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RESEARCH ARTICLE

Comparison of Efficacy, Safety and Cost of Therapy with Oral Ferrous Ascorbate and Ferrous Sulphate in Patients with Iron Deficiency Anemia

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ABSTRACT

Objective: To compare the efficacy and safety of oral ferrous ascorbate and ferrous sulphate in patients with iron deficiency anemia

Methods: An observational, prospective study in patients of anemia in chronic kidney disease (CKD) and pregnancy receiving oral ferrous ascorbate and ferrous sulfate respectively were included. Demographic details, clinical history, baseline hemoglobin, anemia indices data were recorded in a case record form. The patients were followed up monthly for 12 weeks and observed for clinical and hematological improvement and adverse drug reactions (ADRs). The data was analyzed using paired t-test, unpaired t-test and Fisher`s exact test.

Results: Out of 148 anemic patients, 62 CKD patients received ferrous ascorbate and 86 pregnant patients treated with ferrous sulfate. Ferrous ascorbate and ferrous sulphate have significantly (P<0.0001) improved mean hemoglobin and anemia indices at the end of study, however, mean increase in hemoglobin was more and significant (P<0.000) with ferrous ascorbate (3.45 g/dL) as compared to ferrous sulfate (3.3 g/dL). Mean increase in MCV and MCHC were comparable in both ferrous ascorbate and ferrous sulfate treated patients, however, mean increase in MCH was significantly (P <0.005) with ferrous sulfate (4.7 pg/cell) treated patients as compared to ferrous ascorbate (3.15 pg/cell). ADRs were more in patients treated with ferrous sulfate (86%) than ferrous ascorbate (71%). Cost of therapy incurred to patient treated with ferrous ascorbate (Rs. 1269.6) was three time more as compared to ferrous sulfate (Rs. 409.7).

Conclusion: Ferrous ascorbate and ferrous sulfate, both were effective and safe in treating iron deficiency anemia in patients with CKD and pregnancy respectively. However, ferrous ascorbate increased hemoglobin more, with better tolerated by patients. Unfortunately, cost of therapy with ferrous ascorbate was high as compared to ferrous sulfate.

Key words: anemia in pregnancy, chronic kidney disease, ferrous ascorbate, ferrous sulfate

INTRODUCTION:

Anemia is a sign, not a disease of dynamic process. The World Health Organization (WHO) defines anemia as hemoglobin (Hb) below 13 g/dL for adult males and postmenopausal women, and below 12 g/dL for premenopausal women. [1] According to WHO, two billion people (>30% of the world's population) are anemic, mainly due to iron deficiency. The incidence of iron deficiency anemia (IDA) in India is 60% in urban and 69% in the rural population. [2 and 3] Anemia is the commonest medical disorder in pregnancy and also common in patients with chronic kidney disease. [4] Iron deficiency anemia manifests as a hypochromic, microcytic anemia with low hemoglobin, anemia indices (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC)) and serum ferritin. [4] It is commonly seen in populations with inadequate iron intake, inadequate iron absorption or increased iron requirements. These include infants, especially premature infants; children during rapid growth periods; pregnant and lactating women; and patients with chronic kidney disease who lose erythrocytes at a relatively high rate during hemodialysis. [4]

Oral and parenteral iron preparations are used in treatment and prophylaxis of anemia. [5, 6, 7] Oral iron preparations are used to treat mild to moderate iron deficiency anemia. [5, 6] Conventional oral iron preparations include ferrous sulfate, fumarate, succinate while newer preparations include ferrous ascorbate.[5, 6, 7] Though, ferrous ascorbate are widely used for the treatment of iron deficiency in pregnancy and in chronic

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kidney disease patients in India. Although limited literature on the efficacy and safety of ferrous ascorbate in anemia in pregnancy and chronic kidney diseases in Indian patients is available. Thus the present study was conducted to evaluate efficacy and safety of oral ferrous ascorbate and ferrous sulphate in these patients

Aims and Objectives:

The aim of present study is to compare the efficacy and safety and cost of therapy oral ferrous ascorbate and ferrous sulphate in anaemic patients.

Materials and Methods:

This was a continuous, prospective, observational, two centre study conducted at the semi-government hospital and the government tertiary care teaching hospital in an urban setting of western India. The study was approved by Institutional Ethics Committee (IEC) and granted permission by the Director of Institute. Patients of anaemia in pregnancy and chronic kidney disease (CKD) of more than 16 years and either gender receiving ferrous ascorbate and ferrous sulphate, from November 2011 to January 2013, at CHA and IKD were enrolled in the study. However, Patients having anemia due to haemolysis, bone marrow depression, vitamin B_{12} deficiency, transfused blood or blood products in previous two months and with haemochromatosis or other iron storage disorders were excluded. Informed consent was obtained from all patients.

The baseline data of the patients were recorded in pre-tested case record form. Each patient was followed up every month for clinical and hematological improvement and adverse drug reactions (ADRs) for three months. Hemoglobin, anemia indices and serum ferritin (at IKD) were measured at baseline and at the end of each month for subsequent three months. The data was recorded in Microsoft Excel Worksheet and analysed by Fisher's exact test and paired student's 't' test and unpaired student `s 't' test with the help of GraphPad Prism 5.0 software.

RESULT:

Baseline Characteristics:

Out of 148 patients, 41 were men and 107 were women. Out of 148 anemic patients, 62 CKD patients received ferrous ascorbate and 86 pregnant patients treated with ferrous sulfate. The mean age of patients treated with ferrous ascorbate was 53.4 years and 23.6 years with ferrous sulfate. The most frequent presenting complaints of patients were fatigue followed by breathlessness (Table 1). Most common sign was mild to severe pallor of tongue, nail and conjunctiva among patients (Table 1). Mean baseline hemoglobin and anemia indices were comparable in ferrous ascorbate and ferrous sulfate iron preparations treated patients. (Table 1)

Outcome on iron preparations therapy:

Clinical assessment:

Each patient was followed up every month for clinical improvement for three months. There was significant improvement ($p<0.0001$) in fatigue and breathlessness in ferrous ascorbate and ferrous sulfate treated patients at first follow up. Further, all patients were symptomless at the end of 3 months treatment with ferrous ascorbate and ferrous sulfate. (Table 2)

Hematological assessment:

Compared to baseline, there was significant ($p<0.0001$) improvement in mean hemoglobin, and anemia indices (MCV, MCH and MCHC) in patients treated with ferrous ascorbate, ferrous sulfate and iron sucrose at 12 weeks (Table 3).

Comparison between oral ferrous ascorbate and ferrous sulfate:

A significant difference in mean hemoglobin ($p<0.0001$) was observed with ferrous ascorbate at the end of treatment as compared to ferrous sulfate. While mean MCH was significant improvement with ferrous sulfate group at 4 weeks, 8 weeks and 12 weeks as compared to ferrous ascorbate group (Table 4)

Adverse Drug Reactions (ADRs):

A total of 118 ADRs were observed in 148 patients during the study period. The most common ADR was nausea (39) followed by heart burn (26). Out of 118 ADRs, 44 (37.2%) were reported from ferrous ascorbate treated group and 74 (62.7%) from ferrous sulfate (Table 5). ADRs were categorized as mild based on modified Hartwig and Siegel scale. However, none of the ADR required withdrawal of causal drug. Causality assessment showed that majority of ADRs were categorized as possible in nature (118) by WHO-UMC scale, while 118 ADRs were categorized as probable in nature by Naranjo`s scale (Table 6).

Total cost of drug treatment of anemia:

The cost of drug treatment of anemia has been calculated in terms of direct and indirect cost in terms of rupees spent per patient per month.(Table 6)

a) *Direct cost*: This refers to cost incurred to patient for purchase of drugs plus laboratory investigations plus the amount spent towards transportation to hospital. The mean direct cost of therapy in ferrous ascorbate treated patients Rs. 569.39 [95% CI (557.4, 581.38)] and Rs. 113.3 [95% CI (102.4, 125.8)] with sulfate.

b) *Indirect cost*: This refers to the loss of daily wages of the patient and accompanying person. The mean indirect cost of therapy in ferrous ascorbate treated group was

700.3 [95% CI (645.8, 744.4)] and ferrous sulfate group was 295.7 [95% CI (271.9, 323.5)].

c) ***Total cost:***

Mean total cost of therapy in ferrous ascorbate group was Rs. 1269.6 [95% CI (1203.2, 1325.8)] and in ferrous sulfate group was Rs 409.7 [95% CI (378.4, 442.7)] at 12 weeks.

Table 1: Baseline characteristics of the patients with anemia in the study (n=148)

Parameter	Ferrous ascorbate	Ferrous sulphate	Total
Number of patients	62	86	148
Mean age (Years)	53.4 ± 18.3	23.6 ± 5.8	-
Gender			
Men	41	00	41
Women	21	86	107
Clinical symptoms			
Fatigue (%)	62 (100)	86 (100)	-
Breathlessness (%)	9 (14.5)	9 (10.5)	-
Clinical signs (Severity of pallor of tongue, conjunctiva and nail)			
Mild (%)	54 (87)	73 (84.8)	-
Moderate (%)	8 (13)	13(15.2)	-
Severe (%)	0 (0)	0 (0)	-
Laboratory parameters			
Mean Hb (g/dL)	9 ± 0.3	8.9 ± 0.4	-
Mean MCV(µm3)	65.5 ± 7.6	64.6 ± 3.2	-
Mean MCH (pg/cell)	27.6 ± 0.8	25.2 ± 0.8	-
Mean MCHC (g/dl)	31.5 ± 5.8	30.5 ± 6.1	-

Table 2: Comparison of clinical symptoms of patients at different time interval (n=148)

[Values are absolute count (%)]

Study groups	Symptoms	Baseline	1st FU	2nd FU	3rd FU
Ferrous ascorbate (n=62)	Fatigue (%)	62 (100)	6 (9.67)#	0 (0)#	0 (0)#
	Breathlessness (%)	9 (14.5)	0 (0)#	0 (0)#	0 (0)#
Ferrous sulphate (n=86)	Fatigue (%)	86 (100)	11(12.7)#	0 (0)#	0 (0)#
	Breathlessness (%)	9 (10.5)	0 (0)#	0 (0)#	0 (0)#

# P < 0.0001 as compared to baseline (Fisher's exact test). FU= follow up

Table 3: Comparison of laboratory parameters of patients at different time interval (n=232)

[Values are mean ± SEM]

Study groups	Laboratory parameters	Baseline	1st FU	2nd FU	3rd FU
Ferrous ascorbate (n=62)	Mean Hb (gms %)	9 ± 0.3	10.8 ± 0.6*	11.9 ± 0.6*	12.4 ±0.5*
	Mean MCV(μm^3)	65.5 ± 7.6	67.8 ± 7.6*	69.3 ± 7.5*	69.9 ± 7.3*
	Mean MCH (pg/cell)	27.6 ± 0.8	29.3 ± 1.2*	30.2 ± 1.1*	30.8 ± 1*
	Mean MCHC (g/dl)	31.5 ± 5.8	33.1 ± 6.4*	33.8 ± 6.7*	34.1 ± 6.8*
Ferrous sulphate (n=86)	Mean Hb (gms %)	8.9 ± 0.4	10.2 ± 0.2*	11.2 ± 0.1*	12.2 ±0.7*
	Mean MCV(μm^3)	64.6 ± 3.2	66.8 ± 4.2*	68.5 ± 8.1*	69.4 ± 5.2*
	Mean MCH (pg/cell)	25.2 ± 0.8	28.3 ± 4.6*	29.4 ± 5.2*	29.9 ± 2.3*
	Mean MCHC (g/dl)	30.5 ± 6.1	32.5 ± 7.2*	33.2 ± 8.3*	33.7 ± 1.5*

#P < 0.0001 as compared to baseline (Paired student's't' tes). FU= follow up

Table 4: Comparison of difference in mean value of laboratory parameters of patients treated with oral iron preparations (n=148)

[Values are mean ± SEM]

Parameters	Mean difference at first follow up (4 weeks)		Mean difference at second follow up (8 weeks)		Mean difference at third follow up (12 weeks)		Total mean difference (12 weeks)	
	Ferrous ascorbate (n = 62)	Ferrous sulfate (n = 86)	Ferrous ascorbate (n = 62)	Ferrous sulfate (n = 86)	Ferrous ascorbate (n = 62)	Ferrous sulfate (n = 86)	Ferrous ascorbate (n = 62)	Ferrous sulfate (n = 86)
Mean Hb (g/dL)	1.8 ± 0.1*	1.3 ± 0.2	1 ± 0.12	1 ± 0.1	0.47 ± 0.06	1 ± 0.1**	3.45 ± 0.1*	3.3 ± 0.4
Mean MCV(μm^3)	2.3 ± 0.16*	1.2 ± 1	1.5 ± 028	1.7 ± 3.9**	0.64 ± 0.15*	0.9 ± 2.9**	4.3 ± 0.25	4.8 ± 2
Mean MCH (pg/cell)	1.6 ± 0.13	3.1 ± 3.8**	0.87 ± 0.13	1.1 ± 0.6**	0.6 ± 0.12	0.5 ± 2.9	3.15 ± 0.9	4.7 ± 1.5**
Mean MCHC (g/dl)	1.6 ± 0.14	2 ± 1.1	0.64 ± 0.1	0.7 ± 1.6	0.33 ± 0.08	0.5 ± 6.8	2.58 ± 0.21	3.2 ± 4.6

* P <0.0001 as compared to ferrous sulfate treated group (Unpaired student's't' test), **P <0.005 as compared to ascorbate treated group (Unpaired student's't' test). Oral ferrous ascorbate tr ineated patients chronic kidney disease (n=62) and oral ferrous sulfate treated patients in pregnancy (n=86). Hb- Hemoglobin. MCV - Mean corpuscle volume. MCH - Mean corpuscle hemoglobin. MCHC - Mean corpuscle hemoglobin concentration

Table 5: Details of adverse drug reactions (ADRs) observed among patients treated with iron preparations in the study (n=148)

ADRs	Ferrous Ascorbate n (%)	Ferrous sulphate n (%)	WHO-UMC Causality scale
Constipation	8 (18.1)	15 (20.2)	Possible
Heart burn	10 (22.7)	16 (21.6)	Possible
Nausea	16 (36.3)	23 (31)	Possible
Metallic taste	2 (4.5)	5 (6.75)	Possible
Epigastric distress	4 (9)	7 (9.4)	Possible
Headache	2 (4.5)	2 (2.7)	Possible
Vomiting	2 (4.5)	6 (8.1)	Possible
Total	44 (100)	74 (100)	

Table 6: The cost of drug treatment of patients treated with ferrous ascorbate and ferrous sulfate (n=148)

[Values are mean (95 % confidence interval)]

Type of cost	Ferrous ascorbate treated patients (n=62)	Ferrous sulfate treated patients (n=86)
Mean direct cost (Rs.)	569.3 (557.4, 581.38)	113.3 (102.4, 125.8)
Mean indirect cost (Rs.)	700.3(645.8, 744.4)	295.7(271.9, 323.5)
Mean Total cost (Rs.)	1269.6 (1203.2, 1325.8)	409.7(378.4, 442.7)

DISCUSSION:

Iron deficiency anemia (IDA) is one of the most prevalent nutritional deficiencies in the world and 12th most important risk factor for all mortality globally.[8] The iron deficiency can be effectively prevented and treated by using nutritional diet, different oral and parenteral iron preparations as well as with blood transfusion.[9] Blood transfusion associated with risk of infection (bacterial, viral). [9] Conventional oral ferrous salts like sulfate, fumerate and gluconate are most commonly used routinely; however, recently ferrous ascorbate has been widely used effectively to treat iron deficiency in pregnancy and CKD. [10] Ferrous ascorbate, a novel oral iron preparation, claims to enhance the process of iron absorption in gastrointestinal tract. [11, 12]

Our study shows an analysis describing the outcomes of total 148 patients treated with ferrous ascorbate and ferrous sulfate for three months semi-governmental hospital and a tertiary care teaching hospital in an urban setting of western India. After 3 months of follow up, all 148 patients remained on treatment with no deaths or drop outs. Of 148 patients, all 148 had normalized hematological parameters (Hemoglobin and anemia indices) values and clinical improvement, giving 100%

treatment success rate with all three iron preparations at 12 weeks.

Our study showed that the most common age group was 16-30 (37.9%) years followed by 46-60 (21.9%) years. In our study, mean age of ferrous ascorbate treated patients was (higher (53.6 years) as compared to studies carried out by Suheyl Asma et al., 2009 (44.5 years) and Gabriel Mircescu et al., 2006 (52.2 years).[13, 14] There were more women (72.9%) than men (28.8%) in our study indicating high prevalence of iron deficiency women. However, national data shows that 69% of the total iron deficiency anemia patients are young women, which is lower than our finding (80.3 % young women). In our study, we observed fatigue and breathlessness were most common presenting symptoms. This can be because of decrease oxygenation of skeletal muscle as result of low oxygen carrying capacity in anemia patients. [9] Pallor of tongue, nail and conjunctiva was also seen in the patients and its severity was related to hemoglobin concentration. Similar findings had been reported in studies conducted by Tokars ML, 2010 [15]. Different hematological parameters like hemoglobin, anemic indices (MCV, MCH and MCHC) were used to diagnose the anemia, determine its severity and know iron store. The baseline value of laboratory parameters is comparable between ferrous ascorbate and ferrous sulfate. Similar difference in baseline values had been observed in study conducted by John stoves et al., 2001. [16]

Ferrous ascorbate and ferrous sulfate treatment resulted into a significant improvement ($p<0.0001$) in fatigue and breathlessness at first follow up. Further, all patients were symptom free at the end of 3 months treatment with oral and parenteral iron preparations. Similar results were documented in studies carried out by Suheyl Asma et al., 2009 (at 4 weeks) and Gabriel Mircescu et al., 2006 (1 week).[14, 15] As result of treatment with oral iron preparations improves availability of elemental iron for erythropoesis and that improves signs and symptoms of anemia.[17]

A parallel improvement in laboratory parameters was noted in our study. In mild to moderate anemia (Hb between 7 to 10.9 gms) patients treated with ferrous ascorbate and ferrous sulfate, the hemoglobin and anemia indices (MCV, MCH and MCHC) were comparable with maximal improvement at third follow up (12 weeks). However, in our study, we observed more increase in hemoglobin ($p<0.0001$) with patients treated with ferrous ascorbate as compare to ferrous sulfate. This may be due to ferrous ascorbate being a synthetic iron molecule with ascorbate a reducing agent reduces iron in highly soluble ferrous form and enhances its absorption from gastrointestinal tract. [12, 13] Similar observation had observed in studies done by tudies carried out by Suheyl Asma et al., 2009 and Tokars ML, 2010 [13,15]

In our study, all three iron preparations were well tolerated and there no serious adverse event was observed. The most common ADRs documented were heart burn (22%), nausea (33%) and constipation (19.4%). A comparison between two ferrous salts showed that adverse drug reactions with ferrous ascorbate were low (37.3%) as compared to ferrous sulfate (62.7%). This is due to more free elemental iron presents in gastro-intestinal tract which increases gastro-intestinal irritation. Ferrous ascorbate provide better stability of iron-ascorbate complex in gastro-intestinal tract which prevent dissociation of iron from ascorbate.[11,12] In addition, ascorbate prevention of oxidation ferrous form to ferric form which enhances its absorption from upper intestine.[11, 12]

Cost of treatment incurred by patients per month is three times higher with ferrous ascorbate as compared to ferrous sulfate due to following reasons: firstly, the expenditure for ferrous ascorbate (Rs. 1.5/ tablet) was paid out of pocket by patients while ferrous sulfate being essential medicine was provided free at tertiary teaching government hospital and secondly, patients had to incur cost of laboratory tests at semi-governmental hospital which was free of cost at tertiary teaching government hospital. The cost of drug treatment per patient per month was definitely high especially for patients of low income group.

CONCLUSION:

Ferrous ascorbate and ferrous sulfate, both were effective and safe in treating iron deficiency anemia in patients with CKD and pregnancy respectively. However, ferrous ascorbate increased hemoglobin more and better tolerated by patients as compared to ferrous sulfate. But cost of treatment incurred by patients per month is three times higher with ferrous ascorbate as compared to ferrous sulfate. Such higher cost cannot easily afforded by low income group especially when cheaper alternative like ferrous sulfate available.

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