석 사 학 위 논 문

Efficacy and Safety of Intravenous Iron Therapy in Children : Korean Single Center Study

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이 논문을 석사학위 논문으로 제출함

2021년 2월

계명대학교 대학원

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정난이의 석사학위 논문을 인준함

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또, 논문의 방향 설정과 질적 향상을 위해 세심한 배려와 조언을 주신 도영록 교수님, 장효정 교수님께도 감사의 말씀을 드립니다.

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1. Introduction

Intravenous (IV) iron, first introduced in 1947, is absorbed differently from oral iron by directly entering the reticuloendothelial system from the circulating blood.[1,2] By bypassing the intestinal pathway, IV iron has fewer gastrointestinal side effects than oral iron. However, IV iron was used only in cases of failure of oral iron therapy until the early the 1990s due to safety issues.[3] As new formulations with fewer side effects have become available recently, IV iron is now widely used for various indications, including chronic kidney disease, inflammatory bowel disease, heart failure, perioperative anemia, gestational anemia, and restless leg syndrome.[2,4] Despite remarkable efficacy and safety results in adults, IV iron is rarely used in children due to the lack of pediatric data.

The purpose of this study was to investigate the etiologies of anemia and indications for IV iron therapy and to evaluate the efficacy and safety of IV iron therapy in children treated at a single Korean center.

2. Materials and Methods

2.1. Patients and Data Collection:

We retrospectively collected data from children < 18 years of age who received IV iron at the Keimyung University Dongsan Hospital between July 2003 and December 2018. Patients were identified from a review of medical records including demographic information, underlying disease, etiology of anemia, indication for IV iron, formulation and dose of IV iron, laboratory results of pre- and post-infusion of IV iron, and adverse effects. This study was approved by the Institutional Review Board at Keimyung University Dongsan Hospital (approval number: DSMC 2019-09-064).

According to the initial inclusion criteria, data of total children receiving IV iron were analyzed for patient characteristics and safety assessment. Efficacy assessment was performed for the subsequent data after application of the following exclusion criteria; packed red blood cell transfusion, erythropoietin, and concurrent oral iron therapy, as well as significant bleeding before the results of IV iron therapy were obtained, and insufficient laboratory data. We compared the hemoglobin (Hb) concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and serum ferritin between pre- and post-infusion of IV iron to analyze the efficacy of IV iron.

Patients were categorized according to the etiologies of anemia or indications for IV iron therapy. The indications for IV iron therapy were divided into five groups; gastrointestinal disorder, anemia of chronic

disease with iron deficiency, blood loss, nutritional problems, and others. The etiologies of anemia were divided into six groups; blood loss difficult to manage with oral iron therapy, oral iron refractoriness, oral iron intolerance, perioperative management, treatment with erythropoiesis-stimulating agents, and unknown.

2.2. Administration of IV Iron:

IV iron was administered as iron sucrose (IS; Venoferrum®, BYK Gulden, Singen, Germany) or ferric carboxymaltose (FCM; Ferinject®, Vifor Pharma, St. Gallen, Switzerland) according to the physician's decision. The dosage was calculated according to the patient's age and body weight. The IS was diluted using normal saline to a final concentration of ≥ 1 mg/mL and infused over 30 to 60 min. The FCM was mixed in normal saline (diluted to ≥ 2 mg/mL) and infused over 15 to 60 min according to the manufacturer's labeling. All the patients received IV iron without a test dose or routine premedication. Vital signs including heart rate, blood pressure, and oxygen saturation were monitored before the infusion, every 30 minutes during the infusion, and after the infusion.

In this study, one infusion of IV iron was defined as a single dose or multiple doses with an interval of within three months between the initial dose and the next dose. Follow-up laboratory tests were performed within one week to three months after the last dose. When multiple laboratory results were present, the values with the greatest increase in Hb level were chosen for the analysis.

2.3. Statistical Analysis:

All statistical analyses were performed using IBM SPSS software (version 23.0; IBM Corp., Armonk, NY, USA). Variables are shown as median values and ranges. Comparisons of variables between pre- and post-infusion of IV iron were performed using the Wilcoxon signed rank test. A comparison of the increase in laboratory tests between the two groups after IV iron therapy was performed using a generalized estimated equation. Box plots were described by the minimum, maximum, median, and first and third quartiles. P-values of < 0.05 were considered statistically significant.

3. Results

3.1. Patients' Baseline Characteristics:

A total of 68 children (male:female = 34:34) received 85 infusions of IV iron during the study period. Patients' characteristics, etiologies, and indications, as well as safety assessments of the IV iron were investigated in 68 children. After applying exclusion criteria, 35 children received 41 infusions of IV iron. The data were used for the efficacy analysis. The flow chart of this study is shown in Figure 1.

The median age of the 68 children who received IV iron was 7.1 years (range, 0.3 - 17.9 years). Twenty-seven children (39.7%) under five years of age were included. Of the 68 patients, 36 received IS. The median dose of the IS was 4.2 mg/kg (range, 1 - 20.4 mg/kg), and the median number of doses was one (range, 1 - 9). The remaining 49 patients received FCM. The median dose of FCM was 5.1 mg/kg (range, 2.7 - 18.8 mg/kg), and the median number of doses was one (range, 1 - 12). The baseline characteristics of the patients and IV iron are shown in Table 1.

3.2. Etiologies of Anemia and Indications of IV Iron Therapy in Children:

Gastrointestinal disorders (29.4%), anemia of chronic diseases with iron deficiency (25%), and blood loss (22.1%) were common etiologies of anemia. Twenty patients (29.4%) had gastrointestinal disorders, including

eosinophilic gastrointestinal disorders, peptic ulcer, short bowel syndrome, Crohn's disease, varix bleeding, gastritis with *Helicobacter pylori* infection, gastrointestinal graft-versus-host disease, food protein-induced enterocolitis, microvillus inclusion disease, small bowel bleeding, allergic proctocolitis, and juvenile polyps. Among the 20 patients with gastrointestinal disorders, 11 patients also had gastrointestinal bleeding. Seventeen patients (25%) had anemia of chronic disease with iron deficiency, including chronic kidney diseases, cancers, respiratory tract infections, autoimmune disorders, endocrine disorders, neuroinflammation, and allergies. Fifteen patients (22.1%) had blood loss; menorrhagia, intraoperative bleeding, gingival hemorrhage, trauma, hematuria, and epistaxis. Eleven patients (16.2%) had nutritional problems; problems of baby food in infancy, malnutrition associated with developmental disabilities, and cyclic vomiting syndrome. The remaining five patients had sleep disorders or anemia after chemotherapy. Of the 68 patients, there were five patients with congenital bleeding disorders who had hemorrhages needed iron supplementation; two patients with hemophilia, two with von Willebrand disease, and one with Glanzmann thrombasthenia. More details on the etiologies of IV iron therapy are listed in Table 2.

Blood loss difficult to manage with oral iron (26.5%), oral iron refractoriness (25%), and oral iron intolerance (23.5%) were common indications of IV iron therapy for children in this study. More details on the indications are listed in Table 3.

3.3. Safety Assessment for IV Iron Therapy:

Among the 68 patients, two had three adverse events. One patient

was a 1.3-year-old boy who was administered two infusions of IS. He had fever each time for about 3 - 4 hours after the infusions of IS and was managed with antipyretics. The other patient was a 6-year-old girl who underwent FCM. She had headache and facial flushing three days after the infusion of FCM. The guardian reported that her symptoms improved spontaneously. Severe adverse events such as anaphylaxis were not observed.

3.4. Efficacy Assessment for IV Iron Therapy:

The results of pre- and post-infusion laboratory tests for Hb, MCV, MCH, and MCHC were compared in 41 infusions. The levels of serum ferritin before and after infusions were compared in 30 infusions. The median level of Hb increased from 10.2 g/dL (range, 6.1 - 14.0 g/dL) to 12.1 g/dL (range, 7.7 - 14.7 g/dL) with statistical significance ($P < 0.001$). The median value of MCV increased from 77.3 fL (range, 55.9 - 91.1 fL) to 79.8 fL (range, 64.9 - 103.5 fL), with statistical significance ($P < 0.001$). The median value of MCH increased from 25.2 pg (range, 13.6 - 31.8 pg) to 26.3 pg (range, 18.4 - 33.1 pg) with statistical significance ($P < 0.001$). The median value of MCHC increased from 31.8 g/dL (range, 24.4 - 35.4 g/dL) to 32.5 g/dL (range, 28.1 - 35.2 g/dL) with statistical significance ($P < 0.001$). The median level of serum ferritin increased from 27.0 ng/mL (range, 7.0 - 175.0 ng/mL) to 146.4 ng/mL (range, 12.6 - 1007.7 ng/mL) with statistical significance ($P < 0.001$). Among the 83 infusions of IV iron, all infusions showed Hb improvements except for one infusion; a case of active peptic ulcer bleeding. The graphs for the aforementioned data are shown in Figure 2. Box plots were described by the minimum, maximum, median, and

first and third quartiles in the graphs.

3.5. Comparisons in Efficacy of IV Iron Therapy between IS and FCM:

The efficacy of IV iron therapy was compared according to the iron formulation used. The Hb, MCV, MCH, and MCHC were checked for 13 infusions in the IS group and 28 infusions in the FCM group. Serum ferritin levels were analyzed for seven infusions in the IS group and 25 infusions in the FCM group. After comparison between the IS and FCM groups, there were no statistical differences in the increase of Hb ($P \geq 0.05$), MCV ($P \geq 0.05$), MCH ($P \geq 0.05$), MCHC ($P \geq 0.05$), and ferritin ($P \geq 0.05$) after iron infusion. The graphs are shown in Figure 3.

3.5. Comparisons in Efficacy of IV Iron Therapy between Bleeding and Non-bleeding Groups:

The efficacy of IV iron therapy was compared according to the etiologies; bleeding (blood loss, and gastrointestinal disorders with bleeding) and non-bleeding groups. The Hb, MCV, MCH, and MCHC were checked for 12 infusions in the bleeding group and 29 infusions in the non-bleeding group. Serum ferritin levels were analyzed for 10 infusions in the bleeding group and 27 infusions in the non-bleeding group. After comparison between the two groups, there was a statistical

difference in the increase of Hb between the bleeding and non-bleeding groups ($P < 0.01$). In addition to Hb, there were no statistical differences in the increase of MCV ($P \geq 0.05$), MCH ($P \geq 0.05$), MCHC ($P \geq 0.05$), and ferritin ($P \geq 0.05$) between the bleeding and non-bleeding groups. These graphs are shown in Figure 4.

Table 1. Baseline Characteristics of Children who Received Intravenous Iron Therapy

Baseline characteristics	
Male : female	34 : 34
Age (years)	Median 7.1 (range, 0.3 - 17.9)
< 2	17 (25.0%)
≥ 2 and <5	10 (14.7%)
≥ 5 and <12	15 (22.1%)
≥ 12 and <18	26 (38.2%)
Timing of follow-up tests (days)	27 (7 - 175)
Formulation of intravenous iron	Median (range)
Iron sucrose (N = 36)	
Dose (mg/kg)	4.2 (1.0 - 20.4)
Total dose (mg)	135 (24 - 1200)
Total dose per body weight (mg/kg)	5.1 (1.0 - 24.3)
Number of doses	1 (1 - 9)
Ferric carboxymaltose (N = 49)	
Dose (mg/kg)	5.1 (2.7 - 18.8)
Total dose (mg)	200 (58 - 1200)
Total dose per body weight (mg/kg)	6.5 (4.3 - 45)
Number of doses	1 (1 - 12)

Table 2A. Etiologies of Anemia in Children

Etiologies of anemia	N (%)
Gastrointestinal disorders	20 (29.4)
Eosinophilic gastrointestinal disorder	4
Peptic ulcer	3
Short bowel syndrome	2
Crohn's disease	2
Varix bleeding*	2
Gastritis with *Helicobacter pylori* infection	1
Gastrointestinal graft-versus-host disease	1
Food protein induced enterocolitis	1
Microvillus inclusion disease	1
Small bowel bleeding**	1
Allergic proctocolitis	1
Juvenile polyp	1
Anemia of chronic disease with iron deficiency	17 (25.0)
Chronic kidney diseases	4
Cancers (Wilms tumor, leukemia, and stomach cancer)	3
Autoimmune disorders (AIHA, CRMO, and TA)	3
Respiratory tract infection	3
Endocrine disorders (Graves' disease and congenital hypothyroidism)	2
Neuroinflammation (neuronal ceroid lipofuscinosis)	1
Allergic rhinitis	1
Blood loss	15 (22.1)
Menorrhagia***	5
Intraoperative bleedings	4
Gingival hemorrhages§	2
Traumas	2
Hematuria‖	1
Epistaxis¶	1
Nutritional problems	11 (16.2)
Problems of baby food in infancy	8
Malnutrition associated with developmental disabilities	2
Cyclic vomiting syndrome	1
Others	5 (7.4)
Sleep disorders	4
Anemia after chemotherapy	1
Total	68 (100.0)

Table 2B. Etiologies of Anemia in Children (continued)

AIHA: autoimmune hemolytic anemia; CRMO; chronic recurrent multifocal osteomyelitis; TA: Takayasu arteritis.

* Two patients had biliary atresia with biliary cirrhosis. ** The patient had severe hemophilia A with an inhibitor. *** One of the patients had von Willebrand disease. § One patient had Glanzmann thrombasthenia, and the other had moderate hemophilia B. ‖ The patient had chronic kidney disease with IgA nephropathy. ¶ The patient had von Willebrand disease.

Table 3. Indications for Intravenous Iron Therapy in Children

Indications of intravenous iron therapy	N (%)
Blood loss difficult to manage with oral iron therapy	18 (26.5)
Oral iron refractoriness	17 (25.0)
Oral iron intolerance	16 (23.5)
Perioperative management	7 (10.3)
With erythropoiesis-stimulating agent	4 (5.9)
In a situation in which red blood cell transfusion is not possible	2 (2.9)
Unknown	4 (5.9)
Total	68 (100.0)

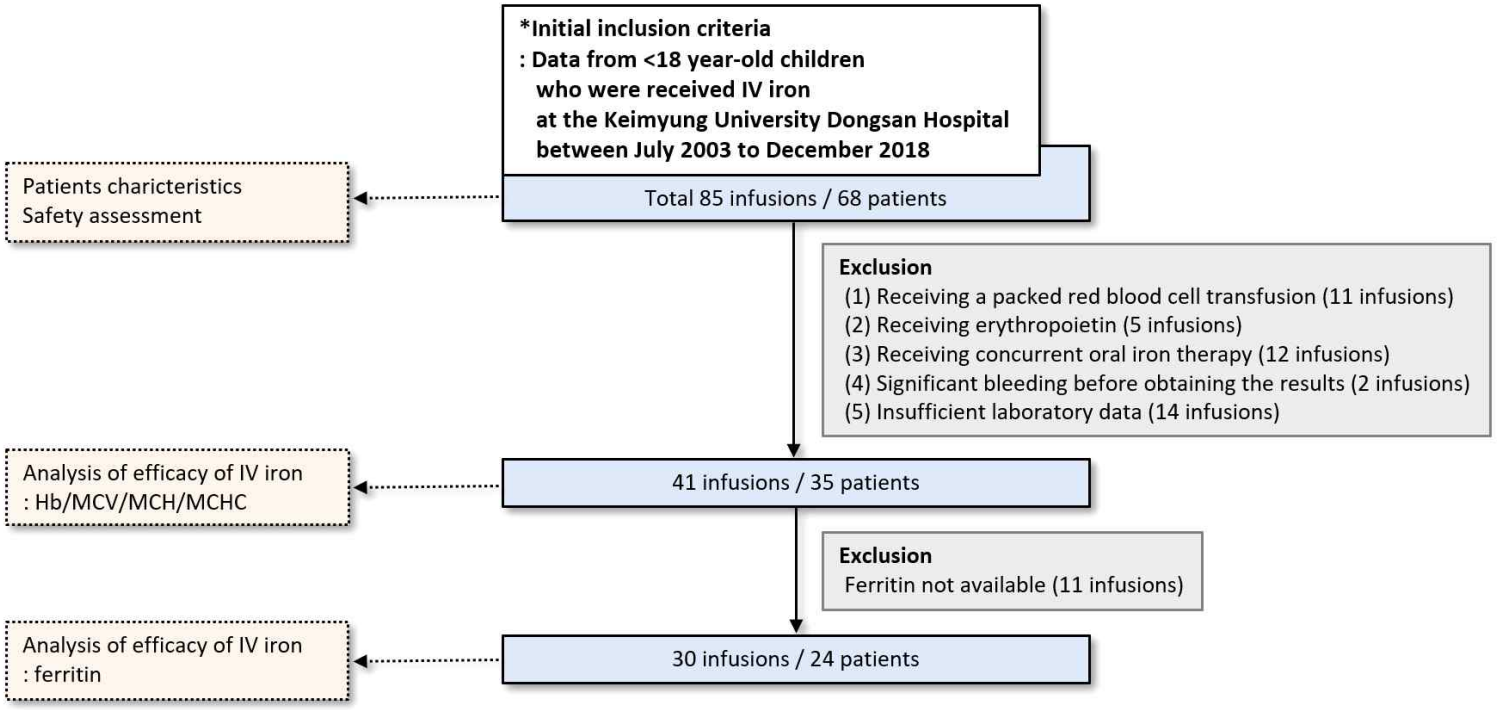

Figure 1. The flow chart of the study.

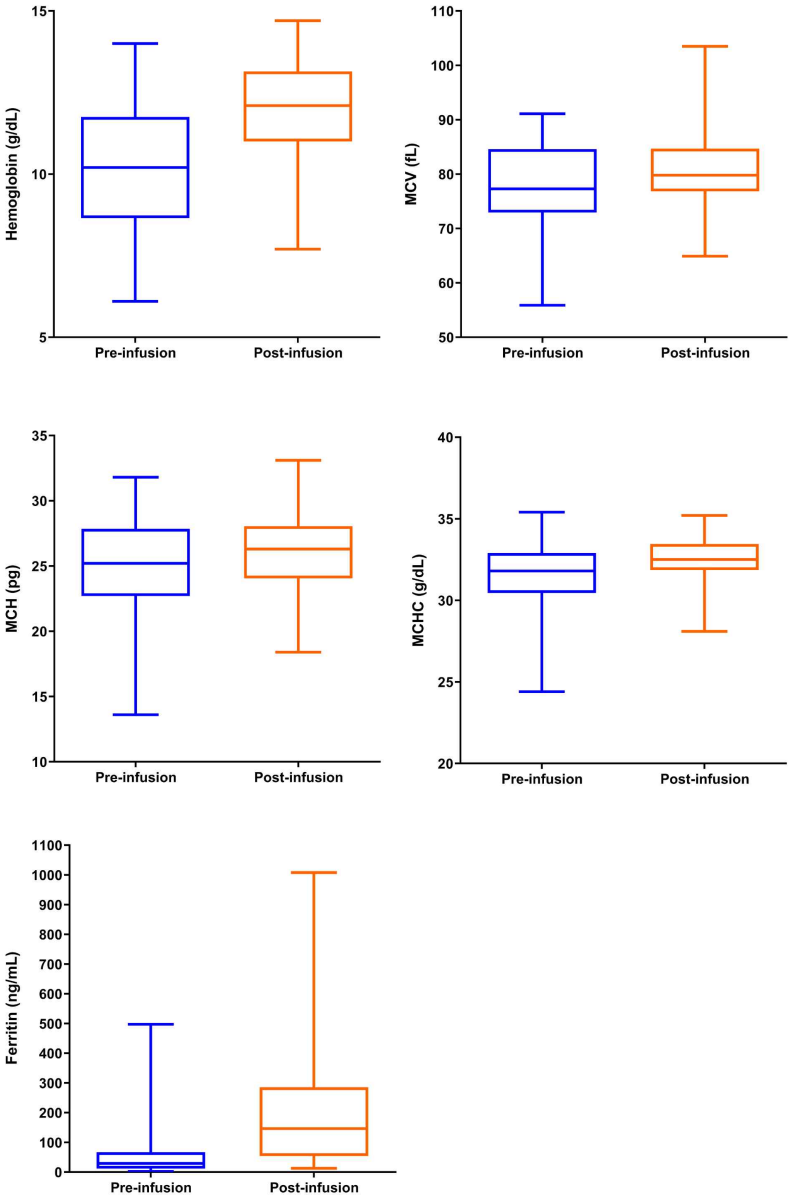

Figure 2. The comparison of hemoglobin, MCV, MCH, MCHC, and ferritin before and after intravenous iron therapy. Box plots were described by the minimum, the maximum, the median, and the first and third quartiles in the graphs. MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume.

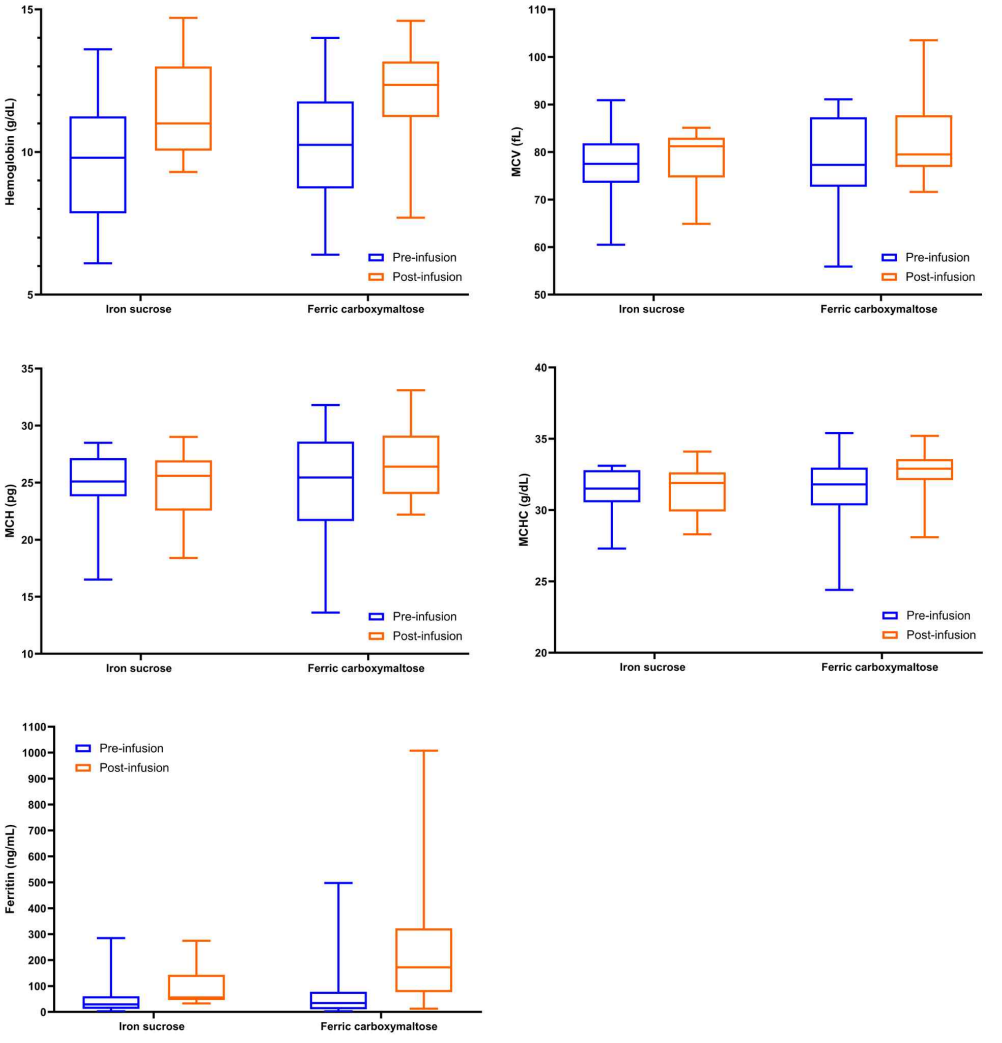

Figure 3. The comparison of the increase in hemoglobin, MCV, MCH, MCHC, and ferritin between iron formulations (iron sucrose and ferric carboxymaltose) after intravenous iron therapy. Box plots were described by the minimum, the maximum, the median, and the first and third quartiles in the graphs. MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume.

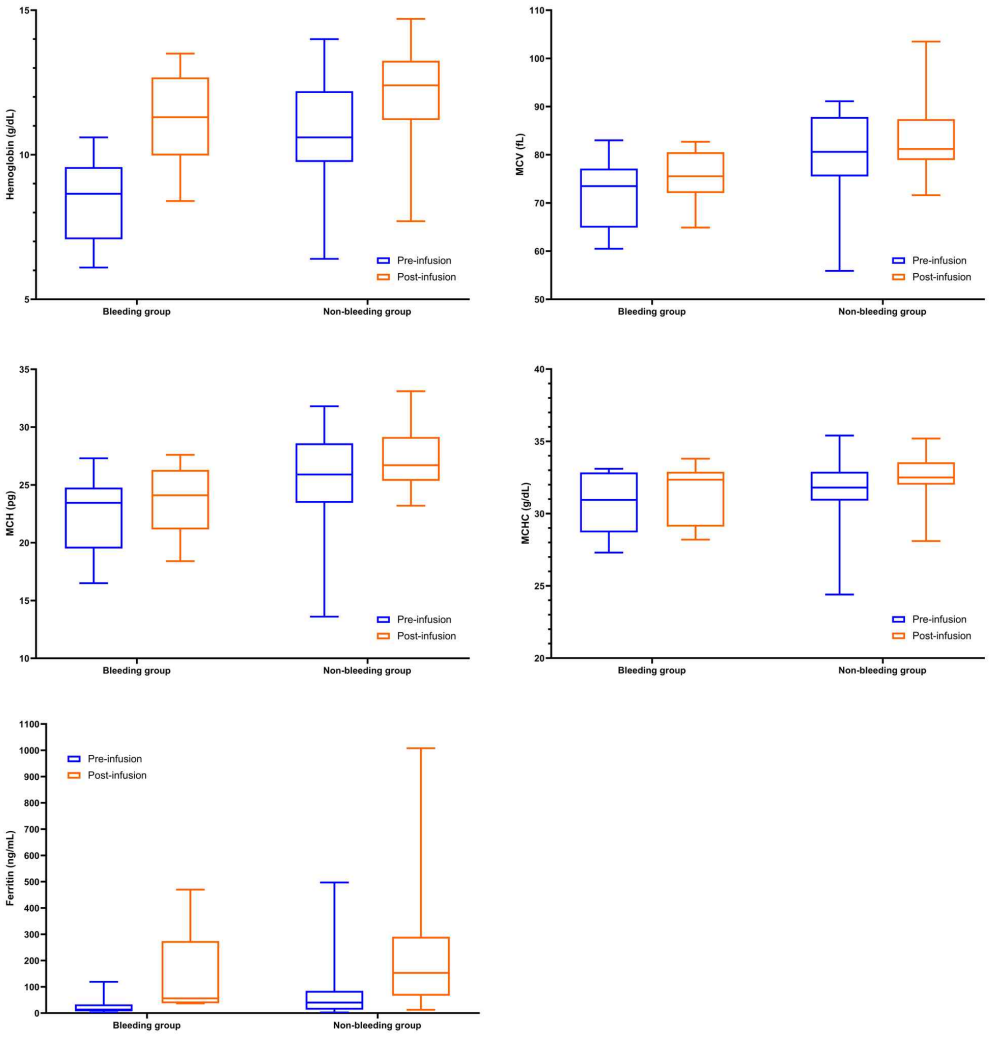

Figure 4. The comparison of the increase in hemoglobin, MCV, MCH, MCHC, and ferritin between bleeding and non-bleeding groups after intravenous iron therapy. Box plots were described by the minimum, the maximum, the median, and the first and third quartiles in the graphs. MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume.

4. Discussion

Iron deficiency is a common hematologic condition particularly in infants and menstruating young women due to the increased physiologic need for iron.[5] Since iron deficiency affects childhood development, cognitive function, and the immune system, it should be treated properly.[6-8] Oral iron has been used as an inexpensive and effective initial treatment for iron deficiency anemia. However, frequent gastrointestinal adverse effects such as nausea, vomiting, constipation, and diarrhea cause oral iron intolerance.[9] In addition, destruction of gastrointestinal mucosal integrity or high serum hepcidin levels interferes with oral iron absorption.[2]

On the other hand, due to its high cost, invasiveness, and risk of side effects, IV iron has been used as an alternative option in situations of unresponsiveness to oral iron or the need for rapid anemia correction.[10] For this reason, the majority of patients who received IV iron in this study had complex pathologic conditions. These conditions included various gastrointestinal disorders and chronic diseases such as chronic kidney diseases, cancers, autoimmune disorders, endocrine disorders, neurologic disorders, or congenital bleeding disorders. Even in the nutritional problem group, three patients had underlying diseases, such as developmental disabilities and cyclic vomiting syndrome. In the blood loss group, four patients had congenital bleeding disorders and one had chronic kidney disease.

There have been no long-term prospective studies of IV iron therapy in children: however, several studies have shown pediatric data of IV iron. They all showed IV iron was effective in Hb increment and had no severe adverse effects.[11-13] Until now, well-established indications of

IV iron therapy in children are iron deficiency anemia unresponsive to oral iron, inflammatory bowel disease, and chronic kidney disease.[11] We used IV iron in patients with various anemia situations, such as cancer, perioperative anemia, and restless leg syndrome. Similar to previously established indications, Hb, red cell indices, and ferritin levels were significantly increased after IV iron infusions. Therefore, in children with complicated conditions, who are likely not to respond to oral iron, IV iron should be considered as an important option to reduce the complication of anemia and avoid red blood cell transfusion.

Safety issues such as anaphylaxis are one of the most significant limitations of the use of IV iron before the introduction of novel iron preparations.[14] Recent systematic meta-analyses have shown serious adverse events, including infection, infusion, cardiovascular, neurologic, respiratory, gastrointestinal, thromboembolic, and constitutional severe reactions, were extremely rare (less than 1 in 200,000) with novel IV iron preparations such as IS and FCM.[15] We encountered two suspicious cases: one had a fever with coughing, and the other had a headache. Both symptoms were mild and self-limited. As no further evaluation was made, the relationship between symptoms and IV iron infusions was not clear. No serious adverse effects were recorded in the medical charts.

Although both IS and FCM are safe and effective preparations, FCM is one of the newer IV iron preparations. Because FCM has a high stability, it can be administered rapidly at high doses (infusion of 1000 mg elemental iron over 15 min).[16] In adults, a total dose infusion of IV iron is available instead of repeated infusions.[17] Although there is insufficient pediatric data on total dose infusions, total infusion can be considered a possible choice in children to reduce the number of infusions.

This study had some limitations. First, it was a retrospective, single-center study. Thus, IV iron was administered with wide variations of infusion doses, numbers, and intervals. Second, the timing of the follow-up laboratory test was also variable. Despite these limitations, this was the first study to report the efficacy and safety of IV iron in Korean children with various etiologies of anemia. In addition, young children under the age of five made up a quarter of the patients included in the study. Our results may encourage the use of IV iron in children of a wide range of ages and various indications.

5. Summary

In conclusion, we investigated the safety and efficacy of IV iron in various groups of children. The most common etiologies of anemia were gastrointestinal disorders. Blood loss difficult to manage with oral iron therapy, oral iron refractoriness, and oral iron intolerance were common, with similar proportions. The use of IV iron was effective and safe in children with various etiologies of anemia. Prospective controlled studies of IV iron in children using standardized guidelines are needed.

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Efficacy and Safety of Intravenous Iron Therapy in Children: Korean Single Center Study

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(Abstract)

Administration of intravenous (IV) iron is rarely used in children due to lack of data. The aim of this study was to determine the etiologies of anemia and indications for IV iron and to evaluate the efficacy and safety of IV iron infusions to children. This retrospective study collected data from < 18 year-old children who received IV iron at Keimyung University Dongsan Hospital between July 2003 and December 2019. Total 68 children received total 85 infusions of IV iron. The most common etiologies of anemia were gastrointestinal disorders (29.4%). Blood loss difficult to manage with oral iron therapy (26.5%), oral iron refractoriness (25%) and oral iron intolerance (23.5%) were common indications for IV iron. Twenty-eight patients received a total of 36 infusions of iron sucrose (median dose, 4.2 mg/kg), 43 patients received

a total of 49 infusions of ferric carboxymaltose (median dose, 5.1 mg/kg). Hemoglobin, red cell indices, and ferritin levels showed a statistically significant improvement after IV iron infusions. No patients experienced severe adverse effects. The use of IV iron was effective and safe in children with anemia.

소아에서 주사용 철분제 사용의 효과와 안전성

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(초록)

주사용 철분제는 소아에서의 연구 결과가 부족하여 소아 빈혈의 치료로는 잘 사용되지 않고 있다. 이 연구의 목적은 소아에서 주사용 철분제를 사용한 증례를 모아, 빈혈의 원인과 주사용 철분제의 적응증을 확인하고, 그 효과와 안전성을 평가하는 것이다. 본 연구는 후향적 연구로, 2003 년 7 월부터 2019 년 12 월까지 계명대학교 동산병원에서 주사용 철분제를 투여한 18 세 미만 소아의 자료를 조사하였다. 총 68 명의 환자들이 85 번의 주사용 철분제를 투여받았다. 빈혈의 가장 많은 원인은 소화기 질환(29.4%)이었다. 경구용 철분제로 조절이 어려운 출혈(26.5%), 경구용 철분제에 반응이 없는 경우(25%), 경구용 철분제를 못 먹는 경우(23.5%)가 주사용 철분제 사용의 흔한 적응증이었다. 28 명의 환자들이 36 번의 iron sucrose(중간 용량, 4.2 mg/kg)를 투여받았고, 43 명의 환자들이 총 49 번의 ferric carboxymaltose(중간 용량, 5.1 mg/kg)를 투여받았다. 혈색소, 적혈구 지수와 페리틴 수치는 주사용 철분제 투여 후 통계적으로 유의한 호전을

보였다. 심각한 부작용을 보인 환자는 없었다. 따라서 주사용 철분제 치료는 소아에서 효과적이고 안전하였다.