Safety, Tolerability and Efficacy of Melt-In-Mouth Oral Iron and Folic Acid Supplement in an Urban Non-Pregnant Population

Hema Divakar[1], Rita Singh[2], Poorni Narayanan[3], Divakar G. V.[4], Shyam Sundar Pani[5], Twinkle Bellani[6], Raksha Suvarna[7]

[1]Medical Director and Senior OBGYN Consultant, Divakars Speciality Hospital, Bengaluru, Karnataka, India. [2]Associate Consultant, Department of Obstetrics and Gynaecology, Divakars Speciality Hospital, Bengaluru, Karnataka, India. [3]Associate Consultant, Department of Obstetrics and Gynaecology, Divakars Speciality Hospital, Bengaluru, Karnataka, India. [4]Managing Director and Ophthalmologist, Divakars Speciality Hospital, Bengaluru, Karnataka, India. [5]Director, Hlthistyl, Bengaluru, Karnataka, India. [6]Chief, Nutrition and Regulatory affairs, Hlthistyl, Bengaluru, Karnataka, India. [7]Research Co-ordinator, Artist, Asian Research and Training Institute for Skill Transfer, Bengaluru, Karnataka, India.

ABSTRACT

BACKGROUND

In this study, we determined the safety, tolerability, efficacy and compliance of 'Positeve' melt-in-mouth tablets, an oral iron preparation along with micronutrients crucial for healthy blood cells and women's health. The tablets were administered to young girls and non-pregnant women as part of daily dietary supplementation in maintaining an anaemia free status as determined by measuring the haemoglobin status pre- and post-intervention.

METHODS

A prospective study was conducted (July 2019 - November 2019) at Divakars Speciality Hospital, Bengaluru, India. One hundred and seven subjects were enrolled as per the inclusion criteria. Baseline Hb levels were measured and additional measurements were recorded at the completion of the study period i.e. 6 weeks. A daily dose of melt-in-mouth tablets delivering 11.5 mg of elemental iron and 100 mcg of folic acid (along with other micronutrients) was administered to the study participants, once daily, after meals, for a period of 6 weeks.

RESULTS

Of the 107 enrolled, 7 dropped out and were not available for follow up. Of the 100 study subjects, 58 women took Positeve melted mouth tablets regularly; 42 women were noted to be partially compliant. In 59 subjects, there was a haemoglobin raise of 0.1 g/dL - 0.6 g/dL. By applying students paired t test we could see that the difference was found to be statistically significant. In 32 subjects, there was a drop of 0.1 g/dL - 0.7 g/dL. In 4 subjects, it did not make any difference in their Hb level. No major side effects or anaphylactic reactions were noted during study period.

CONCLUSIONS

The findings of the study suggest that Positeve melt-in-mouths by Hlthistyl is safe and well tolerated and helps in maintaining iron sufficiency among young girls and non-pregnant women. The elemental iron formulated along with crucial micronutrients is suggested to be effective in the supplementary treatment of IDA among the young girls and non-pregnant women. Compliance is found to be better with minimal adverse effects**.**

KEYWORDS

Iron Deficiency Anaemia, IDA, Anaemia, Adolescent, Women, India, Positeve Melt-In-Mouth, Oral Iron

Corresponding Author:
Dr. Hema Divakar,
Hema Divakars Speciality Hospital,
No. 220, 9th Main Cross,
J. P. Nagar, 2nd Phase,
Bengaluru- 560078, Karnataka, India.
E-mail: drhemadivakar@gmail.com

DOI: 10.18410/jebmh/2020/306

How to Cite This Article:
Hema D, Rita S, Poorni N, et al. Safety, tolerability and efficacy of melt-in- mouth oral iron and folic acid supplement in an urban non-pregnant population. J. Evid. Based Med. Healthc. 2020; 7(30),1448-1452. DOI: 10.18410/jebmh/2020/306

Submission 09-01-2020,
Peer Review 17-01-2020,
Acceptance 17-06-2020,
Published 27-07-2020.

BACKGROUND

Anaemia, defined as a reduction in haemoglobin concentration, red-cell count, or packed-cell volume below established cut-off levels, is a widely discussed public health challenge that India is facing. According to the World Health Organization (WHO), anaemia among women is defined as a haemoglobin concentration of <120 g/L for non-pregnant women aged 15 years and above, and a haemoglobin concentration of <110-g/L for pregnant women.[1] In particular, a persistently high level of anaemia among women in India (53% of all women have anaemia as per the National Family Health Survey 2015-2016)[2] is of great concern, and the 2017 National Health Policy tabled by the Ministry of Health and Family Welfare, Government of India, acknowledges this high burden.[3] Iron-deficiency anaemia (IDA) is a common problem among women, primarily due to their recurrent menstrual loss. Demand for iron is higher among pregnant women, and women with anaemia in combination with early onset of childbearing, a high number of births, short intervals between births and poor access to antenatal care and supplementation are likely to experience poor pregnancy outcome.[4] Presently, the situation is being handled as a crisis correction for short term benefits.

Prevention and management of IDA demands adequate iron intake and provision of bioavailable iron on a continuous basis.[5] The most recent estimates reflect an unacceptably low consumption of iron (median: 13.7 mg/day per person) among women in India aged ≥18 years and 51-83% of pregnant women in India are deprived of the recommended daily allowance of iron of 15-18 mg/day.[6] Women in India largely derive iron from non-haem, inorganic sources, including grains, plants, cereals, lentils and vegetables; and, to a small extent, from iron supplements, such as iron or iron and folic acid (IFA) tablets for pregnant women, and iron-fortified foods, as compared to sources of haem iron such as meat and fish, which have a higher rate of absorption.[7,8]

Oral and intravenous iron therapies have been indicated for the treatment of IDA.[9] However, the utility of oral iron is limited by gastrointestinal side-effects[10,11] and patient non-adherence.[12] Furthermore, although intravenous iron therapies rapidly increase blood haemoglobin levels,[13] they can provoke severe life threatening immune and allergic responses[14,15] or may require multiple low-doses[16] and long infusion times.[17] Thus, there is a need for effective iron therapies that are simple to administer and effective and safe .This can address the limitations of current treatments of choice. We need a shift of mind set of clinicians and women for long-term preventive care.

A daily dose of melt-in-mouth tablets of 11.5 mg of elemental iron and 100 mcg folic acid along with other crucial micronutrients was administered orally to the study participants, once daily, after meals for a period of 6 weeks. The goal of this study was to determine its efficacy, safety, compliance with least adverse effects in preventing IDA in the young girls and non-pregnant women.

The study was aimed to evaluate the safety, tolerability and efficacy of Positeve melt-in mouth tablets.

METHODS

The test substance Positeve is an iron-based supplement for adolescent girls and women, formulated and branded by Hlthistyl, Bangalore, India. It is a melt-in-mouth tablet which bridges the daily nutritional gap for micronutrients crucial for women's health- Iron (Ferrous Bisglycinate), Vitamin C, B complex vitamins, Zinc and Selenium.

This was an open-label, prospective, single centre study conducted with institutional review board approval. Girls and non-pregnant Women attending the outpatient Department of Divakars Speciality Hospital, Bengaluru, India willing to participate, were recruited to take part in the study. Positeve melt-in-mouth tablet delivering 11.5 mg of elemental iron and 100 mcg folic acid (along with other micronutrients) was administered to the study participants, once daily, after meals for a period of 6 weeks. All the subjects gave written informed consent before enrolling in the study and explained the details of the product and protocol, in the language understandable to them.

Study Period

July 2019 - November 2019.

Study Participants

Women who visited Divakar Speciality hospital and camps conducted (July 2019 - November 2019) by Divakar Speciality hospital were recruited and enrolled. Provision of appropriate consent and assent, willingness and ability to participate in study procedure was made.

Inclusion Criteria

1. The subjects were girls and women aged 10-65 years old,
2. Hb more than 9 gm/dL
3. IDA confirmed by haematological tests

Exclusion Criteria

We excluded girls and women-

1. whose anaemia was the result of conditions other than iron deficiency (e.g. Vitamin B12 or folate deficiency, infection, chronic bleeding or renal failure)
2. who had Recent blood transfusion,
3. Current treatment with myelosuppressive therapy,
4. Intolerance to iron derivatives,
5. Pregnancy,
6. Menorrhagia,
7. Severely iron deficient,
8. H/ o chronic illness on medication.

Primary End Point - Efficacy

The study was designed to establish the efficacy of Positeve melt-in-mouth tablets in prevention of iron deficiency

anaemia among adolescent girls and women via maintaining a state of iron sufficiency among the participants. The primary efficacy endpoint, therefore, was a change in Hb from baseline to 6 weeks pre and post intervention of the tablets. Subjects were also asked to record their responses on the questionnaire provided that focussed on their experiences with their energy levels pre and post intervention.

Intervention

In this study, a daily dose of 11.5 mg elementary iron and 100 mcg of folic acid preparation (with stated micronutrients) was administered orally to the study participants, once daily, after meals for a period of 6 weeks. Repeat estimates of Hb at 6 weeks were performed.

The secondary endpoints were safety, tolerability and compliance. The participants were alerted to report any adverse effects experienced with the tablet ingestion i.e. nausea, vomiting, GI irritation, constipation, rashes, etc., The subjects were requested to keep a journal and record any side-effects experienced associated with the tablets. Adverse events were spontaneously reported, elicited, or observed effects determined by the investigator to be probably or possibly treatment-emergent adverse events.

Compliance among subjects was ensured via a weekly telephonic conversion update from the subjects on their tablet administration schedule. The subjects were called in for a follow up after 6 weeks to assess the status of haemoglobin levels using previously mentioned parameters. Qualitative response to a question on energy levels was noted.

RESULTS

Hundred and seven women were enrolled in the study, from 7th July 2019. 7 dropped out and were not available for follow up.

Of the 100 study subjects, 59% Subjects, there was haemoglobin raise from 0.1 g/dL - 0.6 g/dL. Of these 1% woman had 0.5 g/dL and 0.6 g/dL, 9% women had 0.4 g/dL, 13% women had raised of 0.3 g/dL, 20% women had raised of 0.2 g/dL, 15% women had 0.1 g/dL, Overall rise was 0.2 to 0.4 g/dL in majority of the women with an average baseline Hb in the range of 9.8 to 10.8 gm/dL at baseline. In 32% Subjects there was drop of 0.1 g/dL - 0.7 g/dL. 8% women had drop of 0.1 g/dL, 11% women had 0.2 g/dL, 8% women had drop 0.3 g/dL, 3% women had 0.4 g/dL and 2% women had 0.7 g/dL (Figure 1). This may be due to irregular intake or a short-term comorbidity (acute infection or a bout of menorrhagia) In 4 subjects did not make any difference in their Hb level. Mean Hb value before was found to be 11.256 and that of after was 11.457 with the difference of 0.201 increase. By applying students paired t test we could see that the difference was found to be statistically significant. (Table 1)

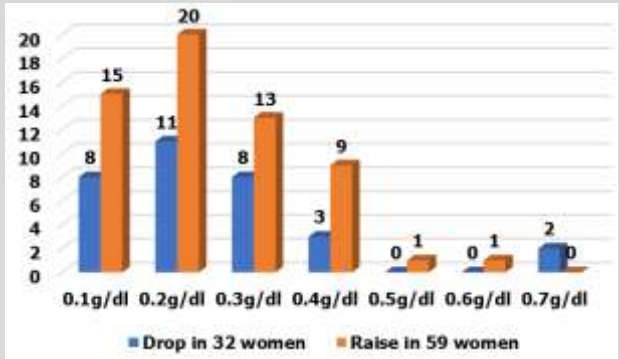

Figure 1. Raise and Drop in Haemoglobin Level

Haemoglobin level	Raise in 59 women
0.1 g/dL	15%
0.2 g/dL	20%
0.3 g/dL	13%
0.4 g/dL	09%
0.5 g/dL	01%
0.6 g/dL	01%
0.7 g/dL	0%

Table 1. Raise in Haemoglobin Level

Compliance was reasonably good. 58% of the girls and non-pregnant women took Positeve melt-in-mouth tablets regularly, rest were noted to be partially compliant and took Positeve melt-in-mouth tablets irregularly. (Figure 2)

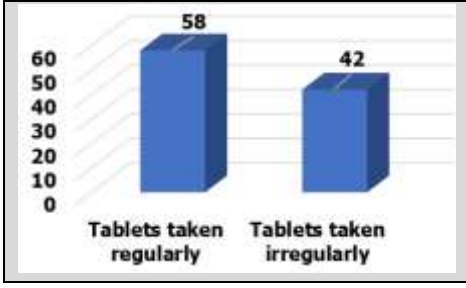

Figure 2. Overall Compliance

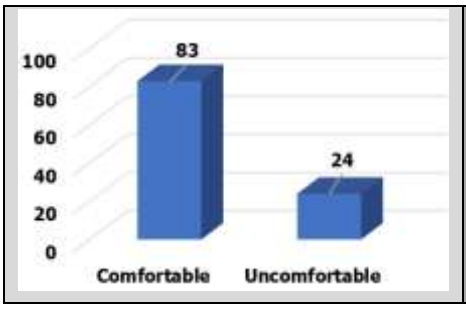

Figure 3. Overall Tolerability

83% women were comfortable and did not report any minor or major adverse effects. 24% women were uncomfortable with the tablets (Figure 3). We could see that only 7.5% were having side effects of Vomiting but nausea was seen among 18.7% of the people. Similarly, constipation was in 15% of the subjects and rest did not report any side effects (Figure 4).

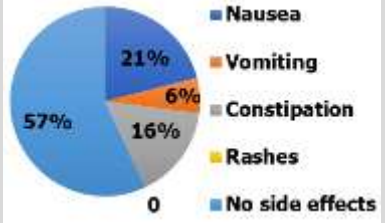

Figure 4. Side Effects

The difference between Hb value before and after was compared between Energy levels. Energy level- 12% women felt energetic. 88% women said they did not notice any difference in their energy levels. The mean Hb difference in Energetic group was 0.967 and that of No difference it was just 0.152. This difference was also found to be statistically significant by applying students unpaired t test (Table 2).

Haemoglobin level	Drop in 32 women
0.1 g/dL	08%
0.2 g/dL	11%
0.3 g/dL	08%
0.4 g/dL	03%
0.5 g/dL	0%
0.6 g/dL	0%
0.7 g/dL	02%

Table 2. Drop in Haemoglobin Level

Data Analysis

Analysis was done by Descriptive statistics. Comparison of Hb level from pre to post was done by student's paired t test. Comparison of this mean difference of Hb in comfortable and uncomfortable group and with energy levels was done by students unpaired t test. A statistical package SPSS ver. 23.0 was used to do this analysis. $p<0.05$ was considered as significant.

DISCUSSION

The incidence of IDA in pregnant women in India is quite high.[18] World Health Organization (WHO) estimates that two billion people are anaemic worldwide and attribute approximately 50% of all anaemia to iron deficiency.[19] It occurs at all stages of the life cycle but is more prevalent in pregnant women and young children.[20]

The goal of this study was to determine the efficacy of Positeve melt-in-mouth in preventing Iron Deficiency Anaemia through maintaining a state of iron sufficiency among the young girls and non-pregnant women in India over a period of 6 weeks

Positeve is an iron based supplement for women, formulated and branded by Hlthistyl, Bangalore, India. It is a melt-in-mouth tablet which bridges the daily nutritional gap for micronutrients crucial for women's health and comprises of Iron (Ferrous Bisglycinate), Vitamin C, B complex vitamins, Zinc and Selenium. Vitamin C aids in effective absorption of iron while the B complex vitamins support in releasing energy and contribute to a healthier blood profile. The tablets formulated by Hlthistyl supports immunity and healthy blood cells.

It was established that a daily administration of Positeve melt-in-mouth tablets containing 11.5 mg iron and 100 mcg folic acid (and with listed micronutrients) resulted a rise of Hb level among 59% study subjects from baseline to 6 weeks. Among the study subjects 32% also reported a drop in the Hb levels.

The raise of Hb is contributed from iron and folic acid along with other crucial micronutrients that contributes to a healthy blood profile via supporting effective absorption of iron by the body (Vitamin C), the synthesis of its oxygen transport proteins, in particular haemoglobin and myoglobin, and for the formation of heme enzymes and other iron-containing enzymes involved in electron transfer and oxidation-reductions thereby contributing to a rise in the haemoglobin levels among subjects.[21]

The drop in Hb level may be due to menstruation, other bleeding, iron is highly conserved and not readily lost from the body.[22] There is some obligatory loss of iron from the body that results from the physiologic exfoliation of cells from epithelial surfaces,[23] including the skin, genitourinary tract, and gastrointestinal tract.[20] However, these losses are estimated to be very limited (≈1 mg/day).[24] Iron losses through bleeding can be substantial and excessive menstrual blood loss is the most common cause of iron deficiency in women.[25]

Also 42% subjects were not taking the tablets regularly. In 18% subjects in spite of taking iron tablets irregularly there was a raise of 0.1 g/dL of Hb seen, this can be because of the Iron tablets and dietary impact which did not let a decline in the haemoglobin level.

Recent Indian study (2019) reported poor compliance in almost 75% patients irrespective of the type of oral iron formulation mainly due to GI side effects.[26]

As against this, the compliance in our study, due to the melt in mouth approach to oral medication, the compliance is far greater, with least amount of adverse effects.

Major Adverse effect was not reported.

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.

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 women and girls would have been useful in determining the effect of Positeve melt-in-mouth tablets on the iron stores.

CONCLUSIONS

The findings of the study suggest that Positeve melt-in-mouths by Hlthistyl is safe and well tolerated. It helps in maintaining iron sufficiency among young girls and non-pregnant women. The elemental iron formulation along with crucial micronutrients is effective, in the treatment of IDA among young girls and non-pregnant women. Pharma economic studies need to be performed to compare the cost utilization of tablets in India to determine where in the IDA

prevention chain, Positeve melt-in-mouth tablets would be more effective. It is likely to find its place as a standalone therapy as an adjunct / supplement in view of melt-in-mouth form of drug delivery with improved compliance.

All authors report grants from Hltistyl.

FSS License number- 10018043002349

REFERENCES

[1] Nutritional anaemias: tools for effective prevention and control. Geneva: World Health Organization, 2017. (Accessed on 15th January, 2018). http://apps.who.int/iris/bitstream/10665/259425/1/9789241513067-eng.pdf

[2] Ministry of Health and Family Welfare, Government of India. India National Family Health Survey (NFHS4) 2015-16. Mumbai: International Institute for Population Sciences, 2017. (Accessed on 15 January 2018). http://rchiips.org/nfhs/NFHS-4Reports/India.pdf

[3] National Health Policy 2017. New Delhi: Ministry of Health and Family Welfare, Government of India. 2017. (Accessed on 15th January, 2018). http://cdsco.nic.in/writereaddata/National-Health-Policy.pdf

[4] Balarajan Y, Ramakrishnan U, Ozaltin E, et al. Anaemia in low-income and middle-income countries. Lancet 2011;378(9809):2123-2135.

[5] Camaschella C. Iron-deficiency anemia. N Engl J Med 2015;372(19):1832-1843.

[6] Shankar B, Agrawal S, Beaudreault AR, et al. Dietary and nutritional change in India: implications for strategies, policies and interventions. Ann N Y Acad Sci 2017;1395(1):49-59.

[7] Deaton A, Drèze J. Food and nutrition in India: facts and interpretations. Econ Polit Wkly 2009;44:42-65. Accessed on 15th January 2018. https://www.princeton.edu/~deaton/downloads/Food_and_Nutrition_in_India_Facts_and_Interpretations.pdf

[8] Mehta R, Platt AC, Sun X, et al. Efficacy of Iron-supplement bars to reduce anemia in urban Indian women: a cluster-randomized controlled trial. Am J Clin Nutr 2017;105(3):746-757.

[9] Dodd JM, Dare MR, Middleton P. Treatment for women with postpartum iron deficiency anaemia. The Cochrane Database Syst Rev 2004;18(4): Art. No. CD004222.

[10] Sharma N. Iron absorption: IPC therapy is superior to conventional Iron salts. Obstet Gynaecol 2001:515-519.

[11] Geisser P. In vitro studies on interactions of Iron salts and complexes with food-stuffs and medicaments. Arzneimittelforschung 1990;40(7):754-760.

[12] Van Wyck DB, Martens MG, Seid MH, et al. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anaemia: a randomized controlled trial. Obstet Gynaecol 2007;110(2 Pt 1):267-278.

[13] Seid MH, Derman RJ, Baker JB, et al. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anaemia: a randomized controlled clinical trial. Am J Obstet Gynecol 2008;199(4):435.e1-435.e7.

[14] Walters BAJ, Van Wyck DB. Benchmarking Iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients. Nephrol Dial Transplant 2005;20(7):1438-1442.

[15] Fishbane S, Ungureanu VD, Maesaka JK, et al. The safety of intravenous iron dextran in hemodialysis patients. Am J Kidney Dis 1996;28(4):529-534.

[16] Breymann C, Richter C, Huttner C, et al. Effectiveness of recombinant erythropoietin and Iron Sucrose vs. Iron therapy only, in patients with postpartum anaemia and blunted erythropoiesis. Eur J Clin Invest 2000;30(2):154-161.

[17] Bhandal N, Russell R. Intravenous versus oral Iron therapy for postpartum anaemia. BJOG 2006;113(11):1248-1252.

[18] Kalaivani K. Prevalence and consequences of anaemia in pregnancy. Indian Journal of Medical Research 2009;130(5):627-633.

[19] Murray CJL, Salomon JA, Mathers CD, et al. The global burden of disease. Geneva: World Health Organization, 2002.

[20] World Health Organization. The World Health Report 2002: reducing risks, promoting healthy life. Geneva: WHO, 2002.

[21] Hurrell RF. Bioavailability of Iron. Eur J Clin Nutr 1997;51 Suppl 1:S4-S8.

[22] Hunt JR, Zito CA, Johnson LK. Body Iron excretion by healthy men and women. Am J Clin Nutr 2009;89(6):1792-1798.

[23] McDowell LR. Minerals in animal and human nutrition. 2nd edn. Amsterdam: Elsevier Science 2003: p. 660.

[24] Fairbanks VF. Iron in medicine and nutrition. In: Shils ME, Shike M, Ross AC, et al. eds. Modern nutrition in health and disease. 10th edn. Baltimore: Lippincott Williams & Wilkins 1999: p. 193-221.

[25] Abbaspur N, Hurrell R, Kelishadi R. Review on Iron and its importance for human health. Journal of Research in Medical Sciences 2014;19(2):164-174.

[26] Srivastava R, Kant S, Singh AK, et al. Effect of Iron and Folic acid tablet versus capsule formulation on treatment compliance and Iron status among pregnant women: a randomized controlled trial. J Family Med Prim Care 2019;8(2):378-384.