Original Article

Comparison of Conventional and Newer Iron Preparations for the Treatment of Iron Deficiency Anaemia in Children

Asmat Parveen[1], Naima Fazil Raja[2], Imran Mehmood Khan[3], Hijab Shaheen[4], Muhammad Imran[5], Rizwan Shafeeq Ahmed[6]

[1] Consultant Pediatrician, Maryam Memorial Hospital, Rawalpindi.
[2] Consultant Pediatrician, Tehsil Headquarter Hospital, Taxila.
[3] Associate Professor, Islamabad Medical & Dental College, Islamabad.
[4] Medical Officer, Pakistan Institute of Medical Sciences, Islamabad.
[5] Senior Registrar, Shifa College of Medicine, Islamabad.
[6] Assistant Professor, Islamabad Medical & Dental College, Islamabad.

Author`s Contribution
[1,2,3,4,5,6] *Conception of study*
[1,4,5] *Experimentation/Study conduction*
[1,2,3,4,5] *Analysis/Interpretation/Discussion*
[1,2,3,6] *Manuscript Writing*
[2,3,6] *Critical Review*

Corresponding Author
Dr. Imran Mehmood Khan
Associate Professor,
Islamabad Medical & Dental College,
Islamabad
Email: lifesaverforu@yahoo.com

Article Processing
Received: 13/7/2019
Accepted: 13/5/2020

Cite this Article: *Parveen, A., Raja, N.F., Khan, I.M., Shaheen, H., Imran, M. & Ahmed, R.S.(2020). Comparison of Conventional and Newer Iron Preparations for the Treatment of Iron Deficiency Anaemia in Children. 24(2), 40-45.*
DOI: https://doi.org/10.37939/jrmc.v24i2.1160

Conflict of Interest: *Nil*
Funding Source:
Pakistan Institute of Medical Sciences, Islamabad.

Access Online:

Abstract

Introduction: Commonly used iron salt, ferrous sulphate for the treatment of iron deficiency anemia, has several gastrointestinal side effects. Nowadays new iron salts such as ferrous bisglycinate are marketed with claims of raising hemoglobin faster with fewer gastrointestinal side effects.

Objective: To compare the efficacy of ferrous sulphate with ferrous bisglycinate for the treatment of iron deficiency anemia in children.

Methods: This randomized controlled trial was carried out at Children Hospital, PIMS, Islamabad from July 2015 to June 2016. A total of 136 children were selected through systematic sampling and randomized into 2 groups using a computer-generated table of random numbers; ferrous sulphate as group 1 and ferrous bisglycinate as group 2. Clinical outcome was assessed based on a mean increase in hemoglobin after 12 weeks of therapy in both groups. The data was entered and analyzed using SPSS version 20.

Results: The baseline characteristics i.e. mean age, mean hemoglobin levels were similar in both study groups. After 12 weeks of treatment, the mean increase in hemoglobin was 1.8 ±1.59 g/dl in the ferrous sulphate group as compare to 2.5 ±1.31g/dl in ferrous bisglycinate group showing the higher level of rising with ferrous bisglycinate than ferrous sulphate, P =0.0033.

Conclusion: Newer iron preparation, ferrous bisglycinate is a better treatment option than conventional preparation of ferrous sulphate for increasing hemoglobin in iron deficiency anemia in children.

Keywords: Hemoglobin, iron, ferrous sulphate, ferrous bisglycinate, iron deficiency, anemia.

Introduction

Anemia is defined as "a hemoglobin level of less than the 5th percentile for age".[1,2] About 30% of the world's population is suffering from iron deficiency anemia (IDA) mostly residing in developing countries.[3] In Pakistan, 65% of the general population including children and adults, is having IDA.[4] WHO statistics shows that in the world 43% & in Pakistan 29% of children are suffering from iron deficiency.[4]

Children less than 2 years of age have the highest risk due to the increasing demand for rapid growth.[5,6] Other causes of IDA are premature births, early clamping of the umbilical cord, prolonged exclusive breastfeeding greater than 6 months without iron supplementation, delayed weaning, excessive intake of cow milk, low iron absorption, chronic blood loss, and parasite infestation.[3,7,8,9,10]

The most common sign of anemia is pallor which does not appear until hemoglobin (Hb) falls to 7-8 g/dl. So IDA is commonly missed by parents in early stages. Other than anemia, iron deficiency also causes fatigue, poor concentration, and memory resulting in poor school performance.[11,12,6] It also leads to pica and pagophagia (desire to ingest rice).[3,13] There is a positive association of iron deficiency with febrile seizures, breath-holding spells, irritability, nausea and reduced immunity.[3,14,13,6]

To prevent IDA, WHO recommends daily doses of 30 mg of iron and 250 µg of folic acid for 3 months.[9,15] Two commonly used iron preparations in children are ferrous sulphate and iron polymaltose complex. Ferrous sulphate raises Hb faster than iron polymaltose complex but has more side effects and less tolerability as compared to iron polymaltose complex.[7,16,5] The side effects of ferrous sulphate include nausea, vomiting, abdominal pain, constipation, diarrhea and staining of teeth.[16]

So we need such iron preparation which rapidly increases Hb level with good tolerability and fewer side effects. One such preparation is ferrous bisglycinate which is an amino acid chelate. It has higher bioavailability (90.9%) as compared to ferrous sulphate (26.7%).[17,18] This is because it does not form insoluble compounds with iron absorption inhibitor found in high quantity in cereal-based diets like phytates, oxalates, and tannins.[6]

Trials of ferrous bisglycinate versus ferrous sulphate in pregnant women showed that ferrous bisglycinate raises Hb faster and has high compliance due to fewer side effects.[19]

One study in children showed that although Hb increases significantly in both ferrous sulphate and ferrous bisglycinate group plasma ferritin which represents iron stores in the body increases significantly only in ferrous bisglycinate group.[17]

To date, no study has been conducted in Pakistan to compare the efficacy of ferrous sulphate with ferrous bisglycinate for the treatment of newly diagnosed IDA in children. Therefore, we are going to conduct this study to compare the efficacy of ferrous sulphate with ferrous bisglycinate for the treatment of iron deficiency anemia in children.

Material & Methods

After seeking permission from the Institutional Ethics Review Board of Pakistan Institute of Medical Sciences (PIMS), Islamabad, this randomized controlled trial was done at Children Hospital's OPD of PIMS, from July 2015 to June 2016. Children of either gender with age ranging from 6 months to 60 months who were recently diagnosed as having IDA with serum Hb levels between 7 and 10.9 g/dl, MCV < 70, MCHC < 20p g/dl; Serum ferritin <10 µg/L were included in the study. Children who have β thalassemia trait, chronic inflammatory diseases, renal insufficiency, active infections, or have been treated with drugs that interfered with iron absorption were excluded from our study.

Total 136 children (68 in each group) were taken as sample size by using WHO sample size calculator with following values of calculations; Level of significance = 5%, Power of test = 80%, Mean Hb P1 = $2.5^{17}\pm1.31$, Mean Hb P2=$1.8^{17}\pm1.59$, Pooled SD = 1.45.

A total of 136 children fulfilling the above-mentioned inclusion criteria were enrolled in the study by using systematic sampling. A computer-generated table of random numbers was used to randomize the enrolled children into two study groups; ferrous sulphate as group 1 and ferrous bisglycinate as group 2. Demographic features such as age and gender were asked and noted on a specially designed proforma. Children randomized to group 1 were advised syrup ferrous sulphate with a daily dose of 5 mg of iron/kilogram of body weight in 2 divided doses for 12 weeks. Children randomized to group 2 were advised syrup ferrous bisglycinate with a daily dose of 5 mg of iron/kilogram of body weight in 2 divided doses for 12 weeks.

Afterward, all the children in both the study groups were sent home with the advice of a follow-up visit

after 4 weeks of starting iron therapy. On 4 week follow up visit, history regarding the compliance of the patient to iron supplementation and any of the associated side effects was asked from mothers/ caregivers and advised another follow-up visit after 12 weeks of starting iron therapy. In this 2nd follow up visit, a blood sample was obtained from each enrolled child to examine the serum Hb levels. All the laboratory data was recorded on specially designed proforma and analyzed using SPSS version 20. For continuous variables such as age and Hb (at baseline, at 12 weeks and the increase in Hb) mean ± standard deviation was calculated. Frequencies and percentages were measured for categorical variables such as gender. For comparison of the increase in Hb between the two study drugs, the Student t-test was used and p-values were obtained. P-value ≤0.05 was considered significant.

Results

In this study 136 children with IDA were enrolled, 68 in each group. The mean age of children was 24±1.26 months in the ferrous sulphate group while it was 25±1.74 months in the ferrous bisglycinate group. In the ferrous sulphate group, 39 (57%) children were male and 29 (43%) children were female. Whereas in the ferrous bisglycinate group 40 (59%) children were male and 28 (41%) children were female.

Baseline serum Hb and post-treatment serum Hb were analysed in both groups showing the more level of rising in ferrous bisglycinate group than ferrous sulphate group over the same period as shown in Table 1.

Table 1: Comparison between Ferrous Sulphate and Ferrous Bisglycinate Groups

Parameters	*Ferrous sulphate Mean±SD*	*Ferrous bisglycinate Mean±SD*	*p-value*
Baseline Hb (g/dl)	8.7±1.64	8.0±1.49	0.995
Post Treatment Hb (g/dl)	10.5±0.81	10.5±0.22	0.500
Increase in Hb (g/dl)	1.8±1.59	2.5±1.31	0.0033

Discussion

Iron deficiency is the most common micronutrient deficiency in the world.[6] Our study shows that in the ferrous sulphate group means the age of children was 24±1.26 months while it was 25±1.74 months in the ferrous bisglycinate group. In the ferrous sulphate group, 39 (57%) children were male and 29 (43%) children were female. Whereas in the ferrous bisglycinate group 40 (59%) children were male and 28 (41%) children were female. Baseline serum Hb analysis shows that in the ferrous sulphate group means Hb level was 8.7 ±1.64 while in ferrous bisglycinate groups mean Hb level was 8.0 ±1.49. Post-treatment serum Hb analysis shows that in the ferrous sulphate group means Hb level was 10.5 ±0.81 and in ferrous bisglycinate group mean Hb level was 10.5 ±0.22. It shows that Hb raises more with ferrous bisglycinate than ferrous sulphate over the same period. The findings of the current study are comparable to other similar studies.

In a study conducted by Duque et al on school children of Mexico City, 200 children with decreased ferritin levels were compared and randomly assigned to two groups. One group was given ferrous sulphate and the other was given ferrous bisglycinate at a dose of 30 mg /day for 12 weeks. Serum ferritin concentration was almost the same in both groups after 1 week of completing iron supplementation but after 6 months of completing iron supplementation; it was significantly higher in ferrous bisglycinate group as compared to ferrous sulphate group.[6]

In another study by Ribeiro and Sigulem showed that ferrous bisglycinate cause a significant increase in Hb in children when given at the dose of 5mg/kg/day. In that study, the effect on serum ferritin concentration was not checked.[20]

Rojas and her colleague did their study on preschool children by giving milk fortified with ferrous sulphate to one group and milk fortified with ferrous bisglycinate to other groups. After 2 months they found a significant increase in serum ferritin in the ferrous bisglycinate group as compared to the ferrous sulphate group (p=0.022). Hb, hematocrit and adverse reactions were the same in both groups.[21]

A study by Pineda et al. showed that although Hb increases significantly in both ferrous sulphate and ferrous bisglycinate group serum ferritin increases significantly only in iron bisglycinate group after 28 days of iron supplementation at the rate of 5mg/kg/day ($P < 0.005$).[17]

Bovell-Benjamin et al studied college students who were given ferrous sulphate and ferrous bis-glycinate mixed with maize porridge in a breakfast meal. The iron from the ferrous bisglycinate was absorbed 4

times more than that from the ferrous sulfate ($p < 0.05$).[18]

Iost et al. also reported that low Hb concentrations in young children can be increased through daily consumption of fluid milk fortified with 3 mg of ferrous bisglycinate.[22]

Various studies show that ferrous bisglycinate has lesser gastrointestinal side effects than ferrous sulphate. Coplin et al reported that ferrous bisglycinate has better tolerability as compared to ferrous sulphate.[23]

Although the current study shows that ferrous bisglycinate is better in terms of improvement in Hb level. However, this study has a few limitations. Serum ferritin levels which are more significant tests for the evaluation of IDA could not be performed after completion of therapy. The study would have become more powerful if the tolerability of both forms of iron was assessed and compared.

It is suggested that further studies should be done on related research areas so that the efficacy and tolerability of newer iron preparations are further evaluated.

Conclusion

Newer iron preparation, ferrous bisglycinate is a better treatment option than conventional preparations of ferrous sulphate for increasing Hb in IDA in children.

Acknowledgements

We are thankful to all patients and their parents who participated in our study.

References

1. Janus J. Evaluation of Anemia in Children. Am Fam Physician [Internet]. 2010;81(12):1462–71. Available from: www.aafp.org/afp.
2. Ahsan S, Noether J. The Harriet Lane handbook. 21st ed. Flerlage J, Engorn B, editors. Philadelphia: Elsevier; 2017. 1272 p.
3. Sills R. Nelson Textbook of Pediatrics. 20th ed. Kliegman RM, Stanton BF, Schor NF, editors. Philadelphia: Elsevier; 2016. 3473 p.
4. Afzal M, Qureshi SM, Lutafullah M, Iqbal M, Sultan M, Khan SA. 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. J Pak Med Assoc. 2009 Nov 15;59(11):764-8.
5. Mahmood T. Comparison of Ferrous Sulphate with Iron Polymaltose in Treating Iron Deficiency Anaemia in Children. Journal of Rawalpindi Medical College. 2017 Dec 30;21(4):376-9.
6. Duque X, Martinez H, Vilchis-Gil J, Mendoza E, Flores-Hernández S, Morán S, Navarro F, Roque-Evangelista V, Serrano A, Mera RM. Effect of supplementation with ferrous sulfate or iron bis-glycinate chelate on ferritin concentration in Mexican schoolchildren: a randomized controlled trial. Nutrition journal. 2014 Dec 1;13(1):71.
7. Akhtar S, Ahmed A, Ahmad A, Ali Z, Riaz M, Ismail T. Iron status of the Pakistani population-current issues and strategies. Asia Pacific Journal of clinical nutrition. 2013;22(3):340.
8. Powers JM, Buchanan GR, Adix L, Zhang S, Gao A, McCavit TL. Effect of low-dose ferrous sulfate vs iron polysaccharide complex on hemoglobin concentration in young children with nutritional iron-deficiency anemia: a randomized clinical trial. Jama. 2017 Jun 13;317(22):2297-304. DOI:10.1001/jama.2017.6846
9. De□Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane Database of Systematic Reviews. 2011(12). https://doi.org/10.1002/14651858.CD009085.pub2
10. Balarajan Y, Ramakrishnan U, Özaltin E, Shankar AH, Subramanian SV. Anaemia in low-income and middle-income countries. The lancet. 2011 Dec 17;378(9809):2123-35. https://doi.org/10.1016/S0140-6736(10)62304-5
11. Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Poorer behavioral and developmental outcome more than 10 years after treatment for iron deficiency in infancy. Pediatrics. 2000 Apr 1;105(4):e51. DOI: https://doi.org/10.1542/peds.105.4.e51
12. Lukowski AF, Koss M, Burden MJ, Jonides J, Nelson CA, Kaciroti N, Jimenez E, Lozoff B. Iron deficiency in infancy and neurocognitive functioning at 19 years: evidence of long-term deficits in executive function and recognition memory. Nutritional neuroscience. 2010 Apr 1;13(2):54-70. https://doi.org/10.1179/147683010X12611460763689
13. Sajid A, Ikram MA, Shahid HM, Saeed SM. Iron Deficiency Anemia in Children; Common But Commonly Missed. Pak Pediatr J [Internet]. 2014;38(2):91–5.
14. Saeed T. Association of iron deficiency anaemia and febrile seizures in children. Journal of Rawalpindi Medical College. 2013 Dec 30;17(2):175-7.
15. World Health Organization, World Health Organization. Iron deficiency anaemia: Assessment. Prevention and Control. A guide for programme managers. Geneva: WHO. 2001:99.
16. Khalid J, Ahmed MM, Khalid M, Butt MA, Akhtar KM. IRON DEFICIENCY ANEMIA; COMPARISON OF EFFICACY OF FERROUS SULPHATE WITH IRON POLYMALTOSE COMPLEX FOR TREATMENT OF IRON DEFICIENCY ANEMIA. Professional Medical Journal. 2018 Apr 1;25(4).
17. Pineda O, Ashmead HD. Effectiveness of treatment of iron-deficiency anemia in infants and young children with ferrous bis-glycinate chelate. Nutrition. 2001 May 1;17(5):381-4. https://doi.org/10.1016/S0899-9007(01)00519-6
18. Bovell-Benjamin AC, Viteri FE, Allen LH. Iron absorption from ferrous bisglycinate and ferric trisglycinate in whole maize is regulated by iron status. The American journal of clinical nutrition. 2000 Jun 1;71(6):1563-9. https://doi.org/10.1093/ajcn/71.6.1563
19. Abbas AM, Abdelbadee SA, Alanwar A, Mostafa S. Efficacy of ferrous bis-glycinate versus ferrous glycine sulfate in the treatment of iron deficiency anemia with pregnancy: a randomized double-blind clinical trial. The Journal of Maternal-Fetal & Neonatal Medicine. 2019 Dec 17;32(24):4139-45. https://doi.org/10.1080/14767058.2018.1482871
20. Ribeiro LC, Sigulem DM. Tratamento da anemia ferropriva com ferro quelato glicinato e crescimento de crianças na primeira infância. Revista de Nutrição. 2008 Oct;21(5):483-90. https://doi.org/10.1590/S1415-52732008000500001

21. Rojas ML, Sánchez J, Villada Ó, Montoya L, Díaz A, Vargas C, Chica J, Herrera AM. Effectiveness of iron amino acid chelate versus ferrous sulfate as part of a food complement in preschool children with iron deficiency, Medellín, 2011. Biomédica. 2013 Sep;33(3):350-60. doi: http://dx.doi.org/10.7705/biomedica.v33i3.775
22. Iost C, Name JJ, Jeppsen RB, DeWayne Ashmead H. Repleting hemoglobin in iron deficiency anemia in young children through liquid milk fortification with bioavailable iron amino acid chelate. Journal of the American College of Nutrition. 1998 Apr 1;17(2):187-94. https://doi.org/10.1080/07315724.1998.10718745
23. Coplin M, Schuette S, Leichtmann G, Lashner B. Tolerability of iron: a comparison of bis-glycino iron II and ferrous sulfate. Clinical therapeutics. 1991;13(5):606-12.