IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 14, Issue 1 Ver. II (Jan. 2015), PP 52-60
www.iosrjournals.org

Effectiveness of Intravenous Iron Sucrose versus Oral Iron in Iron Deficiency Anemia in Pregnancy

Dr Sunita V .N[1] Dr Rutuja Kolekar[2], Dr. Shivanand Gundalli[3]
Dr Vikrant Nandurkar[4]

Assistant professor Department of obstetrics and gynaecology Devraj urs Medical college Kolar [1]
Senior resident, Department of obstetrics and gynaecology SNMC Bagalkot [2]
Assistant professor Department of pathology SNMC Bagalkot [3]
Assistant professor Department of surgery Devraj urs Medical college Kolar [4]

Abstract: *Anaemia in pregnancy is a public health problem in India, where nutrition mass education and availabiliaty and blood are far from satisfactory. It is paradoxical that the while iron is one of the least expensive and most readily available medicinal substance, its deficiency particularly in female population still presents serious problems. Low availability and absorptions of iron and repeated and closely spaced pregnancies place a constant drain on the iron stores of pregnanct women resulting in development of iron deficientl anaemia. All women who were attending antenatal check ups were asked to participate diagnosis of moderate deficiency was done by Hb and Sr. Ferritin and those who have fulfilled the criteria were enrolled after written informed consent. All patients were asked to come at day 14 and day 28 for laboratory tests. On day 14, Hb was done and on day 28 CBC, Sr. Feritin were done and at delivery Sr. Ferritin, CBC were done. The prevalence of anaemia was similar in both supplemented (88.1%) and the unsupplemented groups (87.5%) suggesting that the supplement provided was not adequate or the compliance was poor . The choice of treatment of iron deficiency anemia is oral iron replacement because it is the safest and least expensive.*

Keywords: *Anaemia ,iron,Hb,deficiency.*

I. Introduction

Anemia is one of the most common debilitating conditions affecting the health and well being of women in South East Asia, with India having the highest prevalence of anaemia in the world

In India, the most common reason for developing anaemia is iron deficiency. Around 52% of Indian women suffer from iron deficiency anaemia (IDA).

Anemia is defined as hemoglobin concentration less than 12g/dl in non-pregnant women and less than 10g/dl in pregnancyor the pnerperium. The center for Disease Control and Prevention (CDC) and prevention (1990) defined anaemia as less than 11g/dl in the first and third trimester and less than 10.5g/dl in the second trimester.

Iron deficiency anaemia is more common in Adolescents, pregnancy, child bearing age group because of increasing demand for iron.

In adolescence, there are period intense growth, not only physically but also mentally and socially. During the time 20% of final adult weight and 50% adult weight are attained. Because of this rapid growth, adolescents are vulnerable to anaemia. Whereas in pregnancy, average women of reproductive age needs about 350 -500mg addition iron to maintain iron balance during pregnancy however, it is not reasonable to expect that the additional iron can cause from iron stores, since they very seldom reach this level in women in developing countries. Because of more incidence of early pregnancy. Rapid succession of pregnancy inadequate diet, lower socio-economic status male dominated socialy and etc.

The other cause for iron deficiency are decreased iron intake, In India, since create are not routinely fortified with iron, the total iron consumption is still less. Also a large proportion of Indian population is strictly vegetarine and most of the vegetables and fruits are poor in iron content. Increasing use of refined and junk foods leads to consumption of a diet poor in iron.

Components in the diet like vitamin C and meat enhance iron abortion whereas posphates, phytakes and tannic acid re…..absorption are the responsible factors for decreased absorption of iron from the of Hookworm infection is very common in India each adult hook worm sucks 0.1ml of blood every day and menstrual blood loss are very common cause of iron deficiency of anaemia in India.

With all these difficult circumstance to deal with there are other problems too problems with formulation of iron preparations, poor compliance by the beneficiaries, failure to replenish the stocks at the beneficiary level and of antenatal check-ups or registration and supervision and hence, the National Nutritional Anaemia Control Programme of India has failed to reach its target since last 30 years.

Iron deficiency in pregnancy has varied adverse consequences on both the mother and the fetus. Apart from anemia, iron deficiency is also associated with preterm labor (28.2%) pre-eclampsia (31%), sepsis, hemorrhage and low birth weight delivery. It was also postulate that the pregnant women with iron deficiency anemia may give birth to infants with low iron stores, which may result in abnormal child development (Physical and congnitive), if deficiencies are not corrected early.

A varied away of interventions exist that are designed to prevent and correct iron deficiency anemia. These include dietary improvement fortification of food with iron, iron supplementation and other public health measures, such as helminth control. Iron supplementation can be done by various methods such as oral iron, intramuscular oral iron salts has got many disadvantages when compared to other routes of intervention because for binding to other routes of ferritin and transferritin ferrous iron has to be converted into ferric iron by oxidation highly reactive free radicals are produced during this process. This causes the damage to be mucosal lining of gastrointestinal nausea, diarrhoea or constipation more common with the oral salts. And the other demerit is the bioavailability of oral iron salts depends upon the iron preparation and environment of intestines are presence of other food substances in the human.

But coinciding the convenience and cost, oral salts are still the first line therapy in the treatment and prevention of Iron deficiency anemia. But severe anaemia is an imaginary and should be corrected promptly.

Blood transfusion is given in emergency to correct severe anemia. Though it corrects and effectively the blood transfusion is associated the risk of transmission of serious infection like HIV, HBV, HCV, bacterial and protozoal infection. Transfusion reactions and mismatch may occur. The mode of treatment depends upon the availability of blood donors. There is unnecessary administration of WBSs, plasma, platelets and always possible of iron overload. Also it requires a prolonged IV administration.

In last 10 years, there is a newer intravenous iron preparation has evolved (i.e.) iron sucrose complex (ISC) which has got good safety profile, faster achievement of target .....and no test dose required.

There are studies which had shown the safety and faster achievement of target aemoglobin when compared to oral iron during iron deficiency anemia of pregnancy. In another study, it has shown that even though the rise in haemoglobin is equal in both the groups but eh se ferritin was more in the ISC group when compared to oral group.

The present study was done to compare the efficiency and safety of Intravenous iron sucrose versus oral iron for treatment of iron deficiency anemia of pregnancy.

Statement of hypothesis

"Intravenous Iron Sucrose could have better safety and efficiency when compared to oral iron in the treatment of iron deficiency anemia of pregnancy.

II. Aims And Objectives

II.1. Aim:

To correct iron deficiency Anemia and Iron deficiency during pregnancy

II.2 .Objectives:

1. To compare effectiveness of intravenous iron sucrose versus oral iron deficiency anemia of pregnancy.
2. To compare safety of intravenous iron deficiency versus oral iron.

III. Materials And Methods

1. Study design:

- This was an open labelled randomized controlled trial
- Randomisation is done by using simple Randomisation tables.
- Blinding was not possible as two different drugs were administrated in different preparation forms by different routes

2. Study settings:

The trial was conducted at department of obstetrics and gynaecology, Government medical college and hospital, Nagpur.

3. Study period:

The study was performed between 2008 to 2011.and was approved by the Ethics committee.

4. Inclusion criteria:

- Pregnant women more than 18 years old
- Gestational age between 26 to 32 weeks

- Haemoglobin level between 8 to 10g/dl
- Sr. Ferritin level <13µg/L

5. Exclusion criteria

- Anemia not linked to iron deficiency such as haemoglobinopathies, Haceocyttic anaemia
- Multiple pregnancy
- Intolerance to iron derivatives
- Previous blood transfusion
- Suspected acute infection
- Parental iron treatment

6. Sample size Sample sized was calculated by computer generated formula (i.e)

Epi – Info – version = 3.5.1.

Power – 80%
CL – 95%
Ratio 1:L
Hg sample size came out to be
Iron sucrose : 45
Oral iron : 45

7. Intervention:

Subjects were assigned to Intravenous iron sucrose group or oral iron by simple RandomisationIn the group A the dose of total iron sucrose was calculated from the following formula: weight (target haemoglobin – acute haemoglobin) x 2.4 + 500mg. Target haemoglobin in grams per litre was set at 11mg/dL. In each infusion, the maximum total dose administrated 200mg elemental iron in 100ml 0.9% infused over 20 to 30minutes. No test dose was given.

A total dose minimum of 200mg to maximum of 950mg administered over 1 day to 8 days respectively. Most of the patients received iron sucrose at the rate of 200mg every other day. Treatment was completed after administration of the calculated dose.

In group B, three 100mg iron tablets per day were given (i.e. a total of 300mg of elemental iron per day) throughout their pregnancy. Patients were instructed to take the tablets on an empty stomach, 2 hours before or after their meals. Both groups were supplemented by 0.5mg folic acid treatment per day for 4 weeks. Additional multivitamin or vitamin C preparations were not given during study. All adverse events after each infection of elemental iron were identified. Blood pressure was measured before due and after each infusion and hypotene was recorded as an adverse event if it was clinically significant. All patients were asked to come at day 14 and day 28 for laboratory tests. On day 14, Hb was done and on day 28 CBC, Sr. Feritin were done and at delivery Sr. Ferritin, CBC were done.

8. Outcome measures:

Primary measure:
Change in haemoglobin concentration on day 14, 28 and at the delivery.
Secondary measure:
Change in Sr. Ferritin levels at day 28, at delivery.

- Adverse effects
- Fetal birth weight

Follow up:

During each visit, all adverse events related or possibly related to the drugs were recorded after physical examinations and direct inquires of the patient. In Group B treatment was assessed by number of returned tablets.

After delivary pregnancy outcomes were obtained from each women's medical records. These included type of birth, transfusion history, fetal birth weight and hospitalization time.

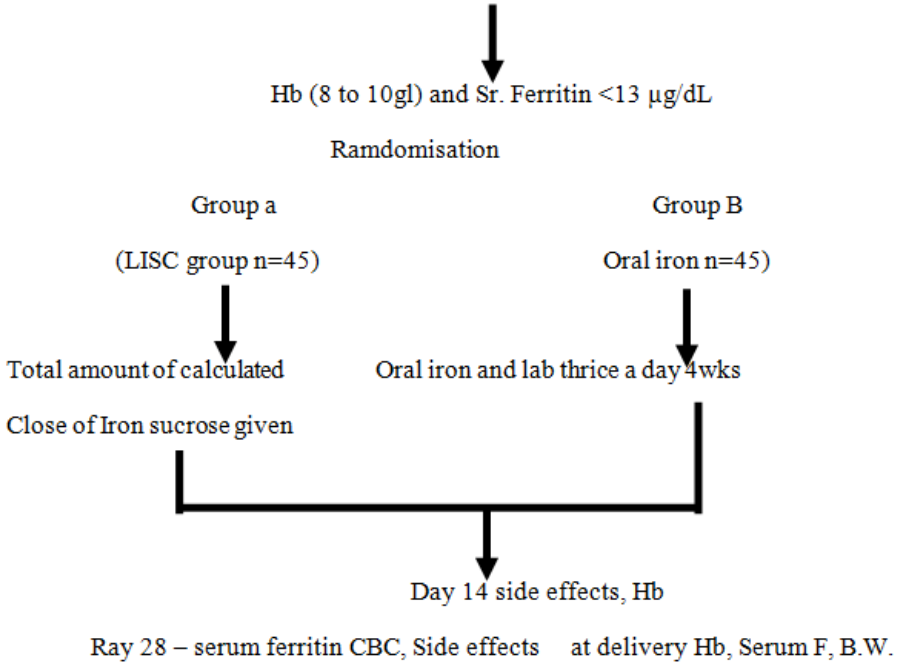
Study population:

All women who were attending antenatal check ups were asked to participate diagnosis of moderate deficiency was done by Hb and Sr. Ferritin and those who have fulfilled the criteria were enrolled after written informed consent (Aneexure I). Women were randomised according to Randomisation table (Annexure II) and grouped into group A (ISC) group B (Oral Iron)

A detailed menstrual and obstetrical history was taken and recored in case record form sheet.

Statistical Analysis: The data was analysed by stat 10.1 version – 2009 used for statistical analysis.
Continuous variable with help of paired and unpaired 't' test.
Categorical variable with help of Chi – square test. The p value was considered to be significant when it was less than 0.05.

Protocol Of The Study Pregnent women between 26-32 weeks



Observations

In the present study pregnant women (n=90) were enrolled and randomly assigned to receive either intravenous ISC or oral iron.

Table 1 Background characteristics

Demographic	Group A (n=45)	Group B (n=45)	P Value	
Age in years Mean ± SD	24.2 ±2.82	24.4 ± 2.71	0.7314	NS
BMI Mean ± SD	20.9 ± 4.21	21.2 ± 4.20	0.7379	NS
Gestational age at enrollement Mean ± SD	27.06 ± 1.51	27.11 ± 1.57	0.8756	NS
Parity Primi (n(%) Multi(n(%)	 25(55.5%) 20(44.5%)	 28(62.2%) 17 (37.8%)	 0.521 (Chi test)	NS

The demographic characteristics of the study population are summarised in Table No.1. the distribution of patients (year), Body Mass Index, Gravidity, Parity and gestational age an distribution were comparable.

Table 2 Background characteristics

Laboratory findings at enrollment	Group A (n=42)	Group B (n=37)	P Value	
Hemoglobin in mg/dl	8.7 ± 0.55	8.69 ±0.47	0.9315	NS
Serum ferritin in µg/L	11.7 ±1.47	11.5 ± 1.37	0.5325	NS

There were no significant difference of laboratory findings at the time of enrolment between the two groups.

Table 3

Hemoglobin in mg/dl	Group A (n=42)	Group B (n=37)	P Value	
8-9	22(52.3%)	25 (47.5%)	0.624	NS
9.1-10	14(33.3%)	12 (32.4%)	0.524	NS

There were no significant difference of hemoglobin level between the two groups.

Table 4

Serum ferritin in µg/L	Group A (n=42)	Group B (n=37)	P Value	
10-11	24(57.1%)	22(59.45%)	0.624	NS
11.1-12	14(33.3%)	11(29.72%)	0.524	NS
12.1-13	4(9.8%)	4 (10.8%)	0.64	NS

There were no significant difference of Serum ferritin level between the two groups.

Table 5

Number of tablets taken	Number of patients n(%)
64-84 (88.09-100%)	36(97.29%)
44-63 (52.3-75%)	1(2.70%)
<44 (<75%)	0

5 patients discontinued the treatment due to side effects and 3 patients lost to follow up, so, number of women included in the oral group were 37, among these 36 (97.29) women took more than 88-100% of their supplements. Only one patient (2.7%) took less than 52.32-75% of their supplements

Table 6

Total dose of iron sucrose complex given	Number of patients n(%)
750-950	22(52.38%)
550-749	17(40.47%)
<549 mg	3(7.14%)

In the study population of iron sucrose group one patient discontinued the treatment because of hypotension and 2 patients lost to follow up and hence 43 patients were included. All patients were administrated the calculated the dose of iron sucrose. The median dose administered was 850mg.

Table 7

Hemoglobin at each interval	Group A (n=42)	Group B (n=37)	P Value	
Hb_{14}	9.97 ±0.531	8.92 ± 0.49	0.001	S
Hb_{28}	10.98 ± 0.54	9.42 ± 0.49	0.001	S
Hb at delivery	11.08 ± 0.65	10.03 ± 0.46	0.001	S

The average hemoglobin values was shown in the table at each interval. Haemoglobin value were different for each groups. (p=0.01) when analysis across the time the haemoglobin value were found to vary significantly within the individuals. The mean haemoglobin of each groups was compared to the mean hemoglobin of subsequent level. The increase in hemoglobin level was significantly higher in this intravenous iron groups than that of oral iron group at the second and 4th week.

Table 8

Difference in the Hemoglobin in between the interval	Group A (n=42)	Group B (n=37)	P Value	
2w-baseline	1.2 ±0.05	0.3 ± 0.02	0.0001	S
4w- 2w	1.01 ± 0.01	0.50 ± 0.001	0.0001	S
Delivery – 4w	0.70 ± 0.11	0.50 ± 0.03	0.0001	S

The average hemoglobin values in between the intervals were significantly higher in iron sucrose group compare to oral group.

Table 9

Period interval	Group A (n=42)	Group B (n=37)	P Value
At 2nd week	7(16.6%)	2(5.4%)	0.0001
At 4th week	24(57.1%)	13 (35.1%)	0.0001
At delivery	39(92.8%)	25(67.5%)	0.0001

13 patients (35.1%) reached the target haemoglobin of 11gm/dl in the oral group and 24(57.1%) in the intravenous group at weeks. (p=0.0001)
At birth, 25 patients (67.5%) reached the target haemoglobin of 11gm/dl in the oral group and 39(92.8%) in the intravenous group at weeks. (p=0.0001) Table 10

Serum ferritin in µg/l	Group A (n=42)	Group B (n=37)	P Value
Day 28	30.66 ±4.93	19.96 ± 2.38	0.001
At delivery	28.78 ± 5.18	27.32 ± 3.81	0.1624
At delivery	39(92.8%)	25(67.5%)	0.0001

Serum ferritin were significantly higher in the intravenous group at 4th week when compared to serum ferritin at delivery.

Table 10

Complications	Group A (n=42)	Group B (n=37)	P Value
Yes	14(37.8%)	4(9.82%)	0.001
No	23(62.2%)	38(90.1%)	
N	37	43	

The complication rate were 3 times more common in oral group when compare to intravenous group.

Table 11

Sideeffects	Group A (n=42)	Group B (n=37)
Nausea	Nil	10(27.0%)
Diarrhoea	Nil	2(5.4%)
Rash	Nil	Nil
Dizziness	1(2.3%)	Nil
Headache	1(2.3%)	Nil
Hypertension	Nil	Nil
Hypotension	1(2.3%)	Nil
Upper GI discomfort	Nil	10(27.02%)
Metalic taste	Nil	2(5.4%)
Local infiltration	1(2.3%)	Nil
Others	Nil	Nil

Table 12

Outcome	Group A (n=42)	Group B (n=37)	P Value
Maternal hospital stay	3.66 ± 2.61	4.02 ± 2.81	0.72
Gestational age at delivery	38.80 ± 2.17	40.2 ±2.08	0.62
Mode of delivery LSCS FTND	 10(23.8%) 32(76.1%)	 10(27.7%) 27(72.9%)	 0.1
Blood transfusion	1(2.38%)	3(8%)	0.52
Birthweight	2590± 508.3	2700±492.0	0.72

The mean hospitalisation time was the same in the two groups. There was no significant difference between the mean birth weight of neonates in each groups. 3 women in oral group received blood transfusion, 1 is for traumatic PPH and other 2 for …… 1 patient has got blood transfusion in intravenous group because of severe blood loss in antepartum.

IV. Discussion

It is paradoxical that the while iron is one of the least expensive and m,ost readily available medicinal substance, its deficiency particularly in female population still presents serious problems.

Evaluation of this program showed that 80% of pregnant women were never offered tablets, which 4% out of 20% who did receive the pills refuse to take them and 25% discontinued taking them (43). Not only pregnant women default in taking oral iron, but also government or ther agencies are not able to ensure smooth and continuous supply of tablets and the mean body ,ass iondex in study group was 20.9 when compared to compared group i.e. 21.2.

Bayoumeu et al in 2002 done a open labelled randomised controlled study of 50 patients at France. The average age of the patients w\in both study and control group were 25 years.

The average weight of the patients were 55kg in study group when compared to control group, it was 53 kg.

All Ragip et al in 2005 done a open labelled prospective study where the mean group of the patient in study group were 26.5 in control group. The mean weight in study group was 58.2 kg where in control group.

Alternative counts for iron therapy need to be considered till such time as the commonly is educated and communication channels are established.

Women with moderate anemia were recruited and not those with severe anemia because the patients with severe anemia should get. The treatment within short period of time. In such patients blood transfusions are preferred.

In the present study commonest age of the patient ranged from 20 to 25 years with mean age group of 24.2 years in study group [Group A] and 24.4 years in control group [group B]

Studies	No of patient	Study group	Control group
Bayameu et al 2002	50	25	25
Ragip et al 2005	90	26.5	24.9
Present study	90	24.2	24.4

Studies	No of patient	Study group	Control group
Bayameu et al 2002	50	55	53
Ragip et al 2005	90	58.2	56.0
Present study	90	49.9	47.68

There were no differences in age in our present study, when compared to other studies. There was a difference in weight because of change in.... There will be change in bode built and that doesn't affect in the treatment because to total than dose required was calculated individually depending on the weight of the patient. In the present study mean gestational age at the time of enrolment was 27 weeks in both the groups. 55.5% were primiparous and 62.2% in study and control group respectively.

The mean gestational age at time of enrolment in other studies were also in the 2nd trimester i.e. 25 wks and 28 wks for Bayameu and Ragip et al respectively.

Studies	No of patient	Study group	Control group
Bayameu et al 2002	50	25	25
Ragip et al 2005	90	28.9	29.7
Present study	90	27.06	27.11

In the present study, the mean haemoglobin level at the time of enrolment were 8.7mg/dL and 8.69 in study and control group respectively.

The mean serum Ferritin were 9.7 and 9.5 in study and control group respectively whereas in other studies the Hb level were 9.6 and 9.7 in study and control group (Bayameu et al) 9.8 and 9.9 mg/dl in study and control group (Ragip et al) Sr. Ferrtin levels, were 6.5 in control and 8µg/L in Bayameu et al and 5 and 4.1 µg/L by Ragip et al

Studies		ISC	POI	ISG	PO
Bayameu et al 2002	50	9.6	9.7	6.5	8
Ragip et al 2005	90	9.8	9.9	5	4.1
Present study	90	8.7	8.69	9.7	9.5

Change in Haemoglobin

In the present study there was an 37 patients were treated with 200mg of ferrous sulphate. But there was significant rise in haemoglobin in study group i.e. from 8.7 ± 0.55 mg/dL to 9.97 ± 0.531 mg/dL when compare to 8.69 ± 0.47 to 9.92 ± 0.49 mg/dl. And at day 14 haemoglobin level 10.98 ± 0.54, 9.42 ± 0.49 at day 28. There was raise in 1.2mg/dl of haemoglobin in level. In first 14 days in study group whereas in control group there was only 0.3mg/dl which is significant. At day 28 significant rising in haemoglobin 2.21 in study group when compare to 0.80 in oral group.

RAgip etal has shown that the same observations there was rise in 1.2mg/dl of haemoglobin in study group when compared to only 0.6mg/dl in control group. A clear in haemoglobin was observed in the two group raising from 9.6 ± 0.79 to 9.1mg/dl to 11.11 ± 1.3 mg/dl on day 30 in the study group and 9.7 ± 0.5 to 11 .1 ± 1.25 which was not significant. In their study 24 women given intravenous sucrose were compared with 23 women given 240mg of oral ferros sulphate.by Bayameu et al. However there are difference between our study and the one who carried out by Bayameu et al. That might explained in the different results.

First, they administered the total iron sucrose over 21 days which was relatively longer than our study.

Second the sample size of the study was smaller than that of study. The success of oral iron treatement depends on various factors. Especially patient dietary habit influence the success of treatment because the nature of the mean affects obsoprtion. Absorption also decrease when iron is takenafter to during meal. It is difficult to control this confounding factors even when good adherents to treatment is achieved.

This confounding factors may be represented variously in small groups.

Studies	Hb Day 0	Hb Day 8	Protein Day 0	Day 28
Bayameu et al 2002	9.6	11.11	9.7	11
Ragip et al 2005	9.8	10.8	9.9	10.5
Present study	8.7	9.7	8.6	8.9

This study confirmed that parenterally administered iron sucrose elevates haemoglobin and restores better the iron stores better than oral iron polymaltose complex during the treatment of moderate iron deficiency anaemia during pregnancy. The mean haemoglobin ferritin levels throughout the treatment were significantly higher in the intravenously administered group. The rise in the haemoglobin concentration was significantly faster than that observed with orally administered iron and a significantly higher number of patients achieved the targeted haemoglobin at the fourth week and at delivery . It is generally accepted that intravenous iron therapy induces a similar or slightly more rapid erythropoietic response than oral iron replacement [36]. this statement has been justified extensively by the results obtained with the iron dextran treatments but may not be generalised for iron sucrose treatments . the rate of iron delivery to the marrow is a major factor in the regulation of marrow proliferation .[37] iron sucrose and iron dextran have different pharmacokinetic properties . iron sucrose complex has an intermediate stability and strength . it is quickly cleared from serum with a terminal half life of approximately 5 to 6 hours compared with iron dextran , which has a serum half life of 3 to 4 days .it is more rapidly available for eyrthropoiesis .[38 to 39] intravenous iron sucrose produces more rapid increase in haemoglobulin concentration when compared oral iron and intramuscular iron dextran. [40] in the current study maternal iron stores were restored more rapidly with intravenously administered iron than orally administered iron as reported in early studies[11,12,13].

In the present study sr. Ferritin i.e. iron stores. Restored very rapidly in iron sucrose group, than in oral group. There was significant difference in list in sr. Ferritin. At day 28, at delivery, there was increase sr ferrin level but the it was not signficnat when compared to oral group.

In the present study the complication rate were 3 lines higher when compared to intravenous group. 27.02% complined of GI symptoms.

Ragdip have got similar findings 18% have got upper GI syndromes

Pregnancy puts the women at risk of major peripartum blood loss, and women who have severe anemia constitute a high risk group for blood transfusions. There is no clear evidence from randomised trials to show whether clinical outcomes may be modified by using available treatments in women with iron deficiency anemia during pregnancy. The choice of treatment of iron deficiency anemia is oral iron replacement because it is the safest and least expensive. However. It seem that intravenous iron sucrose is a safe and effective alternative to oral iron in treatment of iron deficiency anemia of pregnancy. It restores blood stores more rapidly, and a prompt increase in haemoglobin may be achieved. It may reduce the blood transfusion rates in pregnant women who have severe anemia near term. Major disadvantages of intravenous treatment are cost, need for hospitalization or an outpatient setting, and the invasive nature of the procedure. However, it may be considered an alternative to oral iron in the treatment of pregnant women with severe iron deficiency anemia during the third trimester.

Acknowledgement

DR Sunita and Dr Vikrant were postgraduate students in gmc nagapur during that period the study was conducted.Thanks to ALL STAFF MEMBERS OF Department of obstetrics and gynaecology Nagpur , statician , nursing staff for providing valuable support for study.

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