included (34 patients did not fulfill the inclusion criteria). A questionnaire was filled by parents which included major presenting complaints and detailed medical history. Thorough, physical examination was carried out followed by a battery of tests including Hb%, MCV, MCHC, MCH, RBC morphology, reticulocyte count in all cases and serum ferritin (few cases) to have base line values. Stool and urine examination were also done and all cases were dewormed with mebendazole (Anthelminthic effective for threadworms (enterobiasis), whipworms (trichuriasis), roundworms (ascariasis), hookworms (ankylostoma duodenale).

These cases were randomly distributed into three groups by random number tables. These groups were also used as controls for each other. Group A (64 cases) were given oral sodium iron edetate (SIE) at dose of 6mg/kg/day. Group B (40 cases) received oral iron polymaltose complex (IPC) at the dose of 3mg/kg/day and Group C (42 cases) were given iron sorbitol (IS) parenterally in the form of single intramuscular injection daily at dose of 1.5 mg/kg/day. Rise in Hb>10gm% was kept as desired target. Duration of treatment planned was 2 weeks for parenteral group (C) and 12 weeks for oral groups (A and B). Cases were followed and monitored at 2 weeks, 4 weeks, 8 weeks and 12 weeks after starting treatment and above mentioned haematological parameters measured on each visit. Adverse effects were recorded and compliance rate calculated on every visit.

Data was analyzed by using SPSS version 10.0. Mean  $\pm$  SD and percentages were used to describe the data. The difference in rise in Hb% at different time intervals was analyzed using ANOVA. Z-test was applied to check the compliance rate in groups A and B. P value < 0.05 was considered significant.

### Results

A total of 146 children were randomly distributed

**Table-1: Age, weight, sex, presenting complaints and baseline hematological parameter of group A, B and C with haemoglobin less than 8gm/dL.**

Clinical parameters	Total	SIE (group A) n (%)	IPC (group B) n (%)	IS (group C) n (%)
No of pts	146	64 (43.8%)	40 (27.4%)	42 (28.8%)
Mean age in yrs $\pm$ SD	2.6 $\pm$ 1.46	3.09 $\pm$ 3.06	1.68 $\pm$ 0.8	2.77 $\pm$ 2.75
Wt (Kg) mean $\pm$ SD	10.8 $\pm$ 4.8	11.27 $\pm$ 5.3	9.5 $\pm$ 2.3	11.25 $\pm$ 5.7
Male n (%)	97 (66.4%)	42(65.6)	28(70)	27(64.2)
Female n (%)	49 (33.6%)	22(34.3)	12(30)	15(35.7)
Pallor n (%)	144(98.6)	63(98.4)	39(97.5)	42(100)
Breathlessness n (%)	14(9.5)	6(9.3)	5(12.5)	3(7.1)
Anorexia n (%)	82(56.1)	33(51.5)	22(55)	27(64.2)
Irritability n (%)	79(54.1)	31(48.4)	22(55)	27(64.2)
Easy fatigability n (%)	54(36.9)	20(31.2)	16(40)	18(42.8)
Breath holding spells n (%)	9(6.1)	3(4.6)	4(10)	2(4.7)
<b>Haematological parameters</b>				
Mean Hb (g/dl) $\pm$ SD	7.44 $\pm$ 0.54	7.54 $\pm$ 0.42	7.60 $\pm$ 0.38	6.75 $\pm$ 1.08
MCV (fl) $\pm$ SD	58.5 $\pm$ 10.4	60.7 $\pm$ 9.8	58.2 $\pm$ 9.3	55.4 $\pm$ 10.4
MCH (pg) $\pm$ SD	16.9 $\pm$ 5.1	17.7 $\pm$ 6.2	16.9 $\pm$ 3.5	15.8 $\pm$ 4.2
MCHC (g/l) $\pm$ SD	27.2 $\pm$ 3.3	27.6 $\pm$ 3.1	27.3 $\pm$ 3.5	26.5 $\pm$ 3.3

SIE = Sodium Iron Edetate. IPC = Iron Polymaltose Complex. IS = Iron Sorbitol. Hb = Haemoglobin. MCV = Mean Corpuscular Volume. MCH = Mean Corpuscular Haemoglobin. MCHC = Mean Corpuscular Haemoglobin Concentration.

**Table-2: Effect of SIE, IPC and IS on Hb%, MCV, MCH and MCHC.**

Parameter	Hb (g/dl)			MCV (fl)			MCH (pg)			MCHC (g/dl)		
	SIE (n=64)	IPC (n=40)	IS(n=42)	SIE	IPC	IS	SIE	IPC	IS	SIE	IPC	IS
Baseline	7.54±0.42	7.60±0.38	6.75±1.08	60.7±9.8	58.2±9.3	55.4±10.4	17.7±6.2	16.9±3.5	15.8±4.2	27.6±3.1	27.3±3.5	26.5±3.3
After 2 wks treatment	8.42±0.54	8.12±0.98	10.40±1.45	62.3±10.8	58.9±5.6	63.1±10.4	18.2±10.4	17.0±3.1	18.1±3.1	27.7±2.6	27.9±3.1	27.3±3.0
Rise in 2 wks	0.88±0.15	0.52±0.10	3.65±0.57	1.6±1.0	0.7±3.7	7.7±0.03	0.5±4.2	0.1±0.4	2.3±1.1	0.1±0.5	0.6±0.4	0.8±0.3
After 4 wks treatment	9.2±1.2	8.80±1.2		62.8±11.4	59.7±11.9		19.2±3.8	17.5±3.6		28.8±2.4	28.2±2.9	
Rise in 4 wks	1.66±0.2	1.20±0.1		2.1±5.8	1.5±2.6		1.5±2.4	0.6±0.1		1.2±1.7	0.9±1.6	
After 8 wks treatment	10.2±1.0	9.7±1.3		64.7±4.0	62.0±8.2		19.6±2.0	18.1±3.3		29.4±1.4	28.5±2.2	
Rise in 8 wks	2.76±0.02	2.10±0.01		4.0±5.8	3.8±1.1		1.9±4.2	1.2±0.2		1.8±1.7	1.2±1.3	
After 12 wks treatment	10.9±0.75	10.5±0.74		66.5±5.2	71.1±6.7		20.4±2.6	21.4±2.9		30.8±1.6	30.5±2.0	
Rise in 12 wks	3.36±0.34	2.90±0.64		5.8±3.6	12.9±2.6		2.7±3.8	4.5±1.6		3.2±1.5	3.2±1.5	

SIE = Sodium Iron Edetate-Oral. IPC = Iron Polymaltose Complex-Oral. IS = Intramuscular Iron Sorbital. MCV = Mean Corpuscular Volume. MCH = Mean Corpuscular Haemoglobin. MCHC = Mean Corpuscular Haemoglobin Concentration. Wks = Weeks.  
All parameters are expressed as Mean ± ISD.

into three groups; Group A, 64 (43.8%), Group B, 40 (27.4%) and Group C, 42 (28.8%). Mean age was 2.6 ± 1.46 years. Males were 97 (66.4%) while 49 (33.6%) were female children. Commonest presenting complaint was pallor in 144 (98.6%), followed by anorexia in 82 (56.1%), irritability in 79 (54.1%) and easy fatigability in 54 (36.9%) cases as shown in Table-1. Breathlessness was reported in only 14 (9.5%) and breath holding spells in 9 (6.1%) cases.

Baseline mean Hb% was 7.54 ± 0.42 in group A, 7.60 ± 0.38 in group B and 6.75 ± 1.08 in group C (cases with comparatively low Hb%). Similarly MCV, MCH, and MCHC, were recorded as baseline parameters at time of induction in all groups as shown in Table-1. After 02 weeks treatment mean Hb% in group A became 8.42 ± 0.54 gm%, in group B 8.12 ± 0.98 gm%, and in group C 10.4 ± 1.45 gm%. Mean rise noted was 0.88 ± 0.15 gm%, 0.52±0.10 gm%, and 3.65±0.57 gm% in group A, B and C respectively. Difference was significant in group C as compared to A and B group (P<0.001) as shown in Table-2. Hence, maximum rise was seen in group C. Patients in group C achieved target Hb%.

After 04 weeks treatment mean Hb% noted was 9.2 ± 1.2 gm%, 8.80 ± 1.2 gm% in groups A and B respectively while mean rise in Hb% was 1.66 ± 0.2 gm% and 1.20 ± 0.1 gm% respectively. After 8 weeks treatment, mean Hb% was 10.2 ± 1.0 gm% and 9.7 ± 1.3 gm% in groups A and B respectively while rise in Hb% was 2.76 ± 0.02 gm% and 2.10 ± 0.01 gm% respectively. Hence, group A patients also achieved mean target Hb% after 8 weeks. Difference was significant when A and B groups were compared with each other. (p<0.05) After 12 weeks mean Hb% noted was 10.9 ± 0.75 gm% and 10.5 ± 0.74 gm% in groups A and B respectively while rise noted was 3.36 ± 0.34 gm% and 2.90

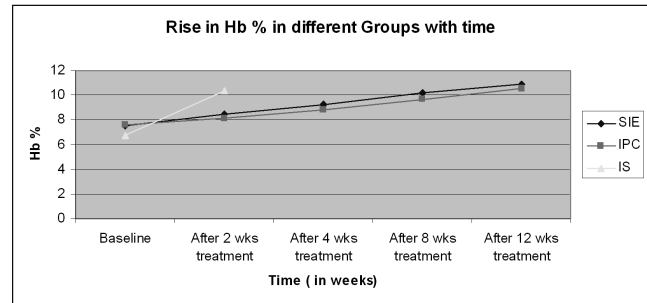


Figure: Rise in Hb% in group A (oral sodium edetate, SIE), group B (oral iron polymaltose complex IPC), group C (intramuscular iron sorbital, IS) after 2, 4, 8 and 12 weeks of treatment.

± 0.64 gm% respectively. Therefore, group B patients also achieved target Hb% after 12 weeks of treatment. Similar rise was noted in other haematological parameters (MCV, MCHC and MCH) as well (Table-2).

Rise in Hb% was most rapid in group C (IS) as compared to oral treatment groups. While comparing oral groups with each other slowest rise was witnessed in group B (IPC) as shown in Figure. On, overall, evaluation after 12 weeks, in group A, 25 patients achieved target Hb% thus making compliance rate of 39% while in group B only 12 patients were able to achieve target, thus making compliance rate of 30%. In group C, 17 patients achieved target Hb% thus making success rate of 40.5%. For compliance, difference between group A and B is significant (P < 0.05) while difference between group A, and C, is not significant. Duration of treatment required to raise mean Hb% > 10 gm% was 2 weeks, 8 weeks, and 12 weeks in group C, A and B respectively. Adverse effects noted were maximum with group A e.g. nausea, vomiting, gastritis and constipation. However, adverse effects were less in group B. In group C local staining of skin was seen

in 10 (23.81%) patients only.

## Discussion

Anaemia is a problem of global significance as WHO estimates that more than 1/3rd of world population is anaemic.<sup>4</sup> IDA is the commonest type and is of serious public health significance having its impact on psychological and physical development, behaviour and work performance.<sup>6,9</sup> Highest prevalence of IDA is found among infants born preterm or low birth weight (LBW), children between 6 months to preschool age and pregnant women.<sup>14</sup> This problem is even more grave in our society where IDA affects about 58.3% school children as reported by Manzoor et al in his study from Lahore.<sup>15</sup>

Studies have proved that children with IDA are at increased risk of long term impairment of psychomotor development, lower IQ level, lack of concentration, poor school performance and decreased physical activity. Iron deficiency also affects the immune system thus making these children vulnerable to recurrent infections. These facts warrant that prevention, identification, and treatment of IDA in infants and preschool children must be taken as a challenge. Treatment strategies adopted should be more definitive, sure and practically implementable. Daily recommended iron requirement is 2mg/kg/day in children and if this is provided through dietary sources, IDA can be prevented effectively. However, in established cases of IDA, usually recommended dose varies from 3-6mg/kg/day.<sup>10,11</sup>

Oral iron supplementation is well established, effective and worldwide accepted mode of treatment in IDA. There are very few indications for blood transfusion or parenteral iron therapy. Various forms of oral iron preparations are available.<sup>11,16</sup> However, patients do not always respond adequately to oral iron therapy because of non compliance due to side effects and prolonged duration of treatment.<sup>17</sup> Gastrointestinal disturbances with oral iron have been reported to be 6-12% in different studies.<sup>18</sup> The most widely recommended and used oral iron preparations are ferrous salts. However, use of these salts is limited by low and variable absorption, chelation by food products and free radical mediated mucosal damage.<sup>19</sup> Ferric compounds were introduced to avoid these problems. However, they have poor bioavailability due to their less solubility and tendency to precipitate intraluminally.<sup>18,19</sup> To overcome these problems, iron polymaltose complex (IPC) was developed as a molecule that is soluble at neutral PH and is not chelated by other substances. Various studies have claimed that IPC is as effective or even superior to ferrous salts but others contradict these results.<sup>17-20</sup> We have compared these oral preparations and our results are superior with ferrous form as also documented by Abdul

Rahman et al in a local study.<sup>21</sup> However, at the same time IPC is preferable and tolerable as far as side effects are concerned.<sup>18</sup> Our results are also consistent with this observation.

Another factor is duration of treatment which plays an important role in compliance. Usually recommended period with oral treatment ranges from 3-6 months.<sup>11</sup> This is an important factor especially in our society where poverty, lack of education, long distances from health facility and false satisfaction with partial treatment compound the problems of compliance. In the present study we have tried parenteral (intramuscular iron sorbitol) route for iron supplementation. We observed very rapid and definitive rise in Hb% in very short time and target Hb% was achieved within 2 weeks only. IS is widely used in pregnant women but scanty data is available regarding its use in children.<sup>13</sup> Surico G et al. have proved and recommended efficacy of I/M iron in their study in children.<sup>22</sup> Majority studies of parenteral iron therapy in pregnant women and few in children have been done with I/V preparations like ferrous succinate, iron dextran etc. Intravenous therapy has its own limitations of hospitalization and serious side effects including death.<sup>23</sup> So although quite effective this mode has not gained popularity in paediatric patients.<sup>12,24</sup> Intramuscular iron dextran has been associated with development of malignancy (sarcomas) at local injection sites in experimental animals.<sup>25</sup> No other significant side effects except local pain and skin staining have been reported with I/M iron sorbitol.<sup>19</sup> These are also quite negligible and no patient discontinued treatment due to them in our study. It is easy to administer I/M injections as out patient. Definitive rise and shorter duration improves the compliance. In our study however compliance of oral ferrous group and parenteral IS group is comparable. We have found I/M IS more definitive, and a rapid alternative mode for treatment of IDA in children with fewer side effects.

IPC is now the most promoted salt for oral treatment due to fewer side effects.<sup>18</sup> However, a slow rise in Hb% and longer duration of treatment are limiting factors. In our study, it took about 12 weeks to achieve target Hb% which was the slowest one as compared to 8 weeks for SIE and 2 weeks for IS. Hence, compliance rate was also the lowest, 30% as compared to 39% in SIE and 40.5% in IS groups respectively. However, this observation is not consistent with other studies where they claim it to be almost equivalent to other oral preparations.<sup>16,18</sup> Therefore, this aspect, needs to be studied further.

## Conclusion

IDA in children needs effective treatment modalities to be adopted. Compliance plays an important role in this

easily treatable problem. Oral ferrous preparations have superior results but increased side effects limit its compliance. IPC is good alternative to avoid side effects but duration of treatment is relatively prolonged, again a limiting factor for compliance. I/M iron sorbitol can be used as an alternative mode of treatment for more definitive and rapid results. However, larger studies are required to assess side effects on long term basis.

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