Efficacy and Safety of Megafer® Injection versus Venofer® Injection in Pregnant Women with Iron Deficiency Anemia

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Abstract: Anemia is the most commonly found blood disorder worldwide in the pregnant women and most frequently it is brought on by nutritional deficiencies giving rise to the typical Iron Deficiency Anemia (IDA). Intravenous administration of iron sucrose, provides a rapid mean to treat this condition by fulfilling the increased body demand of iron. Various alternate brands of iron sucrose injections are now available in the market place but a rationale is to be developed for a preferred product, based on its safety and efficacy. This retrospective comparative analysis is designed to compare two different brands, Megafer® injection and Venofer® injection, containing the same generic compound of Iron Sucrose, in Asian pregnant women with Iron Deficiency Anemia. The outcome measure for efficacy was targeted as the increase in levels of hemoglobin (Hb) after the drug administration, as per the approved protocol. The Hb levels were evaluated through hematological parameters while safety was analyzed by measuring the vital signs and any adverse event reported during the whole study period. Megafer® Injection was found to be as effective and safe as Venofer® Injection, for the short term treatment of IDA in pregnant women.

Keywords: Anemia, iron deficiency, haemoglobin, gestational age, treatment safety, drug efficacy, adverse event, pregnancy, hypochromic microcytic.

INTRODUCTION

Iron is essential for haematopoiesis, formation of hemoglobin, transport of oxygen in the body, conversion of blood sugar to energy and the production of various enzymes. Nutritional iron deficiency and Iron Deficiency Anemia (IDA) are the frequently found problems in clinical practice globally. Iron deficiency refers to the reduced iron stores of the body while Iron Deficiency Anemia is a more severe form, in which the hypochromic microcytic red blood cells are seen along with reduced iron levels. Though the prevalence of iron deficiency anemia has decreased recently in developed countries, yet the iron deficiency is top ranking cause of anemia among Asian population where the deficiency would become more addressing, when occurred in pregnant women [1]. Insufficient, dietary intake of minerals, lack of knowledge about increased iron requirements, and unhealthful environmental conditions, are some of the factors that contribute to further intensify the anemia in women during pregnancy. All pregnant women with a hemoglobin level less than 11.0 g/dl at sea level are considered as being anemic [2].

A survey data, by the Department of Nutrition for Health and Development, World Health Organization (WHO) date showed that 56 million pregnant women were affected by the anemia [3].

During the pregnancy, the overall physiology of the woman undergoes enormous changes whereas the iron stores of the body do not suffice to cater the increasing needs of iron to synthesize hemoglobin for placental and fetal growth. Anemia during the pregnancy exerts significant impact on the fetal as well as maternal health. Preterm deliveries, low birth weights, neonatal morbidity and perinatal mortality due to the impaired oxygen delivery to placenta and fetus are among the consequences of the maternal anemia during the pregnancy [4-6]. Iron supplementation during this phase prevents the development of iron deficiency anemia which may otherwise result in high maternal mortality and morbidity ultimately increasing the infant mortality rate [7].

Iron supplementation can be provided through both, oral (PO) or parenteral (IV) routes; however, the oral

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supplementation has the disadvantage of reduced patient compliance due to the various undesired gastrointestinal effects and the inability to boost up the iron stores quickly, when either the pregnancy has advanced to terminal phase or the anemia is severe enough to effect the health of growing fetus. Various parenteral preparations of iron are available in clinical practice containing dextran and non-dextran substances. Of these, Iron dextran (ID) formulations have been reported to cause fatal anaphylactic reactions [8, 9]. Intravenous administration of iron sucrose (IV-IS) complexes has relatively better safety and efficacy profile, especially in pregnancy when intolerance, non-compliance or lack of efficacy with oral iron is high, despite the dose and administration protocol modifications, Intestinal mal-absorptive conditions (e.g., inflammatory bowel disease); acute blood losses that exceed absorptive capacity of the gut or where clinical need for a rapid iron supply is demanded.

Untreated depletion of iron stores leads to iron-deficient erythropoiesis and, ultimately, to Iron Deficiency Anemia. Administration of iron sucrose replenishes tissue iron stores, reverses iron depletion and iron-deficient erythropoiesis, and corrects or prevents the progression of Iron Deficiency Anemia. Iron sucrose was approved for intravenous use in the United States and has also been used in Europe for long, with reported good safety profile [10]. Iron sucrose injection is now available as different pharmacological brands, but the patient compliance related to potency, better efficacy, lesser side effects and cost effectiveness is considered to be worthy. This retrospective comparative analysis of four different studies is aimed to evaluate the efficacy and safety of same generic compound, i.e. Iron Sucrose between two different commercial brands (Megafer® Injection and Venofer® Injection, in Asian pregnant women with Iron Deficiency Anemia.

METHOD

Literature Search

In order to analyze the comparative effects of Megafer® Injection with Venofer® Injection, the retrospective data was collected from four different studies of same the generic compound of iron sucrose, wherein these two commercial brands were used intravenously to treat the iron deficient anemic pregnant Asian women. The study of Megafer® injection, labelled as **Study A**, was carried out at *the Department of Gynecology & Obstetrics, Jinnah Post graduate medical college, Karachi, during* the period of 31st July 2015 - 18th January 2016, whereas, the remaining three studies of Venofer® Injection were searched in the literature and the selected studies were labelled as: **Study B** - "*The role of intravenous iron sucrose complex in treatment of iron deficiency anemia in pregnant women; Bushra et al., Department of Gynecology & Obstetrics, Al Tibri Medical College & Hospital, Isra University Karachi campus.",* performed during 1st April 2013 - 30th September 2013 [11], **Study C** - *"Iron sucrose infusion in pregnancy made easy; Dipti et al., Department of Obstetrics and Gynecology, Swami Dayanand Hospital, Dilshad Garden, Delhi.", from July 2013 - June 2014* [12] and **Study D** - *"Comparative Study - Efficacy, Safety and Compliance of Intravenous Iron Sucrose and Intramuscular Iron Sorbitol in Iron Deficiency Anemia of Pregnancy; A.Wali et al., Aga Khan Hospital for Women and Children, Kharadar, Karachi, 2002"* [13]. *A*ll the selected studies were thoroughly reviewed for their performance in accordance with the ethical principles of Good Clinical Practice (GCP) and U.S. FDA regulations for the Clinical Trials, which have their origin in the Declaration of Helsinki.

Study Characteristics

Study A, of the Megafer® Injection was a single armed, open label and observational study. Study B of the Venofer® Injection was an interventional retrospective study. The sample size of both, Study A and Study B, was 50. The Study C on Venofer® Injection was a retrospective observational study with the sample size of 234, while the Study D of Venofer® Injection was a prospective comparative study with a sample size of 15. The Study D was conducted on three different groups, amongst which two groups were given the dose of iron sucrose, based on the same formula as in other two studies, B and C of Venofer® Injection, and the third group was administered with iron sorbitol. From the first two groups of Study D, ***Group A*** was selected who was administered with iron sucrose.

The demographic data of all four studies is given in Table 1. For Study A (Megafer®), the mean age of the study participants was 24.04 years, mean weight 49.957 kg and the gestational ages were among second and third trimester. In Study B (Venofer®), the participating subjects had the mean age of 30.9 years, the mean weight of 54.7 kg and the gestational mean age ranging from 28 - 32 weeks. In the Study C, the mean age of subjects was 26.8 ± 3.75 years and the

Table 1: Summary of Demographic Data of Participating Patients of all Studies

Identification	No. of patients	Mean Age (years)	Mean wt. (kg)	Mean Gestational age (weeks)	Mean duration of Rx (weeks)
Study A (Megafer® Injection)	34	24.04	49.95	20.253	3 to 4
Study B (Venofer® Injection)	50	30.9	54.7	30.2	3+0.5
Study C (Venofer® Injection)	234	26.8 ± 3.75	-	20-32	3 to 4
Study D (Venofer® Injection)	15	25.56	69±18.7	29±5.3	3 to 4

period of gestation was 25.8 (20-32). In the Study D (Group A), the mean age of subjects was 25.6 years, the mean weight was 69±18.7 kg and the gestational age was 29 ±. 4.3 weeks.

The main diagnostic parameters for the inclusion criteria for all the studies included the investigational evidences of Iron Deficiency Anemia i.e. low haemoglobin (Hb) and low serum ferritin (SFe) levels, an obstetrician's clinically established diagnosis of IDA, determined by clinical manifestation of low levels of Hb, hematocrit (MCV, MCH) and the requirement for a pharmacological treatment with a course of intravenous iron. Prospective participants were investigated in detail at the time of screening and those found with other co morbidities i.e. Tuberculosis, diabetes, Thyroid disease, Thalassemia and Megaloblastic anemia were excluded from the study.

Treatment Plan

In all four studies, the laboratory investigations were carried out before starting the treatment which included complete blood picture, blood cell indices and serum ferritin. The investigational drug, Iron sucrose complex, was administered to all the patients according to the Ganzoni Equation, [Total iron deficit (mg) = body wt. (kg) x (target Hb–actual Hb) x 0.24+500)] in order to replenish physiological iron stores. The treatment period was consisted of 3-4 weeks.

A test dose was initially administered to each subject, in order to rule out any allergic reaction. Later, an IV infusion of 200 mg of Iron Sucrose, diluted with 0.9% normal saline, was administered on every drug administration day (twice or thrice per week), in a clinical setting under the supervision of a qualified and experienced medical officer, till the calculated dose for that individual subject was completed according to the iron deficit calculated formula. The treatment period consisted of 3-4 weeks for each study. Side effects were observed and reported during the whole duration of each study.

Safety and Efficacy Endpoints

The Primary outcome for all the studies was to assess the efficacy of the drug under study, by comparing the Haemoglobin levels before and after the treatment for iron deficiency anaemia correction.

Safety assessment was the secondary endpoint in all studies, where the subjects were intermittently asked for any unusual medical occurrence including any abnormal sensation or discomfort during the infusion and were kept under clinical observation to notice and record any allergic or anaphylactic reaction [12].

Statistical Analysis

The hypothesis of the study was that the difference of mean "rise in hemoglobin levels" due to Megafer® and Venofer® Injections is less than 1g/dl, constructing the null hypothesis that the difference is greater than 1.

$$H_0=|u_m - u_v| > 1$$

Against the Alternative hypothesis that the difference is less than 1.

$$H_a=|u_m - u_v| < 1$$

RESULT

In Study A (Megafer®), a total of 50 participants were recruited however, only 34 could completed the study as per the protocol. In Study B (Venofer®), all 50 recruited participants were able to complete the study. In Study C, a total of 445 subjects were enrolled, out of which, only 234 completed the study. In study D, all 15 participants were included and completed the study.

As per the analysis review after the completion of treatment, the amount of Hb was increased in study A, from the mean baseline value of 6.69±0.669 g/dl to 9.82± 0.84 g/dl, with a mean value of 3.17±0.92g/dl.

Table 2: Comparitive Analysis of Mean Hemoglobin (Hb) before and after Treatment of Megafer and Venofer Therapy among Four Studies

Study	N	Mean Hb (Pre-therapy)	S.D.±	Mean Hb (Post-therapy)	S.D±	Rise in Hb (Difference between Pre-therapy and Post -therapy)	S.D±
A	34	6.69	0.66	9.82	0.84	3.12	0.92
B	50	8.40	0.50	11.20	0.40	2.80	0.62
C	234	7.30	0.67	10.80	0.58	3.50	0.84
D	15	8.0	1.10	10.60	0.80	2.70	1.10

In Study B, the baseline mean Hb before treatment was 8.4±0.5 g/dl which was elevated after treatment to 11.2±0.4 g/dl with a mean increase of 2.8 ±0.62 g/dl. In Study C, the mean baseline Hb before treatment was 7.3±0.67 g/dl which was raised to 10.80 ±0.58 g/dl after treatment with a mean rise of 3.5±0.84 g/dl. In study D the mean baseline Hb before the treatment was 8.0±1.10 g/dl and after treatment it increased to 10.6± 0.8 g/dl that gives a mean increase of 2.70±1.10 g/dl in the Hb level. Table **2** shows the comparative analysis of both the products for blood parameters before and after the treatment.

The p-values for difference of mean rise in Hb in Venofer® studies B, C and D and in Megafar® study A were calculated to test the null hypothesis, i.e. the difference is greater than 1 (difference of mean rise in Hb should be less than 1g/dl) when compared individually with the Megafer® study A. The p-values and tabulated t-values are given in Table 3. Since all p-values are close to zero, the null hypothesis is rejected, i.e. the difference of means due to Megafar® and Venofer® is greater than 1 and accept the alternative hypothesis that the difference is less than 1, i.e. the difference between mean rise in Hb due to Venofer® and Megafer is not greater than 1g/dl. The cost of both the brands is compared in Table **4** whereas, Figure **1** shows the comparative p-values.

Table 3: Statistical p-Values for mean rise in Hemoglobin in Venofer® Studies (B, C and D) in comparison to Megafer® Study (A).

	Study B	Study C	Study D
t Calculated	4.56	5.26	2.84
t Tabulated	1.99	1.97	2.01
p-Value	0.00001	0.00000	0.00334

None of the patients in any of the four studies, contracted any serious reaction nor did any participant required discontinuation of therapy owing to any anaphylactic, cardiac or other adverse effects during the course of treatment. However, in Study A, mild gastrointestinal disturbances including nausea and vomiting occurred in 5 subjects. Study B had not reported any adverse event, 3 adverse events were reported in Study C whereas, in Study D moderate abdominal pain, shivering and weakness were reported in less than 3 study subjects.

Table 4: Comparative Analysis of Megafer Injection and Venofer Injection in Terms of Cost

Study	Price in Pakistan (PKRs.)
Megafer® Injection	1150/-
Venofer® Injection	1831/-

DISCUSSION

The retrospective data of four different brands of Iron Sucrose Injections were compared, which were used for the treatment of Iron Deficiency Anemia in pregnancy, primarily in terms of efficacy, cost effectiveness and subsequently for safety. The iron deficiency becomes pronounced during pregnancy because the growing fetus solely depends on maternal stores of iron [14]. This is further aggravated by poor absorption of iron due to physiological changes of pregnancy occurring in the gastrointestinal tract such as hyperemesis, motility disorders with reflux esophagitis and indigestion. In underdeveloped countries, anemia is still a major contributory factor to maternal morbidity and mortality [15]. This analysis of four different studies i.e. Study A, B, C and D of Megafer® and Venofer® Injections showed that both the commercial brands produce their effectiveness to increase the iron stores of the maternal body when given in prenatal period as calculated deficit dose, and resulted in the treatment success in 100% of patients within 2-4 weeks of the study. In another study conducted in Rawalpindi by Raja *et al.* on intravenous iron sucrose complex therapy in Iron Deficiency Anemia in pregnant women showed similar results with mean Hb level increased from 7.5 to 11 gm/dl (16). The

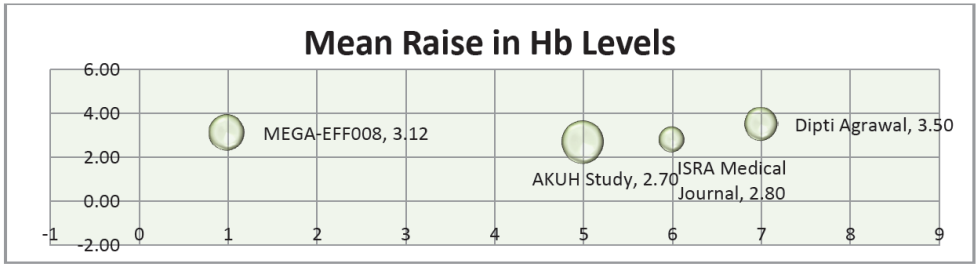

Figure 1: Comparative mean rise in hemoglobin among four studies.

symptoms of anemia including shortness of breath, fatigue, weakness and pallor skin had also been reduced in frequency and severity at the completion of both the studies. This indicates the effectiveness of IV Iron Sucrose (IVIS) in treating the iron deficiency anemia in pregnant women with increase in blood parameters and a decrease in the percentage of hypo chromic microcytic red blood cells. There is no statistically significant difference in the mean rise in the levels of hemoglobin from baseline to the completion of treatment in all four studies so it can be considered that the Megafer® Injection is as effective in the treatment of Iron Deficiency Anemia in pregnant women as Venofer® injection. The cost of Megafer® treatment is 37% low as compared to the Venofer® treatment, that is beneficial in terms of patient compliance. In view of these findings, the Megafer® therapy may be considered as a good adjunct to other intravenous iron preparations while treating pregnant women with Iron Deficiency Anemia, especially in Asian population where dietary habits do not satisfactorily meet the physiological needs of iron. Both the commercial brands are safe to use as no severe adverse effects were found in any of the four studies.

CONCLUSION

This comparative analysis of the retrospective data from the studies of Megafer® Injection and Venofer® Injection concluded that the Intravenous Iron Sucrose therapy of both products is effective and safe in raising the hemoglobin levels to the satisfactory levels in pregnant women with Iron Deficiency Anemia within a short duration. The treatments are equally good and can safely be administered to the pregnant women however, Venofer® is cost effective.

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