THE EFFECTIVENESS OF ORAL HAEMATINIC SYRUP IN CORRECTING IRON DEFICIENCY ANAEMIA IN PREGNANT AND POSTPARTUM WOMEN

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ABSTRACT

BACKGROUND

Although oral and intravenous iron therapies have been indicated for the treatment of iron deficiency anaemia (IDA), their utility is limited. Thus, there is a need for effective iron therapies that can address the limitations of current treatments of choice, given the deleterious effects of IDA. In this study, we determined the effectiveness of syrup, a ferric iron formulation, in correcting IDA in pregnant and postpartum women.

MATERIALS AND METHODS

The exclusion criteria were as follows: history of anaemia other than IDA, recent blood transfusion, current treatment with myelo-suppressive therapy, intolerance to iron derivatives, significant vaginal bleeding, and history of blood loss due to delivery. The inclusion criteria were as follows: 18 years old or older and with a definitive diagnosis of IDA. Baseline Hb and serum ferritin levels were measured, and additional measurements were made at 6 weeks (only Hb) and 12 weeks. A daily dose of 20 ml of syrup was administered orally by the study participants, twice daily, before meals for a period of 12 weeks.

RESULTS

Hb in the pregnant subgroup significantly increased from a baseline level of 10.32 ± 0.89 g/dl to 11.12 ± 1.51 g/dl at 12 weeks ($P < 0.001$). The median serum ferritin median level in this subgroup significantly increased from a baseline concentration of 13.30 ng/ml to a concentration of 28.65 ng/ml at 12 weeks ($P < 0.001$). In the postpartum subgroup, Hb significantly increased from a baseline level of 9.88 ± 1.14 g/dl to 12.01 ± 1.49 g/dl at 12 weeks ($P< 0.001$). A higher percentage of participants in the postpartum subgroup achieved at least an Hb level of 12 g/dl between baseline and 12 weeks ($P< 0.0001$) and at least a 2 g/dl increase in Hb levels between baseline and 12 weeks ($P< 0.0001$). Adverse effects were not observed.

CONCLUSION

Ferric iron oral syrup is effective and safe as an oral iron therapy for the correction of IDA in pregnant and postpartum women. (ferric ammonium citrate (160 mg), folic acid (0.5 mg), cyanocobalamin (Vit. B12) (7.5 mcg), cupric sulphate (30 mcg), and manganese sulphate (30 mcg)).

KEYWORDS

IDA, Anaemia, Postpartum, Pregnancy, India, Oral Iron.

HOW TO CITE THIS ARTICLE: Divakar H, Singh R, Narayanan P, et al. The effectiveness of oral haematinic syrup in correcting iron deficiency anaemia in pregnant and postpartum women. J. Evid. Based Med. Healthc. 2019; 6(8), 612-616. DOI: 10.18410/jebmh/2019/126

BACKGROUND

According to the India National Health Survey 2015–2016,[1] the prevalence of iron deficiency anaemia (IDA) in women between 15-49 years old is 55.3%. In pregnant and postpartum women, the prevalence of IDA is as high as 70%.[2] IDA has been implicated in 36% of all maternal mortality in India.[3] Furthermore, India contributes almost 80% of all maternal deaths due to IDA in South East Asia.[2]

IDA is defined as a haemoglobin (Hb) concentration of less than 12 g/dl in females.[4] It can impair maternal functioning and health, affecting physical performance, mood, cognition and the immune response.[5,6,7,8] These symptoms may, in turn, lead to poor mother–child interactions in the postpartum period, delaying infant development and affecting infant behaviour.[6,9]

Financial or Other, Competing Interest: Dr. Divakar reports grants from Cadila Pharma, during the conduct of the study.
Submission 07-01-2019, Peer Review 09-01-2019,
Acceptance 08-02-2019, Published 25-02-2019.
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DOI: 10.18410/jebmh/2019/126

Oral and intravenous iron therapies have been indicated for the treatment of IDA.[10] However, the utility of oral iron is limited by gastrointestinal side-effects[11,12] and patient non-adherence.[13] Furthermore, although intravenous iron therapies rapidly increase blood haemoglobin levels,[14] they can provoke severe, life threatening immune and allergic responses[15,16] or may require multiple low-doses[17] and long infusion times.[18] Thus, there is a need for effective iron therapies that can address the limitations of current treatments of choice.

Oral syrup is an iron formulation containing ferric ammonium citrate (160 mg), folic acid (0.5 mg), cyanocobalamin (Vit. B12) (7.5 mcg), cupric sulphate (30 mcg), and manganese sulphate (30 mcg) that is indicated for use in children, adolescents, and pregnant women for the treatment of iron deficiency anaemia. The goal of this study was to determine its effectiveness in correcting IDA in the pregnancy and the postpartum periods.

MATERIALS AND METHODS

Study Design

This was an open-label, prospective, multi-center study conducted with institutional review board approval over a period of nine months from February 2018 to October 2018. Women attending the Obstetric Departments of Divakars Speciality Hospital, Bengaluru, India, and Alameen Medical College, Bijapur, India, were recruited to take part in the study. These centres serve high income and low-income strata, respectively. All the subjects gave written informed consent before enrolling in the study.

Study Participants

Women booked for delivery and postpartum care were recruited and enrolled. We included pregnant women who were beyond 12 weeks' gestation and postpartum women who were 10 days and less postpartum. The subjects were 18 years old or older and had a definitive diagnosis of IDA, i.e., with a Hb of 11 gm/dL or less. (up to 7.5 gm/dl) We excluded women whose anaemia was the result of conditions other than iron deficiency (e.g. Vitamin B12 or folate deficiency, infection, chronic bleeding or renal failure) or who had previous blood transfusions, a history of iron intolerance, and a history of hematologic disease (e.g., Thalassemia or sickle cell disease). Patients with postpartum haemorrhage were also excluded. Hb was estimated by collecting a blood sample via finger prick and applying it to a Hemocue (Hb analyser) at bedside to determine inclusion, and those included underwent estimates of Hb and serum ferritin at base line, 6 weeks (only Hb), and 12 weeks by lab analysis.

Intervention

In this study, a daily dose of 20 ml of Heam-Up syrup was administered orally by the study participants, twice daily, before meals for a period of 12 weeks. The participants were requested to keep a journal and record any side-effects associated with taking the syrup. The subjects were followed up after 6 weeks and after 12 weeks to assess the status of iron stores and haemoglobin levels using previously mentioned parameters.

Outcome

The study was designed to establish the effectiveness of Haem-Up syrup in correcting iron deficiency anaemia in pregnant and postpartum women. The primary efficacy endpoint was a change in Hb from baseline to 12 weeks. The secondary endpoints were as follows: the mean change in Hb from baseline to 6 weeks; the mean change in Hb from 6 weeks to 12 weeks; percentage of participants achieving an Hb level of at least 12 g/dl between baseline and 12 weeks; percentage of participants achieving an Hb level of at least 12 g/dl between baseline and 6 weeks; percentage of participants achieving an increase in Hb level of at least 2 g/dl between baseline and 12 weeks; and the mean change in ferritin from baseline to 12 weeks. The safety endpoints were as follows: percentage of study participants reporting treatment-emergent adverse events (overall and related to study drug), whereby adverse events were spontaneously reported, elicited, or observed effects determined by the investigator to be probably or possibly related to study drug; and treatment-emergent serious adverse events (overall and related to study drug).

Statistics

For descriptive statistics, the number of participants, mean, standard deviation (SD), minimum, median and maximum age, weight, Hb, and serum ferritin values were calculated for continuous variables, and the case number and percentage were computed for categorical values. To compare variables at different time points, a paired t-test was applied. To compare proportions, "N-1" Chi-squared test was performed. For ferritin level comparison, a Wilcoxon test was applied, as the variable was not normal distributed. All analyses were performed using IBM SPSS Statistics version 24.

RESULTS

Three hundred and thirty-two women were enrolled in the study, and their available demographic variables are shown in Table 1. Of the 332 women, 211 women were enrolled at Divakars Hospital (Centre A) and 120 were enrolled at Alameen Medical College (Centre B). Furthermore, there were a total of 178 women in the pregnant subgroup and 153 women in the postpartum subgroup.

Characteristics	Centre A		Centre B		Centres A and B	
	Pregnant (n= 108)	Postpartum (n= 103)	Pregnant (n= 70)	Postpartum (n= 50)	Pregnant (n=178)	Postpartum (n= 153)
Age (Years)	22.48±2.55	25.61±4.25	27.94±3.99	29.28 ± 4.82	24.63±4.12	26.81±4.75
Weight (Kg)	50.61±6.2	53.94±5.81	62.29±8.83	63.37±11.24	55.20±9.51	57.02±9.11
BMI (Kg/m^2)	22.08±2.77	23.38±4.03	24.91±4.83	25.81± 4.64	23.19±4.64	24.17±4.364
Height (cm)	151± 4.8	152 ± 7.0	159± 9.2	157±5.5	154 ± 7.7	154 ± 6.8

Table 1. Demographic Characteristics of the Study Participants (All Values are Presented as Mean ± SD)

The primary efficacy endpoint was a change in Hb from baseline to 12 weeks (Table 2). Hb in the pregnant subgroup increased from a baseline level of 10.32 ± 0.89 g/dl to 11.12 ± 1.51 g/dl at 12 weeks. The mean increase was 0.79 ± 1.62 g/dl, and the change was statistically significant (t = –6.092, p < 0.001). In the postpartum subgroup, Hb increased from a baseline level of 9.88 ± 1.14 g/dl to 12.01 ± 1.49 g/dl at 12 weeks. The mean increase was 2.13 ± 1.74 g/dl, and the change was statistically significant (t = –13.989, p <0.001). We also calculated the mean change in Hb from baseline to 6 weeks, and the mean change in Hb from 6 weeks to 12 weeks (Table 2). The mean increase in Hb in the pregnant subgroup from baseline to 6 weeks was 0.54 ± 0.96 g/dl (t = –7.089, p <0.001). In the postpartum group, the mean increase was 1.62 ± 1.27 g/dl (t = –14.061, p < 0.001). The mean increases in Hb from 6 weeks to 12 weeks in the pregnant and postpartum groups were 0.25 ± 1.44 g/dl (t = –4.657, p < 0.001) and .57 ± 1.34 g/dl (t = –4.657, p < 0.001), respectively.

	Baseline	6 Weeks	12 Weeks	Mean Change Baseline to 6 Weeks	Mean Change 6 Weeks to 12 Weeks	Mean Change Baseline to 12 Weeks
Hb, g/dL						
Pregnancy Subgroup	10.33 ±0.90	10.87 ±1.06	11.12 ±1.51	0.54 ±0.96*	0.25 ±1.44*	0.79 ±1.62*
Postpartum Subgroup	9.89 ± 1.14	11.51 ±1.35	12.01 ±1.49	1.62 ±1.27*	0.57 ±1.34*	2.13 ±1.74*

Table 2. Hb Levels and Mean Changes in Hb Levels in Pregnant and Postpartum Groups (Centers A And B)

* P< 0.001

In the pregnant subgroup, a decrease in serum ferritin levels from baseline to 12 weeks was found in 44 cases, and an increase was observed in 108 cases (Table 3). The median serum ferritin median level in this subgroup increased from a baseline concentration of 13.30 ng/ml to a concentration of 28.65 ng/ml at 12 weeks; a Wilcoxon test showed that the change was statistically significant (Z = –5.849, p < 0.001). For the postpartum subgroup, the median serum ferritin decreased from a baseline concentration of 52.48 ng/ml to a concentration of 46.00 ng/ml at 12 weeks; the decrease was not statistically significant (Z = –1.470, p = 0.142). In this subgroup, a decrease was registered in 60 cases, and an increase was registered in 72 cases (Table 3).

As shown in Fig. 1A, the percentage of participants who achieved at least an Hb level of 12 g/dl between baseline and 12 weeks was greater in the postpartum group than in the pregnant group (56.2% vs 22.6%; P< 0.0001). Similarly, the percentage of participants who achieved at least a 2 g/dl increase in Hb levels between baseline and 12 weeks was also higher in the postpartum group than in the pregnant subgroup (60.8% vs. 16.1%; P < 0.0001) (Fig. 1B).

	Baseline	12 Weeks	Number of Participants Registering a Decrease	Number of Participants Registering an Increase	Z	P
Ferritin, ng/ml						
Pregnancy Subgroup	13.30	28.65	44	108	–5.849	0.001
Postpartum Subgroup	52.48	46.00	60	72	–1.470	0.142

Table 3. Median Serum Ferritin Concentration at Baseline and 12 weeks for Pregnant and Postpartum Groups (Centres A+B)

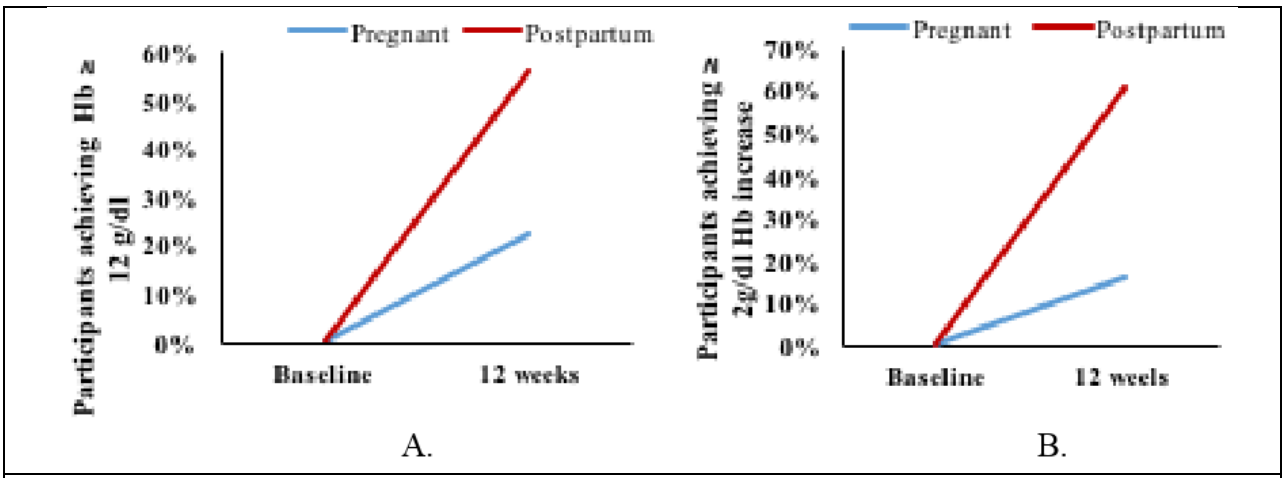

Figure 1a and 1b

Figure 1. A) Percentage of participants achieving aHb≥ than 12.0 g/dL at 12 weeks. The percentage of participants who met the secondary efficacy endpoint (Hb≥ 12.0 g/dL) was significantly greater in the postpartum group than in the pregnant group. **B)** Percentage of participants achieving an increase in Hb of 2.0 g/dL or greater at 12 weeks. The percentage of subjects who had an increase in haemoglobin of 2.0 g/dL or greater was significantly greater in postpartum group than in the pregnant group. P< 0001

DISCUSSION

The goal of the current study was to determine the effectiveness of oral syrup in improving Hb levels and serum ferritin in pregnant and postpartum women with IDA in India over a period of 12 weeks. We found that a daily oral dose of 20 ml of syrup resulted in statistically significant increases in Hb levels in both the pregnant and postpartum subgroups from baseline to 6 weeks, baseline to 12 weeks, and between 6 weeks and 12 weeks. Furthermore, we observed that the proportion of patients who achieved at least an Hb of 12 g/dl between baseline and 12 weeks was 22.6% and 56.2% in the pregnant and postpartum subgroups, respectively, and the proportion of patients who achieved at least a 2 g/dl increase in Hb between baseline and 12 weeks was 16.1% and 60.8% in the pregnant and postpartum subgroups, respectively. For the primary and secondary Hb end points, the greater increases were registered in the postpartum subgroup. The differences between the pregnant and postpartum subgroups might be attributable to the differences in iron demand during pregnancy and the postpartum period. During pregnancy, the demand for iron by mother and fetus is high, with expectant mothers needing about 800 mg of iron, of which about 40% is needed for fetal development.[19] However, the postpartum period is characterized by a low iron demand, although demand is higher for women with prepartum iron deficiency or for whom delivery is marked by a high loss of blood.[20] Owing to these differences, iron reserves may be replenished faster in postpartum women, enabling them to achieve higher Hb levels and Hb normalization sooner than pregnant women.

We found that syrup significantly increased serum ferritin levels in pregnant women from baseline to 12 weeks; however, although a decrease was noted in the postpartum group over the same time period, it was not significant. The results in the pregnant subgroup, together with the Hb findings, show the utility of syrup in safely increasing the iron statuses of pregnant women. A comparison of the serum ferritin levels from baseline to 12 weeks in the postpartum subgroup should not be taken as an indication that syrup reduced serum ferritin and therefore the iron statuses of women in this group. Studies have shown that during puerperium, i.e., the period from delivery to six weeks after delivery, "false normal" and "false high" serum ferritin readings may be obtained,[21] as serum ferritin is an acute phase protein that becomes elevated non-specifically following inflammation,[22] and has been shown to increase in response to the delivery inflammatory reaction.[23] For this group, Hb readings are a more accurate indication of the effectiveness of haematinic syrup in correcting IDA.

The incidence of IDA in pregnant women in India is quite high.[2] Left unmanaged in the postpartum period, IDA can adversely affect the health of both mother and infant.[5,6,7,8] Current WHO guidelines recommend a daily dose of 120 mg of elemental iron in the form of ferrous sulphate heptahydrate, ferrous fumarate, or ferrous gluconate for treatment of IDA during pregnancy.[24] Furthermore, FOGSI recommends 100 mg of elemental iron twice a day with 500 μg folic acid until normalization of Hb levels followed by a prophylactic dose of 60–100 mg for six months.[25] Ferrous iron formulations are preferred to ferric salts in clinical settings owing to their better bio-availability, which is roughly 3 to 4 times higher than that of ferric iron formulations.[26]

CONCLUSION

Although syrup is a ferric iron formulation, our study shows its efficacy, tolerability, and safety in the treatment of IDA in pregnant and postpartum women. Pharmaeconomic studies need to be performed to compare the cost utilization of syrup and the current recommended oral iron therapy for pregnant and postpartum women in India to determine where in the IDA treatment chain haematinic syrup would

be most effective, i.e., as a standalone therapy or as an adjunct.

This study has some limitations. Its open-label, non-blinded design could be seen as a potential source of bias; however, because the study did not have a placebo arm, bias was minimized. Furthermore, the use of the same Heamocue to measure Hb levels at baseline, 6 weeks, and 12 weeks minimized any errors associated with its use. Additionally, the use of an additional iron status marker, such as transferrin saturation (TSAT), considering the lack of reliability of serum ferritin readings early in the postpartum period, would have been useful in determining the effect of haematinic syrup on iron stores.

Acknowledgements
Authors would like to thank the support staff at both centers. This study received funding from Cadila pharma.

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