Indian J Med Res 151, April 2020, pp 371-374
DOI: 10.4103/ijmr.IJMR_1464_18

Quick Response Code:

Fractional iron absorption from enteric-coated ferrous sulphate tablet

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Received August 6, 2018

***Background & objectives*: Iron supplementation is widely used public health measure to manage iron deficiency anaemia. In India, enteric-coated iron tablets are administered to adolescent boys and girls to avoid adverse effects such as gastritis, which reduces compliance, but this may result in poor iron absorption. Data on the absorption of iron from enteric-coated ferrous sulphate tablets are lacking. The present study using stable isotopic approach was aimed to measure iron absorption in iron deficient women.**

***Methods*: Iron absorption was measured from stable isotope-labelled enteric-coated ferrous sulphate (^{57}Fe, ECFS) and uncoated ferrous sulphate (^{58}Fe, UCFS) tablets in iron-deficient (n=9) women, aged 18-40 yr with no infection or inflammation. The two types of tablets (ECFS and UCFS) were administered on consecutive days, 60 min after breakfast, and the sequence being random. Blood samples were collected before dosing, and on day 15, to measure iron absorption from the shift in iron isotopic ratios in haemoglobin.**

***Results*: Eight women completed the iron absorption study. Iron absorption was found to be significantly lower in ECFS compared to UCFS (3.5 vs. 12%, $P<0.05$) consumption.**

***Interpretation & conclusions*: Our study showed poor iron bioavailability from ECFS, and supplementation programmes may consider UCFS tablets for better haematological outcomes.**

Key words Anaemia - enteric-coated tablets - ferrous sulphate - iron deficiency - iron deficiency anaemia - iron supplementation

Anaemia affects nearly 50 per cent of women of reproductive age in India, and iron supplementation is the main approach to reduce this burden, although limited in its success[1]. Currently, the National Iron Plus Initiative (NIPI) programme[2] offers iron supplementation from the age of six months onwards, in vulnerable target groups. To reduce gastrointestinal adverse events and improve compliance, the NIPI programme provides enteric-coated ferrous sulphate (ECFS), which ensures that iron does not come in contact with the gastric mucosa[3]. However, clear evidence on the bioavailability of iron from ECFS is lacking, although available data suggest that iron is poorly absorbed from ECFS[4]. This study was thus undertaken to measure fractional iron absorption from ECFS relative to uncoated ferrous sulphate (UCFS) in iron-deficient young Indian women.

Material & Methods

This study was carried out among young (aged 18-40 yr) non-pregnant non-lactating women from the staff of St. John's Medical College and Hospital, Bengaluru, India. A total of 24 women gave consent

and a venous blood sample (6 ml) was obtained from each for screening of iron status. Haemoglobin was measured using a haematology analyser (ABX Pentra 60C$^+$, HORIBA, France); ferritin was estimated by electrochemiluminescence (E411 immunoassay analyser, Roche Diagnostics, Switzerland) and C-reactive protein (CRP) was measured by immunoturbidometry (COBAS integra 400, Roche Diagnostics, Switzerland). Based on iron status, nine women who were iron deficient (serum ferritin <15 µg/l), with no infection or inflammation (CRP <10 mg/l) were selected for the absorption study. None of the individuals were on any iron supplements or any other medication. In our previous study[5] we have observed a difference of 60 per cent in the relative absorption of iron between the reference meal and the meal with tea. To observe 80 per cent power and 5 per cent level of significance, the sample size required was nine. The study duration was one month (April, 2018). This study was approved by the institutional ethics committee of St. John's Medical College (Approval No. 87/2015) and written informed consent was obtained from all participants.

The preparation of the isotope labelled ferrous sulphate ($FeSO_4$) tablets was similar to the method used in the commercial preparation of the supplementation programme tablets[6]. The elemental ^{57}Fe and ^{58}Fe isotopes (Chemgas, France) were dissolved separately in 0.01 M H_2SO_4 (Merck, Ultrapure grade) solution to get a final concentration of 3 mg ^{57}Fe or ^{58}Fe/ml of iron sulphate solution[5]. All the procedures were carried out in a clean room under the fume hood. The tablets contained $FeSO_4$ equivalent to 100 mg elemental Fe and 0.5 mg folic acid. The elemental iron contained 97 mg of ^{56}Fe and 3 mg of stable isotope of ^{57}Fe as the sulphate salt in the ECFS tablet, and ^{58}Fe in the UCFS tablet. All chemicals were pharma grade (Yarrow Chemical, Mumbai); the $^{57}FeSO_4$ or $^{58}FeSO_4$ was slowly added as a 3 mg $^{57}FeSO_4$ or $^{58}FeSO_4$/ml solution to the natural $FeSO_4$ granules and dried. These were blended with excipients, loaded into a tablet press and punched as tablets in a twelve station-punching machine (CIP Machinery Pvt. Ltd., Ahmedabad). Tablets incorporated with $^{57}FeSO_4$ were then film coated with enteric coating (methahexa copolymer, 6% w/w). Similarly, the tablets incorporated with $^{58}FeSO_4$ were film coated with titanium oxide as a colourant and opacifier. These procedures were carried out at a registered pharmaceutical research facility (Karnataka College of Pharmacy, Bengaluru, registered under the Rajiv Gandhi University of Health Sciences, Bengaluru, Karnataka, India).

Each woman received the isotope labelled ECFS or UCFS in a randomized manner on two consecutive days. On day one, women were asked to report to the metabolic ward in a fasted state, where their anthropometry was measured and a medical history was taken, following which, a rice-based breakfast (Two Idlies with chutney) was served. Sixty minutes after breakfast, the participant consumed either ECFS or UCFS with 100 ml of water, and no food or drink was allowed for 3 h thereafter. The next day, the second isotope labelled tablet was administered with the same process. A blood sample (6 ml) was drawn 15 days after the first day of dosing. Each isotopically enriched blood sample was analyzed in triplicate to measure the shift in isotopic composition of iron in Hb, using a Thermal Ionization Mass Spectrometer (Triton, Thermo Scientific, Germany). The erythrocyte incorporation technique was used to measure fractional iron absorption; the methodology has been described earlier[5].

Statistical analysis: Data are summarized as arithmetic or geometric mean±SD. Paired *t* test of log transformed values was used to compare iron absorption between ECFS and UCFS consumption. Each woman served as her own control.

Results & Discussion

Of the nine women, eight completed the study (one individual dropped out due to gastritis). The baseline characteristics of the study individuals are given in the Table. The mean age was 32 yr; all women were iron deficient and had no infection or inflammation at the time of the study. Fractional iron absorption was significantly (~30%) lower in ECFS (3.5%; minimum 0.46% and maximum 11.85%) while that from UCFS was found to be 12 per cent (minimum 7.05% and maximum 17.40%; $P<0.05$).

In an earlier study, the plasma appearance method showed a 30 per cent bioavailability from ECFS in comparison to $FeSO_4$ provided as a solution[4]. Severely anaemic patients treated with ECFS showed no improvement in their iron status, while replacing their iron tablets with UCFS demonstrated a marked improvement[7]. The enteric coating is applied to shield the iron in the gastric environment and to reduce adverse events. Iron absorption is proton dependent and occurs primarily at the duodenum which is the

Table. Baseline characteristics of and fractional iron absorption in women participating in the iron absorption study

Variable	Iron deficient women (n=8)	Percentage fractional iron absorption (n=8)		
		Individual number	ECFS	UCFS
Age (yr)	33.6±8.35	1	2.22	8.56
Weight (kg)	56.1±9.62	2	0.46	7.05
Height (m)	1.5±0.06	3	3.20	12.61
BMI (kg/m^2)	23.2±3.42	4	3.92	16.50
Haemoglobin (g/dl)	10.4±1.50	5	11.85	17.40
Serum ferritin (µg/l)[#]	6.1 (3.8, 9.5)	6	4.96	17.17
CRP (mg/l)[#]	3.6 (1.5, 8.8)	7	4.50	9.20
		8	6.31	11.03
Total[#]			3.48 (1.3, 9.0)[*]	11.82 (8.4,16.7)

Values are mean ±SD. [*]P<0.05 compared to UCFS, [#]Values are geometric mean (GM − SD, GM + SD). UCFS, uncoated ferrous sulphate; ECFS, enteric coated ferrous sulphate; SD, standard deviation; BMI, body mass index; CRP, C-reactive protein

shortest part of the small intestine. *In vitro* dissolution time has been shown to be markedly longer for ECFS in fluid obtained from perfusion of normal duodenum due to the higher *p*H in this region[8]. The short duodenal transit time may not be sufficient for the enteric coating to dissolve completely and deliver the iron at the duodenum, leading to lower iron absorption. The iron may then be delivered further downstream in the jejunum, ileum or the colon based on the chemistry of the enteric coat used, where the absorption of iron is poor[9]. Iron is highly reactive and induces the formation of reactive oxygen species[10]. The unabsorbed iron also interacts with the gut bacteria adversely, altering the gut microbiome towards an abundance of enterobacteria including enteropathogenic *Escherichia coli*[11]. In real-life situations, iron supplements are taken after habitual foods that are rich in phytates and polyphenols, that may further inhibit the absorption of iron[5]. Previous studies also suggest the need for better operational strategies to reduce non-compliance to iron folic acid (IFA). The major reason for non-adherence to IFA therapy was shown to be the high incidence of gastrointestinal side effects[12]. Based on these, the supplementation policy may need to reconsider the use of ECFS tablets and possibly also use a lower dosage formulation of iron. This will reduce gastric adverse effects, improve compliance and lead to better impact in large scale public health programmes to reduce the burden of iron deficiency and iron deficiency anaemia.

***Acknowledgment*:** Authors acknowledge the staff of St. John's Medical College and Hospital, Bengaluru, for their participation in the study and Shri Charles Milton, Senior Laboratory Technician for blood collection, biochemical analysis and TIMS analysis. Authors thank Dr Tinku Thomas for her technical support in the statistical analysis.

***Financial support & sponsorship*:** This study was financially supported by Margdarshi Fellowship of the Wellcome Trust/DBT India Alliance to the last author (AVK).

***Conflicts of Interest*:** None.

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