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Protocol

Effect of iron folic acid with tablet vitamin C compared to iron folic acid with routine verbal advice of vitamin C rich foods on the hemoglobin levels of anemic pregnant women attending a tertiary care hospital in Puducherry: protocol for a pragmatic trial

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ABSTRACT

Background: In routine practice, pregnant women are advised to take iron folic acid (IFA) tablets with vitamin C-rich foods. If vitamin C tablets are given instead, there may be an improvement in the hemoglobin levels of pregnant women. The study aims to find the effectiveness of IFA tablet with vitamin C tablet compared to IFA tablet with verbal advice of vitamin C rich foods, over 6 weeks, on the hemoglobin levels of anemic pregnant women (13-33 weeks) attending a tertiary care hospital in Puducherry.
Methods: A pragmatic trial will be conducted in the antenatal OPD of a hospital in Puducherry. Anemic pregnant women will be consecutively recruited until a sample size of 86 is attained. Permuted block randomization and allocation concealment will be used. After eligibility assessment, participants will be randomly assigned two arms. The intervention arm will receive IFA tablets with vitamin C tablets, while the control arm will be advised to take IFA tablets with vitamin C-rich food. Participants will be followed up at 6 weeks. The intention-to-treat approach will be used. Linear regression will be performed followed by multivariable linear regression to adjust for confounding variables.
Conclusions: This study protocol is designed to investigate whether the hemoglobin status and control of anemia in anemic mothers can be improved by giving IFA tablets with vitamin C tablets in routine practice, rather than verbal advice to take IFA tablets with vitamin C-rich foods.

Keywords: IFA, Vitamin C, Anemia, Pregnancy

INTRODUCTION

Anemia is a health condition where there is an insufficient amount of red blood cells or a lower-than-normal concentration of hemoglobin within them. Anemia affects around 24.8% of the world's population and is a leading contributor to the global burden of disease.[1] It is one of the most common micronutrient deficiencies among pregnant women. Hemoglobin levels below 11 g/dL are indicative of anemia in pregnant women. In 2019, anemia affected 36.5% of pregnant women aged 15 to 49 years worldwide.[2] According to the NFHS 5 report, almost 53% of pregnant women in India and 42.5% in Puducherry had anemia.[3]

During pregnancy, anemia is associated with adverse reproductive outcomes, such as low birth weight, preterm delivery, diminished iron stores in infants, and fetal death. Maternal complications associated with this condition include pre-eclampsia, antepartum haemorrhage, puerperal sepsis, thromboembolic complications, failure of lactation, spontaneous abortion, and death. Iron

deficiency causes 75% of anemia cases in pregnant women.[4]

Oral IFA tablet is the primary strategy to prevent and control anemia. According to the anemia Mukt Bharat programme guidelines, pregnant women aged 15 to 49 years with mild or moderate anemia (hemoglobin level ranging from 7 to 10.9 g/dL) are advised to take two IFA tablets (60 mg elemental Fe + 500 mcg folic acid) daily. A follow-up to assess their compliance with the treatment is done every two months. In case of improvement in hemoglobin levels, they are asked to switch to the prophylactic dose of IFA tablet for anemia, i.e., one IFA tablet per day. In situations where no improvement is observed, the patients are managed using IV iron sucrose/ferric carboxymaltose (FCM).[5]

Taking iron supplements daily can reduce the risk of maternal anemia at term by 70% and iron deficiency at term by 57%.[6] IFA tablets alone are sufficient to improve the hemoglobin levels. However, only 26% of pregnant women take IFA for 180 days or more during their pregnancy.[3] Therefore, in routine practice, patients are often advised verbally to take IFA tablets with citrus fruit juice or vitamin C-rich food, as these can facilitate iron absorption.

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin that can be found in certain foods and can also be taken as a dietary supplement. Foods rich in vitamin C include citrus fruits like oranges and lemons, Indian gooseberries (amla), tomatoes, potatoes, bell peppers, guava, and more. When iron is ingested orally, it is oxidized from its original form (Fe2+) to the ferric iron (Fe3+) state. Vitamin C supplements or vitamin C-rich foods are known to facilitate increased iron absorption by converting ferric to the more soluble ferrous iron (Fe2+). Additionally, vitamin C's potential to chelate iron contributes to iron absorption and hastens recovery from anemia.[7]

Though patients are advised verbally to take IFA tablets with vitamin C-rich food in routine practice, it's not clear if the patients are following these instructions, and if they are, how often they are doing so. Under these circumstances, prescribing vitamin C tablets along with IFA tablets might result in better outcomes than just providing verbal advice.

To our knowledge, no pragmatic trial has been conducted to determine whether giving vitamin C tablets along with IFA tablets in routine practice will improve hemoglobin status in anemic mothers, compared to simply suggesting that they consume IFA tablets with vitamin C-rich foods. Therefore, this study aims to demonstrate whether administering vitamin C tablets with IFA tablets will improve hemoglobin status and control anemia in anemic mothers, compared to providing only verbal advice to take IFA tablets with vitamin C rich foods.

METHODS

A randomized, parallel, open-blind, two-arm pragmatic clinical trial will be conducted at the antenatal OPD of a tertiary care hospital in Puducherry. The study has been registered with the clinical trial registry of India (CTRI/2022/07/043908).

Adult pregnant women who attend the antenatal OPD of a tertiary care facility in Puducherry will be approached. The purpose of the study will be explained to them, and they will be assessed for eligibility. Written informed consent will be obtained from those found to be eligible. If a prospective participant is not prepared to consent, she will be given the option to take the form home to discuss with her family before signing. Those who give consent will be enrolled in the study. Pregnant women in their second or third trimester of pregnancy (13-33 weeks) with mild to moderate iron deficiency anemia (7-10.9 g/dL) will be included in the study. Patients with conditions in which IFA is contraindicated, such as hypersensitivity, hemoglobinopathies, gastritis, recent repeated blood transfusions, and ulcerative colitis, will be excluded from the trial. Those who are already part of a different trial or taking other medication as part of a trial will also be excluded.

The sample size was calculated using the minimum clinically important difference of 1g/dl between the study and control groups at the end of the follow-up period, based on expert opinion, using Open Epi version 3.03. The total sample size obtained was 72 (i.e., 36 in each arm, with a 95% CI, power of 80%, and 1:1 ratio of study groups). The sample size was increased by 20% to account for potential attrition, resulting in a final sample size of 86 (i.e., 43 in each arm).

Permuted block randomization with block sizes of 2, 4, 6, and 8, and allocation concealment using the SNOSE technique will be done. Initially, a plan with the serial number of subjects in the order of recruitment along with the assignment group will be generated using online randomization software (www.sealedenvelope.com) by a third investigator who is not involved in data collection. The seed of the sequence will be saved by this investigator and will not be shared with others. By the sequentially numbered opaque envelopes (SNOSE) technique, this plan will be used to prepare a set of allocation slips with envelopes. When an eligible person is identified in the OPD, they will be provided with these envelopes sequentially without breaking the seal. Blinding cannot be done in this study as one arm will be provided tablet vitamin C, and the other arm will be given verbal advice. After collecting the baseline information using a semi-structured questionnaire, the envelope seal will be broken to provide the appropriate intervention. Eligible participants will be recruited consecutively until the required sample size is attained.

The baseline hemoglobin levels of the participants will be taken either from their case sheet or accessed from the HIS (Hemoglobin test should have been done within the last 25 days from the date of enrolment). If the test was not done within the last 25 days, participants will be provided with a hemogram investigation form and facilitated to get tested.

The participants selected for the intervention arm will be given IFA tablets (60 mg elemental iron + 500 mcg folic acid BD) and vitamin C supplementation (50 mg BD). They will be asked to take the vitamin C supplementation compulsorily with the IFA tablets. The control group will be given IFA tablets alone (60 mg elemental iron + 500 mcg folic acid BD) and will be advised to take them with vitamin C-rich food or drinks. A health education material will be pasted at the antenatal OPD to facilitate verbal advice. Both groups will be asked to take the medication 1.5 hours after breakfast and dinner. They will be informed to avoid calcium-rich food like mild, curd or supplements while taking IFA tablets.

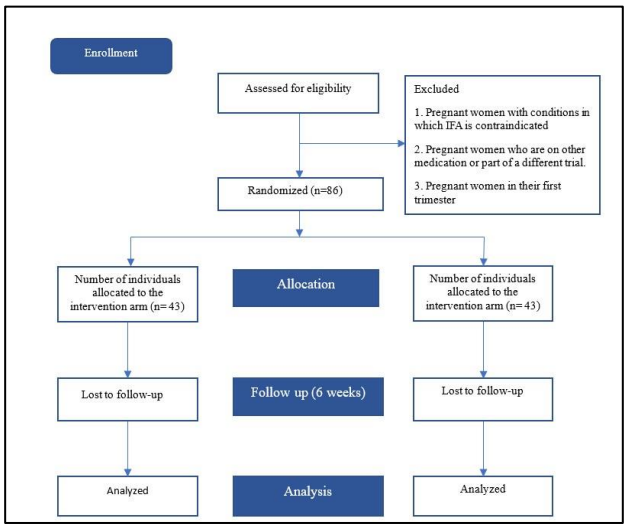

Figure 1: CONSORT diagram of flow of patients through the study.

Adherence will be measured in two ways: Firstly, the patients will be contacted over the phone on any two random days during the 4th to 6th week of follow-up to assess their adherence to the intervention. They will be asked if they consumed two doses of the IFA tablet along with vitamin C (rich diet or tablet) simultaneously on the previous day. In case of non-compliance, the reason will be asked for and noted down. Secondly, adherence to the medication will be assessed using the Medication Adherence Rating Scale -10 (MARS-10) during follow up after 6 weeks.[8] Dietary history will be recorded using a Food Frequency Questionnaire. Participants who took at least three iron-rich food groups more than 2 to 3 times per week were considered to have adequate intake of iron from their diet, while the others were categorized as having inadequate intake of iron.

The participants will be assessed for changes in hemoglobin levels at the end of 6 weeks and will be provided with a hemogram investigation form to get tested. The values obtained will be recorded. The data will be kept confidential in a password-protected system, and accessibility will be restricted only to the investigators. It will be stored for three years.

Data analysis

Data analysis will be performed using SPSS software version 23. Baseline characteristics of the participants in the two arms will be compared to ensure that the randomization was successful and that there are no significant differences between the 2 groups. Continuous variables, such as age and hemoglobin level, will be summarized as mean (SD) or median (IQR) based on the normality of the data. Categorical variables, such as occupation, socioeconomic status, education, etc., will be summarized as frequency or percentage (n, %). The primary outcome is in hemoglobin level taken 6 weeks in the intervention and control arms. The primary effect measure is the mean difference in hemoglobin levels between the intervention and control arms after 6 weeks. An intention to treat analysis approach will be used. Linear regression will be used to estimate the beta coefficient (mean difference in hemoglobin level between intervention and control arms), along with a 95% confidence interval (CI) and p value. Multivariable linear regression will be conducted to account for confounding variables such as such as age, socioeconomic status, education, birth order, baseline hemoglobin level, and iron-rich diet, and to estimate the adjusted beta coefficient, along with a 95% CI and p value.

Ethical aspects

This protocol was approved by the Institutional scientific and ethics committee. A decision to withdraw the participant from the trial will be taken if the participant withdraws her consent or if the intervention is causing harm to the participant's health and safety, as determined by her treating physician. In the event of any adverse events, the participant will be advised to stop the treatment immediately and referred to a physician. All adverse events will be reported to the relevant authorities.

DISCUSSION

All the recommendations in the SPIRIT checklist (Standard protocol items: recommendations for interventional trials) were considered while preparing this protocol. The study's findings will be presented at conferences and published in journals. Vitamin C, in any form, is known to enhance iron absorption. IFA tablets have been used for decades to treat anemia. However, the adherence to IFA among pregnant mothers is quite low.[9] In routine practice, pregnant women are usually advised to consume IFA tablets with vitamin C-rich foods. Though this may improve the iron absorption, pregnant

women may not do so as it is not feasible at all times. Therefore, prescribing vitamin C in tablet form may be an alternative that will improve adherence, and thereby result in increased hemoglobin levels.

If taking vitamin C tablets with IFA tablets is determined to be useful in improving the hemoglobin status of anemic pregnant women, relevant authorities will be notified. This study aims to determine whether taking IFA tablets with vitamin C tablets to treat anemia will help improve the hemoglobin status of anemic pregnant women compared to IFA tablets with verbal advice to take them with vitamin C-rich food. If the intervention is found to be effective, it could potentially reduce the burden of anemia in our country.

CONCLUSION

The study protocol is designed to demonstrate whether the hemoglobin status and the control of anemia in anemic mothers will improve if IFA tablet is given with vitamin C tablet in routine practice instead of mere suggestion or verbal advice to take IFA tablet with vitamin C rich food.

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