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Research Paper

Comparison of Efficacy and Safety of Iron Sucrose in Patients with Anemia in Pregnancy and Chronic Kidney Disease with Historical Control Groups of Different Parenteral Iron Preparations

Pharmacology

KEYWORDS : anemia in pregnancy, chronic kidney disease, iron sucrose, iron dextran, iron sorbitol citrate.

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ABSTRACT

Objective: Comparison of efficacy and safety of iron sucrose in patients with anemia in pregnancy and chronic kidney disease with historical control groups of different parenteral iron preparations

Methods: An observational, prospective, historical controlled study in patients of anemia in pregnancy and chronic kidney disease (CKD) receiving iron sucrose 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). Improvement in laboratory parameters with iron sucrose treated patients were compared with historical control groups of different iron preparations. The data was analyzed using paired t-test, unpaired t-test and Fisher`s exact test.

Results: Out of total 84 iron sucrose treated patients, 47 were pregnant and 37 were CKD patients. One historical control group includes iron dextran treated 78 CKD patients and second group was of 30 anemic pregnant patients treated with iron sorbitol citric acid. Iron sucrose, iron dextran and iron sorbitol citrate significantly (P<0.05) improved mean hemoglobin, anemia indices and serum ferritin at the end of study. Mean increased in hemoglobin from baseline was 4.45 g/dL with iron sucrose (at 12 weeks), 1.45 g/dL with iron sorbitol citrate (at 4 weeks) and 2.4 g/dL with iron dextran (at 6 weeks). Mean improvement in MCV and MCH were 8.4 µm3 and 4.17 pg/cell with iron sucrose (at 12 weeks), 3.53 µm3and 1.63 pg/cell with iron sorbitol citrate (at 4 weeks) and 5.8 µm3 with iron dextran (at 6 weeks) respectively. Mean increases in serum ferritin from baseline was 78.5 ng/ml with iron sucrose treated patients of CKD(at 12 weeks) as compared to 319.7 ng/ml with iron dextran (at 6 weeks). ADRs were more in patients treated with iron sorbitol citrate (103.3%) and iron dextran (151.1%) as compared to iron sucrose (63%).

Conclusion: Iron sucrose improves hemoglobin and anemia indices more efficiently with well tolerated by patients in study

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 is associated with gastrointestinal toxicity occurring in 35% to 59% of patients and a long course needed to resolve anemia and replenish stores. While parenteral iron preparations have the capability of bypassing all these issues, however, there remain concerns about the acute safety profiles of parenteral iron preparation. Parenteral preparations are used to treat severe iron deficiency anemia, intolerance to oral iron preparations and malabsorption. [5, 6]

Novel parenteral iron preparation iron sucrose considered to be better tolerated with few adverse events than conventional parenteral iron dextran and iron sorbitol citrate. [5, 6, 7] Though iron sucrose are widely used for the treatment of iron deficiency in pregnancy and in chronic kidney disease patients in India. Although very few data is available on the efficacy and safety of iron sucrose in anemia in pregnancy and chronic kidney diseases in Indian patients. Thus the present study was conducted to evaluate efficacy and safety of iron sucrose in these patients and compare it with historical control groups of different parenteral iron preparations.

Aims and Objectives:

The aim of present study is to compare efficacy and safety of iron sucrose in patients with anemia in pregnancy and chronic kidney disease with historical control groups of different parenteral iron preparations.

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 iron sucrose from November 2011 to January 2013, at CHA and IKD were enrolled in the study. However, Patients having anemia due to hemolysis, 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 haematological improvement and adverse drug reactions (ADRs) for three months. Hemoglobin, anemia indices and serum ferritin 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. Improvement in laboratory parameters with iron sucrose treated patients were compared with iron dextran treated historical control group of CKD patients in study conducted by Hussain I et al, 2013 and iron sorbitol treated patients of anemia in pregnancy in study carried out by Dhanani JV et al, 2012.[8,9]

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Result:

Baseline Characteristics

In current study, out of total 84 iron sucrose treated patients, 47 were pregnant and 37 were CKD patients. One historical control group includes iron dextran treated 78 CKD patients and second group was of 30 anemic pregnant patients treated with iron sorbitol citric acid. The men to women ratio were 2.3: 1 in current study as compared to 1: 7.6 in iron dextran treated historical control group. The mean age was 23.6 years and 60 years respectively in iron sucrose treated patients with anemia in pregnancy and CKD (Table 1 and 2). While mean age was 22.6 years with iron sorbitol citrate treated pregnant patients and 48.2 years with iron dextran treated CKD patients While mean baseline hemoglobin was 7.7g/dL in iron sucrose treated patients compared to 8.36 g/dL with iron sorbitol citrate and 9.49 ± 0.4 with iron dextran (Table 1and 2). Also, mean baseline serum ferritin was 30 ng/ml in iron sucrose treated patients compared to 9.4 ng/ml with iron sorbitol citrate treated patients and 23.1 ng/ml in iron dextran treated patients (Table 1and 2). Baseline mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) (anemia indices) in iron sucrose treated patients were 61.7 µm3 and 25.7 pg/cell respectively, as compared to 69.4 µm3 and 21.3 pg/cell in iron sorbitol citrate treated patients (Table 1and 2).

Outcome on iron preparations therapy

Laboratory parameters assessment

In current study and even in historical control groups, as compared to baseline, significantly (P<0.05) improved mean hemoglobin, anemia indices and serum ferritin were present at the end of study.

Comparison between treatment groups

a) Comparison between iron sucrose and iron sorbitol citrate treated anemic patients in pregnancy (Table 3)

A significant difference in mean hemoglobin (p<0.05) was observed with iron sucrose at the end of treatment as compared to iron sorbitol citrate. Mean increased in hemoglobin from baseline was more with iron sucrose 4.45 g/dL (at 12 weeks) as compared to 1.45 g/dL with iron sorbitol citrate (at 4 weeks). Mean improvement in MCV and MCH were more with iron sucrose 8.4 µm3 and 4.17 pg/cell (at 12 weeks) respectively, as compared to 3.53 µm3 and 1.63 pg/cell with iron sorbitol citrate (at 4 weeks).

b) Comparison between iron sucrose and iron dextran treated anemic patients in CKD(Table 4)

A significant difference in mean hemoglobin (p<0.05) was observed with iron sucrose at the end of treatment as compared to iron dextran. Mean increased in hemoglobin from baseline was more with iron sucrose 4.45 g/dL (at 12 weeks) as compared to 2.4 g/dL with iron dextran (at 6 weeks). Also, mean improvement in MCV were more with iron sucrose 8.4 µm3 (at 12 weeks) as compared to 5.8 µm3 with iron dextran (at 6 weeks). However, mean increases in serum ferritin from baseline was more with iron dextran 319.7 ng/ml (at 6 weeks) than 78.5 ng/ml with iron sucrose (at 12 weeks).

Adverse Drug Reactions (ADRs)

ADRs were more in patients treated with iron sorbitol citrate 31 (103.3%) and iron dextran 117 (151.1%) as compared to iron sucrose 53 (63%) (Table 5).The most common ADR was heart burns (18) followed by nausea (15) in iron sucrose treated patients, while in iron sorbitol citrate burning/pain at site of injection (11) and blackening at site of injection (7) and with iron dextran were headache (10) and nausea (8) were most common ADRs observed (Table 5). No serious adverse event was noted in iron sucrose and iron sorbitol citrate treated patient, however, one serious adverse event was observed in iron dextran treated patients. None of the ADR required withdrawal of iron sucrose and iron sorbitol citrate, however, 11 iron dextran treated patients who experienced adverse events that led to premature discontinuation from the study (Table 5). Causality assessment of 53 ADRs in iron sucrose treated patients categorized as possible in nature (53) by WHO-UMC scale, while same 53 ADRs were categorized as probable in nature by Naranjo`s scale while 132 ADRs noted in iron dextran treated patients were categorized probable.

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.(10) 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.(11) Blood transfusion associated with risk of infection (bacterial, viral). (11) Conventional oral iron preparations frequently cause side effects and non compliance is common and such therapy had to be given for long time in cases of severe iron deficiency anemia.(11) Absorption of oral iron preparations from gastrointestinal tract and red blood cells production are influenced by additional pathologies such as renal disease and in pregnancy. (11) Iron sucrose is considered to be better tolerated with few adverse events than iron dextran. (12) Iron sucrose had been FDA approved for the treatment of iron deficiency in patients with chronic kidney disease (12). It had also been widely used effectively to treat iron deficiency in pregnancy.

Our study shows an analysis describing the outcomes of total 84 patients treated with iron sucrose for three months at a tertiary care teaching hospital in an urban setting of western India. After 3 months of follow up, all 84 patients remained on treatment with no deaths or drop outs. Of 84 patients, all 84 had normalized hematological parameters (Hemoglobin, anemia indices and serum ferritin) values and clinical improvement, giving 100% treatment success rate with iron sucrose at 12 weeks. Out of total 30 iron sorbitol citrate treated patients, 7 patients were lost to follow up and in iron dextran group out of 78 total patients, 21 patients were discontinued due to various reasons like ADRs, noncompliance, lost to follow up and other.

The mean age was 23.6 years and 60 years respectively in iron sucrose treated patients with anemia in pregnancy and CKD which is lower than mean age of post- partum anemic patients in study done by Khaldoun K at al., 2011(31.1 years) and higher than studies carried out in anemia patient of CKD by Suheyl A et al., 2009 (44.5 years) and Gabriel M at al., 2006 (52.2 years).(13, 14, 15) In our study, men to women ratio were higher (2.3: 1) in iron sucrose treated CKD patients that indicate male preponderance in CKD.(16) Also more number of iron sucrose patients (47) with anemia in pregnancy indicates high prevalence of iron deficiency anemia in younger women in developing countries like India. National data shows that 69% of the total iron deficiency anemia patients are young women, which also supports our finding. (17)

Different hematological parameters like hemoglobin, anemic indices (MCV, MCH and MCHC) and biochemical parameter like serum ferritin was also used to diagnose the anemia, determine its severity and know iron store. The difference in baseline value of laboratory parameters is because of different underlying populations, different criteria for selecting patients, patient care and diagnostic or evaluating criteria in current study and historical control groups of different parenteral iron preparations. In current study, in iron sucrose treated anemic patients in pregnancy, there was more and significant (p<0.05) increase in mean hemoglobin and anemia indices (MCV and MCH) as compared to historical control group of iron sorbitol citrate treated patients. This is because nearly 33- 35% of iron sorbitol citrate is excreted just after the injection and also its release from the reticuloendothelial system is much slower as compared to iron

sucrose.[18, 19] Similar observation were documented in study conducted by Wali et al., 2002.[20] In our study, chronic kidney diseases patients with severe anemia treated with iron sucrose had more significant ($p<0.05$) increase in mean hemoglobin and MCV as compared to historical control group of iron dextran treated patients. Iron sucrose when administered is taken up by reticuloendothelial cell in liver, spleen and bone marrow and gets hydrolysed into sucrose and iron. Sucrose is eliminated by kidney in urine within four hours and iron is quickly available for erythropoiesis to erythroblast progenitor in bone marrow.[14] In contrarily, after iron dextran administration iron transported to reticuloendothelial cells and a significant fraction is only gradually converted to usable iron stores.[5] Similarly, iron sucrose resulted into a rapid and significant ($p<0.0001$) increase with serum ferritin level above minimal require level. Similar observation had documented at Tokars ML, 2010 and Suheyl Asma et al, 2009.[14, 21] However, mean serum ferritin increased more in iron dextran treated patient at the end of study which indicate saturation of reticuloendothelial cells and gradually release of iron from iron-dextran complex.[14] Similar results were observed in study carried out by Dillon R et al., 2011. [22]

In current study in patients treated with iron sucrose most common ADRs were heart burns (18) followed by nausea (15), however, iron sucrose was well tolerated and there no serious adverse event was observed. ADRs were more in patients treated with iron sorbitol citrate (103.3%) and iron dextran (155.1%) as compared to iron sucrose (63%). Most common ADRs documented with iron sorbitol citrate were burning pain (11) and blackening (7) at site of injection. Iron sorbitol produces more ADRs owing to low molecular weight and has high transferring saturation capacity; it cannot be given as intravenous infusion and mainly used as intramuscularly. Similar observations were noted in study done by Wali et al, 2002.[20] With iron dextran produced anaphylactic reaction in one patient and led to premature discontinuation of 11 patients from study due to ADRs. Iron dextran frequently produces acute and delayed type of hypersensitivity reactions and the incidence of severe anaphylactic reactions during iron dextran therapy is 0.6–0.7%.[23, 24] Iron sucrose has low propensity for anaphylactic reaction as compared to iron dextran.[25]

Conclusion:

Both iron sucrose and iron sorbitol citrate are effective and safe in treating patients with anemia in pregnancy. Similarly, iron sucrose and iron dextran both are efficacious with anemia patients in CKD. However, iron sucrose produces more increase in hemoglobin, anemia indices and rapid restoration of iron store with better tolerability of patients with few mild ADRs.

Table-1: Baseline characteristics of the pregnant patients with anemia in the study (n=77) [Values are absolute number or mean ± SEM]

Parameter	Iron sucrose	Iron sorbitol citric acid
Number of patients	47	30
Mean age (Years)	23.6 ± 5.8	22.6 ± 3.26
Laboratory parameters		
Mean Hb (g/dL)	7.7± 0.5	8.34 ± 1.46
Mean MCV(µm3)	61.7±3.5	69.49 ± 9.35
Mean MCH (pg/cell)	25.7± 1.2	21.36 ± 4.56
Mean Serum Ferritin (ng/ml)	-	9.44 ± 7.71

Table-2: Baseline characteristics of the CKD patients with anemia in the study (n=115) [Values are absolute number or mean ± SEM]

Parameter	Iron sucrose	Iron dextran
Number of patients	37	78
Mean age (Years)	60 ± 16.8	48.2 ± 17.1
Gender		
Men	26	9
Women	11	69
Laboratory parameters		
Mean Hb (g/dL)	7.7± 0.5	9.49 ± 1.46
Mean MCV(µm3)	61.7±3.5	58 ± 9.35
Mean Serum Ferritin (ng/ml)	30 ± 6.1	23.12 ± 44.8

Table 3: Comparison of laboratory parameters of pregnant patients with anemia at different time interval (n=69) [Values are mean ± SEM]

Laboratory parameters	Iron sucrose (n=47)		Iron sorbitol citrate (n=23)		Total mean difference (at the end of study)	
	Baseline (0 week)	End of study (12 weeks)	Baseline (0 week)	End of study (4 weeks)	Iron sucrose (n=47)	Iron sorbitol citrate (n=23)
Mean Hb (g/dL)	7.7± 0.5	12.1 ± 0.6*	8.34 ± 1.46	9.77 ± 1.64**	4.42 ± 0.17***	1.43 ± 0.2
Mean MCV(µm3)	61.7±3.5	70.1± 1.4*	69.49 ± 9.35	72.18 ± 8.68**	8.4 ± 0.84***	2.69 ± 0.67
Mean MCH (pg/cell)	25.7± 1.2	29.9 ± 0.8*	21.36 ± 4.56	22.89 ± 4.28**	4.17 ± 0.25***	1.36 ± 0.28
Mean Serum Ferritin (ng/ml)	-	-	9.44 ± 7.71	20.13 ± 11.39**	-	10.69 ± 3.68

*** P<0.0001 as compared to baseline (Paired student's't' test), **P<0.05 as compared to baseline (Paired student's't' test) and *** P<0.05 as compared to iron sorbitol (Unpaired student `s 't'). Iron sucrose treated patients in pregnancy (n=47) and iron sorbitol citrate treated patients in pregnancy (n=23). Hb- Hemoglobin. MCV - Mean corpuscle volume. MCH - Mean corpuscle hemoglobin. MCHC - Mean corpuscle hemoglobin concentration**

Table 4: Comparison of laboratory parameters of CKD patients with anemia at different time interval (n=69) [Values are mean ± SEM]

Laboratory parameters	Iron sucrose		Iron dextran		Total mean difference (at the end of study)	
	Baseline (0 week)	End of study (12 weeks)	Baseline (0 week)	End of study (6 weeks)	Iron sucrose	Iron dextran
Mean Hb (g/dL)	7.9± 0.4	12.1 ± 0.6*	8.34 ± 1.46	9.77 ± 1.64**	4.2 ± 0.17***	1.43 ± 0.2
Mean MCV(µm3)	62.3±4.3	70.1± 1.4*	69.49 ± 9.35	72.18 ± 8.68**	7.8 ± 0.84***	2.69 ± 0.67
Mean MCH (pg/cell)	24.7± 2.3	29.9 ± 0.8*	21.36 ± 4.56	22.89 ± 4.28**	5.2 ± 0.25***	1.36 ± 0.28
Mean Serum Ferritin (ng/ml)	30 ± 7.7	108.6 ± 3.6*	9.44 ± 7.71	20.13 ± 11.39**	78.6 ± 4.1***	10.69 ± 3.68

*** P<0.0001 as compared to baseline (Paired student's't' test), **P<0.05 as compared to baseline (Paired student's't' test) and *****

P<0.05 as compared to iron dextran (Unpaired student `s 't'). Iron sucrose treated patients in CKD (n=37) and iron dextran citrate treated patients in CKD (n=57). 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=154) [Values are absolute number]

ADRs*	Iron sucrose (n= 84)	Iron sorbitol citrate (n=23)	Iron dextran (n=57)	Withdrawal of causal drug
Gastointestinal side effects				
Heart burns	18	4	0	No
Nausea	15	1	8	No
Vomitting	3	1	4	No
Diarrhea	0	0	3	No
Hypersensitivity reaction				
Dyspnea	0	0	10	Yes
Rashes	6	0	5	No
Pruritus	0	0	6	No
Urticaria	0	0	7	No
Anaphylactic reaction	0	0	1	Yes
Reactions at site of injection (buring pain/ blackening)	0	23	0	No
Hypotenion/ dizziness	2	4	4	No
Bodyache and headache	4	0	10	No
Arthralgia	2	0	30	No
Malaise	4	0	29	No
Total	53	31	117	

***All ADRs were probable in nature**

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