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Iron Bisglycinate versus Sucrosomal Iron in Prevention of Iron Deficiency Anemia in Pregnancy: A Randomized Controlled Clinical Trial

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ABSTRACT

Background: Pregnant women with anemia, especially those with severe anemia, run the risk of having poor physical activity levels, higher maternal morbidity, and increased death. Also, their newborns experience adverse effects such as perinatal mortality, intrauterine growth restriction, premature delivery, low birth weight, and fetal anemia.

Objective: The aim of the current study was to compare the bioavailability, safety, efficacy and hematological responses to oral ferrous bisglycinate supplementation and sucrosomal iron in the treatment of iron deficiency anemia (IDA) in pregnant women.

Patients and methods: A clinical trial was conducted at Antenatal Care Outpatient Clinic of Zagazig University Hospitals. The clinical trial included 66 oregnant women in their second and third trimester with IDA (hemoglobin level ≤10 g/dl). Participants were divided two groups; Group 1included cases who received ferrous bisglycinate supplementation and Group 2 included cases who received sucrosomal iron therapy. All Pregnant women were subjected to a full medical history, physical examination, and laboratory testing, including CBC, iron, ferritin, and total iron binding capacity (TIBC).

Results: In groups I and II, there was significant increase of RBCs, hemoglobin, HCT%, MCV, MCHC and ferritin, iron and TIBC at final values compared to the corresponding basal value. The improvement of CBC findings, ferritin, iron and TIBC was more significant in group 2 cases who received sucrosomal iron therapy.

Conclusion: Oral sucrosomal iron therapy is more effective and acceptable than oral iron salts for the treatment of IDA.

Keywords: Iron Bisglycinate, Sucrosomal Iron, Iron Deficiency, Anemia, Clinical trial, Zagazig University.

INTRODUCTION

Pregnant women with anemia, especially those with severe anemia, run the risk of being inactive and having higher rates of maternal morbidity and mortality. Also, their newborns experience adverse effects such as perinatal mortality, intrauterine growth restriction, premature delivery, low birth weight (LBW), and fetal anemia [(1)]. The most frequent causes of anemia in pregnant women are iron and folate deficits [(2)].

If caught early enough, anemia is mostly treatable and easily curable. Treatment of the underlying causes, return of hemoglobin concentration to normal ranges, and prevention and management of consequences all contribute to effective management of anemia [(3)].

Iron supplements, such as ferrous bis-glycinate, are typically started in the second trimester of pregnancy. Unfortunately, traditional iron's therapeutic effectiveness is constrained by inadequate absorption. Moreover, a higher prevalence of anemia in the second part of pregnancy is linked to unfavorable side effects such gastrointestinal (GI) intolerance, dietary interactions, and non-compliance with iron therapy [(1)].

Even though intravenous (IV) iron formulations are getting safer, venous access and infusion monitoring are still necessary and there is a risk of infusion and hypersensitivity reactions [(1)].

An novel oral iron formulation called Sucrosomial® Iron (SI) protects ferric pyrophosphate with a phospholipid bilayer and a sucrester matrix (sucrosome), which is then absorbed via para-cellular and trans-cellular pathways (M cells). Because to its high iron bioavailability and great gastrointestinal tolerance, SI has unique structural, physicochemical, and pharmacokinetic properties [(4)]. The examination of the existing evidence suggests that oral SI iron, which is more effective and acceptable than oral iron salts, is a viable alternative for treating iron deficiency anemia (IDA). As a result, oral SI becomes a good first treatment choice for IDA, especially for patients who are intolerant to iron salts or for whom iron salts are ineffective [(5)] .

Moreover, SI should be taken into account as a substitute for IV iron for initial and/or ongoing treatment in anemic pregnant individuals [(6)]. In order to treat pregnant women with iron deficiency anemia, this study compares the bioavailability, safety, efficacy, and hematological responses to sucrosomal iron and oral ferrous bisglycinate supplementation.

The aim of the current study was to compare the bioavailability, safety, efficacy and hematological responses to oral ferrous bisglycinate supplementation and sucrosomal iron in the treatment of IDA in pregnant women.

PATIENTS AND METHODS

A randomized controlled clinical trial was conducted at Antenatal Care Outpatient Clinic of Zagazig University Hospitals. The clinical trial included 66 oregnant women in their second and third trimester with IDA (hemoglobin level ≤10 g/dl), from April 2022 to October 2022.

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Inclusion criteria: Age: 18- 40 years. Singleton pregnancy. No prior iron supplements in the current pregnancy. Hemoglobin level ≤ 10 g/dL.

Exclusion criteria: Allergy to iron. Multiple pregnancies. History of obstetric hemorrhage in the present pregnancy. Continuous blood loss from any source. History of blood disease (e.g., chronic hemolytic anemia). History of chronic renal, liver disease or chronic peptic ulcer. Malabsorption syndrome.

Eligible cases were randomly divided into two equal groups, with the planned iron therapy. Group 1included cases who received ferrous bisglycinate supplementation and Group 2 included cases who received sucrosomal iron therapy.
The total iron dose calculated by; Total iron dose = weight (Kg) x [Target Hb (gm/dl) – Actual Hb (gm/dl)] x 0.24+500mg**.**

METHODS

All patients were subjected to a full medical history, including symptoms of iron deficiency anemia e.g., Feeling of weakness, exhaustion, loss of appetite, Palpitation, and dyspnea. In addition, take history about the intake of iron containing foods, or foods inhibits iron absorption, previous treatment, and past medical, obstetric and menstrual history to rule out anemia of chronic disease.

Laboratory testing was done for all participants and included CBC, iron, ferritin, and total iron binding capacity (TIBC). Obstetric ultrasonography was done to ensure fetal vitality and determination of gestational age.

Laboratory investigations were done before starting treatment to confirm that the included patient had IDA and then repeated after 8 weeks and 12 weeks of treatment to show the effect of iron taken on the parameters of laboratory investigation. Patients received instructions to take oral iron after meals, preferred with foods which facilitate iron absorption (e.g., ascorbate, citrate). Included patients received treatment, according to randomization tables. We asked patients to bring back the empty packages to monitor treatment compliance.

Dose and administration: Ferrous bisglycinate supplementation was given 27 mg ferrous bisglycinate oral tablet (27 mg of elemental iron) once daily for 12 weeks.
Sucrosomal iron was given as one oral capsule or sachet containing 30 mg of elemental iron daily for 12 weeks.
Follow up: Any symptoms of iron intake e.g., nausea, vomiting, hypotension and bowel disturbances or pain, etc, or drug reaction, hyper-sensitivity and patient compliance were recorded.

Ethical Considerations:

This study was ethically approved by the Institutional Review Board [IRB] of the Faculty of Medicine, Zagazig University (ZUIRB# 9713/17-8-2022). Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

Microsoft Excel software was used to code, enter, and analyze historical data, basic clinical examinations, laboratory investigations, and outcome measurements. The Statistical Package for Social Sciences (SPSS version 20.0) program was then used to import the data and perform the analysis. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD). Independent sample t-test, Mann-Whitney U test and Paired t test were used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

Table 1 showed no statistical significant difference between the 2 studied groups regarding age.

Table (1): Comparison between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) as regard to patient's age (years).

Variable	Mean	S. D	T test	P value
Group I	25.65	3.46	0.74	0.46
Group II	26.22	3.45		
Total	25.93	3.45		

Table 2 showed that there was significant increase of serum ferritin, iron and decrease of TIBC in Group II in comparison to Group I at 8 weeks evaluation time.

Table (2): Comparison between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) as regard to ferritin, iron and TIBC after 8 weeks.

Variable		Mean	SD	t-test	P value
Serum ferritin (ng/ml)	**Group I**	75.69	3.91	19.29	<0.001*
	Group II	100.58	7.52		
	Total	87.63	14.32		
Iron (ug/dl)	**Group I**	100.52	7.70	4.79	<0.001*
	Group II	108.75	7.64		
	Total	105.64	8.67		
TIBC (ug/dl)	**Group I**	250.38	26.56	3.65	<0.001*
	Group II	270.30	19.20		
	Total	260.84	24.92		

Table 3 showed that there was significant increase of RBCs, hemoglobin, HCT and MCHC in group II in comparison to group I at the final evaluation. On the other hand, there was no significant difference between both groups as regard to MCV at the final evaluation**.** This table revealed that, there was significant increase of serum ferritin, iron and decrease of TIBC in group II in comparison to group I at the final evaluation time when compared to oral iron.

Table (3): Comparison between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) as regard to final (after 12 weeks) CBC findings, ferritin, iron and TIBC.

Variable		Mean	SD	t-test	P value
RBCs X10^6/cc	**Group I**	3.864	0.189	4.59	<0.001*
	Group II	4.051	0.173		
	Total	3.958	0.203		
Hemoglobin (g/dl)	**Group I**	9.685	0.502	5.70	<0.001*
	Group II	10.36	0.555		
	Total	10.022	0.626		
HCT%	**Group I**	31.407	1.441	4.36	<0.001*
	Group II	32.917	1.643		
	Total	32.162	1.713		
MCV	**Group I**	88.675	4.984	1.57	0.12
	Group II	90.35	4.526		
	Total	89.512	4.805		
MCHC	**Group I**	30.272	1.754	2.10	0.039*
	Group II	31.07	1.636		
	Total	30.671	1.732		
Serum ferritin	**Group I**	76.69	3.91	19.29	<0.001*
	Group II	102.58	7.52		
	Total	89.63	14.32		
Iron	**Group I**	102.52	7.7	4.79	<0.001*
	Group II	110.75	7.64		
	Total	106.64	8.67		
TIBC	**Group I**	257.38	26.56	3.65	<0.001*
	Group II	276.30	19.20		
	Total	266.84	24.92		

Table 4 showed that there was significant increase of difference between final and basal values of RBCs, hemoglobin and HCT% in group II in comparison to group I. This table revealed that, there was significant increase of difference between final and basal values of ferritin, iron and decrease of TIBC. In studied groups that was higher in group II.

Table (4): Comparison between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) as regard to difference between final and basal values (change) of CBC findings, ferritin, iron and TIBC.

Difference (final-basal)		Mean	SD	t-test	P value
RBCs X10^6/cc	Group I	0.35	0.075	6.52	<0.001*
	Group II	0.45	0.067		
	Total	0.4	0.088		
Hemoglobin (g/dl)	Group I	1.51	0.53	4.07	<0.001*
	Group II	2	0.53		
	Total	1.76	0.58		
HCT%	Group I	3.59	0.055	5.42	<0.001*
	Group II	4.5	0.00		
	Total	4.04	0.87		
MCV	Group I	6.97	0.83	2.06	0.042*
	Group II	7.77	2.30		
	Total	7.37	1.76		
MCHC	Group I	3.58	0.40	1.25	0.21
	Group II	3.72	0.56		
	Total	3.65	0.48		
Serum ferritin (ng/ml)	Group I	65.89	3.72	19.10	<0.001*
	Group II	91.66	7.67		
	Total	78.78	14.28		
Iron (ug/dl)	Group I	47.15	7.44	4.88	<0.001*
	Group II	54.92	6.78		
	Total	51.03	8.08		
TIBC (ug/dl)	Group I	40.65	2.4	6.05	<0.001*
	Group II	53.75	13.45		
	Total	47.2	11.65		

Table 5 showed that in both groups I and II, there was significant increase of RBCs, hemoglobin, HCT%, MCV and MCHC at final values when compared to the corresponding basal value. These results indicated that, both ferrous bisglycinate and sucrosomal iron had a beneficial effect on CBC findings in treatment of IDA in pregnancy.

Table (5): Paired comparison between basal and final values of CBC findings in group I (ferrous bisglycinate group) and group II (sucrosomal iron group).

Variable		Group I			Group II		
		Mean	SD	Test	Mean	SD	Test
RBCs	Basal	3.51	0.21	t= 29.65	3.59	0.21	t= 42.60
	Final	3.86	0.18	P<0.001*	4.05	0.17	P<0.001*
Hembolgobin	Basal	8.16	0.50	t= 18.07	8.35	0.50	t= 23.83
	Final	9.68	0.51	P<0.001*	10.36	0.55	P<0.001*
HCT%	Basal	27.63	2.41	t= 12.30	28.31	1.68	t= 33.12
	Final	31.40	1.44	P<0.001*	32.91	1.64	P<0.001*
MCV	Basal	81.70	5.32	t= 53.04	82.57	4.39	t= 21.34
	Final	88.67	4.98	P<0.001*	90.35	4.52	P<0.001*
MCHC	Basal	26.68	1.65	t= 56.29	27.34	1.53	t= 41.98
	Final	30.27	1.75	P<0.001*	31.07	1.63	P<0.001*

Table 6 showed that, in both groups I and II, there was significant increase of ferritin, iron and TIBC. These results indicated that, both ferrous bisglycinate and sucrosomal iron had a beneficial effect on ferritin, iron and TIBC in treatment of IDA in pregnancy.

Table (6): Paired comparison between basal and final values of ferritin, iron and TIBC.

Variable		Group I (ferrous bisglycinate group)			Group II (sucrosomal iron group)		
		Mean	SD	Test	Mean	SD	test
Ferritin (ng/ml)	Basal	10.8	0.74	t= 111.83	10.9	0.63	t= 75.15
	Final	76.69	3.91	P<0.001*	102.57	7.52	P<0.001*
Iron (ug/dl)	Basal	55.37	3.21	t= 40.04	55.82	3.07	t= 51.20
	Final	102.52	7.7	P<0.001*	110.75	7.64	P<0.001*
TIBC (ug/dl)	Basal	257.37	26.56	t= 107.01	276.3	24.48	t= 25.25
	Final	216.72	26.31	P<0.001*	222.55	19.20	P<0.001*

Table 7 showed that, iron ferrous bisglycinate was associated with significant increase of epigastric discomfort, constipation nausea and vomiting, metallic taste, than sucrosomal iron. On the other hand, No cases in both groups reported diarrhea, anaphylactic reactions, or itching.

Table (7): Comparison between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) regarding adverse effects.

Variable	Group I (N=33)		Group I (N=33)		Total		X^2	P value
	n	%	N	%	N	%		
Nausea and/or vomiting	3	9%	0	0.0%	3	4.5%	3.11	0.07
Epigastric discomfort	9	27%	0	0..0%	9	13.5%	10.14	0.001*
Constipation	12	36%	0	0.0%	12	17%	14.11	<0.001*
Diarrhea	0	0.0%	0	0.0%	0	0.0%	---	
Metallic taste	3	9%	0	0.0%	3	4.5%	3.11	0.07
Anaphylactic reactions	0	0.0%	0	0.0%	0	0.0%	---	
Itching	0	0.0%	0	0.0%	0	0.0%	---	

DISCUSSION

According to the study's findings, the average age of the subjects was 28 years old of 25.93 years and there was statistically no significant difference between group I (ferrous bisglycinate group) and group II (sucrosomal iron group) (25.65±3.46 vs 26.22±3.45, respectively). Also, Group I (ferrous bisglycinate group) and group II (ferrous bisglycinate group) did not significantly differ from one another II (sucrosomal iron group) regarding as weight, height and BMI.

Our results are supported by **Kochhar *et al.*** [7] who reported that from the third week of treatment, there was a statistically significant difference in the rate of Hb growth between the two groups. Hemoglobin levels changed in a statistically significant way on day 30 (mean Hb rose by 3.1 g/dL in group A and 5.1 g/dL in group B; P=0.002) and in the difference between the two groups' increases in ferritin levels (mean ferritin rose by 61.1 ng/mL in the ferrous bisglycinate group and 85.9 ng/ mL in SI group; P= 0.005). Seven days following the start of treatment, the mean hemoglobin and serum ferritin levels in the SI group were 8.8 g/dL and 36.5 ng/dL, respectively, and 12.8 g/dL and 104 ng/mL, respectively, 30 days later. In contrast to this, the increase in hemoglobin and ferritin levels was noticeably slower in the ferrous bisglycinate group.

In agreement with our results, **Parisi *et al.*** [8] in their study, which focused on pregnant women who weren't anemic and had Hb >10.5 g/dL at 12–14 weeks of gestation, they used 28mg of liposomal iron. The study revealed no variations in hematological parameters but significantly greater ferritin and hemoglobin levels at 28 weeks and in the postpartum period**.**

Regarding the side effects of oral iron, our study showed that iron ferrous bisglycinate was associated with significant increase of epigastric discomfort, constipation, nausea and vomiting, metallic taste, in comparison to sucrosomal iron. On the other hand, no cases in both groups reported diarrhea, anaphylactic reactions, or itching. These outcomes correspond to those mentioned by **Milman** [9] who stated that oral iron supplementation is the preferred preventative measure because to its affordability and safety. Yet, in real life, doctors commonly encounter low compliance, which might result in anemia.

In the present study, the rise of hemoglobin in sucrosomal iron group from the start of the research to its conclusion (4 weeks), was 2.0 g/dl compared to 1.51 g/dl in ferrous bisglycinate group, with significant difference between groups (P<0.001). These outcomes correspond to those mentioned by **Gupta *et al.*** [10] that, on day 28, the mean increase in hemoglobin from baseline was 1.9 gm/dL in the sucrosomal iron group

and 1.3 gm/dL in the ferrous bisglycinate group (p value 0.001). Except from that **Ragip *et al.*** [11] found a 1.2 gm/dL increase in the sucrosomal iron group on day 28.

In line with results of the present study, **Deeba *et al.*** [12] reported that both the oral ferrous a scorbate group and the sucrosomal iron group experienced increases in hemoglobin from baseline to six weeks; however, the increases in hemoglobin in the sucrosomal iron group were greater than those in the oral ferrous a scorbate group at each point of measurement. The sucrosomal iron group's hemoglobin levels varied from baseline 1.72 (SD 0.484) at 2 weeks, 2.18 (SD 0.865) at 4 weeks, 2.89 (SD 0.5989) at 6 weeks compared to oral iron, which is 0.5750 (SD 0.456) at 2 weeks, 1.39 (SD 0.4402) at 4 weeks, and 1.9 (SD 0.302) at 6 weeks. The clinically significant P value of 0.000 indicated that the sucrosomal iron group's hemoglobin levels had increased more than that of the control group.

It had been reported that the gold standard for determining iron insufficiency has been serum ferritin, with a commonly acknowledged cutoff level of 15ng/mL; below which iron reserves are deemed to be depleted [13].

Our results are in agreement with, **Ragip *et al.*** [11] who demonstrated that the day 1 increase in serum ferritin 28 was 5 (SD 2.2) to 11 (SD 11) ng/mL serum ferritin increased in the ferrous bisglycinate group compared to the sucrosomal iron group4.1 (SD 2.5) to 28 (SD 26) ng/mL at 4th week, P-value <0.001. Also, patients who come with iron deficiency anemia at an advanced stage of pregnancy can benefit from the early response brought on by iron sucrose.

Also supporting our study **Mafodda *et al.*** [14] According to their randomized clinical trial, sucrosomal iron (30 mg/day for 2 months) increased hemoglobin from 9.4% to 12.7% in patients with solid ovarian tumors who also had anemia, whereas ferric gluconate (60 mg/day for 2 months) increased hemoglobin from 9.2% to 12.1%.

CONCLUSION

The most common nutritional deficiency illness in pregnant women, according to the findings of the current study is IDA. A unique substance called suprasomal iron has improved palatability, increased bioavailability, and great gastrointestinal tolerance. Oral sucrosomal iron is more effective and acceptable than oral iron salts for the treatment of IDA.

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