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ORIGINAL ARTICLE

Pharmacoeconomic Evaluation of Generic Vs Branded preparation of Ferrous Ascorbate in 14 to 24 weeks of Gestational Women

Angadi Eeesha,Karandikar Yogita,Talathi Manju[1]

Abstract

Background: Iron deficiency is a major problem worldwide especially in women of reproductive age. Ferrous Ascorbate has good efficacy, less gastrointestinal side effects and with better patient compliance. **Objective:** Pharmacoeconomic evaluation of branded and generic drug will help to find out the least expensive alternative for treating anaemic pregnant women .This will help in reducing health-economic burden and ensure compliance to minimize morbidity and mortality.**Methods:** We conducted prospective randomized active control open label study in pregnant women between 14-20 weeks. The patients were divided into two groups - Branded and Generic Ferrous Ascorbate groups. Treatment was given orally once a day for a period of 8 weeks. Change in Haemoglobin level,Serum ferritin ,adverse effects were recorded after an interval of 30 and 60 days from baseline. Average and Incremental cost effectiveness ratio was calculated in terms of rupees. **Results:** We observed that there was significant rise in Hb in both groups but therise was greater in Branded group than in Generic (11.86 ± 0.14 Vs10.725 ± 0.14,p-0.001) at the end of 60 days. The average cost-effectiveness ratio (ACER) for Branded group was Rs. 250.77, less than that of Generic gr 269.38 per increase in Hb gm%. The most frequently occurred adverse drug event was constipation which was highest in Generic Group.**Conclusion:** Ferrous Ascorbate caused significant rise in Hb in gm % in both Branded and Generic groups. But Branded Ferrous Ascorbate had better efficacy and was the favourable drug for treatment, as ACER was less and reported less number of adverse events.

Key Words

Ferrous Ascorbate, Generic drugs, anaemia, cost effectiveness, Pharmacoeconomic evaluation

Introduction

Iron deficiency anemia is a major problem in India, especially in women of reproductive age. It has significant impact on health of the fetus as well as the mother. Thus increased need of iron during pregnancy especially after 2nd trimester makes iron supplementation mandatory. [1] Classification derived from an iron-supplemented population lists following levels as anaemic: Hb (g/dl) levels below 11 g/dl in the first trimester; 10.5 g/dl in the second trimester; and 11g/dl in the third trimester. [2,3]

The most common iron salt used for oral administration is Ferrous Sulfate, Ferrous Fumarate and Ferrous Ascorbate. Ferrous Fumarate and Ferrous Ascorbate has less gastrointestinal side effects and is readily absorbed, thus has better patient compliance.[4] Ferrous Ascorbate is a synthetic molecule of ascorbic acid and iron. Ascorbic acid enhances absorption of iron.[5] Hence Ferrous Ascorbate was chosen for this study as it achieves fastest rise in iron levels.

Indian drug market is flooded with more than 7000 drug formulations, where 621 formulations are listed in the Indian Drug Review 2016 (IDR) as hematinic. [6] The prescribing and buying of drugs is an issue of

Department of Pharmacology, & Obst and Gyane[1] BVDU Medical College, Pune, Maharashtra, India

Correspondence to: Dr. Karandikar Yogita. S,Adress:3, Nayananand Society,Anandnagar,Sinhgad road,Pune-51,Maharashtra, India

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unparalleled peculiarity cause the prescriber (Physician) decides what medicine patients should purchase, but he is not the one who pays for drugs, the one who pays and benefits (patient) has no say in what he/she purchases.

India markets two types of drugs, branded generic; considered as Branded drugs and unbranded; considered as Generic drugs. According to Indian drug regulations, the term 'Branded drug' has not been defined. It is a drug formulation manufactured and sold under a popular name. Generic drugs are manufactured by a pharmaceutical company under a brand name which is not promoted and is unpopular.When it comes to pricing, difference in cost between same branded and generic products vary from < 2-fold to >100-fold.[7] Indian pharmaceutical industry today is "considered the world's third-largest by volume and produces approximately 20% of the world's generic drugs. The paradox is that, despite producing huge pharmaceutical products, WHO says 3.2% Indians will fall below the poverty line due to medical expense. Hence, the main purpose of generic drug development is to reduce the cost of marketed drugs, ultimately to lower public health costs. [8] There is a general misconception that Pharmacoeconomic Evaluation is merely a mean to find the least expensive alternative, but a comparison tool, which will not only indicate a clear choice, but will evaluate options quantitatively and objectively based on a defined model. Thus this study will throw light on how to select a drug, keeping the cost, efficacy, tolerance and side effects in mind between branded or generic Ferrous Ascorbate.

Material and Methods

The study was conducted in Obstetrics and Gynecology out Patient Departments (OPD) of a Tertiary Care Teaching Hospital, Pune, for a period of one year (July 2014 to July 2105).The study protocol was approved by Institutional Ethical Committee. [REF: BVDU/MC/64 Dated 2/09/2014] Participants involved in the study were informed and written consent was obtained. The trial is registered with Clinical Trial Registry- India [REF/2016/09/012292]

Inclusion criteria consisted of women with gestational age between 14 -24 weeks, baseline Hemoglobin level > 8gm%. While patients with history of severe oral intolerance for oral Iron preparations, excessive emesis, bleeding piles, active peptic ulcer, other GIT problem, high obstetric risks pregnancies like multifetal pregnancy and any other anemia other than Iron Deficiency Anemia e.g. Megaloblastic Anemia thalassemia, etc. were excluded from the study. 64 willing women fulfilling the above criteria were alternately assigned to group A or group B by simple randomization method. Group A consisting of 32 patients received Branded Ferrous Ascorbate procured from its innovator company. While Group B (n=32) received Generic. Ferrous Ascorbate which were purchased from generic medicine distributor, Mumbai. All 64 were followed up and analyzed. No participants were lost to follow up and there were no dropouts during the study period

Study medication tablets, were administered orally once a day posts prandial for a period of 60 days, with a follow up after 30 days and 60 days. During each follow-up visit; they were subjected to general and obstetric examination and supplied with study medication for the next 30 days. Compliance was checked by verbal enquiry and patient was also provided with a sheet, where patient had to daily tick upon administering drug.Samples for blood investigation were collected at "day 0" (baseline), "day 30" and "day 60" (at end of study) for Hemoglobin and Serum ferritin at "day 0" and "day 60". Patients were trained to record any adverse event like metallic taste, epigastric distress, abdominal pain, nausea, vomiting, diarrhea, constipation and other etc. Cost effectiveness ratio for two groups will be calculated by dividing the cost of treatment by its clinical outcome to yield the ratio in terms of rupees. While Incremental cost effective ratio will be measured as difference in cost (A-B) divided by difference in benefit (A-B). [9,10]

Keeping in account that the Bio-equivalence of both Generic and Branded drugs are same and will yield same results in a fixed time, cost required to attain targeted results was compared. The characteristics of both the treatment groups were compared for both demographic and efficacy variables. In all tests mean values of test groups (A and B) were compared .Students paired t test was used to test the significance of difference in overall efficacy of two treatments resulting in rise in Hemoglobin or change in other parameters. Data was analyzed using graph pad prism software version 6.0.

Results

In this study, 41 (64 %) patients were between 26 - 33 years of age, 35 (55%) were primiparous. There was equal distribution of study population in the diet parameter i.e. 32 vegetarians and 32 on mixed diet.

As seen in *Table I*, The baseline characteristics of the patients in Group A (n = 32) and Group B (n = 32) showed no significant difference in relation to hemoglobin (p=0.52) and Serum ferritin (p=0.82) levels. Thus both the groups were comparable.

Group A shows significant rise in Hb (g/dL) at the end of 1st month of treatment and highly significant rise in Hb (g/dL) at the end of 2nd month of treatment as compared to Group B.

Baseline Serum Ferritin and their levels at the end of

Table.1 Comparison between rise in Hemoglobin and Serum ferritin levels between Branded (Group A) and Generic (Group B) Ferrous Ascorbate

Parameters	Group A	Group B	P value
Baseline Hb (g/dL)	9.41 ± 0.12	9.51 ± 0.11	0.52
Hb after 30 days (g/dL)	10.48 ± 0.14*	10.10 ± 0.11	0.04
Hb after 60 days(g/dL)	11.86 ± 0.14***	10.725 ± 0.14	< 0.0001
Baseline Sr. Ferritin (µg/L)	34.11 ± 1.34	34.44 ± 0.91	0.82
Sr. Ferritin after 60 days (µg/L)	40.10 ± 1.33	38.20 ± 0.96	0.20

*Efficacy variables between groups calculated using Paired t test. Values are expressed as Mean ± SEM (Standard Error Mean)*p<0.05, ***p<0.0001*

Table.2 Cost effective analysis

Intervention	Hb gained (g/dL)	Net cost (Rupees)	ACER (cost/Benefit)	Cost to Rise 1(g/dL) of Hb
Group A (Branded)	2.45	614.40	250.77	250.77
Group B (Generic)	1.225	330	269.38	269.38

Average Cost effectiveness Ratio (ACER) for different groups was calculated by dividing the cost of treatment by its clinical outcome to yield the ratio in terms of rupees

Table.3 Incidence of most common adverse events

ADE	Group A N=32	Group B N=32	P value
Nausea	1	1	1
Vomiting	0	0	-
Constipation	1	5	0.10
Diarrhoea	0	0	-
Abdominal Pain	0	0	-
Metallic Taste	0	1	0.32
Others		0	-
Total	2 (6.25%)	7 (21.87%)	0.02*

Group B reported significantly more events of adverse drug reactions compared to Group A.

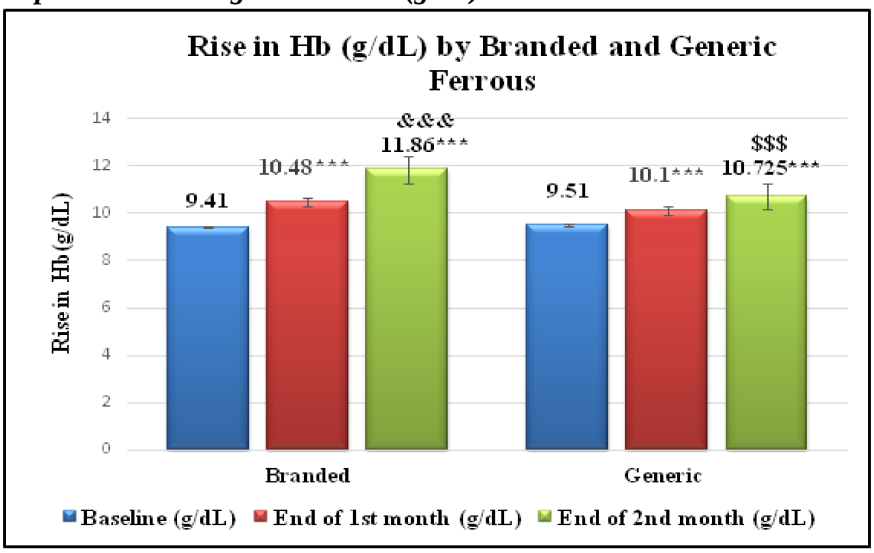
2nd month in Group A and Group B show no statistically significant difference (p=0.82).. Highly statistical significant rise in Serum Ferritin at the end of 2 months of treatment in both Group A and Group B compared to their respective baseline readings was observed.

As seen in *figure I*, Group A shows highly statistical significant rise in Hb (g/dL) at the end of 1st month of treatment as compared to baseline (*** $p < 0.001$) and highly statistical significant at the end of 2nd month as compared to baseline (*** $p < 0.001$).Also there was highly statistical significant rise in Hb (g/dL) at the end of 2nd month as compared to rise observed at the end of 1st month of treatment. (&&& $p < 0.001$).

Similarly, in Group B we observed highly statistical significant rise in Hb (g/dL) at the end of 1st month of treatment as compared to baseline (*** $p < 0.001$). And highly statistical significance at the end of 2nd month as compared to baseline (***$p< 0.001$). Also there was highly statistical significant rise in Hb (g/dL) at the end of 2nd month as compared to rise observed at the end of 1st month of treatment ($$$ $p < 0.001$).

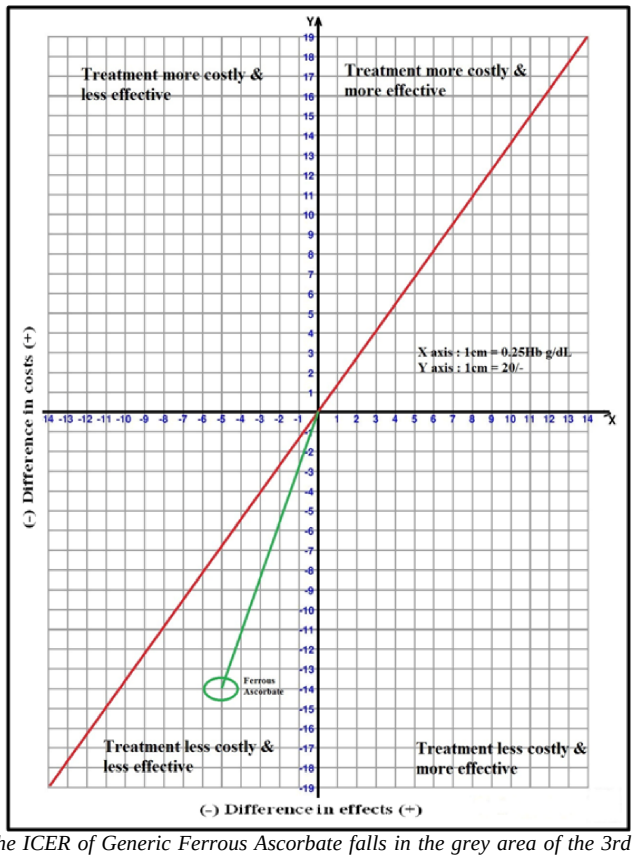
The cost of 10 tablets of branded Ferrous A is Rs.102.40/- while cost of 10 tablets of generic Ferrous Ascorbate is Rs 55/-.As seen in table II, the ACER of Group B (Generic drug) was more than Group A (Branded drug).The mean cost is Group A (Branded drug) is higher than Group B (generic drug). Group A had maximum improvement in Hb gained (g/dL) when

Fig1. Inter Group Rise in Hemoglobin Levels (g/dL)



Efficacy variables between groups calculated using repeated measures of ANOVA followed by Tukey's test.
**** denotes statistical significance p<0.001 as compared Baseline in both groups.*
&&& denotes Statistical significance p<0.001 as compared end of 1st month reading in Branded group.
$$$ denotes statistical significance p<0.001 as compared end of 1st month reading in Generic group.

Fig 2. Incremental Cost Effectiveness Ratio plane of Generic Ferrous Ascorbate



The ICER of Generic Ferrous Ascorbate falls in the grey area of the 3rd i.e. The Southwest quadrant.

compared to Group B.But the cost to rise 1g/dL of Hb it takes Rs 269.38/- for a Generic drug where as it takes Rs 250.77/- for a branded drug. Which means more amount of money needs to be spent to rise 1g/dL of Hb for a Generic drug as compared to a Branded drug.

As seen in *Table III*, the most frequently occurred adverse drug event was constipation (highest in Group B), followed by nausea which was equally seen in both groups and metallic taste in the mouth seen in Group B. Rest no patients reported ADRs like vomiting, diarrhoea, or than others adverse events. Group B reported significantly more total number of adverse drug events compared to group A (0.02*). As seen in *Fig II* The ICER of Generic Ferrous Ascorbate falls in the grey area of the 3rd i.e. The Southwest quadrant which indicate that treatment is less costly but less effective.

Discussion

Despite viable ways to treat, Iron deficiency anemia is the commonest occurring anemia amongst women and children in Indian population. In the present study a parallel improvement in hematological parameters were noted in group A and B (26.03% and 12.89%) with rise in hemoglobin (g/dL) as compared to Baseline. Ferrous form is absorbed thrice as much as ferric form of iron. [11] Ascorbic acid converts the ferric form to ferrous form thus making it absorbable from duodenum and upper jejunum, resulting in considerable enhancement of the absorption of iron and good outcome observed with both Branded (A) and Generic(B) group. Previous studies also

demonstrated similar results with Ferous Ascorbate. [12-14] In Indian market two types of drugs are available, branded generic considered as Branded drugs and unbranded Generic drugs. [15] Indian drug law does not specify definition of generic drug. According to USFDA, generics only become available after the patent of the branded drug expires. [16]

A rise in haemoglobin and serum ferritin was observed in Group A (branded) as compared to Group B (generic) across a duration of 2 months in the study population. Likewise, few other studies with branded drugs also showed better clinical outcome as compared to Generic drugs. [17, 18]

The FDA requires that any approved drug be effective within a 20% range of the brand name drug in bioequivalence study. Thus two generic drugs could contain as much as a 40% difference from each other. Therefore, a drug may be legally chemically equivalent but not at the same time clinically equivalent. [19] Studies have also shown that generics formulations had a more total impurity rate than brand formulation. [20] Thus all of the above factors cumulatively imply better efficacy with branded Ferrous Ascorbate, than the generic drug.

In similar findings, in this study, constipation was the highest noted adverse event, followed by nausea and metallic taste in the mouth. Group B, which received generic drug reported significantly higher adverse incidences compared to group A ($p < 0.05$).

The active pharmaceutical ingredient (API) does not differ between originator and generic medicines. But the difference in other (inactive) ingredients, known as excipients, binder, vehicle and other additives, might change the rates of release and also contribute to adverse drug reactions or side effect. [21]

Pharmacoeconomic studies serve to guide optimal healthcare resource allocation, in a standardized and scientifically grounded manner. [22] Here the price of the branded and generic drugs (1× 10) tablets is, Rs.102.40/ and Rs.55/- respectively. A gestating woman is ideally expected to take iron supplements from 2nd trimester till 6 months of lactation. [23] Thus she has to bear an annual cost of Rs.3686.40/ and Rs.1980/- for branded and generic Ferrous Ascorbate respectively. This difference in the price between generic and branded drugs is huge varying from < 2-fold to >100-fold. [7]

Generic drug manufacturers don't have to invest in research and development like new drugs, and don't have to recover costs of pre-clinical and clinical studies, and hence can price their products lower than the originator product. [7,21] We observed a 1.4 times difference in the Price-to-patient (MRP) and price-to-retailer (PTR) in case of generic Ferrous Ascorbate. The price at which the wholesaler sells the product to the retailer was Rs 55/ for 10 tablets and MRP of the same is Rs.78/. Hence the findings of the study revealed that there are huge mark-ups for retailer on generic medicines.

By switching over to branded generic medicines cost benefit to pharmacist ranged from 270% to 422% but for patients it was only 5%-48.3%. [24] The high mark-ups on generics are totally negating the very concept of affordable generic medicines for patients. Hence, the government should have a policy whereby prices of generic drugs can be made realistic and affordable to the population. In the cost effective analysis considering both groups, Cost effective ratio was least with Group A due to better efficacy and the cost spend to reach such rise in hemoglobin levels compared to generic drug. An individual receiving generic drug, needs to spend Rs 18.61/ - more to gain efficacy obtained by branded drug.The present study therefore indicates that the ICER of the new treatment falls in the grey area of the South West i.e. the 3rd quadrant. When a drug falls in grey areas, drug favourability is subjective from patient to patient and the situation in which patient comes in for treatment. [25-27] If for instance a woman, comes for correction of anemia in her 1st trimester with hemoglobin between 8-10 gm/dL, Group B generic drugs would be favourable as the drug was less costly and shows slow but significant rise in the hemoglobin levels. And targeted levels can be achieved over the time, till the gestating patient is full term. In other scenario, if an anemic, gestating woman comes for correction in the last trimester, the treatment with generic drug is unfavourable, as when we need a rapid rise in hemoglobin levels over a short duration of time. To the best of our knowledge no studies regarding cost effective analysis of Generic and Branded Ferrous Ascorbate were conducted in India. We are not able to compare with other studies. We had not done follow-up of gestating women till term. More generic preparations of Ferrous Ascorbate could have been included in the study. In vitro testing to circumstantiate the reason for difference in efficacy between branded and generic Ferrous Ascorbate should have been done.

Conclusion

In present study, Branded Ferrous Ascorbate had better efficacy and was the favourable drug for treatment, as ACER was less and reported less number of adverse events.As per our study Generic Ferrous Ascorbate should be used if patient comes in during 1st trimester and Branded form should be used if patient comes in late or during 3rd trimester . Need of Pharmacoeconomic studied is the need of time at physician level to ensure

correct selection of drug to decrease health-economic burden and ensure compliance to reduces morbidity and mortality.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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