

Original Research Article

Efficacy and safety of high dose accelerated intravenous iron sucrose in patients of iron deficiency anemia

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ABSTRACT

Background: Low dose (200 mg) extended Intravenous iron sucrose remains the most common treatment option in patients who are intolerant to oral iron therapy in patients with Iron deficiency anemia (IDA). The objective of this study was to evaluate the efficacy and safety of high dose accelerated intravenous iron sucrose (IS) in the treatment of adults with iron deficiency anemia

Methods: One hundred adult patients with iron deficiency anemia, who had intolerance or showed no effect with oral iron therapy, received daily doses of 500 mg of intravenous iron sucrose until the hemoglobin level was corrected or until receiving the total dose of intravenous iron calculated for each patient.

Results: The mean and median Hb (g/dL) 6.47±1.656 and 6.6 (2) at baseline, 9.61±1.629 and 9.6 (2) at 2 weeks of treatment, 11.85±1.277 and 12 (1) at 4 weeks of treatment respectively. The mean rise of Hb was 3.13±1.41 and 5.37±1.50 after 2 and 4 weeks of treatment respectively (p<0.000). A total of 303 intravenous infusions of iron sucrose were administered and iron sucrose was generally well tolerated with twenty-six patients developing mild and one patient developing moderate adverse drug reactions. There was no serious adverse event recorded.

Conclusions: Accelerated high dose intravenous iron sucrose is a safe and cost effective option minimizing frequent hospital visits in the treatment of adults with iron deficiency anemia who are intolerant or lack satisfactory response to oral iron therapy.

Keywords: Anemia, Iron sucrose, Intravenous, Low dose

INTRODUCTION

Iron deficiency remains the most common disorder in the world, the most common cause of anemia and is affecting approximately 25% of the world's population.^{1,2} Globally, 50% of anemia is attributable to iron deficiency and accounts for approximately 841,000 deaths annually worldwide. Africa and parts of Asia bear 71% of the global mortality burden; North America represents only 1.4% of the total morbidity and mortality associated with iron deficiency. The development of iron deficiency, and the rapidity with which it progresses, is dependent upon the individual's initial iron stores which are, in turn, dependent upon age, sex, rate of growth and the balance

between iron absorption and loss. The generally lower value for iron stores in adult women, for example, reflects the composite effect of menstrual losses (approximately 1 mg of iron loss per day), lower caloric intake, use of supplemental iron, and iron losses associated with pregnancy and lactation (about 1000 mg each for pregnancy, delivery, and nursing).

The severity and cause of iron-deficiency anemia will determine the appropriate approach to treatment. As an example, symptomatic elderly patients with severe iron-deficiency anemia and cardiovascular instability may require red cell transfusions. Younger individuals who have compensated for their anemia can be treated more

conservatively with iron replacement. For the majority of cases of iron deficiency (pregnant women, growing children and adolescents, patients with infrequent episodes of bleeding, and those with inadequate dietary intake of iron), oral iron therapy will suffice. Therefore, the first choice in the treatment of iron deficiency anemia (IDA) for almost all patients is oral iron replacement because of its effectiveness, safety and low cost. Of the complications of oral iron therapy, gastrointestinal distress is the most prominent and is seen in 15-20% of patients. Abdominal pain, nausea, vomiting, or constipation may lead to noncompliance. Although small doses of iron or iron preparations with delayed release may help somewhat, the gastrointestinal side effects are a major impediment to the effective treatment of a number of patients. As reported in some studies its efficacy may, however, be limited in many patients because of the side effects related to the drug, particularly gastrointestinal toxicity occurring in up to 35% to 59% of patients and the long course needed to treat anemia and replenish iron stores.^{3,4} Non-adherence to a prescribed course of oral iron is common and, even in adherent patients, poor intestinal absorption fails to compensate for iron need in the presence of ongoing blood losses.^{3,4}

Intravenous iron sucrose can be given to patients who are unable to tolerate oral iron; whose needs are relatively acute; or who need iron on an ongoing basis, usually due to persistent gastrointestinal blood loss. While intravenous (IV) iron has the capability of bypassing all these issues, concerns remain about the acute safety profiles of the available products and the potential for long-term harm from repeated iron administration.^{4,5} The common intravenous regimen utilized for replacement of iron in rural areas consists of multiple injections of 200mg of iron sucrose given over an extended period of two weeks.

The objective of this study was to evaluate the efficacy and safety of accelerated high dose intravenous iron sucrose therapy in patients with IDA as IDA falls into major global mortality burden in our part of the world.

METHODS

This study was conducted in the department of General Medicine, Sher-i-Kashmir Institute of Medical Sciences Medical college and hospital Srinagar, prospectively over a period of one year from April 2015 to March 2016. Informed consent was obtained from all subjects. The study was approved by the Institutional ethical committee of SKIMS MCH Srinagar.

Cases

One hundred patients diagnosed as iron deficiency anemia (IDA) were included in this study. Eligible patients were of age 18 years or older. Patients were selected in accordance with the inclusion criteria of IDA: hemoglobin (Hb) level < 12.0 g/dl for women and < 13.0

g/dL for men, serum ferritin (SF) level < 12 ng/ml. All patients reluctant to oral iron therapy or unable to tolerate oral iron therapy because of gastrointestinal side effects were part of the study group.

Exclusion criteria

Patients having IDA but with other inflammatory diseases, malignancies, diseases of the central nervous system, chronic kidney disease, chronic liver disease, persistent blood loss, reluctant to follow up were excluded from the study. Patients requiring blood transfusions were also excluded from the study.

Clinical assessment

Patients diagnosed as having IDA were recorded for demographic characteristics (like age, sex and residence), marital status, symptoms related to overt blood loss from gastrointestinal tract, genitourinary tract, non-steroidal anti-inflammatory drugs (NSAIDs) usage, steroid usage and associated co-morbid conditions.

Biochemical measures

Biological tests were performed from venous blood samples in a non-fasting state. Complete blood count analysis was done using the Sysmex KX-21N Automated Hematology Analyzer. Iron profile was done which included serum ferritin, serum iron, total iron binding capacity, transferrin saturation. Patients were labelled as having IDA if they had hemoglobin (Hb) level < 12.0 g/dl for women and < 13.0 g/dL for men plus serum ferritin (SF) level < 12 ng/ml.

Treatment plan - Schedule of intravenous infusions

The total iron dose (TID) was calculated according to the Ganzoni's formula: $TID (mg) = \text{weight (Kg)} \times [(\text{ideal Hb} - \text{actual Hb}) \text{ g/dl}] \times 0.24 + 500 \text{ mg (depot iron)}$, rounded up to the nearest multiple of 100 mg.

All eligible patients received daily doses of maximum 500 mg of Iron sucrose till the target was achieved. Iron sucrose was diluted in 250 mL 0.9% sodium chloride solution and administered intravenously over 3.5 hours. Similarly, 400 mg of iron sucrose diluted in 250 ml of normal saline was given over 2.5 hours and 300 mg of iron sucrose diluted in 250 ml of normal saline was given over 1.5 hours. Test doses in the form of 25 mg slow IV push was given prior to total dose iron. Ideal Hb in grams per liter was at 12.0 g/dL for women and 13.0 g/dL for men. Additional oral iron was not administered during the study. No blood transfusion was given during the study.

Safety and efficacy assessments

Iron sucrose infusions was administered in the General Medicine department of SKIMS MCH inpatient setting,

and all patients were observed for two hours after the total dose iron. All adverse events (AE) after IV infusions were identified by physical examination and because of injury to the patient, using standard forms encoded for AE. The blood pressure was measured before, during, and after each infusion.

Study visits and laboratory assessments was performed at screening and 2 and 4 weeks during treatment period. Laboratory assessments performed included complete blood counts with differential counts, reticulocyte count, and markers of iron metabolism (serum ferritin, serum iron and total iron-binding capacity).

The efficacy of IV iron sucrose was evaluated for all participants by determining changes in complete blood counts assessed after 2 and 4 weeks. Responders to IV iron therapy were defined as those patients whose Hb concentration increased by at least 2 g/dL from baseline value by the end of study.

Symptom specific examination and relevant investigations were done to locate the cause of IDA. Lower and upper Gastrointestinal (GI) tract evaluations was performed to diagnose the cause of IDA particularly in men ≥ 50 and in post-menopausal women, in whom IDA was suspected to occur due to bleeding.

RESULTS

A total of one hundred patients having the diagnosis of iron deficiency anemia were included in this study. Most of the patients were females (78 out of 100) and rest 22 were males. The mean \pm SD and median (IQR) age of patients was 37.72 \pm 16.68 and 35 (22) respectively.

The most common cause of anemia was menorrhagia observed in 68 (87.17%) female patients. The most common cause of anemia observed in 16 (72.72%) male patients was gastrointestinal abnormality and duodenal ulcer was found in 8 patients and rest were having erosive gastritis. In rest of patients the cause of anemia was

attributed to hemorrhoids, obscure GI bleed and poor dietary intake.

Changes in hematological parameters

The mean and median Hb was 6.47 \pm 1.656 and 6.6 (2) at baseline, 9.61 \pm 1.629 and 9.6 (2) at 2 weeks of treatment, 11.85 \pm 1.277 and 12 (1) at 4 weeks of treatment respectively. The mean rise of Hb was 3.13 \pm 1.41 and 5.37 \pm 1.50 after 2 and 4 weeks of treatment respectively. The Mean and median MCV was 68.92 \pm 6.02 and 69.2 (7) at baseline, 76.90 \pm 5.19 and 78.2 (7) at 2 weeks of treatment and 81.86 \pm 3.14 and 82 (5) at 4 weeks of treatment respectively. The mean rises of MCV at 2 and 4 weeks was 8.01 \pm 5.65 and 4.96 \pm 3.87 at 8 weeks. The mean and median MCH was 18.3 \pm 2.60 and 18.2 (3) at baseline, 21.71 \pm 2.78 and 21.6 (3) at 2 weeks and 24.62 \pm 2.69 and 24 (4) at 4 weeks of treatment respectively. The mean rise of MCH was 3.38 \pm 2.66 at 2 weeks and 2.90 \pm 2.62 at 4 weeks of treatment. The mean and median MCHC was 25.93 \pm 2.82 and 26.4 (4) at baseline, 28.82 \pm 2.41 and 28.9 (3) at 2 weeks and 31.67 \pm 1.61 and 32.2 (2) at 4 weeks of treatment respectively. Wilcoxon signed ranks test showed significant rise in Hb, MCV, MCH and MCHC after 4 weeks of treatment(p<0.000).

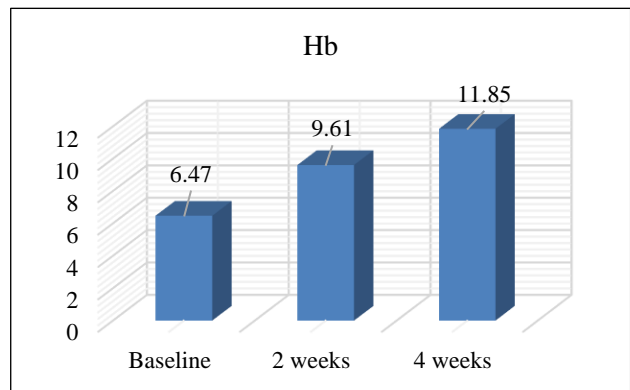


Figure 1: Hemoglobin at baseline, 2 and 4 weeks of treatment.

Table 1: Various parameters before and after start of treatment.

Lab characteristic	Baseline	After 4 weeks	p-value (Wilcoxon signed ranks test)
Hb (g/dL)	6.6 (2)	12 (7)	0.000
MCV (fL)	69.2 (7)	82 (5)	0.000
MCH	18.2 (3)	24 (4)	0.000
MCHC	26.4 (4)	32 (2)	0.000

Treatment characteristics

A total of 303 doses of iron sucrose were given and iron sucrose was well tolerated. There were no deaths or severe reactions during the study period. Twenty-six

patients developed mild reactions to intravenous iron sucrose whereas only one patient developed moderate reaction in the form of urticaria. The most common mild reaction was rash (19%), itching (18%), pain at injection site (18%), headache (8%), vertigo (8%), abdominal pain

(6%), myalgia (6%), vomiting (6%), muscle cramp (4%), fever (4%), metallic taste (3%), hypotension (3%), arthralgia (2%), constipation (2%), chills (1%), hypertension (1%) and urticaria (1%). Five patients had only one adverse event, 18 had up to 4 adverse events and 4 had more than 5 adverse events. One patient with moderate adverse event in the form of urticaria needed discontinuation of treatment and received intravenous anti-histaminic and steroids, while patients with mild adverse events were managed with oral medications only. All the patients were discharged on the same day of iron sucrose infusion. The mean \pm SD intravenous total iron sucrose dose was 1350 \pm 287 mg, median (IQR) iron sucrose dose was 1382 (380) mg.

DISCUSSION

Iron deficiency anemia being the most common cause of anemia also remains the most common disorder in the world. The treatment of IDA is mainly supplementing the deficient iron stores in the form of oral iron or parenteral iron. The oral iron therapy is favored due to affordability and availability however it may get complicated by gastrointestinal side effects in more than 35% of cases.⁵ The net result is poor iron absorption, poor compliance and poor response to treatment. The parenteral iron therapy remains the only alternative to oral iron therapy in such patients to treat iron deficiency anemia and reduces the requirement for blood transfusions. Among the various available parenteral iron compounds, the maximum dose of preparation that can be given in single sitting and the frequency of doses varies tremendously.

The maximum recommended dose for iron gluconate is 62.5-125 mg of iron at a single sitting whereas bolus doses of up to only 200 mg for iron sucrose were recommended.^{6,7} Iron dextran can be administered as a single dose, but this compound needs to be administered over a period of 4-6 hours. Iron dextran has been associated with fatal anaphylactic reactions.⁸ Fatal anaphylactic reactions are rarely reported with iron sucrose, but it is to be given in the form of 5 doses of 200 mg each over 14 days' period to achieve a cumulative dose of 1000 mg.^{9,10} In such condition, multiple doses of iron sucrose over a prolonged period of time have to be given to achieve desired therapeutic effect which leads to multiple hospital visits and chances of drop-out rate increases. To overcome this an accelerated iron sucrose dosing regimen utilizing 500 mg of iron sucrose on daily basis has been given in patients of IDA with chronic kidney disease (CKD), inflammatory bowel disease (IBD) and pregnancy.¹¹⁻¹⁴ An accelerated iron sucrose dosing regimen in which 500 mg of iron sucrose was given over three hours on two consecutive days in chronic kidney disease patients was not only safe and effective but also saved time and improved patient compliance.¹¹ In this study, there were seven minor adverse events reported in two patients. Similarly, in another study accelerated iron sucrose dosing regimen, in which 300 mg of iron sucrose was given on every

alternate day reported twenty-eight low severity adverse events in twenty-two patients.¹²

In India, also high dose iron sucrose therapy in which 500 mg of iron sucrose was given on two consecutive doses in CKD patients reported minor adverse events in 12% of patients.¹⁵ In our study, minor adverse events were recorded in twenty-six patients which are similar to observations made by others.⁹ Only four patients had more than five minor adverse events, while eighteen patients had up to four minor adverse events. Though there have been increase in the tolerable minor side effects only one patient reported moderate intensity adverse event in the form of urticaria and patient refused to continue iron therapy.

CONCLUSION

An accelerated regimen of high dose intravenous iron sucrose therapy in IDA is safe and effective way of improving hemoglobin and may potentially save time of the patient. An accelerated high dose iron sucrose regimen may be an ideal alternative to the low dose extended iron sucrose regimen to manage anemia in IDA especially in developing countries, where it is more practical.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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