

Safety profiles of total dose infusion of low-molecular-weight iron dextran and high-dose iron sucrose in renal patients

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Abstract

Iron sucrose and low-molecular-weight iron dextran (LMW-ID), two commonly used iron solutions, have been compared in terms of allergic adverse event profiles to date. However, the safety of total dose infusion of LMW-ID has been investigated by only one study in chronic kidney disease (CKD) (not dialysis) patients. Thus, we aimed to compare adverse event profiles of total and high-dose LMW-ID and iron sucrose infusions in a heterogenous renal patient group comprising CKD, hemodialysis, and peritoneal dialysis. In this retrospective chart review study, we included 110 predialysis CKD, 101 peritoneal dialysis, and 118 hemodialysis patients. We included a total of 329 patients who were administered parenteral iron sucrose or LMW-ID between September 2006 and April 2010. Adverse events were determined both by medical and nursing follow-up notes. Laboratory data and clinical characteristics were collected from patient charts. Adverse event rates were compared between iron sucrose and LMW-ID infusions. In a total of 329 patients, 530 infusions (3470 ampules) were administered. We detected adverse reaction in only 1 patient. This adverse reaction, which manifested as generalized pruritus, occurred in a patient who received 500 mg of iron sucrose infusion. There were neither anaphylactic reactions nor deaths associated with infusion of either preparation. We did not observe any other adverse event related to administration of 500 and 1000 mg of iron sucrose at single infusion. The results of this study showed comparable safety of total dose LMW-ID and high-dose iron sucrose in a heterogenous group of renal patients.

Key words: Iron sucrose, low-molecular-weight iron dextran, renal patients, total dose infusion

INTRODUCTION

Patients with varying degrees of renal insufficiency, including chronic kidney disease (CKD), hemodialysis, and peritoneal dialysis, frequently have anemia. Anemia is usually multifactorial in these patients, erythropoietin and iron deficiency being the principal culprits. After having entered clinical use, erythropoiesis-stimulating agents (ESAs) redirected the attention on the importance

of iron replacement. Because ESAs render patients with renal insufficiency more dependent on iron due to rapid and brisk erythropoiesis, for a number of reasons, parenteral iron is much more efficacious than oral preparations.¹ However, this efficacy comes with a price: allergic reactions. The first use of parenteral iron in humans was in the form of iron hydroxide and was regarded as unacceptably toxic.¹ Fifteen years later, Nissim² reported safe administration of iron sucrose. This report introduced the concept of encasing the free iron salt in a carbohydrate shell to reduce unwanted severe side effects. Introduction of ESAs during 1990s fostered the evolution of parenteral iron preparations. The distinction among various available parenteral iron preparations is

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determined by their respective carbohydrate shell. High-molecular-weight iron dextran (HMW-ID) became available for intravenous infusion in the United States after 1971. Unfortunately, because of severe allergic reactions and deaths due to anaphylaxis, this preparation has been withdrawn from the market.³ During this time, iron sucrose became widespread due to the better safety profile compared with HMW-ID. Again in early 1990s, iron dextran reemerged in the market, however, this time in the form of low-molecular-weight iron dextran (LMW-ID).⁴ Besides the advantage of low rate of adverse effects, this formulation can also be administered in a total dose infusion (TDI). In a few studies,^{5–7} LMW-ID was compared with other parenteral iron formulation in terms of safety profile. Only 1 retrospective chart study⁸ compared total dose LMW-ID to standard-dose iron sucrose with regard to allergic reactions. Thus, we aimed to compare the safety profile of TDI of LMW-ID with that of high-dose iron sucrose in a heterogeneous group of renal patients who have CKD, and who are undergoing hemodialysis and peritoneal dialysis.

MATERIAL AND METHODS

In this retrospective chart review study, we included 110 predialysis CKD, 101 continuous ambulatory peritoneal dialysis (CAPD), and 118 hemodialysis patients who required parenteral iron treatment sometimes. We included a total of 329 patients who were administered parenteral iron between September 2006 and April 2010 at the outpatient nephrology, CAPD, and inpatient nephrology clinics at Selcuk University Meram School of Medicine Hospitals, Konya, Turkey.

The requirement of parenteral iron was deemed according to NKF-K/DOQI guidelines.⁹ Patients were administered parenteral iron in the forms of either LMW-ID or iron sucrose. Specific form of the iron solution and infusion number and amount of elemental iron administered at each infusion were based on the preference of the attending physician. Commercial preparations of Cosmofer (Say İlaç Sanayi ve Ticaret Ltd. Şti, Istanbul, Turkey) and Venofer (Abdi İbrahim İlaç San ve Tic A.Ş., Istanbul, Turkey) were used as LMW-ID and iron sucrose, respectively. Each 2 mL LMW-ID ampule consists of 625 mg of Fe (III)-hydroxy dextran, which is equivalent to 100 mg of elemental iron, whereas each 5 mL ampule of iron sucrose consists of 2700 mg of Fe (III)-hydroxide in sucrose, which is equivalent to 100 mg of elemental iron.

The parenteral iron infusion protocol at our clinics is as follows:

First, parenteral solution containing 25 mg of elemental iron was slowly infused under close supervision as the test dose. If no allergic reaction was observed 20 minutes after completion of test dose, infusion of the iron solution was commenced. Both parenteral iron solutions were diluted in normal saline. Iron solutions were diluted with 250 mL of normal saline when 100 to 500 mg elemental iron was administered at single infusion. Five hundred milliliter of normal saline was used when 500 to 1000 mg of elemental iron was administered at a single infusion. Total infusion times were 3 and 6 hours for 250 and 500 mL of infusion solutions, respectively. Administration of 125 mg of methylprednisolone is not a routine procedure at our institution before TDI of LMW-ID.

As a general rule, parenteral iron was not used (I) in case of active infection until resolution of the infection, (II) in patients with serum ferritin level >800 ng/mL, and (III) in patients with a known hypersensitivity reaction to oral or parenteral iron preparations.

If any adverse effect that was deemed related to parenteral iron infusion was detected, infusion was promptly stopped and the patient was administered intravenous antihistaminic and 125 mg of methylprednisolone. As a universal practice, in case of an adverse reaction to parenteral iron infusion, the particular kind of adverse reaction and severity were recorded to patient charts.

During infusion, patients were closely monitored for potential adverse reactions by a trained nurse and internal medicine resident. Any adverse reaction related to iron infusion was recorded both by the nurse and the resident to patient charts and nursing follow-up documents, respectively. The patient charts and nursing records were reviewed by two independent internal medicine residents. Data on epidemiological and clinical variables were collected, as well as laboratory data including serum ferritin, hemoglobin, serum iron, iron-binding capacity, C-reactive protein, parathyroid hormone, urea, and creatinine were available. Blood pressures monitoring was performed and adverse reactions were recorded.

The data were evaluated using SPSS 17 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) statistical program. The Student t-test was used for evaluation of the means and standard deviations of the groups.

RESULTS

We included a total of 329 patients in whom 530 infusions (3470 ampules) were administered. One hundred eighty-three patients received 5 ampules 2 times, 18 patients received 10 ampules 2 times, and 128 patients received 10

Table 1 Mean age, gender distribution, and laboratory data of patient groups who were administered LMW-ID and iron sucrose (*P<0.05)

	Total (n: 329)	LMW-ID (n: 269)	Iron sucrose (n: 60)
Age (years)	58.2 ± 15.6	59.2 ± 14.8	53.8 ± 18.6
Gender (F/M)	147/182	114/155	33/27*
Serum iron (mcg/dL)	35.8 ± 32.4	35.5 ± 30.4	37.2 ± 40.7
Iron-binding Capacity (mcg/dL)	190.5 ± 77.7	189.8 ± 76.7	193.4 ± 82.7
Ferritin (ng/mL)	253.1 ± 202.5	245.8 ± 180.3	290.3 ± 290.2*
Hemoglobin (g/dL)	9.5 ± 1.5	9.5 ± 1.4	9.6 ± 1.5
C-reactive protein	31.8 ± 38.4	30.7 ± 38.8	37.7 ± 36.3
Parathyroid hormone (pg/mL)	334.8 ± 266.4	335.3 ± 270.1	333.2 ± 253.9
Urea (mg/dL)	124.9 ± 58.4	126.7 ± 61.2	115.1 ± 38.9
Creatinine (mg/dL)	5.1 ± 2.8	5.1 ± 2.8	5.4 ± 3.2

LMW-ID=low-molecular-weight iron dextran.

ampules once. Sociodemographic and clinical characteristics and laboratory data of patients are shown in Table 1. Totally, we detected adverse reactions in only 1 patient. This adverse event occurred in a patient who received 500 mg of iron sucrose infusion. There were neither anaphylactic reactions nor deaths associated with iron infusion. Amount of elemental iron administered at a single infusion and the type of parenteral iron preparation are shown in Figure 1. Fifty-two and 8 patients were administered 5 and 10 ampules of iron sucrose at a single infusion, respectively. Infusion of LMW-ID and iron sucrose with various infusion types in renal patient groups are seen in the figure. In general, there was no difference between LMW-ID and iron sucrose infusions in terms of adverse events in all renal patient groups.

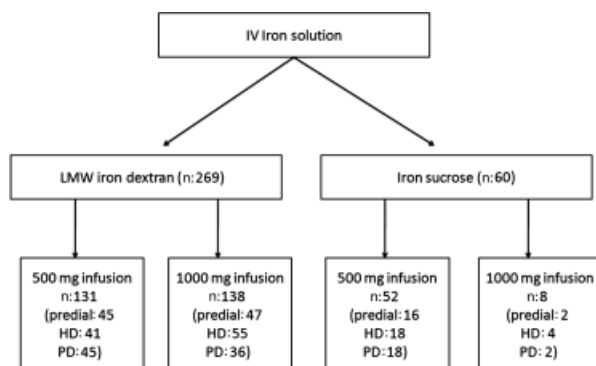
DISCUSSION

The results of this study showed that TDI of LMW-ID and high-dose iron sucrose had comparable safety profiles in

hemodialysis, CAPD and predialytic CKD patients. To the best of our knowledge, this current study is the second study investigating the safety of infusion of total dose iron therapy. However, our study extends previous findings to encompass hemodialysis and peritoneal dialysis patients in addition to CKD patients.

Iron encased with dextran has the advantage of longer half-life and slow sustained release of elemental free iron into the circulation. This feature allows one to administer total dose needed to replenish iron stores at one infusion. Unfortunately, due to unacceptably higher anaphylaxis rates and related mortalities at modern times, the parent molecule, iron dextran has been withdrawn from the market. Later on, realization that the higher molecular weight dextran was the main culprit in allergic reactions led to the development of LMW-ID. LMW-ID has been shown to have a comparable safety profile with a number of other parenteral iron formulations, including iron sucrose^{6,7} and sodium ferricgluconate.⁵

Despite widespread experience with total dose HMW-ID infusion,^{10,11} data are limited regarding safety and efficacy of total dose LMW-ID infusion. Total dose infusion of LMW-ID has been shown to be safe in a number of non-renal patient populations, including inflammatory bowel disease¹² and pregnancy.¹³ Insignificant allergic reactions were seen only in a minority of patients. However, only one study investigated whether TDI of LMW-ID was safe compared with iron sucrose in renal patients. Sinha et al.⁸ retrospectively evaluated adverse events related to 979 TDI of LMW-ID and 504 iron sucrose infusions in CKD patients of different stages. The mean LMW-ID dose was 1100 ± 126 mg and the dose for per infusion of iron sucrose was 200 ± 12 mg. The authors found that there was a total of 3 minor adverse events in patients undergoing LMW-ID infusion (0.3%) and only 1 adverse event in a

**Figure 1** Schematic representation of type and amount of elemental iron in various renal patient groups.

patient undergoing iron sucrose infusion (0.2%). There was no statistically significant difference between the groups.

Because of shorter half-life and more rapid release of elemental iron into circulation, tolerability of high doses of iron sucrose is more difficult.⁴ Usual practice is to administer intravenous push doses up to 200 mg over 2 to 5 minutes in CKD patients and 100 mg 1 to 3 times per week during dialysis. However, Chandler et al.¹⁴ evaluated the safety profile of iron sucrose in three different dosing regimens. They found no adverse reactions in 89 patients who were administered 200 mg of iron sucrose. However, they ended the second phase of the study early in which 500 mg of iron sucrose was administered over 2 hours when 8 out of 22 patients developed infusion-related dizziness, hypotension, and nausea. Thus, due to high adverse-effect rates 500 mg infusion of iron sucrose was not approved.¹⁵ Our results are not in agreement with previous reports that investigated the safety of higher than standard doses of iron sucrose infusion. Only one patient who was administered 500 mg or 1000 mg single-dose iron sucrose infusion developed an adverse event. This may be explained in part by relatively the small number of patients. Nevertheless, our study design and small number of such infusions preclude recommending that this practice is totally safe.

The main advantage of TDI is cost saving. In a cost analysis of TDI of LMW-ID, this method has been estimated to save approximately a quarter of a billion US dollars in the entire hemodialysis population in the United States.¹⁶ In addition to cost saving in outpatient clinics, this method has the potential to shorten hospital stay and consequently may cut costs further in inpatient nephrology practice. Results of our study with respect to total dose LMW-ID infusion are in line with previous reports. None of our patients developed anaphylactic reactions. There were no adverse reactions in patients undergoing total dose LMW-ID infusion.

In two large adverse events reviews from Food and Drug Administration database, Chertow et al.¹⁷ investigated differences among reported adverse effects related to parenteral iron preparations. The authors reported that total major adverse drug reactions were significantly increased among recipients of HMW-ID (OR 5.5) and sodium ferric gluconate complex (OR 6.2) compared with recipients of LMW-ID. In their subsequent study, total and life-threatening adverse events were significantly more frequent among recipients of HMW-ID and significantly less frequent among recipients of sodium ferric gluconate complex and iron sucrose when compared with LMW-ID.¹⁸ One limitation of these studies was the lack of detailed patient data. Even the mode of dialysis or the

stage of CKD was missing in the database. In addition, several life-threatening adverse events were linked with iron dextran without designation of a specific formulation. Thus, one must be cautious when evaluating the results of these large surveys, in which adverse reactions linked to LMW-ID might have been overestimated. Indeed, other studies, including prospective randomized ones, found no difference between LMW-ID and iron sucrose or sodium ferric gluconate.^{6,7} Our results are also in agreement with latter studies. There was no significant difference in terms of allergic reactions between LMW-ID and iron sucrose. We did not observe any anaphylaxis or death associated either with LMW-ID or iron sucrose infusions.

This study has several strengths worth mentioning. This is the first study evaluating safety of total dose LMW-ID infusion against high-dose iron sucrose infusion. The difference between this and other retrospective studies is that we double checked the allergic reactions both from medical records and nursing records. Thus, we assume that the error of overlooking even a subtle reaction due to iron infusion should be low. Meanwhile, a few limitations deserve consideration. First, our study is also subject to limitations, which are inherent to retrospective studies. Given that a heterogeneous group of patients were included, patient numbers in each individual group may be limited.

In conclusion, this study showed equivalent safety profile of LMW-ID and iron sucrose in a heterogeneous group of renal patients. Total dose infusion of LMW-ID was also found to be equally safe compared with infusion of high-dose iron sucrose. No anaphylactic reaction or death was observed with either iron preparations. Obviously, large-scale prospective studies are needed to settle the issue further.

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