Research Article

Comparison of Efficacy and Safety Profile of Oral Iron Formulations in Patients with Iron Deficiency Anemia

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ABSTRACT

The aim of the study is to compare the efficacy and safety profile of oral iron formulations in iron deficiency anemia. A prospective study in patients with anemia receiving oral ferric ammonium citrate, ferrous fumarate, ferrous sulfate and ferrous calcium citrate respectively were included. Demographic details, clinical history, baseline hemoglobin, anemia indices data were recorded in a case record form. The patients were followed up once in 3 weeks for 3 months and observed for hematological improvement and adverse drug reactions (ADRs). The data was analyzed using paired t-test, ANOVA and Pearson Chi square test. Out of 66 patients, 11 patients received ferric ammonium citrate, 23 received ferrous fumarate, 20 received ferrous sulfate and 12 received ferrous calcium citrate. Ferric ammonium citrate, ferrous fumarate ferrous sulfate and ferrous calcium citrate have significantly ($P<0.0001$) improved mean hemoglobin and anemia indices at the end of study, however, there was no significant differences between the groups when compared. All four formulations showed similar ADR profile, there was no significant difference in adverse reactions. Cost of therapy incurred to patients treated with ferrous fumarate was low when compared to other drugs.

Keywords: IDA, Ferric ammonium Citrate, Ferrous Fumarate, Ferrous sulfate, Ferric Calcium Citrate, Hb and Ferritin.

INTRODUCTION

Deficiency of iron is one of the most common nutritional disorder in the society.[1] Iron deficiency anemia is described as decreased production in red blood cells (RBCs) due to low body iron stores.[2] According to World Health Organisation (WHO) Anemia is defined as a hemoglobin count below 13g/dl for adult males and post menopausal women women and below 12g/dl for premenopausal women. More than 30% of worlds population are anemic according to WHO, holding a majority share in iron deficiency anemia.[3] Iron Deficiency Anemia manifests as a hypochromic, microcytic anemia with low ferritin, hemoglobin and anemia indices MCH (mean corpuscular hemoglobin), MCV (mean corpuscular volume) and MCHC (mean corpuscular hemoglobin concentration).[4] The main signs and symptoms of IDA are fatigue, breathlessness, weakness (Because in anemic patients the oxygen carrying capacity will be low, as a result it can lead to decreased oxygenation of skeletal muscle), pallor and rapid heartbeats.[5]

The main causes of iron deficiency are inadequate iron absorption or increased iron requirements and inadequate iron intake.[6]

Management of iron deficiency anemia involves two components, Identifying and eradicating the cause of iron deficiency. Correction of anemia which mainly includes dietary improvement, oral iron supplementation and parenteral iron therapy.[7] Oral and parenteral iron preparations are used in the prophylaxis and treatment of anemia. The oral route is preferred to replace iron stores and mild to moderate iron deficiency anemia are treated using oral iron supplements.[8]

The present study was undertaken to evaluate the efficacy and toxicity profile of four oral iron preparations in iron deficiency anemia.

Aims and Objectives

The aim of the present study is to compare the efficacy, safety and cost of therapy of oral ferric ammonium citrate, ferrous fumarate, ferrous sulfate and ferrous calcium citrate in anemic patients.

Methodology

A prospective study was carried out on outpatients in the department of medical oncology and hematology of Amrita Institute of Medical Sciences (AIMS), Kochi from October 2015 to April 2016.

A patient information sheet was given to the patients and informed consent was obtained from the patient and/or care givers.

Patients with nutritional iron deficiency anemia with Hb <9.5g% and ferritin value <20mcg/l of more than 18 years of age where selected for the study and iron preparations were given in doses as follows.

1. Ferric ammonium citrate (elemental iron 32.8mg/tablet): 2-1-2

2. Ferrous sulphate (elemental iron 46.8mg/capsule): 1-1-1

3. Ferrous calcium citrate (elemental iron 25mg/ tablet): 2-2-2

4. Ferrous fumarate (elemental iron 50mg/tablet): 1-1-1

However patients with gastric blood loss, renal disorders, hemoglobinopathies, vitamin B12 and folic acid deficiency were excluded.

The data of the patients were recorded in data collection record. Patients were followed up every 3 weeks for 3 months for hematological improvement and adverse reactions for three months. The data was recorded in Microsoft Excel Worksheet and analysed by paired 't' test, ANOVA and Pearson Chi square test with the aid of statistical package for social science (SPSS software, version 20.0).

RESULTS

Out of 66 patients, 20 (30%) were male and 46 (70%) were female. Of 66 patients, 23 received ferrous fumarate, 20 received ferrous sulfate, 12 received ferrous calcium citrate and 11 received ferric ammonium citrate. The mean age of the patients treated with iron supplements was 44.86 ± 16.29 years with a minimum age of 18 years and maximum of 85 years.

The most common presenting complaints of patients were pallor (97%) and fatigue (97%) followed by breathlessness (60.6%), brittle nails (24.2%), pica (15.2%) and angular stomatitis (10.6%).

Iron Preparations Therapy Outcome

All patients were followed up every 3 weeks for hematological improvement for 3 months. As compared to baseline, significant improvement (<0.0001) was seen in red cell indices (MCV, MCH and MCHC), and mean hemoglobin in patients treated with ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate at 3 weeks, 6 weeks and 9 weeks. And there is also a significant increase in mean ferritin after 3 months (Table 1). Out of 66 patients, 1 patient's follow up was lost after baseline, 2 patients after 1st follow up and 2 patients after 2nd follow up (Table 2).

Table 2: Comparison of Mean Hb and Ferritin of Patients at each Follow Up

Laboratory Parameters	N	Mean ± SD	P-value
Hb baseline	65	8.0406 ± 1.400	<0.001
Hb 1st FU	65	9.662 ± 1.314	
Hb baseline	63	7.999 ± 1.402	<0.001
Hb 2nd FU	63	11.279 ± 1.464	
Hb baseline	61	7.997 ± 1.426	<0.001
Hb 3rd FU	61	12.638 ± 1.535	
FERRITIN baseline	61	10.400 ± 5.767	<0.001
FERRITIN 3rd FU	61	42.42 ± 9.746	

Comparison between oral ferric ammonium citrate, ferrous fumarate, ferrous sulfate and ferrous calcium citrate

There was no significant difference in mean hemoglobin, red cell distribution width (RDW), anemia indices (MCV, MCH and MCHC) and ferritin in patients treated with ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate at the end of the treatment (Table 3-7).

Table 3: Comparison of Mean increase in Hb of Patients Treated with Oral Iron Formulations

Parameter	Hemoglobin			
	Baseline	Mean increase at 1st follow up 3 weeks.	Mean increase at 2nd follow up 6 weeks.	Mean increase at 3rd follow up 9 weeks.
Ferric ammonium citrate	7.861 ± 1.606	9.878 ± 1.546	11.710 ± 1.782	12.442 ± 1.913
Ferrous Sulfate	8.327 ± 1.402	9.750 ± 1.125	11.35 ± 0.890	12.847 ± 0.873
Ferrous Fumarate	7.85 ± 1.494	9.400 ± 1.504	11.030 ± 1.557	12.716 ± 1.570
Ferrous Calcium Citrate	8.170 ± 1.028	9.798 ± 1.314	11.250 ± 1.804	12.282 ± 2.096
P-value	0.691	0.717	0.678	0.775

Table 4: Comparison of Increase in Mean MCV of Patients Treated with Oral Iron Formulations

Parameter	MCV			
	Baseline	Mean increase at 1st follow up 3 weeks.	Mean increase at 2nd follow up 6 weeks.	Mean increase at 3rd follow up 9 weeks.
Ferric ammonium citrate	65.400 ± 8.930	69.889 ± 7.988	73.140 ± 8.518	76.889 ± 8.351
Ferrous Sulfate	70.865 ± 10.54	74.616 ± 8.192	77.216 ± 7.443	80.142 ± 7.305
Ferrous Fumarate	65.504 ± 6.744	71.550 ± 6.51	77.277 ± 7.625	80.909 ± 7.387
Ferrous Calcium Citrate	71.350 ± 9.775	73.892 ± 7.613	77.133 ± 8.07	80.536 ± 7.171
P-value	0.104	0.306	0.516	0.506

Table 5: Comparison of Mean Increase in MCH of Patients Treated with Oral Iron Formulations

Parameter	MCH			
	Baseline	Mean increase at 1st follow up 3 weeks.	Mean increase at 2nd follow up 6 weeks.	Mean increase at 3rd follow up 9 weeks.
Ferric ammonium citrate	17.964 ± 4.082	20.527 ± 3.667	22.45 ± 3.422	23.689 ± 3.904
Ferrous sulfate	21.375 ± 4.19	22.685 ± 3.454	24.43 ± 3.178	26.00 ± 3.119
Ferrous fumarate	19.257 ± 2.693	21.436 ± 2.767	22.936 ± 2.888	24.432 ± 2.646
Ferrous calcium citrate	21.992 ± 3.833	22.95 ± 3.234	24.05 ± 2.865	26.764 ± 3.045
p-value	0.019	0.193	0.265	0.063

Table 6: Comparison of Mean Increase in MCHC of Patients Treated with Oral Iron Formulations

Parameter	MCHC			
	Baseline	Mean increase at 1st follow up 3 weeks.	Mean increase at 2nd follow up 6 weeks.	Mean increase at 3rd follow up 9 weeks.
Ferric ammonium citrate	26.927 ± 5.022	29.682 ± 1.981	31.350 ± 1.670	31.456 ± 2.215
Ferrous sulfate	29.825 ± 1.982	30.560 ± 1.753	31.453 ± 1.734	32.389 ± 1.718
Ferrous fumarate	29.317 ± 2.072	30.286 ± 1.917	31.105 ± 2.211	32.005 ± 2.535
Ferrous calcium citrate	30.692 ± 0.466	30.383 ± 2.175	31.308 ± 1.854	32.718 ± 2.024
p-value	0.009	0.681	0.950	0.523

Table 7: Comparison of Mean Increase in Ferritin of Patients Treated with Oral Iron Formulations

Parameter	Ferritin	
	Baseline	Mean Increase after 3 Months
Ferric ammonium citrate	8.110 ± 4.670	37.67 ± 11.332
Ferrous sulfate	10.26 ± 6.340	42.35 ± 9.758
Ferrous fumarate	10.60 ± 5.932	41.45 ± 5.489
Ferrous calcium citrate	10.696 ± 5.166	41.45 ± 5.489
p-value	0.653	0.087

Table 8: Details of Adverse Drug Reactions (ADRs) Observed among Patients Treated with Iron Preparations in the Study (n=66)

ADRs	Ferric ammonium citrate	Ferrous sulfate	Ferrous fumarate	Ferrous calcium citrate
Constipation	45.5(5)	45(9)	39.1(9)	33.3(4)
Heart burn	54.5(6)	50(10)	56.5(13)	41.7(5)
Diarrheoa	27.3(3)	10(2)	0(0)	8.3(1)
Nausea	18.2(2)	30(6)	13(3)	8.3(1)
Metallic taste	9.1(1)	10(2)	21.7(5)	0(0)
Epigastric pain	9.1(1)	25(5)	13(3)	8.3(1)
Vomiting	18.2(2)	0(0)	8.7(2)	0(0)

Adverse Drug Reactions (ADRs)

A total of 101 ADR's where observed in 66 patients during the study period. The most often seen adverse reactions were heart burn (51.5%) followed by constipation (40.9), Nausea(18.2%), Epigastric pain(15.2%), Metallic taste(12.1%), Diarrhea(9.1%) and Vomiting(6.1%) . Causalty assessment, majority of ADR's were probable in nature by Naranjo's scale. All four formulations shows similar ADR profile, there is no significant difference in adverse reactions (Table 8).

Total Cost of Drug Treatment of Anemia

The cost of treatment of anemia has been summed up in terms of rupees spent per patient per month for purchasing the drug for 6 months. Mean total cost of therapy for ferric ammonium nitrate is Rs.2118, ferrous

sulfate is Rs. 1686, ferrous fumarate is Rs.912 and for ferrous calcium citrate is Rs. 3006 (Table 9).

Table 9: Cost of Therapy

Groups	Mean Total Cost (6 months)
Ferric ammonium citrate	Rs.2118
Ferrous sulfate	Rs.1686
Ferrous fumarate	Rs.912
Ferrous calcium citrate	Rs.3006

DISCUSSION

Iron deficiency anemia is a serious problem, which has greater impact on behaviour, psychological, physical development, and work performance.[9] Iron deficiency is the 12th most important risk factor for all mortality globally and one of the most prevalent nutritional deficiencies in the world. It can be prevented to a certain extent and treated through nutritional diet, different oral and parenteral iron preparations. Blood transfusion may also be done.[10]

Oral iron administration is the first line treatment of choice. Parenteral iron administration is reserved for patients who show intolerance to oral iron. Blood transfusions is done only in severe cases in which haemoglobin concentration is less than 3 g/dl.[9] Apart from few studies comparing the efficacy, toxicity and cost of few oral iron formulations in pediatrics, pregnancy and CKD patients, there are no studies available that were conducted in general population.

Our study describes the outcomes of 66 patients treated with ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate for 3 months in a tertiary care hospital setting. At the end of 3 months of follow up, 61 patients remained in the study with 5 lost in follow up. All patients showed a significant improvement in hematological parameters in every follow up showing the efficacy of all the four preparations.

In our study, the most common age group was 38-48 years (39.39%), followed by 28-38 years. In our study, mean age of patients treated with iron preparations was higher (44.86 ± 16.29 years) as compared to study carried out by **Adsul BB** (32.18 years).[11] There were 70% women and 30% men in our study indicating higher prevalence of iron deficiency anemia in females, menstrual bleed being a contributory factor. We observed that about 66% of patients have a peripheral smear with microcytic hypochromic cells.

Majority of the patients had fatigue (97%) and pallor (97%) as the most common presenting complaints followed by breathlessness (60%). In anemic patients due to low oxygen carrying capacity, oxygen supply to skeletal muscle decreases which results in fatigue and breathlessness.

Pallor is due to the low serum hemoglobin concentration[10]. A study conducted by **Adsul BB**[11] also reported pallor (88%) and fatigue (74%) as the most common presenting complaints followed by breathlessness (4%).

Hematological parameters like hemoglobin, ferritin (blood hemoglobin level and ferritin level are the most accurate measure of the degree of anemia in iron deficiency), red cell indices (MCV, MCH and MCHC) and RDW were used to diagnose anemia, to determine its severity and to know iron stores. Patients with moderate anemia (hemoglobin < 9.5g/dl) were treated with ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate. In each follow up a significant improvement ($p > 0.001$) was seen in hemoglobin, red cell distribution and red cell indices width. But significant improvement was not seen in mean increase in hemoglobin, red cell indices and red cell distribution width value within each group while comparison.

Similar study was conducted by **Bhoomi AD**[7] Ferrous sulfate and ferrous fumarate were compared in this study and reported that ferrous sulfate is more effective than ferrous fumarate in improving mean hemoglobin level and mean MCV value at the end of one month of treatment, but the study was conducted in girls of age group 12-17 years.

In our study all the four iron preparations were seen to be well tolerated with no serious adverse events reported. The most often seen ADRs reported were heart burn (51.5%), constipation (40.9%) and nausea (18.2%). This may due to the presence of free elemental iron in the gastro intestinal tract which causes gastro intestinal irritation.[5] A pilot study conducted by **leonard AJ**[12] compared two doses of elemental iron (ferrous sulfate) and reported side effects such as nausea, darkening of stool and constipation.

A comparison between ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate doesn't show a significant difference in adverse effects, all show a similar ADR profile. The frequency of side effects is directly related to dose of iron. In the study, all the four preparations are administered in same dose.[9]

The average cost incurred to the patient treated with ferrous calcium citrate was highest, followed by ferric ammonium citrate, ferrous sulfate and ferrous fumarate. The cost of therapy per patient for 3 weeks with ferrous calcium citrate was Rs.501. While with ferric ammonium citrate, it was Rs.353, ferrous sulfate it was Rs.281 and Rs.152 with ferrous fumarate.

The average cost for drug incurred to the patients was more with ferrous calcium citrate as compared to other three preparations. Ferrous fumarate was the best cost effective drug when compared to other three preparations. A study conducted by **Patil SS**[13] compared cost of ferrous fumarate, ferrous bisglycinate and

carbonyl iron and reported that ferrous fumarate is the best cost effective drug compared to other two drugs.

CONCLUSION

The present study was aimed to select the best effective drug for the treatment of iron deficiency anemia from the four drugs currently available in the market, ferric ammonium citrate, ferrous sulfate, ferrous fumarate and ferrous calcium citrate. Our results showed no significant differences in the efficacy and safety in between the treatment groups for treating iron deficiency anemia. Therefore, Ferrous fumarate can be considered as best cost effective choice for treatment of iron deficiency anemia.

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