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Original Article

Efficacy of Ferrous Bis-Glycinate versus Ferrous Sulphate in Children with Iron Deficiency Anemia

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ABSTRACT

Iron deficiency anemia is a common pediatric disease and oral iron supplementation is the usual treatment. Newer formulations has been developed to treat iron deficiency anemia in children. **Objective:** To compare the efficacy of ferrous Bis-Glycinate in children with iron deficiency anemia to the conventional therapy with ferrous sulphate. **Methods:** In this open labelled prospective clinical trial was performed in children with iron deficiency anemia. Two groups were made, one group was given ferrous sulphate and the other group ferrous bis-glycinate at a dose of 5 mg/kg/day, single daily dose. Patient were followed 04 weekly till 12 weeks and then baselines reviewed. **Results:** Out of these total 108 children, 64 (59.3%) were male while the remaining 40.7% were female, with mean age was 27.48 in months with SD of 14.1. Iron therapy succefully raised Hb by 3.49 gm/dl as a whole with in Iron Bis -glycinate group as 3.85d/dl while 3.13gm /dl in ferrous sulphate group. The frequency of gastrointestinal adverse symptoms were less in bis-glycinate group. **Conclusions:** It was concluded that ferrous bis-glyicante has better efficacy to ferrous sulphate in term of Hb rising and has less gastrointestinal side effects.

INTRODUCTION

Anaemia, a condition in which the haemoglobin of the blood is lower than normal, is primarily a nutritional problem in most developing countries due to the economic, social, and other negative consequences of this condition [1]. Anaemia results from poor nutritional status of children in Pakistan [2]. Anaemia is caused by a lack of one or more essential nutrients such as iron, vitamin B12, or folic acid. Using haemoglobin levels as a criterion for iron deficiency anaemia, serum haemoglobin levels of 7–10.9 and 7 g/dl represent moderate and severe anaemia, respectively [3]. Iron deficiency is the most frequent malnutrition, affecting up to 20% of the global population, according to the WHO. It occurs when dietary iron fails to meet the body's iron requirements. Reduced iron transport to target areas such as the liver parenchyma, bone marrow, and muscle myoglobin impairs iron-dependent activities like erythropoiesis. A decrease in the quantity of red blood cells may be accompanied by a drop in mean cell size (microcytic anaemia). The net result is decreased oxygen carrying capacity and, as a result, tissue hypoxia [4]. In Pakistan, the prevalence of iron deficiency anemia ranged from 64% to 79% in children aged 5 years [3]. Common causes of iron deficiency include insufficient dietary iron intake, insufficient iron

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utilization during chronic and inflammatory diseases, impaired iron absorption, or excess iron loss. The cause of iron deficiency anemia is avoidable and reversible in the vast majority of cases by increasing iron supplementation or reducing iron loss [2]. It is common in children during rapid growth and erythroid expansion, particularly in premature or low-birth-weight babies, toddlers, and preschool children, and during adolescence. Iron deficiency anemia is linked to delayed cognitive development in preschool-aged children as well as lower work productivity and cognitive and behavioral issues in adults [5-13]. Although ferrous sulfate is the most often used iron salt for oral delivery, it is known to cause intestinal side effects such as nausea, vomiting, abdominal pain, constipation, and diarrhea in many users. Various novel iron salts are being introduced that are claimed to have minimal gastrointestinal intolerance and thus higher patient compliance [14]. A few of these novel preparations are also reported to boost hemoglobin levels faster and improve iron storage better than traditional ferrous sulfate and ferrous fumarate. Ferrous Bis-glycinate is one of them. Ferrous Bis-glycinate is an amino acid chelate that has shown great efficacy, less gastrointestinal irritation, and its absorption is not hampered by the presence of phytates [2]. A study reported a significant increase in the hemoglobin level from 8.0 g/dl to 10.5 g/dl, a change of 2.5 g/dl with ferrous Bis-glycinate compared to 8.7 g/dl to 10.5 g/dl [15]. In Pakistan, there have been few studies comparing the efficiency of ferrous sulfate. As a result, we will undertake a study to establish the advantages of ferrous Bis-glycinate over ferrous sulfate in terms of change in mean hemoglobin levels after 12 weeks of therapy and gastrointestinal tolerability. The study's findings could provide additional evidence for physicians to use ferrous bis-glycinate as a regular medication for the treatment of iron-deficient anemia in children.

METHODS

It was a Randomized Controlled Trial (RCT) conducted at Lady Reading Hospital's Pediatrics Department in Peshawar for six months following after approval from Institutional Research Board. The sample size was estimated using the WHO sample size calculation using 90% confidence interval, 80% power of test, and mean Hb P2 = 1.86 1.59 (15), Hb P1 = 2.56 1.31 (15). The sample size required each group to have 54 children of iron-deficiency anemia (54 in group 1 and 54 in group 2). Non-probability consecutive sampling was the sampling approach used. Inclusion criteria was a child newly diagnosed with Iron deficiency anemia as per operational definition and has the following features; 1. Age range: 6 to 60 months. 2. Both genders. The following children were excluded from the study; 1. Children with Thalassemia trait. 2. Children with chronic inflammatory disease. 3. Children with renal insufficiency. 4. Children with intestinal surgeries requiring resection. 5. Parents not willing to give informed consent. Before the study conducted, permission from Institutional Research Board was obtained. In order to participate in the study, parents or guardians informed consent was sought. All children aged 6 to 60 months who met the above-mentioned inclusion criteria for iron deficiency anemia presenting to the outpatient department of the hospital were included in the study. A random table generated by a computer for selection of patient to clinical trial group. The enrolled children were randomly assigned to one of two trial groups: ferrous sulfate or ferrous bisglycinate. Group 1 received a daily dose of 5 mg of iron per kilogram of body weight of ferrous sulphate, while group 2 received 5mg/kg of iron of ferrous bisglycinate. Both groups received a daily dose of 5 mg of iron per kilogram of body weight. Characteristics of the population—age and gender—were inquired about and recorded on a specifically developed proforma. Laboratory findings were also recorded in proforma. After every 04 weeks of therapy with ferrous sulphate or ferrous bisglycinate patients were followed in outdoor and checked compliance and adverse effects if they have experienced. After 12 weeks of therapy Hb of all patients were repeated and recorded in the proforma. The difference between the last visit (after therapy) and 1st visit (at the start of therapy) were calculated and recorded. SPSS version 20.0 was used to enter and evaluate the data. Continuous variables, such as age and hemoglobin change were calculated. The frequencies and, for categorical factors such as gender, percentages will be calculated. The Student t test was applied to compare the change in Hb between the two study groups. P-values were calculated. The level of significance p-value < 0.05 was considered. Furthermore, for effect modifiers, comparison will be done by stratifying the child's sex and age. The student t-test was used after stratification.

RESULTS

The total subjects (children with iron deficiency anemia) in this study were 108 divided in two groups equally (54 in either group), one group patients were treated with ferrous sulfate while the other with ferrous Bis-glycinate. Out of these total 108 children (patients), 64 (59.3%) were male while the remaining 40.7% were female, whose mean age was 27.48 in month with SD of 14.1. The frequency of nausea, vomiting and diarrhea after iron therapy were 5(4.6%), 12(11.1%) and 32(29.6%) respectively. After the iron therapy the mean change in Hb level in g/dl as whole was 3.49 with SD of 0.143, while in Group 1 the mean change in Hb level in g/dl was 3.13 with SD of 0.146, while in Group 2

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the mean change in Hb level was 3.85with SD of 0.140, applying the independent t-test the p value is 0.000001 which is significant. More over the chi-square test was used to compare the adverse effects of either therapy which concluded that only 3 patient had complained of nausea taking FeSO4 while 2 patients reported with nausea treated with ferrous Bis-glycinate (p-vale of 0.647), vomiting was noted in 9 patients who were given FeSO4, while in case of ferrous Bis-glycinate therapy only 3 patient had complained of vomiting (p-value (0.066). Similarly with FeSO4 therapy the diarrhea was reported in 21 patients while diarrhea was noted in 11 patients who had taken ferrous Bis-glycinate with 0.035 p-value. Table 1 shows that total subjects (children with iron deficiency anemia) in this study were 108(54 in either group), out of these 64(59.3%) were male while the remaining 40.7% were female. The frequency of nausea, vomiting and diarrhea after iron therapy were 5(4.6%), 12(11.1%) and 32(29.62%) respectively.

Table 1: Frequency and percentage

Variable		Frequency (%)
Gender	Male	64 (59.3)
	Female	44 (40.7)
	Total	108 (100.0)
Nausea	Yes	5 (4.6)
	No	103 (95.3)
	Total	108 (100.0)
Vomiting	Yes	12 (11.1)
	No	96 (88.9)
	Total	108 (100.0)
Diarrhea	Yes	32 (29.62)
	No	76 (70.37)
	Total	108 (100.0)

Table 2 shows that 54 subjects (children with IDA) the mean change in Hb level in g/dl was 3.85 with SD of 0.140 who were given Ferrous Bis-glycinate, while the remaining 54 subject treated with Feso4 the mean change in Hb level was 3.13 with SD of 0.140, applying the independent t-test the p-value is 0.000001 which is significant.

Table 2: Mean change in Hb

Change in HB	Mean ± SD	t-test for Equality of Means p-value
FeSO4	3.133±0.146	.0000001
Iron Bis-glycinate	3.855±0.140	

Table 3 shows that only 3 patient had complained of nausea taking FeSO4 while nausea was reported in 2 patients treated with ferrous Bis-glycinate (p-vale of 0.0647), vomiting was noted in 9 patients who were given FeSO4, while in case of ferrous Bis-glycinate therapy only 3 patient had complained of vomiting (p-value 0.066) similarly with FeSO4 therapy the diarrhea was reported in 21 patients while diarrhea was noted in 11 patients who had taken ferrous Bis-glycinate with 0.035 p-value.

Table 3: Symptoms after iron therapy

Iron therapy	Mean ± SD	Vomiting	Diarrhea
FeSO4	3	9	21
Ferrous Bis-glycinat	2	3	11
P-value	0.0647	0.066	0.035

DISCUSSION

Iron deficiency anemia is widespread in children and has significant impact on their health and development [16]. A proper history, clinical examination, and baseline work up can lead to diagnosis of iron deficiency anemia. Iron supplementation therapy is a successful treatment technique that has been used for a long time [17]. As science advances, attempts are undertaken to create various iron formulations for the treatment of iron deficiency anemia [18]. Our research is part of an effort to find a better treatment option for iron deficient anemia. We compared traditional iron (ferrous sulphate) therapy to a novel preparation (ferrous Bis-glycinate) in our study. Our study found that ferrous Bis-glycinate was more effective than ferrous sulfate in boosting hemoglobin levels in children with IDA to an average of 3.8 g/dl. With a value of 0.000, the p value was significant. Furthermore, ferrous sulfate was associated with higher adverse effects. Vomiting was more common in the ferrous sulfate group (6 patients, approximately 10%) and occurred in only one patient in the Iron Bis-glycinate group. Similarly, diarrhea was detected in 14 patients receiving ferrous sulfate therapy, while diarrhea was noted in 5 patients receiving ferrous Bis-glycinate with a 0.025 p-value. Yasa *et al.*, did a study identical to ours with 103 children ranging in age from 6 months to 17 years with 42 females and 61 boys and mean age of 29 months [19]. Our study has a similar gender ratio of 71 (58%) males and 51 (42%) girls. Yasa *et al.*, go on to say that long-term compliance in infants and children was challenging and that the gastrointestinal side effects of ferrous sulfate were an additional risk factor for poor compliance. The incidence of nausea or abdominal pain is the same in both the iron polymaltose complex (IPC) and ferrous sulfate groups (09, 09); however, nausea or abdominal pain plus constipation was recorded in 13 children in the ferrous sulfate group and just one child in the iron polymaltose group. Large amounts of research have been conducted to compare traditional iron supplements to newer formulations, with mixed outcomes. Similarly, Toblli *et al.*, performed a meta-analysis and discovered that comparing ferrous sulfate to IPC in adults in equal doses raised hemoglobin levels comparable to IPC, which was determined to have comparable efficacy [20]. However, the adverse effects of IPC were much lower than those of

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ferrous sulfate, indicating improved tolerance [17]. A similar trial was undertaken in youngsters by Pineda *et al.*, [14]. They compared iron bis-glycinate to FeSO4. For 28 days, they used 5mg/kg/day of both FeSO4 and Iron Bis-glycinate. There was a significant increase in Hb in both groups, but serum ferritin was significantly higher in children treated with Iron Bis-glycinate, with a p-value of 0.005. FeSO4 had an estimated bioavailability of 26.7%, while ferrous Bis-glycinate had a bioavailability of 90.9%. Their research demonstrated a definite advantage for iron bisglycinate. However, this trial had a small number of patients and lasted only 28 days a shorter duration than usually required for IDA [14]. Rosli *et al.*, conducted a comprehensive review and meta-analysis, which revealed that IPC had no advantage over FeSO4 [21]. However, their chosen trials did not include any study that has used Iron Bis-glycinate and did not assess the acceptability of these formulations. In our study, we employed Iron Bis-Glycinate and FeSO4 and found that they were superior to Ferrous sulfate in terms of side effects and tolerability. Our study had limitations in that we conducted it on a hospital-based small sample without interfering with their dietary routines.

CONCLUSIONS

Iron Bis-glycinate has better efficacy in rising haemoglobin (3.8gm/dl) in children with iron deficiency anemia as compared to ferrous sulphate (3.14gm/dl). Similarly tolerability was better for iron Bis-Glycinate as compared to ferous sulphate as diarrhea was not in 9% with ferrous Bis-Glycinate and 26% with ferrous sulphate. So newer iron formulation makes it better treatment option.

Authors Contribution

Conceptualization: AK
Methodology: SA
Formal analysis: I, AA, ZR
Writing-review and editing: AK, LM, I, SA, AA, ZR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The author declares no conflict of interest.

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REFERENCES

[1] Nisar YB, Aurangzeb B, Hazir T. Nutritional status of hospitalized children with nutritional anaemia: a cross sectional study. Annals of Pakistan Institute of Medical Science. 2013; 9(3): 122-5.

[2] Santiago P. Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview. The Scientific World Journal. 2012 Oct; 2012: 846824. doi: 10.1100/2012/846824.

[3] 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 Jan; 22(3): 340-7.

[4] Zariwala MG, Somavarapu S, Farnaud S, Renshaw D. Comparison study of oral iron preparations using a human intestinal model. Scientia Pharmaceutica. 2013 Dec; 81(4): 1123-40. doi: 10.3797/scipharm.1304-03.

[5] Baird-Gunning J and Bromley J. Correcting iron deficiency. Australian Prescriber. 2016 Dec; 39(6): 193. doi: 10.18773/austprescr.2016.069.

[6] Taghvaei T, Fakheri H, Sartip MA, Mohammadpour RA, Maleki I. Role of upper and lower gastrointestinal endoscopy in investigating the etiologies of iron deficiency anemia in postmenopausal women. Govaresh. 2017 May; 22(2): 119-25.

[7] Rizzo S. Iron requirements in pregnancy. Australian Midwifery News. 2022 Dec; 31(1): 46-7.

[8] Balendran S and Forsyth C. Non-anaemic iron deficiency. Australian Prescriber. 2021 Dec; 44(6): 193. doi: 10.18773/austprescr.2021.052.

[9] Habib MA, Black K, Soofi SB, Hussain I, Bhatti Z, Bhutta ZA, *et al.* Prevalence and predictors of iron deficiency anemia in children under five years of age in Pakistan, a secondary analysis of national nutrition survey data 2011–2012. PloS One. 2016 May; 11(5): e0155051. doi: 10.1371/journal.pone.0155051.

[10] Albaroudi IN, Khodder M, Al Saadi T, Turk T, Youssef LA. Prevalence, diagnosis, and management of iron deficiency and iron deficiency anemia among Syrian children in a major outpatient center in Damascus, Syria. Avicenna Journal of Medicine. 2018 Jul; 8(03): 92-103. doi: 10.4103/ajm.AJM_169_17.

[11] Zahmatkeshan M, Fallahzadeh E, Najib K, Geramizadeh B, Haghighat M, Imanieh MH. Etiology of lower gastrointestinal bleeding in children: a single center experience from southern iran. Middle East Journal of Digestive Diseases. 2012 Oct; 4(4): 216.

[12] Joshi R, Shrestha DB, Shah DR, Khadka S. Iron Deficiency Anemia: A profile of a tertiary care hospital. Journal of Advances in Internal Medicine. 2018 Apr; 7(1): 1-5. doi: 10.3126/jaim.v7i1.19575.

[13] Sarakul O, Kotepui M, Marasa R, Thepwarin W. Anemia and iron deficiency anemia in high school girls in Nakhon Si Thammarat, Thailand. Journal of Health Science and Medical Research. 2018 Aug; 36(3): 197-204. doi: 10.31584/jhsmr.2018.36.3.11.

DOI:http://doi.org/10.54393/pjhs.v4i11.1128

[14] Parveen A, Raja NF, Khan IM, Shaheen H, Imran M, Ahmed RS. Comparison of conventional and newer iron preparations for the treatment of iron deficiency anaemia in children. Journal of Rawalpindi Medical College. 2020 Jun; 24(2): 1160. doi: 10.37939/jrmc.v24i2.1160.

[15] Pineda O and Ashmead HD. Effectiveness of treatment of iron-deficiency anemia in infants and young children with ferrous bis-glycinate chelate. Nutrition. 2001 May; 17(5): 381-4. doi: 10.1016/S0899-9007(01)00519-6.

[16] Natekar P, Deshmukh C, Limaye D, Ramanathan V, Pawar A. A micro review of a nutritional public health challenge: iron deficiency anemia in India. Clinical Epidemiology and Global Health. 2022 Mar; 14: 100992. doi: 10.1016/j.cegh.2022.100992.

[17] Mantadakis E, Chatzimichael E, Zikidou P. Iron deficiency anemia in children residing in high and low-income countries: risk factors, prevention, diagnosis and therapy. Mediterranean journal of hematology and infectious diseases. 2020 Jul; 12(1): e2020041. doi: 10.4084/MJHID.2020.041.

[18] Kontoghiorghes GJ, Kolnagou A, Demetriou T, Neocleous M, Kontoghiorghe CN. New era in the treatment of iron deficiency anaemia using trimaltol iron and other lipophilic iron chelator complexes: historical perspectives of discovery and future applications. International Journal of Molecular Sciences. 2021 May; 22(11): 5546. doi: 10.3390/ijms22115546.

[19] Yasa B, Agaoglu L, Unuvar E. Efficacy, tolerability, and acceptability of iron hydroxide polymaltose complex versus ferrous sulfate: a randomized trial in pediatric patients with iron deficiency anemia. International Journal of Pediatrics. 2011 Sep; 2011: 524520. doi: 10.1155/2011/524520.

[20] Toblli JE and Brignoli R. Iron (III)-hydroxide polymaltose complex in iron deficiency anemia. Arzneimittelforschung. 2007; 57(06): 431-8. doi: 10.1055/s-0031-1296692.

[21] Rosli RR, Norhayati MN, Ismail SB. Effectiveness of iron polymaltose complex in treatment and prevention of iron deficiency anemia in children: a systematic review and meta-analysis. PeerJ. 2021 Jan; 9: e10527. doi: 10.7717/peerj.10527.