

ANALYSIS OF HAEMATINIC PREPARATIONS AVAILABLE IN INDIAN MARKET

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ABSTRACT

To analyze Haematinic formulations available in Indian market for their varieties of dosage forms, iron salts used, content of elemental iron, frequency of administration required, presence of additional nutrients, rationality and cost. Haematinic formulations listed in IDR 2018, were analysed for salts of Iron present. Preparations of ferrous fumarate were further analysed for Iron content, presence of folic acid and other added additional components. A total of 522 formulations, 291 (55.74%) were oral solid dosage form, 206 (39.46%) were oral liquids and 25 (4.7%) were parenteral. Iron salts in these formulations were in form of ferrous fumarate, carbonyl iron, iron ascorbate, iron ammonium citrate, ferric hydroxide polymaltose complex, ferrous sulphate, sodium hydrate. Carbonyl iron was present in 92 preparations and was most commonly used preparation in oral solid formulations. Some formulations additionally contained Vitamin B12, zinc sulphate, histidine, lysine other multivitamins and calcium preparations in variable proportion. Out of 291 oral solid, 45 (15.46 %) preparations required administration > three times a day to achieve the therapeutic concentration. Average cost of the rational preparation was more than average cost of irrational preparation. Analysis of various haematinics shows there is no uniformity in formulations. Iron and folic acid are added in wide variable range moreover other substances were also added without any well proven evidence. Steps should be taken to standardize these formulations.

INTRODUCTION

Anemia is a global public health problem affecting both developing and developed countries with major consequences for human health as well as social and economic development. It occurs at all stages of the life cycle, but is more prevalent in pregnant women and young children although are most susceptible, which may increase the risk of impaired cognitive and physical development and increased mortality and morbidity rate.¹

According to WHO report in 2001, around two billion individuals in the worldwide have been estimated to suffer from anemia with 50% of all anemia was documented to Iron deficiency anemia².

Iron deficiency ranks number 9 among 26 risk factors included in the GBD 2000, and accounts for 841,000 deaths and 35,057,000 disability-adjusted life years lost. Africa and parts of Asia bear 71% of the global mortality burden and 65% of the disability-adjusted life years lost, whereas North America bears 1.4% of the global burden. There is an urgent need to develop effective and sustainable interventions to control iron-deficiency anemia.³

Until today, IDA is still the most prevalent and common type of micronutrient deficiency in the developing countries,⁴ which results from long-term negative iron imbalance. Usually, deficiency of iron develops gradually and does not have clinically apparent symptoms until anemia becomes severe.⁵

The main risk factors for IDA include a low intake of iron, poor absorption of iron from diets high in phytate or phenolic compounds, and period of life when iron requirements are especially high (i.e. growth and pregnancy). Among the other causes of anemia, heavy blood loss as a result of menstruation, or parasite infections such as hookworms, ascaris, and schistosomiasis can lower blood hemoglobin (Hb) concentrations. Acute and chronic infections, including malaria, cancer, tuberculosis, and HIV can also lower blood Hb concentrations. The presence of other micronutrient deficiencies, including vitamins A and B12, folate, riboflavin, and copper can increase the risk of anemia.⁶

Haematinics are drugs used for the treatment and prevention of anemia. Haemopoiesis requires adequate supplies of minerals like iron and copper; vitamins like folic acid,

vitamin B₁₂, vitamin C, pyridoxine, riboflavin; and various hematopoietic growth factors.⁷ Reducing anemia is recognized as an important component of the health of women and children, and the second global nutrition target for 2025 calls for a 50% reduction of anemia in women of reproductive age.⁸

Indian drug market is flooded with various combinations of drug formulations, the majority of which are proprietary multidrug combinations and most of the patients are being made to ingest totally unnecessary drugs. So it is a need to the drug regulatory authorities to pay attention towards rationality of these drug formulations so as to reduce the cost of therapy and also to improve the quality of treatment.

MATERIALS AND METHODS

In this observational study, detailed information about the Haematinic formulations was obtained from the Indian Drug Review (IDR) issue 1, 2018. The formulations were analysed according to route of administration, rationality and cost of daily treatment.

The formulations were classified into the following categories: (A) Oral solid formulations, (B) Oral liquid formulations,

and (C) Parenteral formulations. Each category was further subdivided into formulations containing:

1. Iron salts alone
2. Iron salts + folic acid + others (vitamins, minerals, essential amino acids and other chemicals)
3. Iron salts + folic acid + vitamins C + others
4. Iron salts + others
5. Folic acid + others

Apart from deficiency of iron, deficiency of folic acid is also a common cause of anemia prophylaxis program advices to provide iron along with folic acid.⁹

Besides, vitamin C is known to increase absorption of iron.¹⁰ by facilitating its transport into intestinal cells. Hence inclusion of folic acid and vitamin C in the formulations having iron salts were considered as "rational formulations". Iron preparations containing iron salts along with other vitamins, minerals, etc., were considered as "irrational formulations".

The recommended therapeutic dose of elemental iron being 100-200mg iron per day in three divided doses¹¹ for comparison cost of 100-200mg daily dose of elemental iron in a given formulation was calculated.

The average cost of rational iron formulations was calculated and compared with that of irrational ones.¹⁰

RESULTS

Out of 522 formulations listed in IDR 2018 under hematinic section, 291 (55.74%) were oral solid formulations (Category A), 206 (39.46%) were oral liquids (Category B), and 25 (4.7%) were parenteral (Category C).

If information about the type of iron salt, quantity, and cost were not available, such formulations were not included for the cost analysis. Thus, from category A (solid oral), 30 formulations were dropped and from category B (liquid oral) and C (parenteral), 24 and 5 formulations were not included for cost analysis, respectively.

As shown in table 1: There were only 7 solid oral iron preparations containing iron salts alone. Among the liquid and parenteral formulations there were 36 and 22 respectively. There were 3 solid oral preparations containing folic acid alone.

Among the 291 (55.74%) oral solid formulations, iron salts + folic acid + other ingredient combination was the commonest formulation available 166 (57.04%). Second most common formulation was Iron salt +

folic acid + Vitamin C + other ingredient 111(38.14%).

Among the 206 (39.46%) oral liquid formulations, iron salts + folic acid + other ingredient combination was the commonest formulation available 123 (59.70%). The second commonest formulation was containing only Iron salts 36 (17.47%). Other oral liquid formulations contained Iron salt + folic acid + Vitamin C + other ingredient 21(10.19%), and Iron salt + other ingredient comprised 23 (11.16%).

In 25 (4.7%) parenteral formulations 22 (88%) contained only iron salts while 3 (12%) formulations contained iron salts + folic acid + other ingredient.

Table No. 1: Iron Formulations

Contents	Oral solid (n=291; 55.74%)	Oral liquids (n=206; 39.46%)	Parenteral (n=25; 4.7%)
Iron salts only	7 (2.40%)	36 (17.47%)	22 (88%)
Iron salt + folic acid + others	166 (57.04%)	123 (59.70%)	03 (12%)
Iron salt + folic acid + Vit C + others	111(38.14%)	21(10.19%)	0
Iron salt + others	4 (1.37%)	23 (11.16%)	0
Folic acid +	3 (1.03%)	0	0

others			
Haematinic	0	3 (1.45%)	0

As many as 73% of the solid oral preparations, 66% of the liquid oral preparations and 14% of parenteral iron formulations were classified as irrational.

Table No.2: Irrational and Rational Iron Formulations

Formulations	Irrational	Rational
Oral solid	73%	27 %
Oral liquid	66 %	34%
Parenteral	14%	86%

Table No.3: Average Mean costs of Irrational and Rational Iron Formulations

Formulations	Irrational	Rational
Oral solid	26.34	15.32
Oral liquid	28.1	16.34
Parenteral	298	126

It was found that the mean average price of irrational oral solid and liquid Formulations was higher than the rational ones.

DISCUSSION

Iron deficiency is one of the most common disorders affecting humans and it is considered one of the top 10 contributors to the global burden of disease. The World Health Organization (WHO) describe iron-deficiency anemia as "the most common and widespread nutritional deficiency in the world." ¹

In our study, among the 522 iron formulations found in IDR 2018, 291 were oral solid formulations, 206 were oral liquid formulations and 25 were parenteral formulations. As many as 73% of the solid oral preparations, 66% of the liquid oral preparations and 14% of the parenteral preparations were classified as irrational.

Most of the formulations were classified under iron with folic acid and others subgroup. There were only 7 solid oral iron preparations, 36 liquid oral iron and 22 parenteral formulations containing iron salts alone. Carbonyl iron was contained by 92 preparations and was most commonly used salt in oral solid formulations as it gives high bioavailability and has less side effects than that of conventional iron preparations⁷. Carbonyl iron is absorbed at the rate of gastric acid production which makes carbonyl iron soluble, thus it enters the system much more gradually as compare to other salts.

The most common salt found in liquid oral preparations, Ferric ammonium citrate is claimed to have good GI tolerability, but is less effective, as ferric salts are poorly absorbed than ferrous salts.¹² Iron sucrose which is commonly found in parenteral preparations is a complex of poly nuclear ferric hydroxide in sucrose. It is effective, better tolerated and does not require test dose.⁷

The list of other nutrients added in the various hematinic formulations was quite long:

- Vitamins: Vitamin A, D, E, K, C, B-complex, pantothenic acid, biotin.
- Minerals and other chemicals: zinc, copper, manganese, calcium, sodium, potassium, iodine, selenium, chromium, magnesium, phosphate, molybdate, chlorine.
- Essential amino acids like histidine, lysine, glycine, glutamic acid.
- Miscellaneous nutrients like fat, protein, carbohydrate, inositol, saffron, dioctyl sodium sulfosuccinate, succinic acid, hemoglobin, yeast, alcohol, sorbitol, Menadione, docusate, lactate.

Combination of iron with other nutrients increase the cost as well as the frequency of side effects and hence leads to non-compliance.¹³ they are irrational preparations.

The Drugs Technical Advisory Board (DTAB) of India has recommended that vitamin B complex and zinc should not be included in iron- and folic acid-containing hematinic preparations.¹²

There has been concern that the nutrients other than iron in the multiple micronutrients (MM) supplements could interfere with the absorption of iron and, therefore, these supplements are not as efficacious in treating anemia.¹⁴

Studies have shown that iron absorption is poor in the presence of other minerals such as calcium, magnesium, and zinc.¹⁵ Three randomized controlled trials (RCT) from Tanzania, Mexico and Nepal have found that multiple micronutrients did not improve hematologic indicators when compared to patients who received iron-folic acid supplements.¹⁶

To provide 100 mg of elemental iron per day in not more than three doses, the formulation should deliver approximately 33 mg elemental iron per dose. We found that 45 (15.46 %) out of 291 oral solid iron

formulations would require administration more than 3 times a day to provide the 100 mg of elemental iron necessary for therapeutic purposes, and this can adversely affect patient compliance.

When we compared the prices of rational iron preparations with that of irrational formulations, we found that the rational products were costlier than the irrational ones to a significant extent. The higher cost of irrational preparations might be because of addition of more than one ingredient. These findings are similar to previous reports.^{17,18}

Formulations containing iron salts like ferrous sulphate, carbonyl iron, and ferrous fumarate were cheaper than formulations containing other newer iron salts.

CONCLUSION

Indian drug market is flooded with various drug formulations, the majority of which are proprietary multi-drug combinations. Patients are being made to ingest totally unnecessary drugs. One of the major principles of rational use of drugs is to prescribe only those drugs that are really indicated; unnecessary drugs should not be prescribed and thus will improve the quality and cost of treatment.

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