Original Paper

Acta Hæmatologica

Acta Haematol 2009;121:37–41
DOI: 10.1159/000210062

Received: October 2, 2008
Accepted after revision: December 1, 2008
Published online: March 31, 2009

Safety and Usefulness of Intravenous Iron Sucrose in the Management of Preoperative Anemia in Patients with Menorrhagia: A Phase IV, Open-Label, Prospective, Randomized Study

Yun Hwan Kim[a] Hyun Hoon Chung[a] Soon-Beom Kang[a] Seung Cheol Kim[b]
Young Tae Kim[c]

[a]Department of Obstetrics and Gynecology, College of Medicine, Seoul National University,
[b]Department of Obstetrics and Gynecology, College of Medicine, Ewha Woman's University, and
[c]Department of Obstetrics and Gynecology, Yonsei University College of Medicine, Seoul, Korea

Key Words
Intravenous iron therapy · Iron deficiency anemia · Menorrhagia · Oral iron

Abstract
Background: The aim of this study was to compare the efficacy, safety and achievement of the target hemoglobin level (Hb ≥10 g/dl) in patients with preoperative anemia due to menorrhagia who received intravenous iron sucrose compared with oral iron protein succinylate for anemia management. ***Methods:*** Seventy-six patients with Hb levels <9.0 g/dl who were scheduled to undergo surgical treatment were randomized to receive either intravenous iron sucrose (based on the calculated total iron deficit divided into 2 ampoule infusions intravenously 3 times a week, beginning 3 weeks before surgery) or oral iron (80 mg/day of oral iron protein succinylate daily). ***Results:*** The intravenous iron group had higher increases in Hb (3.0 vs. 0.8 g/dl; $p < 0.0001$) and ferritin levels (170.1 vs. 4.1 μg/l; $p < 0.0001$) than the oral iron group. Achieving the target Hb was also higher in the intravenous iron group than in the oral iron group (76.7 vs. 11.5%; $p < 0.0001$). There were tolerable adverse events in both groups. ***Conclusion:*** Preoperative intravenous iron sucrose administration is more effective than oral iron and is as safe as oral iron therapy in the correction of preoperative anemia due to menorrhagia.

Introduction

Menorrhagia is a significant cause of ill health in women and the main symptom for gynecologic surgeries, including hysterectomy. It is clinically defined as a blood loss of ≥80 ml per menstrual cycle and it is estimated that approximately 30% of women complain of menorrhagia [1–3]. Menorrhagia has a detrimental impact on the quality of life and can adversely affect the physical and mental health of those affected. Moreover, menorrhagia is also associated with disruption to vocational, family and social life [4, 5].

Although medical therapies for menorrhagia have been used primarily, surgical treatments are often definitive in many cases of recurrent, severe bleeding and failed medical therapies. However, preoperative anemia

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0001–5792/09/1211–0037$26.00/0

Accessible online at:
www.karger.com/aha

Soon-Beom Kang, MD
Department of Obstetrics and Gynecology, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu
Seoul 110-744 (Republic of Korea)
Tel. +82 2 2072 2380, Fax +82 2 762 3599, E-Mail ksboo308@plaza.snu.ac.kr

can be an obstacle to optimal surgery because anemia is associated with an increased risk of transfusion, surgical morbidity, mortality and delayed rehabilitation [6, 7].

Traditionally, preoperative oral iron supplementation has been the mainstay for preoperative anemia correction. However, oral iron replacement therapy is limited by poor absorption and gastrointestinal disturbances, thereby straining resources of clinicians and challenging the patient's compliance [8–10].

In recent years, it has been reported that intravenous administration of iron could ameliorate anemia more rapidly and effectively than oral iron in the following conditions: pregnancy [11], postpartum period [12], inflammatory bowel disease [13], malignancies [14] and chronic hemodialysis [15]. Evidence pertaining to safety has also been accumulated without initial concern about anaphylactic reactions [16].

However, studies regarding the role of preoperative intravenous iron treatment for the patients of menorrhagia are few in number, despite the high prevalence and clinical significance of menorrhagia. Therefore, we aimed to evaluate the efficacy and safety of intravenous iron sucrose compared with oral iron protein succinylate for the preoperative control of iron deficiency anemia (IDA) in patients with menorrhagia.

Materials and Methods

This study was an open-label, prospective, randomized, multicenter trial carried out at Seoul National University Hospital, Ewha Woman's University Hospital and Yonsei University Hospital in Seoul, Korea. Approval was obtained from each institutional review board, and written informed consent from all patients was provided prior to participation in the study.

Patients were recruited from the women's clinics in the 3 hospitals. Eligible participants were menorrhagic patients with established IDA who had hemoglobin (Hb) levels <9.0 g/dl and were scheduled to undergo surgical treatment. Exclusion criteria were anemia from causes other than IDA, current administration of iron, previous iron therapy or transfusion within 3 months, a history of hematologic disease, and chronic disease not appropriate for clinical trial.

According to the computer-generated randomization table, the participants were randomly assigned to either the intravenous iron sucrose (Venoferrum®; Vifor International, Ltd., St. Gallen, Switzerland) or the oral iron protein succinylate (Hemo-Q Soln®; Italfarmaco SpA, Milan, Italia) treatment group. Group allocation was determined by one of the authors who was not involved in patient care. As each patient gave consent for the study, the patient was consecutively assigned to 1 of the 2 treatment groups according to the number of a randomization table.

In the group of patients where iron was administered intravenously, the dose for total iron sucrose was calculated from the following formula: weight (kg) × [target Hb (g/dl) – actual Hb (g/dl)] × 2.4 + 500 mg, and rounded up to the nearest multiple of 100 mg [11]. Target Hb was established to be 10 g/dl in our study. In each infusion, the maximum total dose administered was 200 mg of elemental iron in 100 ml of 0.9% NaCl, infused over 20–30 min. No test dose was given. Most of the patients received iron sucrose at the rate of 200 mg every other day, 3 times per week, beginning 3 weeks before surgery. Treatment was completed after administration of the calculated dose. Additional oral iron was not administered during the study. Patients were asked to note any symptoms or adverse effects of treatment, and some physical findings were recorded, including vital signs, which were measured before, during and after each infusion.

In the group of patients to whom iron was administered orally, 2 ampoules of oral protein succinylate (a total of 80 mg of elementary iron) per day, beginning 3 weeks before surgery, were given until the time of surgery. Among various oral iron materials, iron protein succinylate was chosen in the current study because it is a physiologic preparation in which the iron is reversibly bound to a protein carrier, thus having less of an adverse effect and showing more efficacy than ferrous sulfate [8, 17]. Patients were instructed to take an ampoule on an empty stomach, 2 h before or after their meals, twice daily. Patient compliance and physical findings, including the measurement of vital signs, were checked by regular contact with study nurses.

A laboratory evaluation was performed at the time of inclusion in the study and just prior to surgery. The initial evaluation included a complete blood count, serum ferritin level and peripheral blood smear. All laboratory tests were performed immediately after sampling.

A sample size analysis was performed before initiation of the study. We estimated the standard deviation of the Hb values to be approximately 1.5 g/dl. Based on a 2-tailed α of 0.05, it was determined that 36 patients per group were required to detect a 1-g/dl Hb difference in the primary outcome variable with a power of 80%. On the assumption of an overall rate of loss to follow-up of 10%, 40 subjects per group were required.

Participants who had ≥80% compliance were included in the analysis for efficacy. However, to analyze safety, we included all the patients who underwent 1 or more administration of drugs, coupled with follow-up.

All analyses were conducted using SPSS, version 12.0 (SPSS, Inc., Chicago, Ill., USA). To analyze the difference between groups, Student's t test, the Wilcoxon rank-sum test, a χ^2 test and Fisher's exact test were used.

Results

Seventy-six eligible patients were enrolled in the trial and randomly assigned to receive either intravenous (n = 39) or oral iron (n = 37) between December 2005 and January 2007. All the patients received 1 or more administration of drugs coupled with follow-up. Fifty-six participants with >80% compliance completed the trial in the intravenous iron (n = 30, 76.9%) and oral iron (n = 26, 70.3%) groups.

Baseline demographic and clinical characteristics were similar in the 2 groups. No significant difference was demonstrated between the 2 groups in age, baseline vital signs, bleeding episodes, comorbidities and history of past iron therapy (table 1).

The intravenous iron group had a greater increases in the Hb level than the oral iron group (3.0 vs. 0.8 g/dl, respectively; $p < 0.0001$) and a prominent success rate (76.7 vs. 11.5%; $p < 0.0001$) with statistical significance. An increase in the ferritin level (170.1 vs. 4.1 μg/l; $p < 0.0001$) and mean cell volume (11.8 vs. 3.9 fl; $p < 0.0001$) was also significant in the intravenous iron group (table 2), although a few patient data were missing due to protocol violations.

During the study, no severe adverse events were observed in the 2 groups, and only some tolerable adverse events were observed in each group. Two cases of myalgia and 1 case of injection pain developed in the intravenous iron group and 1 event of nausea and 1 event of dyspepsia was observed in the oral iron group.

Discussion

The aim of this investigation was to evaluate the efficacy and safety of intravenous iron sucrose as compared with oral iron protein succinylate for the preoperative control of IDA in patients with menorrhagia. In our study, preoperative intravenous iron sucrose administration was more effective than oral iron therapy and as safe as oral iron therapy in the correction of preoperative anemia due to menorrhagia.

Table 1. Baseline data (mean ± SD)

Variables	Category	Frequency		p value
		IV iron (n = 30)	Oral iron (n = 26)	
Mean age ± SD		42.0 ± 7.4	42.3 ± 8.0	0.87[1]
Bleeding episode	minimal	5 (19.2)	5 (26.3)	0.90[2]
	mild	8 (30.8)	6 (31.6)	
	moderate	5 (19.2)	4 (21.1)	
	severe	4 (15.4)	1 5.3)	
	none	4 (15.4)	3 (15.8)	
Comorbidity	none	23 (76.7)	20 (80.0)	0.77[3]
	yes	7 (23.3)	5 (20.0)	
Hx of previous iron treatment	none	21 (70.0)	19 (73.1)	0.80[3]
	yes	9 (30.0)	7 (26.9)	

Figures in parentheses are percentages. IV = Intravenous; SD = standard deviation; Hx = history.
[1] Two-sample t test. [2] Fisher's exact test. [3] χ^2 test.

Table 2. Results of treatment

Variables	IV iron (n = 30)		Oral iron (n = 26)		p value
	mean ± SD	median	mean ± SD	median	
Preoperative Hb, g/dl	7.5 ± 1.2	7.7 (4.8–9.1)	7.8 ± 1.1	8.2 (4.8–9.2)	<0.0001[1]
Postoperative Hb, g/dl	10.5 ± 1.4	10.7 (5.9–13.3)	8.6 ± 1.4	8.7 (5.9–11.8)	
Difference in Hb, g/dl	3.0 ± 1.6	2.9 (–1.9 to 6.1)	0.8 ± 1.2	0.7 (–1.9 to 3.0)	
Target Hb					
Success	23 [76.7]		3 [11.5]		<0.0001[2]
Failure	7 [23.3]		23 [88.5]		
Preoperative ferritin, μg/l	81.7 ± 272.1	3.7 (1.2–1,205.8)	5.9 ± 5.0	3.6 (1.9–15.1)	<0.0001[3]
Postoperative ferritin, μg/l	231.4 ± 561.7	72.4 (25.0–1,989.4)	9.7 ± 10.3	5.3 (0.7–41.0)	
Difference in ferritin, μg/l	170.1 ± 418.8	80.9 (–366.3 to 783.6)	4.1 ± 7.2	2.7 (6.9–25.9)	
Preoperative MCV, fl	69.4 ± 10.0	65.5 (55.3–89.9)	67.2 ± 6.2	66.0 (59.0–80.0)	<0.0001[3]
Postoperative MCV, fl	81.2 ± 6.8	80.8 (71.4–95.5)	71.4 ± 5.4	70.8 (63.9–82.3)	
Difference in MCV, fl	11.8 ± 7.1	10.4 (0.1–33.1)	3.9 ± 3.7	3.8 (–3.6 to 13.6)	

Figures in parentheses are ranges; figures in brackets are percentages. IV = Intravenous; SD = standard deviation; MCV = mean cell volume; RBC = red blood cell. Ferritin data are limited: the number of patients in the IV iron and oral iron group is 19 and 16, respectively. MCV data are limited: the number of patients in the IV iron and oral iron group is 29 and 25, respectively.
[1] Two-sample t test. [2] χ^2 test. [3] Wilcoxon rank-sum test.

Iron sucrose is effective because of the rapid removal from the plasma and the availability for erythropoiesis [15, 18]. After a bolus dose of iron sucrose, the plasma level peak occurs at 10 min. Twenty-four hours after administration, the plasma level is negligible, indicating rapid bone marrow uptake; this has been shown by positron emission tomography studies [18]. From these studies, 70–97% of the iron is used for erythropoiesis, with only a 4–6% elimination rate. Because of this biologic advantage, intravenous iron sucrose has been approved for the treatment of IDA in the following conditions: pregnancy [11], postpartum state [12], inflammatory bowel disease [13], malignancies [14] and chronic hemodialysis [15].

Similar to other previous investigations, we observed a significant increase in the Hb level (3.0 vs. 0.8 g/dl; $p < 0.0001$) and success in achieving the target Hb level (76.7 vs. 11.5%; $p < 0.0001$) in the intravenous iron sucrose group compared with the oral iron group. Some have suggested that the endpoint of treatment should be surgical outcome; however, we did not plan to compare the transfusion rate or surgical morbidity between the 2 groups. Because the number in the study population was relatively small and the cause and severity of disease were variable, the confounding effect was likely high. Therefore, we planned to study the change in Hb level to evaluate the efficacy between the 2 routes of iron therapy.

Contrary to previous studies [7, 8, 10], compliance with oral iron treatment was considerably high compared with the intravenous iron treatment (70.3 vs. 76.9%, respectively) in our study. It is difficult to explain, but it should be emphasized that the women waiting for surgery were highly motivated and had a fear of the potential risk of transfusion. If verified, the patients would tolerate mild or moderate adverse effects for safe operations, and the complaints about the treatment might be underexpressed in either the intravenous or the oral iron group. In fact, in our study, the rate of reporting adverse effects was small and compliance was high in both treatment groups.

In this study, there were no serious adverse effects. Historically, there have been 3 types of parenteral iron materials (iron dextran, ferric gluconate and iron sucrose). The parenteral use of iron dextran has been associated with significant morbidity and fatal anaphylactic reactions; the incidence of serious, life-threatening anaphylaxis with iron dextran has been reported to be 0.6–0.7% [19]. From this clinical experience, there has been great concern regarding hypersensitivity. However, ferric gluconate and iron sucrose have shown allergy event reporting rates of 0.04 [20] and 0.002% [21], respectively. Moreover, fatal hypersensitivity reactions have not been reported with ferric gluconate or iron sucrose. In addition, intravenous iron sucrose has been reported to be safe with an excellent profile in clinical use [16].

The limitations of our study were mainly due to the premature cessation of the oral iron arm. Because intravenous iron sucrose was significantly superior to oral iron treatment in preoperative anemia correction, delays in surgical procedures were also significantly reduced. Preoperative oral iron replacement was no longer appropriate for patients who had been suffering from menorrhagia and symptoms related to anemia (the success rates of target Hb were 76.7 vs. 11.5%, respectively). For these reasons, the total number of participants in the current study was relatively small and we could not exclude some protocol violations that limited the clinical and laboratory data. However, the superior efficacy of intravenous iron sucrose over oral iron succinylate was still maintained.

The treatment period was another limitation of our study design because 3 weeks of follow-up may be insufficient for oral iron treatment in general medical conditions. However, the patients who decided to have surgical treatment had suffered from symptoms of menorrhagia and associated anemia chronically, and in many cases, had been frustrated with the ineffective medical interventions. Moreover, patients waiting for gynecologic surgery have high levels of psychiatric disorders, including anxiety and depression [22, 23]. Based on this clinical situation, we reasoned that long-term preoperative treatment for iron replacement would have little clinical benefit.

In this study, we demonstrated that preoperative intravenous iron sucrose administration is more effective than oral iron therapy and as safe as oral iron in the correction of preoperative anemia due to menorrhagia. The more extended use of intravenous iron therapy is expected in various anemic preoperative settings.

References

1 Cole SK, Billewicz WZ, Thomson AM: Sources of variation in menstrual blood loss. J Obstet Gynaecol Br Commonw 1971;78: 933–939.
2 Hallberg L, Hogdahl AM, Nilsson L, Rybo G: Menstrual blood loss – a population study. Variation at different ages and attempts to define normality. Acta Obstet Gynecol Scand 1966;45:320–351.
3 Oehler MK, Rees MC: Menorrhagia: an update. Acta Obstet Gynecol Scand 2003;82: 405–422.
4 Coulter A, Peto V, Jenkinson C: Quality of life and patient satisfaction following treatment for menorrhagia. Fam Pract 1994;11: 394–401.
5 Shaw RW, Brickley MR, Evans L, Edwards MJ: Perceptions of women on the impact of menorrhagia on their health using multi-attribute utility assessment. Br J Obstet Gynaecol 1998;105:1155–1159.
6 Kuriyan M, Carson JL: Anemia and clinical outcomes. Anesthesiol Clin North Am 2005; 23:315–325, vii.
7 Carson JL, Terrin ML, Jay M: Anemia and postoperative rehabilitation. Can J Anaesth 2003;50:S60–S64.
8 Liguori L: Iron protein succinylate in the treatment of iron deficiency: controlled, double-blind, multicenter clinical trial on over 1,000 patients. Int J Clin Pharmacol Ther Toxicol 1993;31:103–123.
9 Coplin M, Schuette S, Leichtmann G, Lashner B: Tolerability of iron: a comparison of bis-glycino iron II and ferrous sulfate. Clin Ther 1991;13:606–612.
10 Farley PC, Foland J: Iron deficiency anemia. How to diagnose and correct. Postgrad Med 1990;87:89–93, 96, 101.
11 Al RA, Unlubilgin E, Kandemir O, Yalvac S, Cakir L, Haberal A: Intravenous versus oral iron for treatment of anemia in pregnancy: a randomized trial. Obstet Gynecol 2005;106: 1335–1340.
12 Bhandal N, Russell R: Intravenous versus oral iron therapy for postpartum anaemia. BJOG 2006;113:1248–1252.
13 Schroder O, Mickisch O, Seidler U, de Weerth A, Dignass AU, Herfarth H, Reinshagen M, Schreiber S, Junge U, Schrott M, Stein J: Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease – a randomized, controlled, open-label, multicenter study. Am J Gastroenterol 2005;100:2503–2509.
14 Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, Balan S, Barker L, Rana J: Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol 2004;22: 1301–1307.
15 Charytan C, Levin N, Al-Saloum M, Hafeez T, Gagnon S, Van Wyck DB: Efficacy and safety of iron sucrose for iron deficiency in patients with dialysis-associated anemia: North American clinical trial. Am J Kidney Dis 2001;37:300–307.
16 Perewusnyk G, Huch R, Huch A, Breymann C: Parenteral iron therapy in obstetrics: 8 years experience with iron-sucrose complex. Br J Nutr 2002;88:3–10.
17 Sifakis S, Angelakis E, Papadopoulou E, Stratoudakis G, Fragouli Y, Koumantakis E: The efficacy and tolerability of iron protein succinylate in the treatment of iron-deficiency anemia in pregnancy. Clin Exp Obstet Gynecol 2005;32:117–122.
18 Beshara S, Lundqvist H, Sundin J, Lubberink M, Tolmachev V, Valind S, Antoni G, Langstrom B, Danielson BG: Pharmacokinetics and red cell utilization of iron(III) hydroxide-sucrose complex in anaemic patients: a study using positron emission tomography. Br J Haematol 1999;104:296–302.
19 Bastani B, Rahman S, Gellens M: Lack of reaction to ferric gluconate in hemodialysis patients with a history of severe reaction to iron dextran. ASAIO J 2002;48:404–406.
20 Faich G, Strobos J: Sodium ferric gluconate complex in sucrose: safer intravenous iron therapy than iron dextrans. Am J Kidney Dis 1999;33:464–470.
21 Macdougall I, Bailie G, Richardson D, Tanner J, Gagnon SP: Worldwide safety profile of iron sucrose injection (Venofer): analysis of 1,044,477 patients from 1992 to 2001. J Am Soc Nephrol 2001;2001:333A.
22 Alexander DA, Naji AA, Pinion SB, Mollison J, Kitchener HC, Parkin DE, Abramovich DR, Russell IT: Randomised trial comparing hysterectomy with endometrial ablation for dysfunctional uterine bleeding: psychiatric and psychosocial aspects. BMJ 1996;312: 280–284.
23 Thornton EW, McQueen C, Rosser R, Kneale T, Dixon K: A prospective study of changes in negative mood states of women undergoing surgical hysterectomy: the relationship to cognitive predisposition and familial support. J Psychosom Obstet Gynaecol 1997;18: 22–30.