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Case Series

A randomized open-label study to compare iron content in the blood of healthy subjects treated with Tasiron tablets containing ferric di-phosphate as compared to tablets containing ferrous ascorbate

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ABSTRACT

Iron deficiency anemia (IDA) frequently affects reproductive-age women, pregnant women, and children of growing age, particularly in developing countries like India. Traditional oral iron supplementation has various side effects, and therefore, liposomal technology has been introduced. This study compared serum iron levels in healthy adult female subjects treated with Tasiron tablets containing 30 mg (elemental iron) of micronized liposomal ferric di-phosphate, with those administered with tablets containing 100 mg (elemental iron) of ferrous ascorbate, over 15 days. The test group (n=7) received 30 mg of micronized liposomal ferric di-phosphate and the control group (n=7) received 100 mg of ferrous ascorbate. Serum levels of iron, hemoglobin, ferritin, and transferrin were measured from samples collected on days 1, 8, and 16 of the treatment periods. Higher iron content and hemoglobin levels were found at day 16 ($p<0.05$) and day 8 ($p<0.05$) as compared to day 1 in both groups. The test group received one-third the dose of iron that was administered to the control group. The group receiving 100 mg ferrous ascorbate had higher ferritin levels at day 8 ($p<0.01$) and day 16 ($p<0.01$) as compared to day 1. In the group receiving ferrous ascorbate, transferrin levels decreased on day 8 and 16. In contrast, there was an increase in transferrin levels in the group receiving liposomal iron. Oral liposomal iron effectively increases iron content and hemoglobin levels at one-third the concentration as compared to ferrous ascorbate. Further studies on larger numbers with a longer follow-up are required.

Keywords: Anemia, Ferric di-phosphate, Ferrous ascorbate, IDA, Tasiron

INTRODUCTION

Iron is essential for performing a multitude of physiological functions like oxidative metabolism, erythropoiesis, and cellular immune responses. It is vital for several molecular functions including hemoglobin synthesis and the catalytic activity of various enzymes such as those involved in oxidative metabolism. Iron is one of the most abundant elements on earth; however, IDA is the most common nutritional disorder.[1,2] It is a highly afflicting condition occurring at all stages of life and particularly affects young children of growing age, women of childbearing age, and pregnant women.[3,4] The World Health Organization (WHO) estimates that 42% of children less than 5 years of age and 40% of pregnant women worldwide are anemic.[5] IDA is a common cause of morbidity and mortality in developing countries.[6]

In India, anemia in children is a major public health problem. Comprehensive national nutrition survey 2016-2018 indicated that more than 50% of anemia in childhood is due to an underlying nutritional deficiency. The statistics from the National Family Health Survey-5 (NFHS-5; 2019-21) have highlighted the rising prevalence of anemia across all ages. The highest spike in the prevalence of anemia over the last 5 years was in the under-five years' age (6-59 months) group from 59% to 67.1%.[7] Children with IDA have impaired psychomotor and/or mental development, decreased exercise capacity, and decreased immunity, and can eventually develop

neurocognitive impairment.[8] IDA is seen among pregnant women in developing countries at a prevalence of 35-75%. It has a significant impact on the health of the mother as well as the fetus and may lead to preterm delivery, low birth weight, intrauterine growth retardation, postpartum hemorrhage, and cardiac failure.[6]

Oral iron therapy using 2-3 mg/kg elemental iron daily is used to treat most cases of IDA.[9] Although oral iron treatment is cheaper and more convenient, it often leads to various side effects,[10] such as gastrointestinal effects (in up to 70% of patients), such as flatulence, nausea/vomiting, constipation or diarrhea, metallic taste, staining of the teeth, or epigastric distress.[11,12] These side effects and bad taste lead to non-adherence to the oral iron treatment.[13] Liposomal technology involves the microencapsulation of iron within phospholipid and sucrose esters of the fatty acid membrane and is the recent approach to improve iron tolerance and absorption. The outer phospholipid protects iron from degrading in the mouth and stomach, and assists in targeted delivery. The iron could be further micronized, the smaller particles thus formed have an increased surface area to drug ratio thereby increasing the dissolution rate of the drug resulting in increased bioavailability. It is a new and promising strategy for oral iron delivery and shows high gastrointestinal absorption and bioavailability with reduced incidence of adverse effects.[1,10]

Tasiron 30 chewable tablets are formulated with proprietary liposomal technology and contain ferric-diphosphate delivering 30 mg of elemental iron per serving. Iron formulations containing salts such as ferrous ascorbate have been used as traditional iron supplements to prevent iron-deficiency anemia. Studies comparing the efficacy of traditional and recent formulations of oral iron therapy have been conducted in European and American regions and need to be better documented in the Indian population. Therefore, the aim of this study is to compare the iron content in the blood of healthy adult female subjects treated with Tasiron tablets containing 30 mg of micronized liposomal ferric di-phosphate, with tablets containing 100 mg of ferrous ascorbate, over a period of fifteen days.

CASE SERIES

This was an open-label study conducted in July 2022, in healthy adult female subjects at institute for advanced training and research in interdisciplinary sciences, Mumbai. Ethical approval for the study was taken from institutional ethics committee. All participants signed a written and informed consent. The study was conducted as per the Indian Council of Medical Research (ICMR) guidelines for biomedical research on human subjects, ICH-GCP guidelines, and in accordance with the Declaration of Helsinki.

This study included 14 healthy adult female participants aged between 18 to 55 years and body mass index (BMI) between 18.5 and 30 kg/m^2. The participants had no medical history of significant diseases. All participants had negative rapid plasma reagin (RPR), hepatitis B surface antigen (HBsAg), antibodies to the human immune-deficiency virus (HIV) I and II, and COVID-19. The urine test for drug abuse and pregnancy and salivary alcohol test was also negative. All participants were non-lactating. Participants with difficulty in donating blood or swallowing solids like lozenges or capsules, and participating in any drug research or donating blood in the past 3 months were excluded. All participants had the right to drop out from the study at any time during the course of the study without prior intimation to investigators with no consequence on their treatment. Patient characteristics are described in Table 1.

Subjects were divided into two groups: test (n=7) and control (n=7). The test group was administered the test formulation (Tasiron tablets containing 30 mg of liposomal ferric di-phosphate), and the control group was administered the reference formulation (tablets containing ferrous ascorbate 100 mg). A single dose per day at night before sleep was taken by both the test and control groups. A diary was maintained by the subject for recording compliance to dosing. The field coordinator further ensured compliance through phone calls and one weekly visit at the home of each subject. Ten ml of blood was collected at each sampling point on day 1, day 8, and day 16 post-dose. Serum hemoglobin, ferritin, and transferrin were measured before the administration of test and reference formulation and after the administration of test and reference formulation on day 8 and day 16.

Statistical analysis of safety and tolerability parameters was calculated by Statistical Analysis Software (SAS) version 8.2 or higher version. No aberrant values were recorded in the study and all the values were included in statistical analysis. All parameters are expressed as mean ± SE.

Compliance and side effects

All the subjects completed the study and complied well with the protocol requirements. The treatment with both the reference and test formulation was well tolerated by all the participants except for the given stances. Two participants in the reference group had vomiting three hours post-dosing which resolved within an hour after taking ondansetron tablet (4 mg). One participant had muscle pain while one had headache and nausea in the test group which resolved completely within one hour after treatment with diclofenac and ondansetron tablets (4 mg) respectively.

Serum levels of iron, hemoglobin, ferritin, and transferrin

The group receiving 100 mg ferrous ascorbate (Reference group) had higher iron content at day 16 ($p<0.01$) as compared to the iron content on day 1 (10.77 mg/dl vs. 10.21 mg/dl). Similarly, in the group receiving 30 mg

liposomal iron (Test group), there was an increase in iron on day 16 ($p<0.05$) as compared to the iron content on day 1 (10.87 mg/dl vs. 11.26 mg/dl).

Both formulations were effective in increasing the hemoglobin levels. Compared with baseline hemoglobin (10.21±0.38 g/dl), the reference group had higher hemoglobin levels at day 8 (10.73±0.36 g/dl; $p<0.05$) and at day 16 (10.77±0.32 g/dl; $p<0.05$). Interestingly, the increase in the hemoglobin levels was higher in the test group at day 8 (11.5±0.24 g/dl; $p<0.01$). The hemoglobin levels also increased at day 16 (11.25±0.30 g/dl; $p=0.055$) as compared to the baseline levels in the reference group. On day 16, 6 patients (85.7%) in each group had a numerical increase in hemoglobin as compared to baseline.

Compared to the ferritin levels on day 1 (15.03±7.74 µg/L), the reference group had higher ferritin levels at day 8 (37.61±9.49 µg/L; $p<0.01$) and at day 16 (51.1±10.58 µg/L; $p<0.01$) as 1. A similar increase in ferritin levels was seen in the test group on day 8 (33.52±19.18 µg/L; $p=0.052$) and day 16 (52.81±32.09 µg/L; $p=0.077$) as compared to the baseline ferritin.

Compared to transferrin levels on day 1 (338.28±20.14 mg/dl), there was a significant decrease in the transferrin levels at day 8 (309.0±17.80 mg/dl; $p<0.01$) and day 16 (284.71±12.98 mg/dl; $p<0.01$) in the reference group as. In contrast, in the test group, there was an increase in the transferrin levels at day 8 (311.28±12.3 mg/dl; $p<0.05$) and day 16 (313.57±15.27 mg/dl; $p<0.05$) as compared to baseline transferrin (294.28±11.5 mg/dl).

Table 1: Demographic and clinical characteristics of participants in the two groups.

Parameters	Reference formulation	Test formulation
Age (In years)	36.7±9.4	38±6.5
Height (cm)	159.1±4.1	153.8±13.7
Weight (kg)	59.3±10.4	64.5±10.4
BMI (kg/m^2)	23.4±3.7	27.3±3.2
Hemoglobin at baseline (g/dl)	10.21±0.38	10.87±0.36
Hemoglobin on day 8 (g/dl)	10.73±0.36	11.5±0.24
Hemoglobin on day 16 (g/dl)	10.77±0.32	11.25±0.30
Patients with numerical increase in haemoglobin on day 16	6; 85.7%	6; 85.7%

Primary and secondary pharmacokinetic parameters

The $AUC_{0\text{-}12hour}$ was comparable between reference and test formulation. The half-life of iron elimination, K_{el} constant were also comparable between reference and test formulation (Table 2).

Table 2: Pharmacokinetic parameters of reference and test formulation.

Pharmacokinetic parameters	Reference formulation	Test formulation
C_{max} (ng/ml)	51.75±7.30	132.726±68.762
$AUC_{0\text{-}12hour}$ (ng/ml*hour)	481.35± 47.22	613.588± 131.486
$AUC_{0\text{-}\alpha}$ (ng/ml*hour)	12190.89± 11158.94	970.927± 205.078
T_{max} (hours)	2.00±2.646	4.00±1.82574
K_{el} Constant (hours^{-1})	0.081±0.036	0.07925± 0.01077
$T_{1/2}$ (hours)	18.84±18.75	9.27724± 0.99330

DISCUSSION

This pilot study has several interesting findings. The study demonstrates that liposomal iron is efficient i.e., it leads to an increase in iron and hemoglobin content, and is well tolerated. The present study reports that liposomal iron at one-third concentration (30 mg) as compared to traditional iron supplementation (100 mg) is equally effective in increasing iron content on day 16. Interestingly, the increase in hemoglobin levels at day 8 was higher in the group receiving liposomal iron as compared to the group receiving ferrous ascorbate. This is in line with another study that reports an increase in serum iron and hemoglobin in inflammatory bowel disease patients after 8 weeks of treatment with oral liposomal iron.[10] Similarly, a study on non-pregnant women with IDA receiving one sachet of microencapsulated liposomal iron pyrophosphate reported an increase in mean serum hemoglobin levels.[3]

Ferritin level is an indicator of the storage of iron in cells. There was an increase in ferritin levels in the group receiving ferrous ascorbate and liposomal iron. However, the increase in ferritin levels in the group receiving liposomal iron was not statistically significant. This could be due to participants in the test formulation group already having higher baseline ferritin levels. Another reason may be attributed to the fact that the concentration used in this group was one-third as compared to the group receiving the reference formulation.

Transferrin is a protein that transports iron and reflects the total iron-binding capacity. Interestingly, transferrin levels showed contradicting results. In the group receiving ferrous ascorbate, transferrin levels decreased on day 8 and 16. This is in line with increased iron content which could have led to more iron getting bound to transferrin and therefore lower transferrin levels. A study in inflammatory bowel disease patients after 8 weeks of treatment with oral liposomal iron reported higher transferrin saturation.[10] In contrast, there was an increase in transferrin levels in the group receiving liposomal iron. This suggests that liposomal iron is absorbed through different channels as compared to traditional iron. The liposome is absorbed by the microfold cells (M cells) of the small intestine, which

originate from the lymphatic system. This may explain the contradicting results for transferrin.

The current study depicts the safety of Tasiron tablets. There were two participants in both groups showing mild adverse reactions which resolved completely within an hour. Therefore, the reference and test formulations are safe to use and have good tolerability. The comparison of pharmacokinetic parameters demonstrates that the bioavailability of the two formulations is comparable, despite the fact that the liposomal iron formulation had one-third the iron content. Therefore, the comparable bioavailability, good safety profile, and efficacy in improving hemoglobin suggests that this liposomal iron formulation could be explored as the treatment of choice for the management of IDA.

The present study has some limitations. Firstly, the study has a relatively small number of participants and it is a single-center pilot study. Moreover, patients were treated with oral liposomal iron for 16 days, whereas the recommended duration of oral iron therapy is commonly between 3 to 6 months.[14] Lastly, better adherence to liposomal iron tablets as compared to ferrous ascorbate tablets could not be reported due to the very short period of the study.

CONCLUSION

The current study provides data supporting the efficacy and safety of liposomal iron. Increased iron content and hemoglobin levels were found in the group receiving oral liposomal iron. These results were obtained by using a one-third concentration as compared to ferrous ascorbate tablets. Therefore, this study provides indicative evidence of the potential of liposomal iron formulations for the management of anemia. Additional studies utilizing higher doses, larger cohorts, and longer follow-ups are required to further evaluate and validate the role of oral liposomal iron.

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REFERENCES

1. Biniwale P, Pal B, Sundari T, Mandrupkar G, Datar N, Khurana A et al. Liposomal iron for iron deficiency anemia in women of reproductive age: review of current evidence. Open J Obstet Gynecol. 2018;11(8):993-1005.
2. Maladkar M, Sankar S, Yadav A. A novel approach for iron deficiency anaemia with liposomal iron: concept to clinic. J Biosci Med. 2020;8(9):27-41.
3. Hussain U, Zia K, Iqbal R, Saeed M, Ashraf N. Efficacy of a novel food supplement (Ferfer®) containing microencapsulated iron in liposomal form in female iron deficiency anemia. Cureus. 2019;11(5):e4603.
4. Malhotra J, Garg R, Malhotra N, Agrawal P. Oral liposomal iron: a treatment proposal for anemia. World J Anemia. 2017;1(4):1-6.
5. World Health Organization. Anaemia. Available at: https://www.who.int/news-room/fact-sheets/detail/anaemia. Accessed on 08 August, 2023.
6. Chavan S, Rana P, Tripathi R, Tekur U. Comparison of efficacy and safety of iron polymaltose complex and ferrous ascorbate with ferrous sulphate in pregnant women with iron-deficiency anaemia. Indian J Med Res. 2021;154(1):78-84.
7. Ministry of Health and Family Welfare. National Family Health Survey (NFHS 5). 2019-2020. Compendium of Fact Sheets: Key indicators India and 14 states/UTs (phase II). Available at: https://main.mohfw.gov.in/sites/default/files/NFHS-5_Phase-II_0.pdf. Accessed on 06 February, 2023.
8. Roganović J, Starinac K. Iron deficiency anemia in children. In: Khan J. Current topics in anemia. IntechOpen. 2018.
9. Chandra J, Dewan P, Kumar P, Mahajan A, Singh P, Dhingra B et al. Diagnosis, treatment and prevention of nutritional anemia in children: recommendations of the Joint Committee of Pediatric Hematology-Oncology Chapter and Pediatric and Adolescent Nutrition Society of the Indian Academy of Pediatrics. Indian Pediatr. 2022;59(10):782-801.
10. De Alvarenga Antunes CV, De Alvarenga Nascimento CR, De Rocha Ribeiro TC, De Alvarenga Antunes P, De Andrade Chebli L, Fava LMG et al. Treatment of iron deficiency anemia with liposomal iron in inflammatory bowel disease: efficacy and impact on quality of life. Int J Clin Pharm. 2020;42(3):895-902.
11. Nguyen M, Tadi P. Iron Supplementation. In: StatPearls. Treasure Island (FL): StatPearls Publishing. 2022.
12. Tolkien Z, Stecher L, Mander AP, Pereira DIA, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. PLoS One. 2015;10(2):e0117383.
13. Powers JM, Nagel M, Raphael JL, Mahoney DH, Buchanan GR, Thompson DI. Barriers to and facilitators of iron therapy in children with iron deficiency anemia. J Pediatr. 2020;219:202-8.
14. Baird-Gunning J, Bromley J. Correcting iron deficiency. Aust Prescr. 2016;39(6):193-9.

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