INTRAVENOUS IRON TREATMENT IN PREGNANCY: COMPARISON OF HIGH DOSE CARBOXYMALTOSE VS IRON SUCROSE

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ABSTRACT

***Objective*:** To determine the efficacy of high dose carboxymaltose vs iron sucrose for anemia among pregnant women managed at our hospital.

***Study Design*:** Comparative cross-sectional study.

Place and Duration of Study: Gynecology and Obstetrics department, Pak Emirates Military Hospital Rawalpindi, from Jan 2019 to Jan 2020.

Methodology: The study was done on 150 patients receiving carboxymaltose preparation and 150 patients receiving iron sucrose preparation in second or third trimester of pregnancy due to either not responding to or not tolerating the oral preparation. Mean change in hemoglobin was assessed after 12 weeks of standard therapy with both the agents. Complete recovery from anemia (hemoglobin levels), mean corpuscular volume and ferritin levels were also compared in both the groups.

***Results*:** Mean age of participants was 32.89±7.191 years. Mean rise in hemoglobin in carboxymaltose was 3.96 ± 4.19 mg/dl while in iron sucrose group was 2.11±1.72 mg/dl (*p*-value<0.05). With chi-square test it was established that patients achieved normal range of hemoglobin level, mean corpuscular volume and ferritin level statistically more (*p*-value <0.05) with the carboxymaltose preparation as compared to iron sucrose preparation.

Conclusion: Carboxymaltose preparation of iron emerged as more efficacious agent for improving the parameters of anemia in pregnant women when compared with iron sucrose. Not only hemoglobin levels responded better to carboxymaltose but ferritin and mean corpuscular volume also showed marked improvement with carboxymaltose preparation.

Keywords: Anemia, Iron preparations, Parenteral, Pregnancy.

INTRODUCTION

Physiology of body undergoes a lot of strain when a woman becomes pregnant and homeostasis maintenance becomes very difficult[1]. Various endocrine and metabolic pathways get triggered to achieve the hemostatic state with a fetus now relying on mother's resources as well[2]. Glycemic, lipid and hemodynamic changes may occur at any point during the course of pregnancy and if not addressed in time may lead to long term untoward consequences both for the mother and baby[3].

Anemia, especially iron deficiency anemias have been the most commonly encountered hematological conditions faced by the pregnant women in all parts of the world. Multiple oral or parenteral treatments have been tried to alleviate the signs and symptoms of this condition and keep all the parameters within range during this period. If not addressed adequately and in time anemias may lead to untoward consequences both for the mother and the baby[4,5].

A lot of work has been done to find the best solution for correction of anemia and improving the blood indices in the pregnant women. Parenteral preparations have also been under a lot of interest of the clinicians and researchers. Christoph *et al*, in 2011 conducted a study with the objective to compare the adverse effects and patients tolerability of carboxymaltose and iron sucrose. They concluded that carboxymaltose preparation is equal in tolerability as compared to sucrose preparation and provides an added

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benefit of provision of larger dose of iron and therefore becomes treatment of choice in last two trimesters for pregnant women with iron deficiency[6]. Pfenniger *et al*, in the same year published their study on post partum anemic females with almost similar objective and concluded that iron carboxymaltose is as safe as iron sucrose in the management of postpartum (IDA) iron deficiency anemia despite five times of higher dosage. Both drugs are effective and offer a rapid normalization of Hb after delivery. The single application of carboxymaltose preparation shows advantages of lower incidence of side effects at the injection site, a shorter treatment period, and better patient compliance[7]. Jose *et al*, in 2019 published a well designed randomized controlled trial in this regard. Pregnant women diagnosed with moderate to severe iron deficiency anemia were screened for the study. They concluded that treatment with carboxymaltose preparation resulted in rapid replenishment of iron stores in pregnant women with significantly higher Hb rise over a 12-week period. The convenient dosing with lesser number of total doses to complete the treatment will lead to better compliance in community setting[8]. Naqash *et al*, did a similar study in India and revealed that parenteral therapy is effective in women with iron deficiency anemia in pregnancy, but carboxymaltose preparation elevates hemoglobin level and restored iron stores faster than iron sucrose with minimum adverse drug reactions[9].

Maternal and fetal complications could be prevented if anemia gets addressed in time among the pregnant women. A study has been done in our part of the world by Wali *et al*, in 2002 and showed that Intravenous iron therapy is safe, convenient and more effective then intramuscular iron therapy in treatment of iron deficiency anemia during pregnancy. The intravenous iron therapy can replace blood transfusion in antenatal period[10]. Limited data has been available regarding the best parenteral preparation for pregnant women to alleviate their anemic symptomatology. We therefore conducted this study with the objective to determine the efficacy of high dose carboxymaltose vs iron sucrose for anemia among pregnant women managed at our hospital.

METHODOLOGY

This study was a comparative cross sectional study conducted in Gynecology and Obstetrics Department Pak Emirates Military Hospital Rawalpindi, from January 2019 to January 2020. WHO Sample Size Calculator was used for sample size calculation with population prevalence proportion of response to iron therapy 23.6%[11]. Sample was drawn from the registers from the patients who were in second or third trimesters of pregnancy and put on parenteral iron therapy either due to lack of response of tolerability issues with oral preparation were included in the study. Non probability consecutive sampling technique was used. Exclusion criteria were the diagnosed cases of any medical conditions like hypertension, type II diabetes mellitus, gestational diabetes mellitus, ischemic heart disease, morbid obesity or any metabolic or endocrine disorder. Patients with history of anemias prior to pregnancy or any nutritional deficiencies were also excluded from the study. Patients with past or current history of iron lowering drugs or any medications interfering with the blood indices or iron metabolism were also excluded from the study. Patients who could not be followed up till the end of pregnancy and had incomplete data in the system and registers were also not included in the final analysis.

Ethics approval was obtained from Internal Review Board of Pak Emirates Military Hospital (IREB Letter no: A/28/dated 20 Dec 2018). Patients were taken from the data base of the department and those fulfilling the above-mentioned inclusion/exclusion criteria were included in the study. Those who had iron deficiency anemia not responding to oral preparation or those who could not tolerate oral iron in second or third trimester were included in the study. Complete blood count (CBC) and serum ferritin were measured from the venous sample of the pregnant women from laboratory of our own

hospital and repeated after the 12 weeks of the therapy. CBC was measured using a flow cytometer and an automated analyzer. Iron deficiency anemia was defined as blood hemoglobin values of <12 g/dl and serum ferritin levels 15 ng/mL[12]. Blood tests were repeated after 12 weeks of the therapy and change in hemoglobin along with all other parameters was noted. All parameters were observed at 12 weeks of treatment that whether they are in normal range or not.

Test dose was given for both the preparations of iron before starting the infusion. 200 mg of iron sucrose was diluted in 200 ml of sterile normal saline 0.9% and was given as slow infusion over 30 min. The rest of the doses, as and when required, were given on alternate days following the same procedure[13]. For caboxymaltose preparation, the maximum single dose of 1000 mg diluted in 250 ml of sterile normal saline 0.9% was given as slow infusion over 45 min. If needed, rest of the doses were given on the 8th and the 15th day[13,14].

All statistical analysis was performed by using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation for the age of study participants and rise in hemoglobin in both the groups was calculated. Frequency and percentages for patients with abnormal hematological parameters like hemoglobin, mean corpuscular volume and ferritin values were calculated for patients in both the groups. Chi-square was applied to look for any association between the variables with the type of parental iron therapy. The *p*-values of ≤ 0.05 were considered as significant. Student t-test was applied to compare the mean rise in hemoglobin levels in both the groups.

RESULTS

Target population was all pregnant women who were put on parenteral iron therapy in second trimester due to any reason but with the application of inclusion and exclusion criteria and consent of the individuals. 300 women were finally recruited in the study which were included in the final analysis and divided into two equal groups. Mean age of participants was 32.89 ± 7.191 years. Table-I shows that patients achieved normal range of hemoglobin level, mean corpuscular volume and ferritin level more with the carboxymaltose preparation as compared to iron sucrose preparation (*p*-value <0.05). Table-II depicts that mean rise in hemoglobin in carboxymaltose was 3.96 ± 4.19 mg/dl while in iron sucrose group was 2.11 ± 1.72 mg/dl (*p*-value <0.05).

Table-I: Outcome of various variables studied in the analysis: Chi-square test.

Factors Studied	Ferric carboxymaltose Group	Iron Sucrose Group	*p*-value
Hemoglobin Level			
>12mg/dl	131 (87.3%)	112 (74.7%)	0.005
<12mg/dl	19 (12.7%)	38 (25.3%)	
Mean Corpuscular Volume			
Normal level	109 (72.7%)	85 (56.7%)	0.004
<80 fl/cell	41 (27.3%)	65 (43.3%)	
Ferritin levels			
Normal level	132 (88%)	114 (76%)	0.006
<12ng/ml	18 (12%)	36 (24%)	

Table-II: Comparison of mean rise in hemoglobin of both groups.

	Ferric Carboxymaltose	Iron Sucrose	*p*-value
Rise in Hemoglobin (mg/dl)	3.96 ± 4.19	2.11 ± 1.72	<0.001

DISCUSSION

Anemia has been one of the most commonly encountered clinical condition during the pregnancy. Timely detection and adequate management can save the mother and child from long term consequences. Mumtaz *et al*, published an interesting study in this regard and came up with the findings that in case of anemia among pregnant women of developing countries, continuation of daily iron supplementation is a preferred option as compared to the intermittent iron supplementation[15]. Oral supplementation of iron has been discussed frequently but less attention has been paid to the parenteral formulations. We therefore planned this study with the rationale to determine the efficacy of high dose carboxymaltose vs iron sucrose for anemia among pregnant women managed at our hospital.

Bhavi *et al,* conducted a randomized controlled trial in our neighboring country India comparing intravenous iron sucrose and oral ferrous in terms of efficacy and side effect profile among the pregnant ladies. They came up with the findings that in terms of efficacy parenteral iron preparation was clearly superior and both hemoglobin and ferritin were significantly more improved in women taking parenteral iron preparation as compared to those taking oral iron preparation[16]. Iron sucrose was one of the agents used in our study. Though Bhavi *et al*, established its superiority as compared to oral preparation but we found it inferior to carboxymaltose parenteral preparation[16].

An open-label, multicenter, randomized study was published by Lee *et al*, in 2019 with the objective to compare ferric carboxymaltose (FCM) with iron sucrose (IS) for the effective and timely treatment of preoperative iron deficiency anemia (IDA) in women with menorrhagia. Their findings were quite interesting and comprehensive, and they concluded that ferric carboxymaltose is as effective as IS in correcting preoperative IDA among patients with menorrhagia. The added benefits of FCM over IS included significant rapid correction of IDA, replenishment of iron stores and reduced hospital visits[17]. Our target population was slightly different and we did a retrospective analysis instead to a prospective trial but our findings were very similar to that of Lee *et al*[17].

Mahey *et al*, in 2016 published a randomized controlled trial in adult patients with uterine bleeding. They compared iron sucrose and ferric carboxymaltose and concluded that ferric carboxymaltose has been superior in efficacy among these patients to increase the hemoglobin levels[18]. All the studies done in neighboring countries or west mentioned in discussion section have more or less same findings as that of our study that carboxymaltose preparation has been superior in all the aspects of correcting the anemia.

A prospective randomized control trial should have been the best study design to conduct this study and generate findings that could be generalizable. Clinical indicators and symptoms were not addressed or made part of this study and only focus was laboratory parameters which is another main limitation of this study. Future trials with adequate blinding and better methodology may generate better results in this regard.

CONCLUSION

Carboxymaltose preparation of iron emerged as more efficacious agent for improving the parameters of anemia in pregnant women when compared with iron sucrose. Not only hemoglobin levels responded better to carboxymaltose but ferritin and mean corpuscular volume also showed marked improvement with carboxymaltose preparation.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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