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COMPARISON OF EFFICACY OF FERROUS CALCIUM CITRATE vs FERROUS ASCORBATE ON Hb STATUS IN ANAEMIC PREGNANT WOMEN

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ABSTRACT: Objectives: To compare the efficacy of ferrous calcium citrate with ferrous ascorbate on Hb levels in anaemic pregnant women. **Method:** In this observational study, patients receiving ferrous ascorbate with elemental iron 100 mg were allocated to group A and those receiving ferrous calcium citrate with elemental iron 50 mg allocated to group B. After recording the baseline data, their Hb levels, side effects at the end of each month were recorded. **Results and discussion:** Change in mean Hb levels from baseline to three months is 1.59 ± 0.74 , 1.94 ± 0.52 in group A and group B respectively with the p value ≤ 0.05 . Group B did show statistically significant difference in terms of change in Hb among primi and multiparous women, contrast to group A. **Conclusion:** Study reveals that ferrous calcium citrate results in better increase in Hb levels and lesser proportion of side effects in contrast to ferrous ascorbate.

INTRODUCTION: Iron-deficiency anaemia (IDA) is still a global health problem and the most frequent, alarming nutritional deficiency in terms of collective health. Unlike other nutritional deficits, this type of anaemia continues to be present in all continents and social groups, although its occurrence remains associated with negative socio-environmental conditions.¹⁻² According to the 2008 report of WHO, 1.62 billion (24.8%) people are affected globally from anaemia.³ But it is a main public health issue in developing countries where around 52% of pregnant women are anaemic, whereas this proportion is 23% in developed countries¹.

Nutritional IDA is highest in population segments that are at peak rate of growth like, infants, young children and pregnant women. Risk for developing IDA is highest in pregnancy, because iron requirements are substantially greater than average absorbable iron intakes. Physiologic demands for iron increases from 0.8 to ≤ 7.5 mg.^{4,5}

As per WHO guidelines the first and third trimesters, with threshold $Hb \leq 11.0$ g/dl; in the second trimester $Hb \leq 10.5$ g/dl; is considered as anaemia.⁶ With an alarming fact that nearly one third of women of childbearing age are already anaemic even prior to conception, the risk is further enhanced by increased body iron requirement during gestation. To add on, dietary habits in developing countries cannot supply 30 - 40 mg of iron that is required for absorption of 4 - 6 mg, needed during the latter stages of pregnancy⁷⁻⁹. To combat this WHO guidelines recommend iron supplementation for all pregnant women especially in areas with high anaemia prevalence ($\geq 20\%$ -40%).¹⁰⁻¹²

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Anaemia may be due to several reasons, although it is supposed to be mainly caused by iron deficiency especially in developing countries. Deficiency of other micronutrient *e.g.* Vitamins A and B₁₂, riboflavin, and folic acid have also been a cause of anaemia during pregnancy.

The most economical and effective medical treatment for IDA is oral administration of iron salts. The goal of supplementation is two-fold: to reverse the anaemia and to replete iron stores. The most commonly prescribed preparation, the ferrous and ferric salts, include ferrous sulfate, ferrous gluconate, ferrous ascorbate, ferrous fumarate, ferric carboxymaltose *etc.* These ferrous (Fe⁺²) forms are more soluble than the dietary ferric (Fe⁺³) form, with twice the absorbability. The estimated absorption rate of the ferrous salts is 10-15%.¹³

Oral iron therapy is notorious for its side effects, namely constipation, diarrhoea, heartburn, nausea, and epigastric pain, seen in up to 20% of patients and limit compliance to the different iron formulations. The estimated adherence rate hovers around 40 - 60%.¹⁴ The upper GI side effects, such as nausea and epigastric pain, are more dose-dependent and can be managed with lower or less frequent dosing initially. In light of these therapy-limiting side effects, new enteric-coated tablets, modified release formulations of iron with other mineral combination arrived in the market in an attempt to decrease the prevalence of GI upset and reduce the dosing schedule.

However, many studies reflect absorption is interfered, as the iron may not be absorbed in the duodenum. A comparison between enteric-coated and elixir ferrous sulfate in healthy volunteers did not show a statistically significant increase in serum iron concentration from baseline in the enteric-coated group.¹⁵ Moreover, there is also a large variation in the incidence of pregnancy anaemia because of the changes in socioeconomic conditions, lifestyles, and health seeking behaviours of various individuals across different countries and cultures and obstetrics and gynaecological related situation of pregnant mothers. This study tries to evaluate haemoglobin levels and compares haematological and clinical outcome with different iron preparations among residents of Davangere district.

Various studies in the past have compared ferrous Vs ferric salts, different formulations of ferrous, but no direct comparison demonstrating the efficacy of conventional ferrous ascorbate and modified release ferrous calcium citrate has been done. The present study was undertaken to evaluate the following objectives:

- To compare the efficacy of ferrous calcium citrate with ferrous ascorbate on haemoglobin levels in anaemic pregnant women.
- Compare side effects among two groups.

MATERIALS AND METHODS:

Study Design: An open label, observational study designed to conduct in pregnant women visiting OBG department of Chigateri hospital attached to JJM Medical College, Davangere. Patients receiving ferrous calcium citrate or ferrous ascorbate orally for three month were analyzed as two different groups.

Group A: preparation - ferrous ascorbate, containing elemental iron 100 mg

Group B: preparation -Ferrous calcium citrate with elemental iron 50 mg at bet time + calcium carbonate 500 mg, Vitamin D₃ 200 IU, Magnesium hydroxide 90 mg, Zinc Sulfate Monohydrate USP 4 mg.

Pregnant ladies in both groups after filling the informed consent form were asked to attend OPD at regular predetermined dates for ANC. Till 100 patients were added to the study screening went on as per the inclusion criteria and exclusion criteria.

Inclusion Criteria:

- Pregnant women not taking any iron preparations. Pregnant women with gestational age less than 6 months.
- Anaemia with Hb ≤ 10.5 gm%.

Exclusion Criteria:

- High risk pregnancy with cardiac and other complications.
- Multiple pregnancies

Patient were instructed to report for the follow up after every month for successive three months at their first visit. To improve the follow up rates patients were informed over the phone. At each

visit patient's Hb level were assessed using Sahli's haemoglobinometer.

Change in weight and any side effects if any were recorded in patient case report form. Out of 100 patients 7 patients were lost to follow up hence only 93 patients were included in statistical analysis.

List of Safety Measurements:

- Patient Hb assessment were done under aseptic precautions.
- Patient informed consent was compulsory Approval of ethical committee was obtained.

RESULTS AND DISCUSSION:

TABLE 1: COMPARISON OF MEAN Hb LEVEL BETWEEN TWO GROUPS

	Ferrous ascorbate (Mean \pm Sd)	Ferrous calcium citrate (Mean \pm Sd)	Mean difference	T value	P value
Baseline	9.02 \pm .98	8.72 \pm .99	0.30	1.2	0.23 (NS)
1 Month	9.88 \pm .90	9.53 \pm 1.01	0.35	1.4	0.16 (NS)
2 Months	10.35 \pm .66	10.33 \pm .75	0.02	0.07	0.94 (NS)
3 Months	10.62 \pm .72	10.67 \pm .51	0.05	0.26	0.79 (NS)

TABLE 2: COMPARISON OF Hb LEVEL AT BASELINE – (UNPAIRED T TEST)

Hb	Primi (Mean \pm S.D)	Multi (Mean \pm S.D)	Statistical analysis		
			Mean Difference \pm SE of Diff	T value	(Mean \pm S.D)
Ferrous ascorbate	9.3 \pm 1.08	8.57 \pm 0.56	0.71 \pm 0.35	2.03(2.4)	0.052 (0.024)
Ferrous calcium citrate	8.9 \pm 0.99	8.61 \pm 1.00	0.27 \pm 0.37	0.73	0.473

TABLE 3: COMPARISON OF Hb LEVEL AT 3 MONTHS- PRIMI & MULTI (UNPAIRED T TEST)

	Primi (Mean \pm S.D)	Multi (Mean \pm S.D)	Statistical analysis		
			Mean Difference \pm SE of Diff	T value	P value
Ferrous ascorbate	10.74 \pm 0.71	10.42 \pm 0.74	0.31 \pm 0.27	1.15	0.260
Ferrous calcium citrate	10.9 \pm 0.29	10.52 \pm 0.58	0.38 \pm 0.16	2.1	0.045

TABLE 4: MEAN CHANGES IN Hb IN TWO GROUPS

	Ferrous ascorbate	Ferrous calcium citrate
Baseline to 1 month	0.86	0.813
1 st month – 2 nd month	0.463	0.803
2 nd month – 3 rd month	0.277	0.333

TABLE 5: ADVERSE EFFECTS

Adverse effects	Ferrous ascorbate				Ferrous calcium citrate			
	Baseline	1 month	2 month	3 month	Baseline	1 month	2 month	3 month
Nausea	9 (30%)	4 (13.3%)	2 (6.7%)	3 (10%)	10(33.3%)	7(23.3%)	0(0%)	0(0%)
Vomiting	9 (30%)	6 (20%)	1 (3.3%)	2 (6.7%)	11(36.7%)	2(6.7%)	0(0%)	0(0%)
Gastric irritation	4 (13.3%)	0 (0%)	0 (0%)	0 (0%)	2(6.7%)	0(0%)	0(0%)	0(0%)
giddiness	3 (10%)	0 (0%)	0 (0%)	1 (3.3%)	3(10%)	0(0%)	0(0%)	0(0%)
Lethargy	3 (10%)	0 (0%)	1 (3.3%)	0 (0%)	6(20%)	2(6.7%)	0(0%)	0(0%)
Headache	1 (1.1%)	1 (3.3%)	0 (0%)	0 (0%)	0(0%)	0(0%)	0(0%)	0(0%)
Pain	3 (10%)	1 (3.3%)	1 (3.3%)	2 (6.7%)	3(10%)	2(6.7%)	3(10%)	3(10%)
Reduced appetite	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0(0%)	0(0%)	0(0%)	0(0%)

Increased risk of IDA during pregnancy is due to increased maternal iron needs and demands from the growing fetus and placenta; increased erythrocyte mass; and, in the third trimester, expanded maternal blood volume.^{16 - 20} Suggested prophylaxis for IDA in high-risk populations is 60 to 100 mg of elemental iron daily.²¹

In our study we compared two supplements with different iron composition. In this follow up study, no evidence of harm was identified from iron

supplementation of pregnant women who were iron replete and anaemic at initiation of antenatal care. The expected response to a course of iron is a reticulocytosis in 3-5 days, followed shortly by a rise in Hb. Gain in Hb by 1g/dL after one month qualifies as an adequate response accordingly we evaluated patient's Hb at the end of 1 month.

In our study, mean Hb in both groups did not show significant difference at baseline. Independent student t test showed that there was no significant

difference in mean Hb level between the two groups at different times (Baseline, 1 month, 2 months & 3 months).

Ferrous ascorbate: A repeated measures ANOVA determined that mean Hb levels were statistically significantly different between time points ($F = 54.38, P < 0.001$).

Post hoc tests using the Bonferroni correction revealed that increase in Hb level from baseline to 1 month ($9.02 \pm .98 \text{ gm\%}$ Vs $9.8 \pm .90 \text{ gm\%}$), baseline to 2 month ($9.02 \pm .98 \text{ gm\%}$ Vs $10.35 \pm .66 \text{ gm\%}$), baseline to 3 months ($9.02 \pm .98 \text{ gm\%}$ Vs $10.62 \pm .72$) was also statistically significant ($p < .001$). Also, there was a statistically significant increase in Hb level from 1st month to 2nd month ($9.8 \pm .90 \text{ gm\%}$ to $10.35 \pm .66 \text{ gm\%}$, $p < .001$), 1st month to 3rd month ($9.8 \pm .90 \text{ gm\%}$ to $10.62 \pm .72$, $p < .001$).

However, among ferrous ascorbate group there was statistically significant increase in Hb from baseline to 3 months, there was a slight increase in Hb level between 2nd month & 3rd month, but it was not statistically significant ($p = 0.204$).

Ferrous Calcium Citrate: A repeated measures ANOVA determined that mean Hb levels were statistically significantly different between time points ($F = 76.56, P < 0.001$).

Post hoc tests using the Bonferroni correction revealed that Hb level increased from baseline to 1 month ($8.72 \pm .99 \text{ gm\%}$ Vs $9.53 \pm 1.01 \text{ gm\%}$), baseline to 2 month ($8.72 \pm .99 \text{ gm\%}$ Vs $10.33 \pm .75 \text{ gm\%}$), baseline to 3 months ($8.72 \pm .99 \text{ gm\%}$ Vs $10.67 \pm .51$) was statistically significant ($p < .001$). Also, there was a statistically significant increase in Hb level from 1st month to 2nd month ($9.53 \pm 1.01 \text{ gm\%}$ to $10.33 \pm .75 \text{ gm\%}$, $p < .001$), 1st month to 3rd month ($9.53 \pm 1.01 \text{ gm\%}$ to $10.67 \pm .51$, $p < .001$) & 2nd month to 3rd month ($10.33 \pm .75 \text{ gm\%}$ to $10.67 \pm .51$, $p = 0.046$).

In Ferrous calcium citrate group mean change in Hb from 2nd to 3rd month also was statistically significant.

Comparison of amount of Hb increased at different time periods shows that in ferrous ascorbate group absolute increase from baseline to 1st month is

higher than ferrous calcium citrate group. But subsequent follow up data revealed that rate of rise of Hb has reduced by 50 % every month. In contrast ferrous calcium citrate group showed similar rate of increase in Hb upto 2 months of follow up period.

At the end of 3 months 10 % had nausea and 6.7 % had vomiting in ferrous ascorbate group but ferrous calcium citrate group it was 2% and 1% respectively. Overall proportion of adverse effects were less at subsequent 2nd, 3rd month follow up among Ferrous calcium citrate group in contrast to ferrous ascorbate group.

CONCLUSION: After statistical analysis, study reveals that ferrous calcium citrate with elemental iron 50 mg shows better increase in Hb levels and lesser proportion of side effects in comparison with ferrous ascorbate having 100 mg of elemental iron. Ferrous calcium citrate's better efficacy can be attributed to higher rate of absorption by means of its formulation *i.e* ferrous citrate combined with calcium. Calcium citrate gets dissociated in stomach and binds to phytates / phosphates in food, thus attenuating their inhibitory effect on iron absorption. Reduced rate of side effects can be due to lesser amount of elemental iron concentration present in formulation. In comparison of ferrous calcium citrate Vs ferrous ascorbate group, statistically significant difference is found in mean change Hb during 3 months among ferrous ascorbate group but not among ferrous calcium citrate group.

Drawbacks of the Study:

- Cost effectiveness was not studied.
- Other laboratory parameters not used.
- Anaemia may be due to causes other than iron deficiency.

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CONFLICT OF INTEREST: None

REFERENCES:

1. WHO-World Health Organization. Iron deficiency anaemia assessment, prevention and control: a guide for programme managers. Geneva; 2001.

2. Batista M Filho, Souza AI, Bresani CC. Anemia como problema de saúde pública: uma realidade atual. *Ciênc Saúde Colet* 2008; 13(6): 1917-22.
3. WHO, Worldwide Prevalence of Anaemia 1993–2005: WHO Global Database on Anaemia, WHO, Geneva, Switzerland, 2008.8. Sight and Life, “Nutritional Anaemia,” Sight and Life Press, 2007. http://www.sightandlife.org/fileadmin/data/Books/Nutritional_anaemia_book.
4. Viteri F. Iron supplementation for the control of iron deficiency anaemia in population at risk. *Nutr Rev* 1997; 55:189-203.
5. Allen L. Pregnancy and iron deficiency: unresolved issues. *Nutr Rev* 1997; 55:91-101.
6. The clinical use of blood in general medicine, obstetrics, paediatrics, surgery & anaesthesia, trauma & burns. Geneva, World Health Organization; 1998. (http://www.who.int/bloodsafety/clinical_use/en/Manual_EN.pdf).
7. Sharma JB, Soni D, Murthy NS, Malhotra M. Effect of dietary habits on prevalence of anaemia in pregnant women of Delhi. *J Obstet Gynaeco Res* 2003; 29:73-8.
8. Sharma JB. Medical complications in pregnancy. In: Sharma JB, Eds. *The obstetric protocol*. 1st ed. Delhi, India: Jaypee Brothers, 1998:78-98.
9. Sharma JB. Nutritional anaemia during pregnancy in non industrialised countries. In: Studd J, ed. *Progress in obstetrics and gynaecology*. Edinburgh: Churchill Livingstone, 2003:103-22.
10. World Health Organization. *Iron Deficiency Anaemia: Assessment, Prevention and Control*. Geneva, Switzerland; World Health Organization; 2001.
11. World Health Organization. *Intermittent Iron and Folic Acid Supplementation in Menstruating Women*. Geneva, Switzerland; World Health Organization; 2011.
12. World Health Organization. *Daily Iron and Folic Acid Supplementation in Pregnant Women*. Geneva Switzerland: World Health Organization; 2012
13. Brise H, Hallberg L. Absorbability of different iron compounds. *Acta Med Scand Suppl* 1962; 376: 23-37. <http://www.ncbi.nlm.nih.gov/pubmed/13873149>.
14. Cancelo-Hidalgo MJ, Castelo-Branco C, Palacios S, et al. Tolerability of different oral iron supplements: a systematic review. *Current Med Research & Opinion*. 2013; 29(4): 291-303. <http://www.ncbi.nlm.nih.gov/pubmed/23252877>
15. Walker SE, Paton TW, Cowan DH. Bioavailability of iron in oral ferrous sulfate preparations in healthy volunteers. *Canadian Med Assoc Jour* 1989; 141(6):543-547. <http://www.ncbi.nlm.nih.gov/pubmed/2776093>.
16. Recommendations to prevent and control iron deficiency in the United States. Centers for Disease Control and Prevention. *MMWR Recomm Rep*. 1998; 47:1-29. [PMID: 9563847]
17. Earl R, Woteki CE, eds. *Iron Deficiency Anemia: Recommended Guidelines for the Prevention, Detection, and Management among U.S. Children and Women of Childbearing Age*. Washington, DC: National Academies Press; 1993.
18. Krishnamurti L.: Iron-deficiency anemia. In: McInerney TK, Adam HM, Campbell DE, Kamat DM, Kelleher KJ, eds. *American Academy of Pediatrics Textbook of Pediatric Care*. Elk Grove Village, IL: American Academy of Pediatrics; Part 9, 2009.
19. Scholl TO. Iron status during pregnancy: setting the stage for mother and infant. *Am J Clin Nutr*. 2005; 81:1218S-1222S. [PMID: 15883455]
20. World Health Organization. *Iron and Folate Supplementation. Standards for Maternal and Neonatal Care. Integrated Management of Pregnancy and Childbirth (IMPAC). Volume 1.8*. Geneva: World Health Organization; 2006.
21. Short MW, Domagalski JE. Iron deficiency anemia: evaluation and management. *Am Fam Physician* 201387(2): 98-104. <http://www.ncbi.nlm.nih.gov/pubmed/23317073>

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