ORIGINAL ARTICLE

CONTENTS

Effectiveness and safety of intravenous iron sucrose in correcting ferritin level for female patients with iron deficiency anemia

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ABSTRACT

Aim: The study aims to evaluate the effectiveness and safety of intravenous iron sucrose in correcting serum ferritin in female patients with iron deficiency anemia.
Materials and Methods: A prospective clinical study was conducted at Alsader Medical City in AlNajaf City/ Iraq. We enrolled 100 female patients with iron deficiency anemia, and hemoglobin less than 12 mg/dl. Two hundred mg of elemental iron was given twice weekly over 2.5 hours, and the patients were observed closely for any potential side effects. The main effectiveness endpoint gained from variation in serum ferritin and hemoglobin from baseline to end of the study. The safety evaluation includes recording any side effects developed either during or after intravenous administration.
Results: The mean of hemoglobin concentration at bassline was 8.05±0.891 mg/dl, and the mean of hemoglobin after one month of treatment was 11.234±1.232G/dl,($p < 0.0001$). There was an increase in serum ferritin concentration from the beginning of the study with 10.2±0.23ng/dl to 224.12±0.772 ng/dl, ($p<0.0001$) after 1 month of treatment. No one of the patients had any serious or lethal side effects.
Conclusions: Intravenous iron sucrose is an effective and safe option for the correction of serum ferritin in female patients with iron deficiency anemia.

KEY WORDS: Ferritin, intravenous iron sucrose, IDA

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INTRODUCTION

Iron is important for almost all organisms and vital for growth and survival [1]. It plays a vital role in numerous biological activities, including DNA biosynthesis, transport of oxygen, and generation of cellular energy [2]. Most of the body's iron is used in erythrocytes to bind and transport oxygen [3]. Iron deficiency is the diminution of total-body iron, particularly of hepatocyte iron stores and macrophages. Because most of the body's iron is used for hemoglobin synthesis, anemia is the most apparent sign of iron deficiency [4]. WHO defines anemia as Hb <13 g/dL in adult males and Hb <12 g/dL in adult females [5]. Anemia affects quality of life and is associated with fatigue, impaired cognitive function, and decreased capacity for work [6, 7]. The major cause of iron deficiency is blood loss, especially during menstruation or due to bleeding from the gastrointestinal tract; the next most common reason is poor absorption [8]. Women have a higher incidence of iron deficiency [9].

Serum ferritin is the most dependable early test for diagnosing of iron deficiency anemia (IDA) [10]. Ferritin is present in most tissues as a cytosolic protein, and extracellular ferritin plays a role as an iron carrier to deliver iron to cells. A single ferritin molecule can sequester up to 4500 iron atoms, thus making it potentially a very effective iron delivery system [10]. In the treatment of IDA, oral iron supplements are an inexpensive and available effective option. There are many formulations of oral iron like iron salt example, ferrous sulfate, ferrous gluconate, and ferrous fumarate. Other public iron formulations include ferrous succinate, ferrous ascorbate, ferric citrate, carbonyl iron, liposomal iron, heme iron polypeptide, and polysaccharide iron complexes (PICs) [11]. The problem with oral iron is the long duration of treatment; it requires 3-6 months for serum ferritin to normalize. On the other hand, serum ferritin does not rise with the oral iron treatment of IDA until hemoglobin levels are normal and the initial elevation seen with a double dose is most likely due to the absorption of iron exceeding the utilization for erythropoiesis causing brief storage, that rapidly decreased as reflected by the rapid decrease in serum ferritin when iron stopped [12]. In addition, the response to oral iron is unpredictable,

most likely due to malabsorption of iron and poor compliance with medication [13]. Common adverse effects of oral iron include gastric upset, vomiting, diarrhea, constipation, metallic taste, and dark stool [14]. Intravenous iron can avoid all these problems, and it is a good alternative to oral iron. In addition to that, there are certain situations in which intravenous iron is considered as a first choice like cases of severe anemia, the need for rapid correction of iron before surgery [15], or in patients with IDA and congestive heart failure [16]. An important concern is the safety of the available formulation. Although most of the newer generations of intravenous iron show a good safety profile, its use has been limited to treating IDA in patients with renal impairment on hemodialysis [17].

Iron sucrose is one of the first intravenous iron preparations; it is one of the oldest therapeutic agents still widely used today. Without a doubt, it is the most frequently used intravenous iron preparation worldwide [18, 19]. Despite its safety, iron sucrose has many adverse effects including allergic reaction**s** (e.g. rash, pruritus, urticaria, flushing), gastrointestinal (e.g. diarrhea, nausea, and vomiting), systemic (e.g fever, tachycardia, headache, and hypotension), respiratory (e.g. wheezing or dyspnea) and serious side effects (e.g. cardiac arrest, death, anaphylactic reactions, and shock [20].

AIM

This study aims to evaluate the effectiveness and safety of intravenous iron sucrose in the correction of serum ferritin in female patients with iron deficiency anemia.

MATERIALS AND METHODS

A prospective clinical study was conducted at Alsader Medical City in AlNajaf / Iraq. The study was carried out from June 2017 to April 2023. We enrolled 100 female patients with iron deficiency anemia with hemoglobin less than 12 g/dl.

The cause of anemia is mostly due to menstruation and abnormal uterine bleeding. Patients with anemia due to causes other than iron deficiency, patients with hypersensitivity to iron, patients with acute inflammation, and pregnant women were excluded from the study.

The current study was conducted following the Declaration of Helsinki (as revised in 2013), and approved by an Ethics committee of the medical college/Kufa University.

The subjective of the study was explained to the patients in Arabic language, and informed consent was taken from all the participants. After careful history and examination of all participants, age, and weight were reordered. A specimen of whole blood was collected in ethylene diamine tetra acetic acid (EDTA) containing a Vacutainer tube (purple top) for complete blood count with reticulocyte count, RBC indices, and ESR measurement, before iron administration and four weeks later.

CBC analysis was performed using the Sysmex XN-550 hematology analyzer, while serum ferritin levels were measured using the Roche Cobas e 411 immunoassay analyzer.

To ensure the reliability of laboratory measurements, duplicate sample testing was performed on a subset of blood samples, and all hematology and immunoassay analyzers were calibrated daily using manufacturer-provided standards. Additionally, the intra-assay and inter-assay coefficient of variation (CV) was calculated for ferritin and hemoglobin measurements to assess reproducibility.

The iron dose is calculated according to Ganzoni Equation [21]**:**

Total iron deficit [mg] = body weight [kg] x (target Hb-actual Hb) [g/dl] x 2.4 + depot iron [mg].

The target hemoglobin is 12 g/dl.

Iron sucrose diluted in 0.9% NaCl solution, final concentration range is 1-2 mg of elemental iron/mL

Two hundred mg of elemental iron was given twice weekly over 2.5 hours, and the patients were observed closely for potential side effects.

All patients completed the study.

The main effectiveness endpoint gained from variation in serum ferritin and hemoglobin from baseline to end of the study.

The safety evaluation include**s** recording any side effect**s** developed either during or after intravenous administration.

The Statistical Package for the Social Sciences (SPSS) was used to analyze all data; data are presented as mean and standard deviation. A paired sample t-test was used to compare the latest and baseline ferritin concentrations.

RESULT

The mean age of the patient was 32.3±0.36 years, ranging between 16-55 years old. The mean BMI was 24.7±0.14 (Table 1).

The mean of hemoglobin concentration at bassline was 8.05±0.891 G/dl, and the mean of hemoglobin after one month of treatment was 11.234±1.232G/dl, ($p < 0.0001$). There was an increase in serum ferritin concentration from the beginning of the study with 10.2±0.23ng/dl, to 224.12±0.772 ng/dl, ($p<0.0001$) after 1 month of treatment (Table 2).

Table 1. Baseline characteristic of the study population

Parameters	mean±sd
Age, year	32.3±0.36
BMI	24.7±0.14
Hemoglobin, g/dl	8.05±0.891
Ferritin, ng/ml	10.2±0.23

The pretreatment mean of corpuscular hemoglobin (MCH) was 18.236 ±0.934 pg/cell, which increased to 29.48±1.350 pg/cell (p <0.0001) after 1 month. Likewise, there is an increase in mean corpuscular volume (MCV) from 64.124±0.12 fL to 75.56± 0.255 fL (p <0.0001). The mean corpuscular hemoglobin concentration (MCHC) increased from 23.54±0.14 pg/cell at the bassline to 30.25±0.654 pg/cell at the end of the end of the study (p <0.0001). The reticulocyte count mean before treatment was 0.468± 0.115% increased to 1.664± 0.224% (p <0.0001) post-treatment. RDW-CV change from 16.76±0.776% pretreatment to14.53±0.132% (p <0.0001) after 1 month of treatment. ESR mean was 27.9±0.13 mm/hr at the beginning of the study changed to 18.9±0.82 mm/hr (p <0.0001) at the end of it (Table 3).

Over the study period, only one patient developed hypotension. 10 patients had dizziness, 5 patients developed fatigue, 1 patient had vomiting and 7 patients had nausea. 2 patients had pruritus and 15 patients had burning at the injection site. No one of the patients had any serious or lethal side effects. Most of the side effects are related to methods of administration, rapid administration of the drug is the leading cause of the side effects, when we changed the duration and rate of administration, most of the side effects disappeared.

DISCUSSION

Serum ferritin is a useful and convenient test to assess the status of iron storage; Low serum ferritin is very specific for iron deficiency anemia [10]. The duration of serum ferritin correction is 3-6 months with oral iron therapy, which is one of the drawbacks of oral treatment. Poor adherence to oral iron leads to the ineffectiveness of the treatment in the correction of serum ferritin and the importance of an alternative measure [22].

Intravenous iron sucrose is cleared rapidly from the serum of the patient, with a terminal half-life of 5.3 ± 1.6 h and total body clearance of 1.23 ± 0.22 L/h (20.5 ± 3.7 mL/min) [23]. Following intravenous administration of iron sucrose into patients with anemia, the liver, spleen, and bone marrow rapidly take up iron. Most (97%) of injected iron is used for red blood cell (RBC) synthesis in these patients [24].

Previously, the use of intravenous iron sucrose was restricted to patients with chronic kidney disease on regular hemodialysis, nowadays many promising attempts to use intravenous iron sucrose in the treatment of IDA in patients without hemodialysis.

In this study, the average increase in hemoglobin was > 3 mg/dl after 4 weeks of treatment, which is consistent with other studies that found intravenous iron sucrose is effective in correcting hemoglobin in IDA [25, 26].

The important finding in this study is that Serum ferritin increased> 200ng/ml, after 4 weeks of treatment even before hemoglobin returns normal. There are few studies focused on the effect of intravenous iron on ferritin levels, Blunden RW, *et al*. found that serum ferritin peaks 7-9 days after intravenous iron dextran [27]. The results of the current study were similar to the results of other studies which show that serum ferritin increase with intravenous iron sucrose administration [28, 29].

The safety of iron sucrose was evaluated by the appearance of side effects during or after infusion. Our result found that most of the side effects during administration were due to the rate of administration and when we changed it, most of the side effects disap-

Table 2. Hemoglobin and serum ferritin before treatment and after 4 weeks of treatment

Parameters	Pretreatment level (mean±sd)	Post-treatment level (mean±sd)	P-value
Hemoglobin, g/dl	8.05±0.891	11.234±1.232	< 0.0001
Ferritin, ng/ml	10.2±0.23	224.12±0.772	< 0.0001

Table 3. RBC indices before treatment and after 4 weeks of treatment

Parameter	Pretreatment level (mean±sd)	Post-treatment level (mean±sd)	P-value
MCH pg/cell	18.236 ±0.934	29.48± 1.350	<0.0001
MCV Fl	64.124±0.12	75.56± 0.255	< 0.0001
MCHC pg/cell	23.54±0.14	30.25±0.654	<0.0001
Reticulocyte count %	0.468± 0.115	1.664± 0.224	<0.0001
RDW-CV%	16.76±0.776	14.53±0.132	<0.0001
ESR mm/hr	27.9±0.13	18.9±0.82	<0.0001

peared and the patients continued their doses without any side effects. Most of the side effects were minor, this finding is consistent with other studies that found iron sucrose is safe in the management of IDA [30].

CONCLUSIONS

Intravenous iron sucrose is an effective and safe option for the correction of serum ferritin in female patients with IDA.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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