COMPARISON OF EFFICACY OF ORAL AND INTRAMUSCULAR IRON SUPPLEMENTATION FOR TREATMENT OF IRON DEFICIENCY ANEMIA IN CHILDREN

Shabbir Hussain, Tariq Mahmood Ahmad, Moin Ud Din Sabir, Saba Haider Tarar

Combined Military Hospital Kharian

ABSTRACT

Objective: To compare the efficacy of oral iron preparation with intramuscular iron sorbitol in treatment of iron deficiency anemia in children.

Study Design: Randomized controlled trial.

Place and Duration of Study: Paediatric department of Combined Military Hospital Kharian, Pakistan, from October 2011 to March 2013.

Patients and Methods: In total 200 anemic children from 6 months to 5 years of age were included. Cut off value for Hb was < 8 gm/dl. Patients were divided into two groups, each of 100, randomly. Group A received oral sodium feredetate (iron edetate) and group B received intramuscular iron sorbitol. Rise in Hb > 10 gm/dl was kept as the desired value. Maximum duration of treatment planned was 12 weeks for group A and 2 weeks for group B. Laboratory parameters such as Hb%, mean corpuscular volume (MCV), retic count and serum ferritin level were used to detect the responses in both groups at one week, two weeks, four weeks and twelve weeks of treatment.

Results: Among 200 patients, male and female distribution was 45% and 55% respectively.. Desired rise in Hb in group B was achieved much earlier i.e. at two weeks as compared to group A. Progressive rise in laboratory parameters was observed but this rise was more evident in group B as compared to group A. After one week treatment in group A, rise in retic count, Hb, ferritin and MCV was 0.759 ± 0.318, 0.814 ± 0.387, 0.47 ± 0.154 and 4.28 ± 2.468 respectively. But rise in these values in group B was 2.235±0.632, 2.335 ± 0.135, 6.31 ± 1.123 and 12.11 ± 0.414 respectively. Same persistent different trend was observed at 2 and 4 weeks. After 12 weeks treatment in group A, rise in retic count, Hb, ferritin and MCV was 1.044 ± 0.222, 5.204 ± 0.134, 17.39 ± 2.551 and 16.61 ± 1.214 respectively but rise in these laboratory indices in group B was 0.551 ± 0.261, 6.097 ± 0.21, 42.49 ± 2.768 and 20.68 ± 2.233 respectively. The comparison of hematological indices after 12 weeks in A and B groups show significant differences. All these parameters improved in both groups but improvement in group B was drastically more prominent when compared with group A (p-value < *0.05)*.

Conclusion: Intramuscular iron sorbitol therapy is an alternative and comparatively better treatment option as compared to oral iron therapy, sodium feredetate, in regards of treatment duration and earlier rise in the laboratory indices.

Keywords*:* Anaemia, Children, Intramuscular iron, Oral iron, Therapy.

INTRODUCTION

Iron deficiency anemia (IDA) is the most common nutritional deficiency of paediatric age group in developing world[1]. Prevalence of IDA is more in 2nd year of life as compared to 3rd to 5th year[2]. This nutritional disorder frequently affects the pregnant women and children[3]. Among preschool- aged children in South East Asia, IDA is the commonest cause of anemia, in addition to hemoglobinopathies and vit A deficiency[4]. Iron deficiency is the commonest among three (iron, vitamin A, iodine) common micronutrient deficiencies that affects the malnourished children in developing world[4]. IDA commonly affects the people belonging to lower socioeconomic group[5]. In socioeconomically poor countries due to lack of sanitation, hook worm infestation is also a contributory factor to develop IDA[6]. Prevalence of iron deficiency anemia in Pakistan is around 65%[7]. Prevalence is highest

Correspondence: Dr Shabbir Hussain, Consultant Paediatrician, CMH Kharian.
Email: shabbirmoeez@yahoo.com
Received: 23 Dec 2013; Accepted: 06 Mar 2014

among infants born as preterm low birth weight and from 6 months to 5 years of age[3].

IDA to some extent is a preventable disease and can be prevented by the use of oral iron in the form of dietary sources. Daily requirement of iron in children in food intake is 2 mg/kg/day[3]. It has both physical and psychosocial impact on development of growing child[8]. Different studies have proved that IDA adversely affects IQ level, concentration level, immune system and school performance[3]. IDA is a multiorgan disease and it affects synthesis of dopamine, serotonin, gama aminobutyric acid and myeline leading to a plethora of symptoms[2]. It has a vast clinical presentation ranging from pallor, anorexia, irritability, pagophagia, breath holding spells[9] to febrile seizures[10] impaired psychomotor and mental development [1,2,4,8]. Iron supplementation is supposed to improve these developmental features but some are irreversible[11].

Laboratory indices of iron deficiency anemia are hypochromic, microcytic morphology, decreased serum ferritin level and raised red cell distribution width. Various routes of delivery of treatment are available like oral, intravenous and intramuscular[12,13]. Oral iron therapy is associated with gastrointestinal side effects, poor compliance and prolonged duration of therapy issues[3]. Parenteral intravenous preparations are associated with anaphylactic reactions and require hospitalization[14]. Association between iron supplementation, especially intramuscular, and risk of infectious illnesses is considered a hazard but remains controversial[15].

Considering various limitations associated with oral iron and intravenous iron therapy, we conducted this study to document and compare the efficacy of oral and intramuscular iron preparations. Results of our study may help the policy makers and physicians to understand the benefits of alternative routes of iron supplementation in children

PATIENTS AND METHODS

This study was an RCT carried out in Combined Military Hospital (CMH) Kharian, Pakistan, from Oct 2011 to Mar 2013. Children presenting in out patient department (OPD) with diagnosis of anemia were included. Cut off level for Hb was < 8 gm/dl. Age criteria was from 6 months to 5 years. This study was irrespective of sex, race, ethnicity, geographical distribution and socioeconomic status. IDA was diagnosed on the basis of low haemoglobin (Hb) hypochromic microcytic morphology, increased red cell distribution width, mentzer index of > 14 and low serum ferritin levels. Patients with severe anemia (Hb < 5 gm%), anemia due to chronic systemic diseases, acute infection with IDA, hemoglobinopathies and anemia's other than IDA were excluded.

A total of 215 patients were enrolled, who underwent randomization process. Written consent of parents for participation in study was taken and details of medication, procedure, blood sampling and adverse events explained. Simple randomization was done to divide patients into two groups. A total of 110 patients were assigned group A and 105 group B. But 10 participants in group A and 5 in group B were lost to complete the study period due to financial, logistic and social reasons. None of these were lost due to adverse events, hospital admission or mortality. In total 200 patients, 100 in each group, could be followed up throughout study period. Presumed worm infestation was treated with albendazole, 400mg single dose, in all patients before start of treatment. Group A was given oral iron, sodium feredetate, in dose of 6mg/kg/day for twelve weeks and group B was given intramuscular iron sorbitol 1.5 mg/kg/day for two weeks. In group A, specific dose for patients was calculated in ml and parents counseled and guided regarding its administration. Compliance was assessed from record endorsed on a written form that was handed over to parents at initiation of treatment. In group B, intramuscular administration was done in hospital under supervision of consultant. Response to treatment was judged by retic count, Hb , MCV and serum ferritin levels at one , two , four and twelve weeks of treatment. Adverse events were asked and recorded, although it was

not part of the study. Minor side effects in group B such as immediate local pain, redness and swelling were observed. No anaphylactic reaction or any other life threatening event was observed.

Table-1: Base line parameters comparison of group A and B.

Parameter	Total Patients	Group A	Group B
Sex			
Male	110	57	53
Female	90	43	47
Age			
6-12 month	47	23	24
13-24	58	28	30
25-36	21	13	8
37-48	53	26	27
49-60	21	10	11
Income Status			
PRs 5000-10000	79	36	43
10001-20000	53	25	28
20001-30000	36	20	16
30001-40000	16	9	7
>40000	16	10	6
Symptoms			
Pallor	72	40	32
Male	42	22	20
Female	30	18	12
Anorexia	59	25	34
Male	30	12	18
Female	29	13	16
Irritibality	51	24	27
Male	27	10	17
Female	24	14	10
Pagophagia	07	4	3
Male	04	2	2
Female	03	2	1
BHS	03	1	02
Male	01	00	01
Female	02	01	01
Intelectual Abnormalities	08	05	03
Male			
Female	06	04	02
	02	01	01

Statistical analysis

Data was analyzed by using SPSS version 16. Mean ± SD and percentages were used to describe the data. The difference in retic count, Hb, MCV, and serum ferritin level rise was calculated at different intervals. A p value < 0.05 was considered significant.

RESULTS

Out of these 200 cases, 110 (55%) were males and 90 (45%) females. Regarding age parameter,

majority (52.5%) of patients was between 6-24 months. Parents' income status revealed that income of parents of more than half sample was between Rs 5000-2000 and only 16 (8%) cases belonged to families who were earning more than Rs.41000/month. Plethora of symptomatology on presentation revealed that only 72 (36%) patients among study sample had pallor as a prominent symptom. Comparison of different parameters of study in both groups is shown in Table-1.

Four laboratory parameters(Retic count, MCV, Hb and Ferritin level) were compared in both groups at the start of the treatment as baseline values, after 1, 2, 4 and 12 weeks of treatment. It was observed that all the parameters were significantly (*p*-value < 0.05) different in both groups at all these specified times. Exception to this observation was ferritin and MCV levels at start of treatment which were almost the same in both groups (table-2). Desired rise in Hb in group B was achieved much earlier i.e. at two weeks as compared to group A (table-2).

Table-2: Comparison of different laboratory parameters between oral and intra muscular treatment groups at start of the study and after one, two, four and twelve week of treatment.

Laboratory Parameters	Oral Treatment Group	Intra Muscular Treatment Group	*p*-value
	Mean ± SD	Mean ± SD	
Start of Treatment			
Retict (%)	0.746 ± 0.076	0.803 ± 0.078	0.000
Hb (gm/dl)	6.096 ± 0.808	6.323 ± 0.579	0.024
MCV (fl)	64.370 ± 3.457	65.020 ± 2.287	0.118
Ferritin ng/ml	4.530 ± 1.058	4.480 ± 1.020	0.734
After One Week			
Retic	1.505 ± 0.394	3.038 ± 0.710	0.000
Hb	6.910 ± 0.421	8.658 ± 0.444	0.000
MCV	68.650 ± 0.989	77.130 ± 1.873	0.000
Ferritin	5.000 ± 0.904	10.790 ± 2.143	0.000
After Two Week			
Retic	1.823 ± 0.267	3.241 ± 0.693	0.000
Hb	8.627 ± 0.321	10.892 ± 0.937	0.000
MCV	79.200 ± 1.934	82.364 ± 1.437	0.000
Ferritin	7.257 ± 0.834	23.726 ± 3.626	0.000
After Four Week			
Retic	1.928 ± 0.371	3.477 ± 0.599	0.000
Hb	9.227 ± 0.433	11.000 ± 0.725	0.000
MCV	77.800 ± 1.792	85.570 ± 1.402	0.000
Ferritin	8.860 ± 1.491	26.250 ± 5.064	0.000
After Twelve Week			
Retic	1.790 ± 0.298	1.354 ± 0.339	0.000
Hb	11.300 ± 0.674	12.421 ± 0.369	0.000
MCV	80.980 ± 2.243	85.700 ± 4.520	0.000
Ferritin	21.920 ± 3.609	46.970 ± 3.788	0.000

Table-2 shows the Comparison (Mean±SD) of different laboratory parameters between oral and intra muscular treatment groups at start of the study and after one, two, four and twelve week of treatment. It is evident from the results

that there is statistical significant difference *0.000)* difference at 12 weeks of treatment from baseline in all laboratory parameters in both

Table-3: Comparison of rise in different laboratory parameters at different intervals.

		Oral Group	I/M Group
Time Interval	Laboratory Parametrs	Values	Values
After One Week	Retic count (%)	0.759 ± 0.318	2.235 ± 0.632
	Hb gm / dl	0.814 ± 0.387	2.335 ± 0.135
	Ferritin ng / ml	0.47 ± 0.154	6.31 ± 1.123
	MCV (fl)	4.28 ± 2.468	12.11 ± 0.414
After Two Week	Retic count	1.086 ± 0.191	2.438 ± 0.615
	Hb	2.531 ± 0.487	4.569 ± 0.358
	Ferritin	2.727 ± 0.224	19.246 ± 2.606
	MCV	14.83 ± 1.523	17.344 ± 0.85
After Four Week	Retic count	1.182 ± 0.295	2.674 ± 0.521
	Hb	3.131 ± 0.375	4.766 ± 0.146
	Ferritin	4.33 ± 0.433	21.77 ± 4.044
	MCV	13.43 ± 1.665	20.73 ± 0.885
After Twelve Week	Retic count	1.044 ± 0.222	0.551 ± 0.261
	Hb	5.204 ± 0.134	6.097 ± 0.21
	Ferritin	17.39 ± 2.551	42.49 ± 2.768
	MCV	16.61 ± 1.214	20.68 ± 2.233

Table-4: Comparison of laboratory parameters after 12 weeks of treatment with baseline values in both groups.

Parameters	Oral Treatment Group	*p*-value	Intra Muscular Treatment Group	*p*-value
Start Retic (%)	0.746 ± 0.076	0.000	0.803 ± 0.078	0.000
Retic after 12 week	1.790 ± 0.298		1.354 ± 0.339	
Start Hb gm / dl	6.096 ± 0.808	0.000	6.323 ± 0.579	0.000
Hb after 12 week	11.300 ± 0.674		12.421 ± 0.369	
Start MCV (fl)	64.370 ± 3.457	0.000	65.020 ± 2.287	0.000
MCV after 12 week	80.980 ± 2.243		85.700 ± 4.520	
Start Ferritin ng / ml	4.530 ± 1.058	0.000	4.480 ± 1.020	0.000
Ferritin after 12 week	21.920 ± 3.609		46.970 ± 3.788	

between two groups (*p*-value < *0.05).*

Table-3 shows Comparison in rise in different laboratory parameters in both groups at different intervals.There is progressive rise in both groups but this rise is more in intramuscular group as compared to oral group.

Table-4 highlights the comparison of retic, Hb, MCV and ferritin at base line and after 12 weeks of treatment in both groups.It is absolutely clear that there is statistically significant (*p*-value groups. But from the results it is obvious that the improvement in intramuscular treatment group was drastically more prominent as compared with oral treatment group.

DISCUSSION

IDA affects children of lower socioeconomic class more frequently[5]. This fact is also supported by our study results that lesser the earning of the family more frequently the children were suffering from IDA. It is said that in our society

58.3% school aged children are suffering with IDA[16]. So IDA in infants where brain growth is still occurring and preschool aged children is a big challenge for paediatrician community to address it affectively. Presentation of IDA, as stated in introduction, varies. Clinical presentation of children in our study is also consistent with these symptoms and signs of anemia[8,9,10].

Iron deficiency is treated by the use of oral and parenteral preparations. Oral iron therapy is associated with compliance issues and gastrointestinal side effects which have been described in several studies[17]. A number of local studies have proved that parenteral iron preparations are a better choice for the treatment of IDA in the pregnant women[18,19,20]. Only two studies, one conducted by Afzal et al[3] and other by Imran et al[21], have demonstrated the use of intramuscular iron for the treatment of IDA in Pakistani children. Surico et al[22] have also documented the efficacy and safety of intramuscular iron administration in children with severe IDA who failed to respond to oral iron therapy. They have concluded that parenteral iron therapy for IDA treatment is a rapid, easy and definitive solution. They recommend parenteral iron for severe IDA in children who do not recover after oral therapy. Our study results are in agreement with these studies and we have established that intramuscular iron is more effective than the oral preparation[3,21,22]. There was a significant rise in retic count, MCV and Hb after one week in both groups but more in intramuscular treatment group. The work of Afzal et al[3] reported similar responses after two weeks of treatment. Target Hb was achieved in two weeks in parenteral group. In both groups progressive rise in all laboratory indices was observed from the start of treatment till 12 weeks but this trend is more pronounced in parenteral group than oral. All these results are in agreement with Afzal et al and Imran et al [3,21]. The benefits of intramuscular treatment are shorter duration and early recovery. Intramuscular therapy side effects are discomfort, local discoloration, transient metallic taste and palpitations[21]. Association of infection and parenteral, especially intramuscular, iron supplementation is considered a hazard and limiting factor for this mode of therapy[15]. But opinion regarding this aspect is polarized by different research works. ID is considered a defence mechanism and hypoferremia may play a role in preventing bacterial growth. Hence the term nutritional immunity was proposed for hypoferremia. Opponents of this immunity theory suggest that ID is associated with defective neutrophil bactericidal activity and cell mediated immunity thus enhancing susceptibility to infection. In addition, iron supplementation may cause cell damage through free radicals. Trials of iron supplementation have shown either beneficial effects, no effects or an increased rate of infectious illnesses. Gera et al[23] concluded from systemic review analysis of published data that iron supplementation has no harmful effects on the incidence of infectious illnesses in children. Clinical evidence of increased infection rate after the use of parentral iron therapy remains inconclusive. There are animal and human studies in patients undergoing dialysis those have been administered parentral iron and no significant increased risk of infection was observed[24]. In another study conducted in patients undergoing cardiac surgery, overall infection rate was 4.52%, with an infection rate of 3.97% in iron treated versus 4.81% in untreated patients who did not receive parentral iron[25]. Intramuscular iron dextran, another parenteral iron supplement is associated with the development of sarcomas at the injection sites in animal models[21]. No immediate side effect was serious enough to stop this mode of treatment in our study. To study the relationship between iron supplementation and infectious illnesses was beyond the scope of this study.

CONCLUSION

Iron sorbitol is useful for treating iron deficiency anemia with additional benefits of faster, reliable and shorter duration of treatment modality in paediatric population. However

future studies are encouraged to assess the side effects and sustained response to intramuscular iron therapy.

Conflict of Interest

This study has no conflict of interest to declare by any author.

REFERENCES

1. DeBenoist B, McLean E, Egli I, Logswell M. Worldwide prevalence of anaemia 1993-2005: WHO global database on anemia. Report, World Health Organization; (Centers for Disease Control), Geneva, 2008.
2. Bortolini GA,Vitolo MR. Relationship between iron deficiency and anemia in children younger than 4 years. J Pediatr (Rio J). 2010; 86(6): 488–92.
3. Afzal M, Qureshi SM, Lutafullah M, Iqbal M, Sultan M, Khan SA. Comparative study of efficacy, tolerability and compliance of oral iron preparations(iron edentate, iron polymaltose complex) and intramuscular iron sorbitol in iron deficiency anemia in children.J Pak Med Assoc- 2009; 59(11): 764-68.
4. George J, Yiannakis M, Main B, Devernish R, Anderson C. Genetic hemoglobin disorders, infection, and deficiencies of iron and vitamin A determine anemia in young Cambodian children. J Nutr. 2012; 142(4): 781–87.
5. Molla A, Khurshid M, Molla AM. Prevalence of iron deficiency anemia in children of the urban slums of Karachi.J Pak Med Assoc- 1992; 429(5): 118-21.
6. Hotez PJ, Brooker S, Bethony JM, Bottazzi ME, Loukas A, Xiao S. Hookworm infection. N Engl J Med. 2004; 351(8): 799–807.
7. National institute of Health. National Nutritional Survey, 2oo1-2002 .Islamabad.Planning Dvision,Government of Pakistan 2003.
8. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006; 64: S34–43.
9. Ziaullah, Nawaz S, Shah S, Talat A. Iron deficiency anemia as a cause of breath holding spells. JPMI 2005; 19(2): 171-74.
10. Rehman N, Billo AG. Association between iron deficiency anemia and febrile seizures. J Coll Physcians Surg Pak Jun 2005; 15(6): 338-40.
11. Lozoff B,Beard J,Connor J, Felt B, Georgieff M,Schallert T.Long lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev.2006;64:834-43
12. Iqbal MM, Malik BA. Parenteral Iron therapy in malnourished children. Pakistan Armed Forces Med J 2006; 56: 271-75.
13. Wali A, Mushtaq A, Nilofer. Comparative study—efficacy, safety and compliance of intravenous iron sucrose and intramuscular iron sorbitol in iron deficiency anemia of pregnancy. J Pak Med Assoc 2002; 52: 392-5.
14. Wysowski DK, Swartz L, Borders-Hemphill BV, Goulding MR, Dormitzer C, et al. Use of parenteral iron products and serious anaphylactic-type reactions. Am J Hematol 2010; 85(9): 650-54
15. Sazawal S, Black RE, Ramsan M, Chawaya HM, Stoltzfus RJet al. Effects of routine prophylactic supplementation with iron and folic acid on admission to hospital and mortality in preschool children in a high malaria transmission setting: community-based, randomised, placebo-controlled trial. Lancet. 2006; 367(9505): 133–43.
16. Manzoor A, Tayyib M, Tasneem T. Iron status of anemic school children. Pakistan Postgrad Med J 2003; 14(1): 14-7.
17. Saha L, Pandhi P, Gopalan S, Malhotra S, Saha PK. Comparison of efficacy, tolerability and cost of Iron polymaltose complex with ferrous sulphate in the treatment of Iron deficiency anemia in pregnant women. Med Gen Med 2007; 9 (1);1
18. Hasan S, Hashim B, Sultana A. Iron therapy in iron deficiency anemia in Pregnancy: intravenous iron sucrose versus oral iron hydroxide polymaltose complex in anemia.Ann Abbasi Shaheed Hosp Karachi Med Dent Coll Dec 2003; 8(2): 435-40.
19. Tayab S, Hossain N, Fatima TS. Iron Supplement during Pregnancy - A better way of intramuscular iron administration. Med Channel Oct - Dec 1999; 5(4): 20-4.
20. Komolafe JO, Kuti O, Ijadunola KT, Ogunniyi SO. A comparative study between intramuscular iron dextran and oral ferrous sulphate in the treatment of iron deficiency anemia in pregnancy. J Obstet Gynaecol. 2003; 23(6): 628-31.
21. Asghar I, Ahmad KN, Kamran S, Hussain S. Efficacy of parenteral iron as compared to oral iron in the treatment of iron deficiency anemia in children. PAFMJ 2012; 62(2): 55.
22. Surico G, Muggeo P, Muggeo V, Lucarelli A, Martucci T, Daniele M et al.Parenteral iron supplementation for the treatment of iron deficiency anemia in children. Ann Hematol 2002; 81(3): 154-57.
23. Gera T, Sachdev HPS. Effect of iron supplementation on incidence of infectious illness in children: systematic review. BMJ. 2002; 325(7373): 1142.
24. Bullen JJ, Rogers HJ , Spalding PB , Ward CG. Natural resistance, iron and infection: a challenge for clinical medicine. J Med Microbiol. 2006; 55(3): 251-58.
25. Torress S, Kuo YH, Morris K, Neibart R, Holtz JB, David JM. Intravenous Iron following Cardiac surgery does not increase Infection Rate. Surg Infect. 2006; 7(4): 361-66.