Original Article

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IV Ferric Carboxymaltose Vs Oral Iron in the Treatment of Post-partum Iron Deficiency Anaemia

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ABSTRACT

Introduction: Iron deficiency is the most common cause of Post-partum anaemia, reported as 50-60% in India. It is primarily due to inadequate iron intake and due to peripartum blood loss. It has been associated with significant post-partum complications. Therefore, Post-partum iron deficiency warrants greater attention and higher quality care. Oral iron treatment has been considered the standard of care. However, parenteral iron treatment is expected to be advantageous in cases where oral iron therapy is not possible. As a result, there is increased interest in parenteral iron therapy. Recently, a new parenteral iron preparation, Ferric Carboxy Maltose (FCM), was developed to facilitate effective treatment of Iron Deficiency Anaemia (IDA). This study was carried out in women with Post-partum IDA who were expected to benefit from the short treatment period permitted by the larger doses given parenterally.

Aim: To evaluate the efficacy, safety and tolerability of intra venous FCM compared to oral iron in treating Post-partum IDA patients.

Materials and Methods: This was a hospital based prospective comparative study. Women with Haemoglobin (Hb) between 7-10 g/dl and peripheral smear showing microcytic hypochromic anaemia on the first Post-partum day were included in the study. These women were randomised to receive either IV FCM (single dose 1000 mg) or oral ferrous ascorbate (100 mg twice daily for 6 weeks). Statistical analysis was done by student's paired and unpaired t-test and by chi- square test and fischer-exact t-test.

Results: Ninety patients (45 in each group) were followed at one week and six weeks from the start of treatment and their HB were estimated. Significant rise in Hb was observed in subjects treated with FCM compared to oral iron. FCM treated subjects were more likely to achieve an Hb rise greater than or equal to 3.0 g/dL. FCM was better tolerated with complete adherence to treatment as compared to oral ferrous ascorbate.

Conclusion: FCM showed robust evidence of efficacy, tolerability and safety in comparison to oral iron. Collectively, these data support the clinical utility of FCM in treating Post-partum IDA patients.

Keywords: Parenteral iron therapy, Peripartum anaemia, Postnatal period

INTRODUCTION

Anaemia in the postnatal period is a common problem globally [1]. The prevalence of Post-partum anaemia is more in developing countries [2]. It is an important cause of maternal morbidity and mortality in these countries [3]. Of the ~500,000 annual maternal deaths occurring globally in association with delivery, 20% are related to peripartum blood loss and anaemia [4,5]. However, Post-partum anaemia also contributes to a major healthcare problem even in developed countries [6,7].

World Health Organization defines Post-partum Anaemia (PPA) as haemoglobin (Hb) of <10 g% [8]. Iron deficit being the most common cause of anaemia reported as 50-60% in Post-partum females in India. Post-partum Iron Deficiency Anaemia (IDA) is mostly due to poor iron intake before pregnancy and due to peripartum blood loss [7].

Post-partum IDA affects low income women. It has been associated with Post-partum mood disorders, poor mother –infant relationship [9]. Infants of these mothers have low development test scores at 10 weeks, and these iron deficits in infant development have been shown to persist even at 9 months of age [8].

All these imply that Post-partum iron deficiency has significant effect on social and economic aspects of women's lives, including the ability to properly concentrate on child care, household and social activities. Henceforth, Post-partum iron deficiency needs greater consideration and higher quality of care.

IDA should be treated by restoring iron stores either by oral or intravenous (IV) administration of iron depending on the grade of anaemia and how rapid the anaemia needs to be corrected. The main drawback with oral iron therapy is due to noncompliance or impaired gastrointestinal absorption [9-11]. Iron IV formulations contain more or less tightly bound ferric iron. Of these formulations 1st generation products include low molecular weight iron dextran and iron sorbitol citrate. These compounds can be given in higher doses but are associated with anaphylactic reactions. A 2nd generation compounds like iron sucrose require multiple injections to supplement 1000 mg of iron [12,13]. Thus a new parenteral iron molecule with the advantages of both the parenteral preparations is needed. It is important to find a better way of treating the patients with Post-partum anaemia. At present, the principle treatment for anaemia is oral iron supplementation. A recent IV iron preparation, Ferric Carboxy Maltose (FCM), has been newly developed. It provides quick replenishment of iron stores and can be given up to a maximum single dose of 1000 mg in a duration of less than 15 minutes [14,15].

The aim of this study was to evaluate the efficacy, safety and tolerability of IVFCM, in comparison with oral iron in women with Post-partum IDA.

MATERIALS AND METHODS

This was a hospital based prospective comparative study conducted over a period of two years between September 2013 and September 2015 at Kasturba Medical College, Mangalore. Institutional ethics committee approval was taken prior to initiation of the study. A total of 90 subjects were studied. Sample size was calculated based on the mean and standard deviation values of study by van wyck et al., with 95% confidence level and 90% power sample size comes to 45 in each group [15]. All subjects

gave written informed consent before enrolment. Women with history of anaemia other than IDA, current myelosuppresive therapy, recent blood transfusions (within 3 months), therapy with erythropoietin within 3 months prior to screening were excluded. Haemoglobin levels were assessed on the first Post-partum day, though not appropriate due to decrease in plasma volume that follows delivery, so that if needed treatment can be started earlier. Women with Hb between 7-10 g/dl were selected. These patients were subjected to peripheral smear examination. Women with peripheral smear showing microcytic hypochromic anaemia were randomised in a 1:1 ratio to receive either IV FCM or oral Ferrous ascorbate. Single dose Ferric carboxy maltose was given 1000mg IV diluted in 250ml normal saline over 15 minutes for one group and Ferrous ascorbate 100mg BD orally given before meals for six weeks for the other group. Repeat Hb levels were assessed at one week and six weeks after the start of treatment. Patients were observed for side effects after FCM injection for the next 24 hours. This group received no further iron supplementation. Patients on oral iron were questioned about the adherence to treatment and side effects at the end of six weeks. Used blister packs were returned to assess adherence to therapy. The secondary objective of this study was to compare the rate of rise in haemoglobin at one week and six weeks Post-partum among the two groups. The secondary objectives were to study the percentage of patients with rise of haemoglobin of > 3g% after treatment in the two groups and to study the adverse reactions and the compliance associated with the treatment in the two groups. Statistical analysis was done by student's paired and unpaired t-test and by chi- square test and fischer-exact t-test. Statistical package SPSS version 17.0 was used. The p-value of <0.05 was considered statistically significant.

RESULTS

A total of 98 patients were randomized to receive either oral iron supplement (51 patients) or IV FCM (47 patients). Out of these eight patients were lost to follow-up, six patients in oral iron group and two patients in FCM group. Finally 90 patients (45 in each group) were followed at one week and six weeks and their haemoglobin values were estimated. Mean age of the patients in the oral Iron group is 27.4 years and that in the FCM group is 28.044 years [Table/Fig-1]. In the present study, 48.88% patients underwent vaginal delivery and 51.1% patients underwent LSCS in the oral iron group, where as in FCM group 73.33 % patients had vaginal delivery and 26.7% had undergone LSCS. The groups did not differ in baseline characteristics or laboratory data. Though in the oral iron group, number of patients who had LSCS is more their Hb levels were comparable to other group before treatment.

Mean Haemoglobin at the start of treatment in both groups were statistically insignificant. Mean Haemoglobin after 1 week from the start of treatment in the oral iron group was 10.044g/dl whereas in the FCM group it was 10.688 g/dl (p-value <0.001 i.e., high significance). Mean Haemoglobin after 6 weeks from the start of treatment in the oral iron group was 11.156 g/dl whereas in the FCM group it was 11.938 g/dl (p-value <0.001 i.e., high significance) [Table/Fig-2].

Mean rise of haemoglobin after one week of start of treatment in the oral iron group was 1.138gm/dl and in the FCM group it was 1.980 g/dl (p-value <0.001, highly significant). Mean rise of haemoglobin after 6 weeks of start of treatment in the oral iron group was 2.271 g/dl and in the FCM group it was 3.227 g/dl (p-value <0.001, highly significant) [Table/Fig-2].

Eight patients in oral iron group had haemoglobin rise more than 3g/dl after six weeks (17.77%). Twenty two patients in FCM group had haemoglobin rise more than 3g/dl after six weeks (48.88%). No adverse reactions were seen in patients who received FCM. Seventeen patients (p-value<0.001) in oral iron group had GI complications accounting for 33.33%. Of these 3 patients reported constipation, two patients had epigastric pain and eight patients had nausea. Two patients reported both constipation and epigastric pain. No serious drug-related adverse events (e.g., hypersensitivity, anaphylaxis) were reported in either treatment group [Table/Fig-3].

Adherence to therapy was significantly greater among patients in the IV FCM group compared with those in the oral iron group (mean percent adherence 100% compared with 84.4 %). A total of 38 out of 45 patients in the oral iron group were compliant with therapy. Though used blister packs were returned to assess compliance to therapy adherence cannot be assured and this could be even responsible for oral iron to be comparatively less effective than FCM.

parameter	FCM (N=45)	Oral iron supplement (N=45)
Mean age (years)	28.044	27.4
Parity (primi / multi)	26/19	21/24
Antenatal Hb<10 g/dl	13	16
Mean antenatal Hb g/dl	10.03	10.16
Delivery (LSCS / VD)	12/33	23/22
Risk factors antenatally		
Hypertensive disorder	2	3
Malaria	1	0
Diabetes	4	2
PPH	0	0
Baseline Hb (g/dl)	8.71	8.907

[Table/Fig-1]: Demographic distribution and baseline clinical data.

BCC subtype	Group N=45	Mean	Std. Deviation	p-value
Hb at the start of treatment (g/dl)	FCM	8.710	0.835	p=0.206 ns
	Oral iron	8.907	0.617	
Hb after 1 week of start of treatment (g/dl)	FCM	10.688	0.980	p<.001 hs
	Oral iron	10.044	0.750	
Hb after 6 weeks of start of treatment (g/dl)	FCM	11.938	0.874	p<0.001 hs
	Oral iron	11.156	0.744	
Mean rise in Hb at 1 week	FCM	1.980	0.844	p<0.001 hs
	Oral iron	1.138	0.669	
Mean rise in HB at 6 weeks	FCM	3.227	1.242	p<0.001 hs
	Oral iron	2.271	0.711	

[Table/Fig-2]: Mean Hb at 1 week and 6 weeks and mean rise of Hb from the start of treatment.
p-value of <0.05 is considered significant; hs- highly significant

Parameter		Group		Total
		FCM	Oral iron	
Constipation	Count	0	5	5
	%	0.0%	11.1%	5.55%
Epigastric pain	Count	0	4	4
	%	0.0%	8.88%	4.44%
Nausea	Count	0	8	8
		0.0%	17.77%	8.88%
Nil	Count	45	30	75
	%	100%	66.66%	83.3%

[Table/Fig-3]: Adverse reactions in both groups.

DISCUSSION

The present study was conducted to compare IV FCM and oral ferrous ascorbate, for the treatment of a common disorder, Post-partum IDA. In our study, we wanted to study the response to a single dose FCM of 1000 mg and see if it was better than oral iron taken over 6 weeks.

Highly significant rise in Hb was observed in FCM group as compared to oral iron group at one week and six weeks Post-partum in our study. Although rise in Hb within 1 week was seen in patients assigned to oral iron also, some of this increase can be ascribed to the expected decrease in plasma volume that follows delivery [16,17]. In the present study, it was also observed that greater proportion of subjects in FCM group to achieve a target rise of Hb > 3g/dl compared to oral iron treatment group. There was proportionately more number of multigravidas in oral iron group compared to FCM group. This could also affect outcome as generally iron stores will be comparatively less in multigravidas than primigravidas. Similar Hb increase of 3 g/dL or greater was seen in subjects in FCM group in studies by Van wyck et al., and Sied et al., compared to oral iron [15,18]. In a study by Mishra et al., and Rathod et al., statistically significant rise in Hb was seen in the FCM group [19,20]. The response in these studies was greater than our study. The better response with FCM in these studies might be due to the fact that they had given FCM based on the calculated iron requirement in multiple doses. In present study it was found that the response to single dose of FCM of 1000mg was better than oral iron taken over 6 weeks. Also, the subjects in the oral iron group, in present study were less compliant to prescribed therapy when compared to the studies conducted by Van wyck et al., and Breymann et al., studies [15,21]. Reduced compliance in the oral group in our study compared to previous studies might be due to the reason that subjects in the present study did not receive any regular encouragement from study personnel. Complete adherence in the FCM group was seen in current study as it was given as a single dose. True to previous experience, we found significant drawbacks to oral iron treatment. GI disorders are the most common adverse effects with oral iron therapy. It was observed that 33.33% subjects in the oral iron group had Gastro Intestinal (GI) complications, where as no complications were reported in the FCM group. Rathod et al., in his study reported adverse reactions in 51% of subjects of oral iron group [20]. In the studies conducted by Sied et al., and Breymann et al., overall adverse events were experienced by 26.0% and 10.6% of patients in the iron carboxymaltose group respectively [18,21]. In a study by Mishra et al., 9% of patients in FCM group experienced adverse reactions. Serious life threatening events were not reported in any of these studies [19].

Due to this significant rate of noncompliance and GI side effects with oral iron, many patients remain susceptible to anaemia and are prone to the risk of interventions like transfusion. The main advantage of FCM over oral iron was the short treatment period and ensured compliance and no GI side effects. In our study, FCM showed its clinical utility in anaemia without significant safety concerns.

LIMITATION

IDA was confirmed only by peripheral smear showing microcytic hypochromic anaemia. Serum ferritin levels were not estimated in our study. Another limitation of our study was, we did not focus on how maternal quality of life and mother and infant relations were benefitted by correcting Post-partum anaemia. A major limitation of our study was that we did not administer iron as per the calculated requirement.

CONCLUSION

Single dose administration of 1000mg FCM showed robust evidence of efficacy, tolerability and safety in comparison to oral iron. Collectively, these data support the clinical utility of FCM in treating Post-partum IDA patients.

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