Journal of Pharmaceutical Research International

33(45B): 501-509, 2021; Article no.JPRI.73605
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Effect of Oral Iron Therapy in Moderately Affected Anemianic Pregnant Women

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i45B32832
Editor(s):
(1) Dr. Mohamed Fawzy Ramadan Hassanien, Zagazig University, Egypt.
Reviewers:
(1) Niranjan Mayadeo, Kem Hospital, India.
(2) M. Jayanthi, JIPMER, India.
Complete Peer review History: https://www.sdiarticle4.com/review-history/73605

Original Research Article

Received 07 July 2021
Accepted 17 September 2021
Published 11 October 2021

ABSTRACT

In India, Iron deficiency anemia is one of the major causes of maternal deaths, over the past years, various oral and intra muscular & intravenous preparations of iron have been used for correction of iron muscular are associated with significant side effects; Intramuscular (Iron dextran) was used as an alternative to oral iron therapy for those who were not compliant to oral therapy. Iron dextran has a lot of side effects such as fever, arthralgia, even anaphylactic reactions extending to pulmonary edema and even death. Further it is not possible to achieve the target rise in Hemoglobin level in a limited time period, when the patient is approaching term. Whereas Intravenous (Iron sucrose complex) is a relatively new drug which is a BOON to medical therapy and is the BEST OPTION of iron therapy when used as an alternative to oral therapy as it restores iron stores more promptly and is able to raise the hemoglobin to satisfactory level .

Keywords: Maternal deaths; intramuscular; iron sucrose complex; oral iron therapy.

1. INTRODUCTION

Anemia is a condition of low circulating Hemoglobin in which the Hemoglobin concentration has fallen below a threshold lying at 2SDall below the median of healthy population of the same age, sex & stage of pregnancy [1-3]. Anemia in pregnancy is defined by the world

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health organization as a hemoglobin value below 11 g/dl (WHO 1992, 2001 [4-6]. Center for disease control & prevention (1990) defined anemia as 1lg/dl in the 1st & 3rd trimesters and < 10.5 g/dl in the 2nd trimester. Nutritional anemia is believed to be the most widespread nutritional disorders in the world. It essentially affects people in developing countries. According to WHO definition, the "nutritional anemia" encompasses all pathological conditions in which the blood Hemoglobin concentration drops to an abnormally low level owing to a deficiency in one (or) Several essential nutrients, regardless of the causeof this deficiency [7]. The etiology of nutritional deficiency of iron in developing countries is *multifactorial. The* causes *include nutritional* deficiency of iron, folic acid and Vitamin B12, Secondary effects of infections and parasitic infestations [8]. An imbalance occur as a result of low nutrient intake, Poor absorption, Increased demand of nutrients during pregnancy, increased nutrient loss due to repeated pregnancies, decreased inter pregnancy interval & menstruation. Dietary short coming are often associated with low socio economic status and relatedto cooking & dietary habits, local food taboos, ignorance, illiteracy & lack of knowledge regarding nutrition [9]. Increased demand for nutrients is one of the major causes of nutritional anemia during pregnancy [10]. The increased blood volume during pregnancy results in dilution of red cells and a reduction in hemoglobin concentration. This dilutional anemia is potentially accentuated by the increased demands of iron and folic acid leading to anemia. Poor absorption of iron occurs due • to the fact that Indian diet is predominantly cereal based. Though Indian diet has adequate iron content 20 - 25mg/day several factors inhibits absorption, the most important being the phytate from the cereals. Deficiency of ascorbic acid and calcium inhibits iron absorption. Increased demand for nutrients is one of the major causes of nutritional anemia during pregnancy. The increased blood volume during pregnancy results in dilution of red cells and a reduction in Hemoglobin concentration. This dilutional anemia is potentially accentuated by the increased demands of iron & Folic acid leading to anemia [11].

There is increased demand for iron as it is essential for the synthesis of increased Hemoglobin required for the greater maternal blood as well as for the storage of iron in the fetus. When the mother does not meet this demand, she may develop features of Iron deficiency anemia. Previous studies showed that intra venous application is an effective method for iron administration, besides, many women, did not like such invasive method. In such a case, the parenteral and oral iron preparations are another alternative methods that usually followed up. The present study aimed to compare both methods based on the retrospective evaluation.

2. MATERIALS AND METHODS

The "study of outcome of the treatment with intravenous iron sucrose in moderately anemic pregnant women. 200 antenatal patients with moderate iron deficiency anemia with hemoglobin between 7-10 g/dl were selected and included in this study. This study was conducted to prove that iron sucrose is more effective, safer and well tolerated than various forms of oral iron salts in pregnant women with moderate anemia complicating pregnancy.

TYPE OF STUDY: EXPERIMENTAL STUDY.

INCLUSION CRITERIA

Primi and multi gravida between 28-36 weeks of pregnancy.

Pregnant women with hemoglobin between 7-10 g/dl women with established iron deficiency anemia singleton pregnancy are selected.

GROUP A- PARENTRAL IRON THERAPY - IRON SUCROSE

GROUP B1- ORAL IRON THERAPY- FERROUS SULPHATE.

They were explained about repeating investigations during follow-up visits after a period of 4 weeks. The side effects volunteered by the women were noted. Hemoglobin estimation was done by Sahli's method, which is most practical, cost- effective and commonly used method.

Hemoglobinestimation- Sahli's hemoglobinometer merhod.

Fig. 1. Hemoglobin estimation- Sahli' shemoglobinometer method

O. lN Hcl was sucked by an ordinary pipette was poured into the graduated dilution tube upto 20 mark on % side or 2 marks on g% side. Blood was sucked by hemoglobin pipette transfused to dilution tube containingO. lN Hcl stirred with stirrer. The dilution tube was allowed to stand for 5minutes. The color of the dilution tube was compared with that of the standard in day light. Distilled water is added further to equal the color of the mixture with standard, distilled water is added in succession of 3 - 4drops and each time it was mixed with the stirrer. Towards the final point then number of drops may be reduced to get the right point accurately. The scale was read which gave the hemoglobin as g/dl.

Peripheral smear:

Blood smear was stained with leishman stain, morphology of red cells was noted.

Procedure:

A small drop of capillary blood was placed about 1 or 2 cm from one end of a pre cleaned slide. Immediately, another slide with a smooth edge was placed an angle of 250 and moved backwards to make contact with the drop. The drop of blood should spread out quickly along the line of contact of the spreader with the slide. The blood film was then spread by a rapid, smooth, forward movement of the spreader until all the blood has spread or the edge of the slide is reached. The ideal thickness of the smear was such that there was some overlap of red cells throughout majority of the length of the smear with separation and no distortion towards the tail of the film. The air dried blood smear was fixed by covering the film with acetone free methyl alcohol for 1 min.

Denaturation of proteins is required to prevent hemolysis ofthe RBC'S. The slide was flooded with leishman's stain for 5 min.

Double the volume of distilled water was added and left for 10 min. The slide was washed with distilled water. The slide was air dried and the back of the slide was wiped clean and was observed under the microscope, and the type of the anemia was noted.

Visit II:

Patients were evaluated from baseline to 4 week interval adverse effect if any reported were noted, whether the patient could tolerate oral iron

is noted, and vital like blood pressure and pulse rate noted. The patient should bring back the empty packs of tablets and there were enquired about the color of the stool. At the end of 4 weeks repeat hemoglobin estimation was done. The results and data was analyzed with statistical test. If the hemoglobin at the end of 4 weeks was 11gm% then ferrous sulphate 100mg of elemental iron i.e., 1 tablet is continued till 3 months after delivery. If the Hemogllobin is less than 13gms ferrous sulphate 100mg of elemental iron one tablet twice a day is given till 13gms is reached.

After a period of 4 weeks, the pregnant women were examined clinically and maternal weight was noted. Hemoglobin. hematocrit, MCV, MCHC, S. Ferritin, Peripheral smear were done in both groups to note the improvement in values.

Adverse reaction monitoring:

No direct leading questions were asked to elicit side effects. Only those side effects volunteered by pregnant women, were recorded. They were asked to report immediately if there were any unpleasant symptoms during iron sucrose therapy. This report included a detailed description of the symptoms, time of onset and duration, whether treatment was discontinued and corrective measures taken

3. RESULTS AND DISCUSSION

200 antenatal women after confirming iron deficiency anemia were included in this study and the required dosage of iron was infused intravenously in the form of iron sucrose complex in 100 patients and various forms of oral iron salts in 100 patients.

Table 1. Parity Status

Groups	Parity						Chi Square Test
	3		2		1		
	N	%	N	%	N	%	
Iron sucrose	45	45.0%	39	39.0%	16	16.0%	
Ferrous Sulphate	12	36.4%	12	36.4%	9	27.3%	x2=3.96
Ferrous Gluconate	16	47.1%	12	35.3%	6	17.6%	P=0.68
Ferrous Fumarate	18	54.5%	11	33.3%	4	12.1%	

3.1 Obstetric Score

Table 4 shows distribution of patients according to parity, among the studied patients, number and percentage of antenatal women in each group.

Primi-

45(45%) were in group A,
12(36.4%) were in group B_i,
16(47.1%) were in group B_2,
18 (54.5%) were in group B_3.

Gravida II-

39 (39%) were in group A,
12(36.4%) were in group B_1,
12 (35.3%) were in group B2,
11(35.35) were in group B_3

Gravida III-

16 (16%) were in group A,
9(27.3%) were in group B_1,
6(17.6%) were in group B_2,
4(12.1%) were in group B_3

This was found to be statistically insignificant.

Table 2. Hemoglobin Level

Groups	Hb in Baseline		Hb in 4th Week		Paired t-Test
	Mean	SD	Mean	SD	
Iron sucrose	8.35	.71	9.49	.70	t=38.20 p=0.001 *** significant t=32.12 p=0.001***
Ferrous Sulphate	8.12	.51	8.65	.50	significant
Ferrous Gluconate	8.11	.73	8.63	.73	t=32.90 p=0.001 *** significant t=33.53p=0.001 ***
Ferrous Fumarate	8.24	.68	8.76	.68	significant

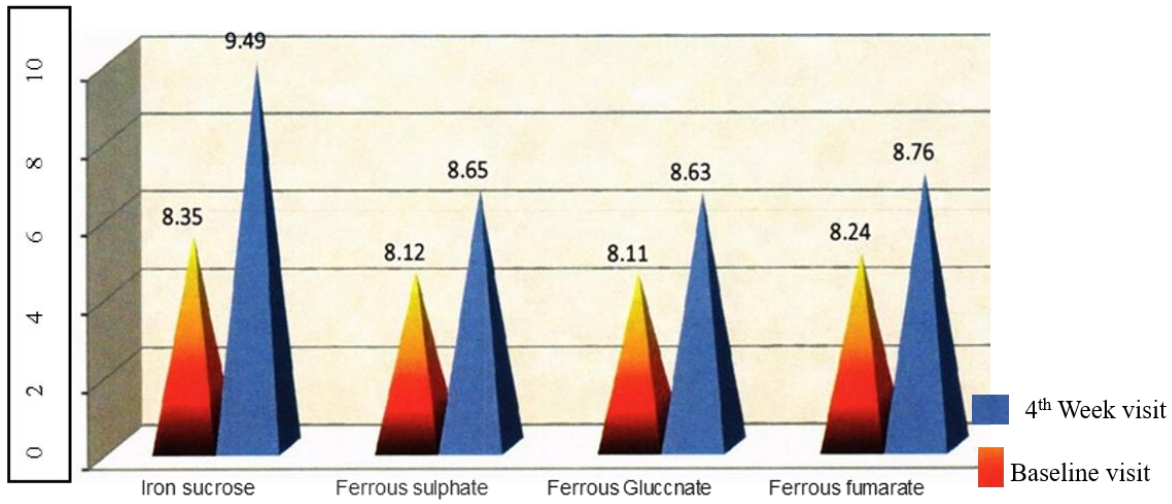

Fig. 2. Showing distribution of patients with Hemoglobin Level

3.2 Change in Hemoglobin Level

Table 3. Hematocrit Level

Groups	PCV in Baseline		PCV in 4th Week		Paired t-Test
	Mean	SD	Mean	SD	
Iron sucrose	28.36	.85	29.38	.85	t=71.48 p=0.001*** significant
Ferrous Sulphate	27.78	.70	27.92	.67	t=2.44 p=0.02* significant
Ferrous Gluconate	28.00	.89	28.15	.89	t=2.39 p=0.02* significant
Ferrous Fumarate	28.21	.96	28.24	.97	t=l.00 p=0.32 not significant

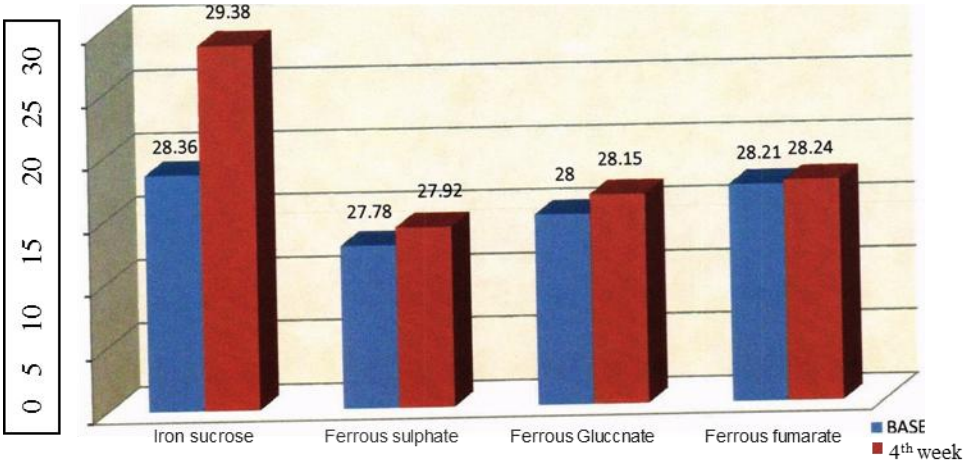

Fig. 3. Showing distribution of patients with hematocrit level

Table 4. MCV Level

Groups	MCV in Baseline		MCV in 4th Week		Paired t-Test
	Mean	SD	Mean	SD	
Iron sucrose	81.08	.77	82.10	.78	t=72.49 p=0.001*** significant
Ferrous Sulphate	80.88	.70	81.00	.66	t=2.10 p=0.04* significant
Ferrous Gluconate	81.00	.74	81.00	.74	t=l.71p=0.09 not significant
Ferrous Fumarate	80.94	.70	80.94	.70	t=l.68 p=0.10 not significant

3.3 Change in MCV Level

Mean Baseline MCV

Group A Iron sucrose: 81.08 +/-0.77 cu microns

Group B1 Ferrous sulphate: 80.88+/-0.70 cu microns

Group B2 Ferrous gluconate: 81+/-0.74 cu microns

Group B3 Ferrous fumarate:80.94+/-0.70 cu microns

Mean MCV after 4 weeks

Group A Iron sucrose: 82.10 +/-0.78 cu microns

Group B1 Ferrous sulphate: 81+/-0.66 cu microns

Group B2 Ferrous gluconate: 81+/-0.74 cu microns

Group B3 Ferrous fumarate: 80.94+/-0.70 cu microns

Change in the mean MCV from baseline to After 4 weeks

Group A Iron. sucrose: 81.08 to 82.10 cu microns and mean rise is l .02cu microns

Group B1 Ferrous sulphate: 80.88 to 81cu microns and mean rise 1s0.12cu microns

Group B2 Ferrous gluconate: 81to 81cu microns and no mean rise

Group B3 Ferrous fumarate: 80.94 to 80.94 cu microns and no mean rise.

P value: 0.0001

The p value is 0.0001 which is statistically significant.

Table 6 shows the mean baseline MCV is 81.08, 80.88, 81, 80.94 cu microns in groups A, B1, B2, B3respectively. The mean MCV after 4 weeks is 82.10, 81, 81, 80.94 cu microns in groups A, B1, B2, B3 respectively. The mean rise in MCV is 1.02, 0.12 cu microns in groups A, B1 and no rise in groups B2, B3. The rise in mean MCV i.e. the difference in the mean MCV before and after treatment was l.02cu microns which is more in intravenous group than in oral groups and the p value is 0.0001 which is statistically significant.

In Ragip et al, Bayoumeu et al, Richa et al, the rise from <82 cu microns to the below value in the table in intravenous group is seen, similar to the present study.

Table 7 shows the mean baseline MCHC is 27.96, 28.42, 28.47, 28.48% in groups A, B1, B2, B3 respectively. The mean MCHC after 4 weeks is 28.97, 28.73, 28.56, 28.55% in groups A, B1, B2, B3 respectively. The mean rise in MCV is 1.01, 0.31, 0.09, 0.07% in groups A, B1, B2, B3• The rise in mean MCHC i.e. the difference in the mean MCHC before and after treatment was 1.01% which is more in theintravenous group than in the oral groups and the p value is 0.0001 which is statistically significant.

Table 5. MCHC Level

Groups	MCHC in Baseline		MCHC in 4th Week		Paired t-Test
	Mean	SD	Mean	SD	
Iron sucrose	27.96	.89	28.97	.87	t=16.16 p=0.001 *** significant
Ferrous Sulphate	28.42	.83	28.73	.91	t=3.73 p=0.01 ** significant
Ferrous Gluconate	28.47	1.02	28.56	1.05	t=l .79p=0.08 not significant
Ferrous Fumarate	28.48	1.09	28.55	1.12	t=l.43 p=0.16 not significant

Table 6. Mean baseline MCV

Studies	Intravenous	Oral	P value
Ragip et al	85.2+/-8 cu microns	86.9+/-6.5 cu microns	P=0.278
Bayoumeu et al.	86.2+/-11.5 cu microns	89.8+/-11.7 cu microns	P<0.001
Richa et al.	88.44+/-3.48 cu microns	82.9+/-2.63 cu microns	P<0.001
Aggarwal et al.	71.28+/-0.9 to	70.1+/-2.9 to 85.8+/-3.9	P<0.001
Present study	81.08+/-0.77 to 82.l+/-0.78	B1 80.88+/-0.7 to 81+/-0.66cum	P=0.001
			P=0.04
		B2 81+/-0.74 to 81+/-0.74cum	P=0.1
		B3 80.94+/-0.7 to 80.94+/-0.7cum	

The rise in the MCHC value is seen more in the intravenous group in Ragip et al, Aggarwal et al group is similar to the present study.

Table 8 shows the maximum number of patients from both the groups had ferritin levels of <20 mcg /1. Mean S.Ferritin among the 200 patients before starting the intravenous therapy was 16.11, 17.02, 16.65, 16.85 mcg/1 in groups A, B1, B2, B3 respectively and the mean S.Ferritin at the end of one month of completing the therapy was 23.45, 1806, 17.56, 18.15 mcg/1 in groups A, Bi, B2, B3 respectively. The rise in mean S.ferritin i.e. the difference in the mean S.Ferritin before and after treatment was 7.34, 1.01,0.91, 1.3 mcg/1 in groups A,B1, B2, B3which is more in the intravenous than in various forms of oral groups. The p value is 0.0001 which is statistically significant.

In the Ragip et al study, Ferritin values were found to be changed significantly across time within both the oral (P value <0.005) and intravenous groups (P value <0.005). The serum ferritin value was higher in the intravenous group than in oral group at each point of measurement. It was 11+/- 11 mcg/1 compared with 28+/-26 mcg/1(P value <0.005) at the fourth week and 18.1+/- 11 mcg/1 compared with 23.7+/-13.8 mcg/1 (P value <0.005) at 8 weeks in the oral and intravenous groups respectively.

In the Bayoumeu et al at the end of 4 weeks there was highly significant difference in the ferritin levels between the 2 groups with iron reserve restored only in the intravenous group (P value <0.0001).

Significant rise in the S.Ferritin value is seen in the intravenous group in the studies conducted by Richa et al and Aggarwal et al. But the present study results are comparable with Ragip et al studyresults.

Table 9 shows that among the 100 antenatal patients in the study group with oral therapy, the side effects were- 36.36% (12/33) had side effects in group B1 in 15.2%(5/33) patients with epigastric pain,6.1%(2/33) in patients with headache, 15.2%(5/33) in patients with vomiting.

Table 7. Mean baseline MCHC

Studies	Intravenous	Oral	Pvalue
Richa et al	28+/-0.86 to 33.87+/-0.86%	28+/-1.13 to 33.3+/-1.13%	P=0.006
Aggarwal et al	26+/-1.73 to 33.1+/-0.97%	25.6+/-2.06 to 32.08+/-l .41%	P=0.0009
Present study	27.96+/-0.89 to 28.97+/-0.87%	B1 28.42+/-0.8 to 28.73+/-0.9% B2 28.47+/- l. 02 to 28.56+/-l .05% B3 28.48+/-l .09 to 28.55+/-l.12%	P=0.001 P=0.08 P=0.16

Table 8. Compar ative study

Studies	Intravenous	Oral	Pvalue
Ragip et al	5+/-2.2 to 28+/-26 mcg/1	4.1+/-2.5 to 11+/-1 lmcg/l	P=0.095
Bayoumeuet al	6.5+/-2.5 mcg/1	8.0+/-4 mcg/1	P<0.001
Richa et al	46.57+/-14.12 mcg/1	13.28+/-5.3 lmcg/l	P<0.001
Aggarwal et al	9.44+/-3.01 to 295.5+/-45. l	10+/-l.9 to 160.8+/-33.lmcg/l	P<0.001
Present study	16.11+/-1.67 to 23.45+/-l.64	B117.02+/-l.35 to 18.03+/-l .33 B216.65+/- l. 52 to 17.56+/-1.54 B316.85+/- 1.44 to 18.15+/-2.28	P=0.001 P=0.001 P=0.001

Table 9. Gastrointestinal side effects

Studies	Intravenous	Oral	P value
Ragip et al	6(13.3%) Epigastric Pain, 1(2.2%) Arthralgia	13(28.9%) Epigastric Pain, 4(8.9%) Diarrhea	
Surraiya et al	17(34%)Nausea, 9(18%) Metallic Taste	23(46%) Constipation	
Agarwal et al	1(4%) Fever 4(16%) Altered Taste 1(4%) Arthritis 1(4%) Thrombophlebitis	2(8%) Nausea 5(20%) Diarrhea 2(8%) Constipation 3(12%) Gastritis	
Present Study	1(1%)Chills and Rigor 1(1%)Nausea and Vomiting	B1-5 (15.2%) Epigastric Pain, 2(6.1%) Headache, 5(15.2) Nausea B2 -3 (8.8%) Epigastric Pain, 2(5.9%) Headache, 4(11.8%) Nausea B3-1(3%) Epigastric Pain, 3(9.09%) Nausea and Vomiting	P=0.001

In group B2 they were 26.5% (9/34) with side effects 8.8% (3/34) with epigastric pain, 5.9% (2/34) with headache and 11.8%(4/34) with vomiting.

In group B3 they were 27.3% (9/33) with side effects 3% (1/33) had epigastric pain and 9.09% (3/33) had vomiting.

Patients with no side effects were in group B163.63%(21/33), in group B2 73.5% (25/34), in group B387.88%(29/33).

4. DISCUSSION

Among the I00 antenatal patients in this study group with intravenous iron therapy, the side effects were very minimal and seen in only 2% (2/100). They were nausea/ vomiting in 1% (I /100) patients and chills and rigors in I% (1/100). There were no anaphylactic reactions noted in the study group. There were no adverse effects noted in 98% (98/100) of the patients. The p value is 0.0001 which_ is statistically significant. There was no hemodynamic disturbance observed either during infusion or after infusion .There were no serious adverse effects in the study .Same observations reported in the other studies like Al-Momen et al, Ragip et al, Surraiya et al and Agarwal et al without any serious adverse effects.

In the Ragip et al study the mean hemoglobin and the ferritin levels throughout the treatment were significantly higher in the intravenously administered iron group than orally administered iron groups.

In the present study regarding the side effect gastrointestinal side effects were more common in the oral group than the parenteral group. The study drugs were well tolerated in all the groups. All those patients who complained epigastric pain were asked to take the tablet along with food, constipation was managed by asking the patient to take high fibre diet. Vomiting and diarrhea subsided within 3 to 4 days by itself no specific medication was given to the patient to stop that recurrence and education about anemia was given to all those patient who complained of side effect. In a country like ours where anemia is widely prevalent, anemia can be cured with ferrous sulphate which is available free of cost in all hospitals and Primary Health Centres.

5. CONCLUSION

As a conclusion, only oral iron sucrose appears to restore iron reserves in case of severe deficiency with a statistical difference at any time of the treatment period. Further the side effects were minimal with parenteral group when compared with the oral group in all the studies.

ETHICAL APPROVAL

After Attaining Ethical Committee Clearence was conducted in Department of Obstetrics & Gynecology, Sri Lakshmi Narayana Institute of Medical Sciences, during the period between NOVEMBER 2011-SEPTEMBER 2013.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle4.com/review-history/73605