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AN ANALYTICAL STUDY ON PARENTERAL AND ORAL IRON THERAPY IN THE TREATMENT OF MODERATE DEGREE OF IRON DEFICIENCY ANEMIA IN PREGNANCY.

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ABSTRACT

Background
Anemia, especially caused by insufficient iron and acute blood loss, is prevalent in pregnancy and the postpartum period. Iron requirements rise significantly during pregnancy to support both maternal and fetal needs.
Aim: To evaluate the efficacy of Intravenous Iron and oral iron therapy in moderate degree of iron deficiency anemia in the second and third trimesters of pregnant women attending Antenatal OPD or labor room in Silchar Medical College and Hospital.

Methods
An Observational Cross-Sectional Study was done on 250 pregnant women attending Antenatal OPD and patients admitted to "The Department of Obstetrics and Gynecology of Silchar Medical College and Hospital" with hemoglobin 7-9.9 g/dl. 250 Population selected randomly, separated into 2 groups with 125 each. The first group of patients who were given IVIS. The second group of people received oral ferrous sulfate tablets twice daily. The patients were asked to report after 4 weeks for estimation of Hb.

Results
Baseline Hb of a group receiving oral iron therapy and parenteral iron therapy was 8.07 ±0.70 and 8.05±0.74 respectively. After 4 weeks of therapy, a mean difference of 0.61±0.53 was found in the oral therapy group and 1.44±0.62 in parenteral therapy where the P value is <0.001. The final rise in hemoglobin in the parenteral iron therapy group was found to be 9.47±0.97 and 8.69±0.86 in the oral receiving group.

Conclusion
Parenteral iron therapy was found to be an effective, safe, and alternative therapy to oral iron therapy in the treatment management of moderate degree of iron deficiency anemia in second and third-trimester pregnant women.

Recommendation
Further studies with newer IV iron formulations to overcome the issue of affordability and the risks of infusion-related complications and increase the sample size.

***Keywords**: Anemia, Iron deficiency anemia, Oral iron therapy, Parenteral iron therapy, Hemoglobin*
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INTRODUCTION

Anemia is a frequent blood condition, that involves lower levels of RBC or hemoglobin in the bloodstream. In pregnancy and after childbirth, the primary causes are typically iron deficiency and sudden blood loss. During pregnancy, inadequate levels can lead to maternal and neonatal harmful changes. According to classifications "based on populations supplemented with iron, anemia is hemoglobin levels below 11 g/dL in the first trimester, 10.5 g/dL in the second trimester, and 11 g/dL in the third trimester". (1)

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Anemia is a major catastrophic issue during pregnancy, especially in developing countries like India, largely due to iron deficiency exacerbated by vegetarian diets. In India, over 90% of cases stem from inadequate iron intake. This deficiency is critical during pregnancy as more iron is needed for fetal development and maternal blood volume expansion. (2)
Iron deficiency anemia (IDA) in pregnancy can lead to serious health issues such as LBW, preterm birth, and even maternal death in severe cases. These outcomes impact the health of mothers and babies and place significant economic strain on families and healthcare systems. Efforts to combat iron deficiency anemia during pregnancy typically include strategies such as iron supplementation, promoting diets rich in iron, and raising awareness about nutrition and healthcare services. These measures are crucial for reducing the prevalence and severity of anemia, thereby improving maternal and child health in the growing nations. (2)

According to the "Fifth National Family Health Survey of 2019-2021",52.7% of women and 52.2% of pregnant women aged 15 to 49 are anemic. (3) An increase in anemia in the Northeastern parts of India is largely credited to the challenging hilly terrain of the region and inaccessible healthcare facility services. Consequently, many women from these areas present at hospitals with complicated states at later stages of pregnancy. (Tigga et al 2020)(2)
Anemia is a significant contributor to maternal mortality, directly or indirectly accounting for 40% of these deaths in India. When hemoglobin levels drop below 5g/dl during pregnancy, there is an alarming 8-to-10-fold increase in maternal mortality rates. Therefore, early detection and effective management of anemia in pregnant women are crucial to mitigate this risk and improve maternal survival rates. Ferdousi et al.2022(4)

Alternatively, treating nutritional anemia during pregnancy with oral iron poses challenges in the form of side effects, often leading to non-compliance. As a result, intravenous iron is used for those who do not tolerate oral iron well, potentially reducing the necessity for blood transfusions during pregnancy. Tigga et al 2020 (2)Intravenous iron, specifically iron sucrose, has become increasingly recognized as a suitable choice for treating iron deficiency in pregnant and postpartum patients. It is effective when oral iron supplements are inadequate or poorly tolerated, or when patients are also undergoing treatment with recombinant human erythropoietin (rHuEPO). Safety data indicate that iron sucrose, when administered according to recommended dosages and protocols, is generally safe for both the mother and the fetus. (Breymann et al.2006) (6)

During pregnancy, the body's iron requirements are substantial and vary based on different factors such as red cell mass expansion, fetal transfer, placental needs, and anticipated blood loss during delivery. Accounting for iron conservation through amenorrhea, additional iron of about 500-600mg is needed throughout pregnancy. This translates to a daily need for 4-6 mg of absorbed iron. Given that iron absorption is generally low, especially in diets with limited bioavailability, pregnant women must ensure their diet includes 40-60 mg of iron daily to meet these increased demands and avoid developing iron-deficiency anemia, which can adversely affect both maternal and fetal health (Kalindi et al.2021) (5)
IV iron infusion is a treatment wherein a mixture of iron & saline solution is injected directly into a vein, typically for patients dealing with iron deficiency, anemia, and chronic kidney disease. This method is recommended when oral iron supplements do not sufficiently restore iron and Hb levels in the blood. IV infusion allows for rapid and efficient delivery of iron throughout the body, offering an immediate administration compared to the gradual absorption process of oral iron supplements. Tigga et al 2020(2)

Ferric carboxymaltose (FCM) is considered safer as compared to Iron sucrose in the case of IDA in expecting women. It facilitates rapid replenishment of iron stores, leading to a significant increase in Hb with fewer side effects. Due to its high efficacy and safety profile, FCM is preferred as the initial treatment option for managing IDA during pregnancy. This strategy seeks to lessen the high prevalence and burden of disease related to this illness in our community. (Ferdousi et al.2022) (4)

Aim

To evaluate the efficacy of Intravenous Iron and oral iron therapy in moderate degree of iron deficiency anemia in the second and third trimesters of pregnant women attending ANOPD or labor room in Silchar Medical College and Hospital

METHODOLOGY

Study design

An Observational Cross-Sectional Study

Study setting

The proposed study will be carried out in the Department of Obstetrics and Gynecology, Silchar Medical College and Hospital for one year

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Study population

250 pregnant women attending ANOPD and patients admitted to the Department of Obstetrics and Gynecology of Silchar Medical College and hospital with hemoglobin 7-9.9 g/dl will be included. 250 Population selected on a random basis will be separated into 2 groups with 125 each randomly.

Sample size

Based on previous literature it was assumed that the prevalence of anemia during pregnancy is as high as 80% in the Indian population. in the study published by Maureen P Tigga and Amulya P Debbarma in 2019 in Northeastern states. The sample size is calculated by using the Daniel sample size formula:
So, using the formula for sample size $N= \{(Z^2) \times p \times q\} /d^2$
Where, N= Sample Size
Z = 1.96 for confidence interval
P= prevalence of anemia in pregnancy = 80%
q= 100 – p =20 %
d = absolute precision = 5%
Hence, the calculated sample size = 245= Rounded to 250

Selection criteria

Inclusion criteria

- Singleton pregnancy.
- Gestational age of 14 -36 weeks
- Hemoglobin concentration of 7 to 9.9 g/dl (moderate)
- Willing to enroll in the study and follow up

Exclusion criteria

- Those known to be allergic to parenteral iron
- Medical disorders like tuberculosis, diabetes hepatic failure, and hemoglobinopathies.
- Patients with Hb less than 7 g/dl and more than 9.9 g/dl
- Patients with obstetrical complications like HDP, APH, multiple pregnancies, etc

Statistical analysis

The data was examined by employing SYSTAT 7.0 software developed by SPSS Inc. in the United States. An independent t-test was used to examine the differences between mean percentages. Any statistical significance was determined at a significance level of $P<0.05$. All measures have been presented as the mean value ± the standard error.

Ethical consideration

This research has been approved by the institutional ethical committee of Silchar Medical College. IRB number: No. SMC/ETHICS/M1/2023/13 Dated on 13/08/2024

Methodology

Patients were divided into 2 groups consisting of 125 people each selected on a random basis. Group 1- Intravenous Iron Sucrose Group [IVIS] had patients who were given IVIS 100mg in 100 mL of normal saline on alternate days after a test dosage. The patients had received injections of iron sucrose at a minimum of 100 mg per day and up to roughly 300 mg per week. The necessary dosage of iron sucrose was determined using the following formula: Body mass in kilograms × (starting – target hemoglobin) × 2.4 + 500 mg. It was determined that 11 g/dL was the target Hb. The patient was observed for anaphylactic reactions during a 15-minute break after a test dosage of 15ml of iron sucrose infusion was given gradually. The rest of the infusion was given if no reactions occurred.
Patients in the second group (the oral group) of 125 received 200 mg of oral ferrous sulfate capsules twice a day, each of which contained 60 mg of elemental iron. Folic acid was given in the same amounts to both groups.
The patients were requested to report for follow-up after 4 weeks to calculate hemoglobin. The mean Hb values before and after treatment were to be examined both separately and between the two groups.

RESULTS

250 pregnant women with moderate IDA were enrolled and randomly assigned to 2 groups: the IV group (n = 125) and the oral group (n = 125). After 4 weeks, 10 women in the iron sucrose group (2 of whom developed hypersensitivity reactions) and 25 women in the oral group who were unable to tolerate the medication (15 of whom did not adhere to the tablet regimen) were counseled and motivated and later they were included in the study (total of 250 pregnant women was present in the study). The majority of patients in both the oral and intravenous groups fell within the age range of 25 to 29 years.

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Table 1 shows the tabulations of both parenteral and oral iron supplementation in moderate-degree pregnant women

	Parenteral iron group (N=125)	Oral iron group (N=125)	P value
Hb before study			
Mean ± SD	8.05±0.74	8.07±0.70	0.787
Median(IQR)	8(7.50-8.50)	8(7.50-8.50)	
Hb after 4 weeks of therapy			
Mean ± SD	9.49±0.97	8.69±0.86	<0.001*
Median(IQR)	9.40(9-10.20)	8.50(8-9.20)	
Increase in Hb			
Mean ± SD	1.44±0.62	0.61±0.53	<0.001*
Median(IQR)	1.50(1-1.80)	0.50(0.30-0.80)	

Following 4 weeks of IV ferrous sucrose therapy, the mean hemoglobin level in the IV group increased significantly from 8.05±0.74 to 9.49±0.97. The median hemoglobin range shifted from 7.50-8.50 to 9.00-10.20. The statistical analysis showed a highly significant p-value> 0.001, indicating a considerable improvement in Hb levels after treatment.

In the oral group, the initial mean Hb level was 8.07±0.70, with a median range of 8 (7.50-8.50), and a p-value of 0.787. After 4 weeks of oral iron supplementation, the mean Hb significantly increased to 8.69±0.86, with a median range of 8.50 (8-9.20) and a p-value>0.001.

Comparatively, in the IV group, the initial mean Hb was 8.05±0.74, and after 4 weeks of IV ferrous sucrose therapy, it increased to 9.49±0.97, with a median range of 9.40 (9.00-10.20) and a p-value>0.001. The net increase in mean Hb levels was 1.44±0.62 in the IV group & 0.61±0.53 in the oral iron group, with a p-value >0.001. This difference indicates a considerable superiority in Hb rises in the IV group compared to the oral group following treatment.

In the study, a paired 't-test' was utilized to assess the statistical importance of Hb improvement after therapy, with a threshold of $p < 0.05$ considered significant. In the intravenous (IV) group, nearly 5 patients experienced

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hypersensitivity reactions to iron sucrose, and 10 patients reported itching at the injection site they were treated symptomatically and continued in the study

Conversely, 26 pregnant women in the oral group demonstrated low compliance due to various adverse drug reactions, such as abdominal pain and metallic taste. They were counseled and later included in the study.

Diagram 1: Comparison of Hb before the study between the two groups

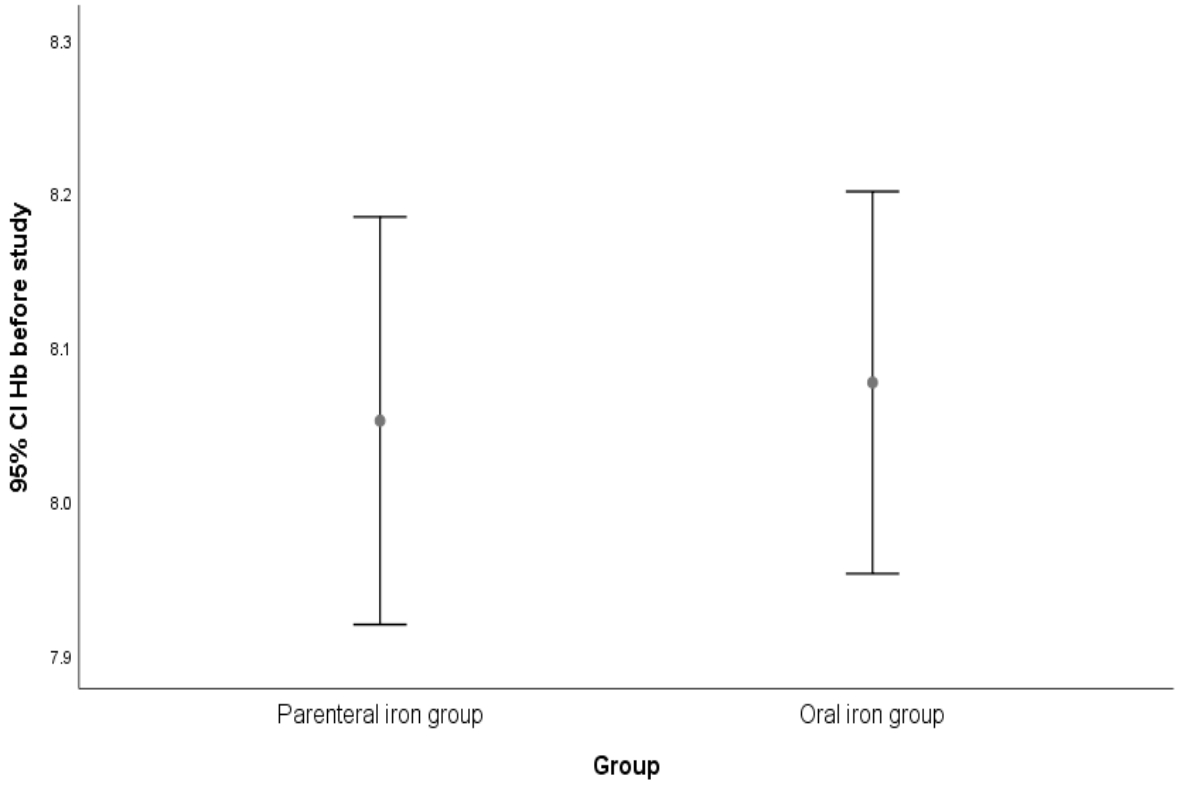

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Diagram 2: Comparison of Hb after 4 weeks of therapy between the two groups

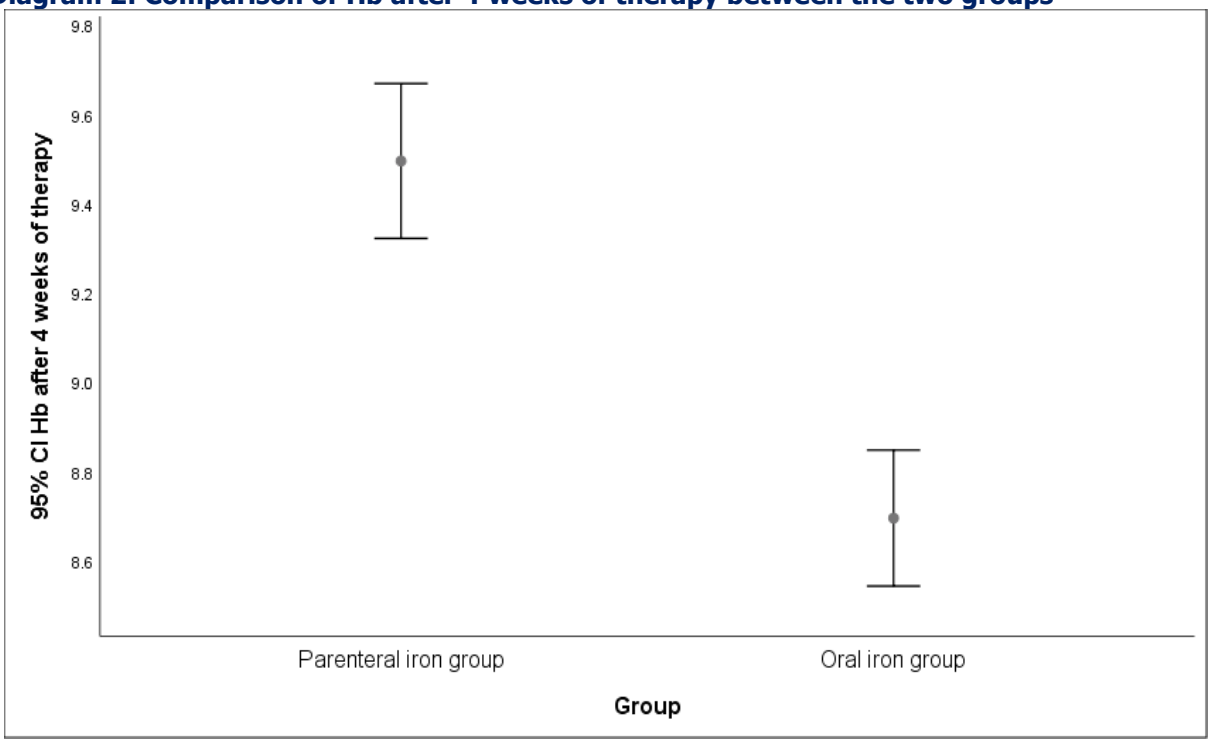

Table 2: showing the increase in hemoglobin in total with parenteral and oral iron.

	Mean increase in Hb± SD	P value
Parenteral iron group	1.44±0.62	<0.001*
Oral iron group	0.61±0.53	<0.001*

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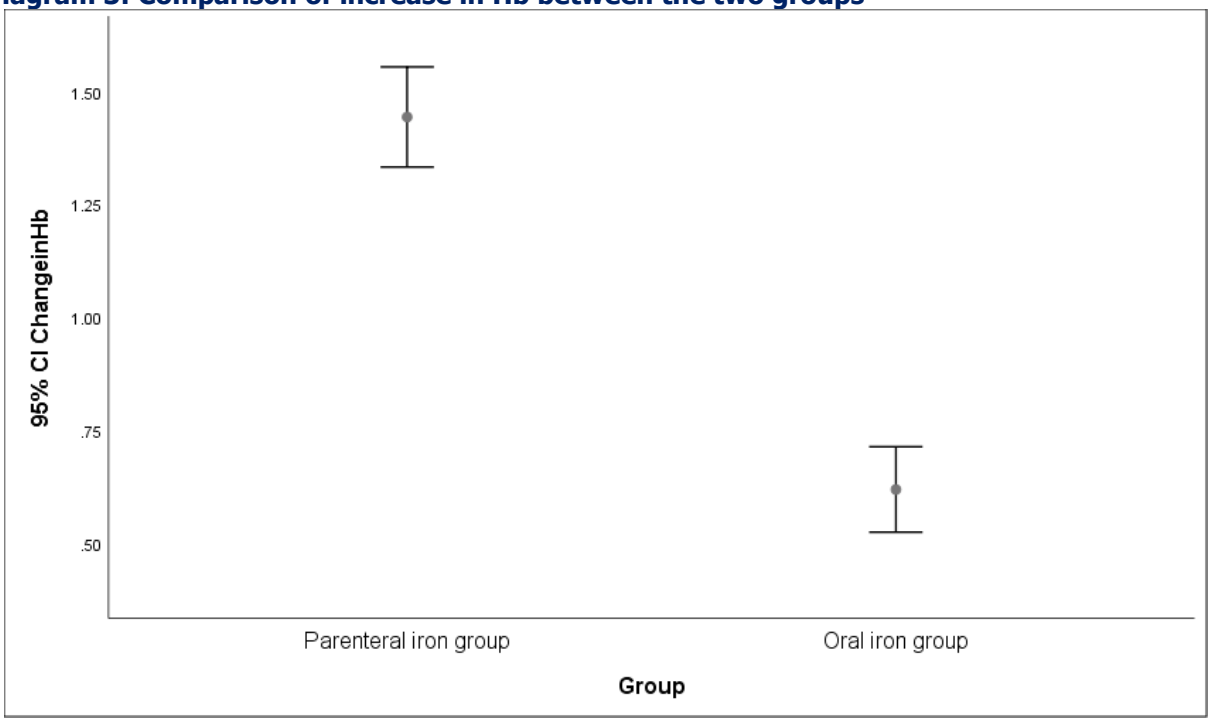
Diagram 3: Comparison of increase in Hb between the two groups



DISCUSSION

This study conducted a comparative analysis of the effectiveness of parenteral vs oral iron supplementation in treating anemia. A significantly greater increase in Hb levels was found in the parenteral group than in the oral group after a month of therapy. Specifically, the mean difference in Hb in the IV iron therapy group at 1 month was 1.44±0.62, with a p-value>0.001, indicating an increased improvement. Similarly, the mean difference in Hb in the oral iron therapy group at 4 weeks was slightly increased at 0.61±0.53, also with a p-value>0.001, showing a significant but lesser improvement compared to the IV group. These findings deemed IV iron therapy to be more effective in raising Hb levels than oral iron supplementation within the study's timeframe.

In an economically deprived area of Northeast India, an investigation by Tigga et al. (2020) found that after one to two months of treatment, the parenteral group's Hb levels increased more than those of the oral group. Before treatment, the mean Hb level in the oral group was 9.6±0.74g/dL. But in the IVIS group, it was 8.84±0.66g/dL. The mean increases in Hb levels in the oral group after 1-2 months of therapy were found to be 1.6g/dL & 2.91g/dL, accordingly. In contrast, the Hb levels in the IVIS group increased by 2.12g/dL after a month and by 4.03g/dL after 2 months. A considerable difference between the 2 groups after a month (P=0.01) and 2 months (P=0.00), shows that IV iron sucrose therapy generated greater improvements in Hb levels compared to oral iron supplementation over both periods studied. (2)

In the research led by Breymann et al. (2006), significant improvements were noted in key blood parameters after eight weeks of treatment: Hemoglobin levels rose significantly from an initial 7.63 ± 0.61 g% to 11.20 ± 0.73 g% (P < 0.001). Serum ferritin level, ls also showed a substantial increase, climbing from 11.2±4.7µg/l to 69±23.1µg/l (P < 0.001).

Additionally, the count of reticulocytes, which are young red blood cells, saw a marked rise from 1.5 ± 0.6% to 4.6 ± 0.8% within two weeks of starting the therapy. These findings highlight the effective outcomes of the treatment regimen in enhancing hemoglobin levels, boosting iron reserves (ferritin), and stimulating the production of new red blood cells (reticulocytes) in the study participants. (6)

In the study by Ferdousi et al. (2022), participants in both the oral and IV groups were included at a comparable mean gestational age of around 27 weeks. Baseline Hb levels ranged from 6.5 to 8.5g/dl, with mean baseline Hb values of 7.82g/dl in the oral group and 7.75g/dl in the IV group, showing no such difference between the groups. After 3 weeks of treatment, the mean Hb levels rose to 8.22g/dl in the oral group & 8.55g/dl in the IV group, with a significant

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difference (p=0.002). At 6 weeks post-treatment, Hb levels further improved to 10.7 g/dl in the IV group (from 7.75±0.57g/dl) as well as to 9.26g/dl in the oral group (from 7.82±0.45g/dl), demonstrating a highly significant difference (p<0.001). By the end of the study, the average increase in Hb was 2.95g/dl in the IV group and 1.44g/dl in the oral group, which was statistically significant. These findings underscore the greater efficacy of IV iron supplementation in achieving higher Hb levels compared to oral supplementation over the study period. (4)

In the study by Kalindi et al. (2021), hematological parameters were compared between two groups receiving intravenous and oral iron medications using an independent sample t-test. Significant differences (p<0.05) were found in the changes in Hb levels across all weeks studied. At the beginning, there was a statistically insignificant difference in the baseline mean hemoglobin levels between the oral iron therapy group & the parenteral iron therapy group (843±0.15g/dl and 8.41±0.13g/dl, respectively). After receiving oral and injectable iron for six weeks, both groups showed a statistically important and substantial increase (p 0.05 or more) in Hb levels. The average increase in Hb was 3.22 g/dl in the group receiving injectable iron (p<0.05), and 1.66g/dl in the group receiving oral iron (p<0.05). These findings are from recent studies that also reported increased Hb levels in both oral and IV iron therapy groups. They underscore the effectiveness of both treatment modalities in improving Hb levels in patients with iron deficiency anemia (5)

CONCLUSION

The study's conclusion indicated that intravenous iron sucrose therapy resulted in a faster improvement in hemoglobin compared to oral iron supplementation. Intravenous sucrose was identified as a safe and efficient alternative for treating IDA during pregnancy, despite its significantly higher treatment costs compared to oral therapy.

RECOMMENDATION

- Universal iron supplementation is recommended for all pregnant women
- We also recommend further studies with newer IV iron formulations to overcome the issue of affordability and the risks of infusion-related complications.
- We recommend new studies to increase the sample size so more accurate significance can be analyzed.
- We recommend follow-up studies after 8 weeks and 12 weeks to check the long-term effect on both classes of supplementation.

LIST OF ABBREVIATION

APH: antepartum hemorrhage
FCM: ferrous carboxy maltose
Hb: hemoglobin
HDP: hypertensive disorder of pregnancy.
IDA: iron deficiency anemia
IV: intravenous route
IVIS: intravenous iron sucrose
LBW: low birth weight
OPD: outpatient department
RBC: red blood cells
rHuEPO: recombinant human erythropoietin

FUNDING

No funding was done for the study since oral and intravenous iron sucrose was provided to the patients free of cost and supplied by the Government of India. The supplementation of oral iron tablets and parenteral iron was provided government of India as normal supplementation for pregnant women as per Anemia Mukt Bharat. In my study, we followed up on the patients who received the normal treatment management.

CONFLICT OF INTEREST

There is no conflict of interest between the authors.

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