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RESEARCH ARTICLE

The Effects of Iron Therapy on Blood Transfusion, Length of Intensive Care Stay and Mortality in Patients with Iron Deficiency Anemia in the Intensive Care Unit

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ABSTRACT

Objectives: The most prevalent form of anemia is iron deficiency anemia (IDA). In the intensive care unit (ICU) setting, frequent blood sampling for diagnostic purposes is one of the most important causes of anemia among patients. In our study, we aimed to retrospectively scan and compare patients diagnosed with IDA in our institution's ICU, with and without iron therapy.

Methods: In this study, patients with IDA who were hospitalized in our ICU for more than 21 days were included. The patients were divided into two groups: group 1 (patients with iron therapy) and group 2 (patients without iron therapy). Information regarding demographics (age and sex), comorbidities, total volume of blood samples drawn, hemoglobin, hematocrit, ferritin values, requirement for blood transfusion, length of ICU stay, Acute Physiology and Chronic Health Evaluation II score, Glasgow coma scale, and mortality rates were recorded.

Results: In this study, 48 patients were analyzed, including 25 (18 women, 7 men) with iron therapy and 23 (13 women, 10 men) without iron therapy. A statistically significant difference was found in the mean blood volume per patient transfused over the 21-day period between the two groups.

Conclusion: We noted that oral iron therapy was effective in reducing blood transfusions in patients with prolonged ICU stays. We believe that studies with larger patient groups are warranted regarding this topic.

Keywords: Anemia, intensive care, iron therapy

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Introduction

In the general population, anemia is a relatively common condition. The most prevalent form of anemia worldwide is iron deficiency anemia (IDA). Although IDA is more common in the elderly and female population, it can occur at any age.[1] According to the World Health Organization, anemia is defined as a hemoglobin (Hb) concentration of <13.0 g/dL in men over 15 years and a Hb concentration of <12.0 g/dL in nonpregnant women over 15 years of age. Moreover, anemia in pregnant women is defined as a Hb concentration <11.0 g/dL. Anemia is also associated with an increased length of postoperative hospital stay and a higher rate of intensive care unit (ICU) admission, morbidity, and mortality.[2]

IDA is a common condition in patients admitted to the ICU. To manage IDA, inexpensive, effective, and reliable oral iron supplements are used.[3] In the literature, doses higher than 60–120 mg of elemental iron per day are not recommended because they are unlikely to offer significant benefit in terms of iron repletion and can cause unintended side effects.[4] It has been reported that providing iron supplements daily as divided doses increases serum hepcidin and reduces iron absorption, and daily oral iron supplements are more effective as a single dose.[5] Moreover, it has been reported that Hb usually responds rapidly to effective oral iron therapy and indicates an adequate therapeutic response as a Hb increase of at least 2 g/dL after 3 weeks of therapy. However, repletion of iron stores may require 4–6 months of treatment.[6]

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Frequent blood sampling from patients for diagnostic purposes is associated with blood loss volume and is one of the most important causes of anemia in the ICU, which is disregarded by clinicians. The average volume of blood samples drawn has been reported to be 40–41 mL/day in studies, and a positive correlation was found between diagnostic phlebotomy and the amount of erythrocyte transfusion.[7,8] A common intervention method for treating anemia in critically ill patients is red blood cell transfusion. Although blood transfusion is life-saving, it is also associated with an increased risk of morbidity and mortality.[3,9,10] An increase in mortality rates has been reported in ICU patients who receive frequent blood transfusions. Transfusion therapy in the ICU is an ever-growing field, with a new understanding of potential complications, new drug therapies to reduce the requirement for transfusion, and new additions in component therapy. Although there have been several large clinical trials that have studied red blood cell transfusion in various ICU patient populations, currently, a widely accepted consensus in terms of its application in the ICU is nonexistent.[11–13]

Iron therapy is a biologically plausible treatment to reduce the need for blood transfusion in ICU patients.[14] This study includes a retrospective comparison of ICU patients diagnosed with IDA with and without iron therapy. This study aimed to reveal the effects of iron therapy through a comparison of the demographic data of the patients, the blood sample volume drawn, Hb, hematocrit, ferritin values, requirement for blood transfusion, and length of ICU stay.

Methods

This study was approved by the Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital (No: 128/17; January 10, 2022). Patients with IDA who were hospitalized in the ICU of our hospital for more than 21 days between July 1, 2021 and January 1, 2022 were included in the study. The exclusion criteria are as follows: patients under 1 year of age, postoperative patients, patients with non-IDA, critically ill patients with active infection, patients with acute and chronic kidney disease, patients with inflammatory diseases, and patients with missing data. Four patients with kidney stones and cysts but with normal kidney function values were not excluded from the study. This research is a descriptive epidemiological study, and it was aimed to include all patients in the study.

Patient data were scanned and recorded retrospectively from the hospital information system and ICU assessment forms. The patients were divided into two groups: group 1 (patients with iron therapy) and group 2 (patients without iron therapy). Oral iron supplementation is not recommended for patients who are allergic to iron preparations and have gastrointestinal system absorption disorders such as inflammatory bowel disease and gastrointestinal malignancy.[15] Therefore, patients who were not administered oral iron therapy were included in the group of patients without iron therapy. Information regarding demographics (age and sex), comorbidities, total volume of blood samples drawn, Hb, hematocrit, ferritin values, requirement for blood transfusion, length of ICU stay, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Glasgow coma scale (GCS), and mortality rates were recorded.

Laboratory evaluation is required for a definitive diagnosis of the type of anemia. As appropriate to this aim, various blood tests are performed to diagnose anemia in ICU patients on the first day of hospitalization, such as hemogram, iron, ferritin, iron binding capacity, vitamin B12, and folate. After excluding other causes of anemia such as vitamin B12 and folate deficiencies, iron replacement therapy is used in patients with IDA. Hemoglobin levels below 13 g/dL in men and 12 g/dL in women were considered as anemia. In patients with anemia with ferritin levels below 30 µg/L and iron levels below 33 µg/dL, iron deficiency was considered.

In this study, the effects of daily oral iron treatment in a single dose for 21 days were examined. Patients in the ICU in our institution diagnosed with IDA were administered 270 mg/day of ferrous sulfate (80 mg elemental iron) orally as a single daily dose for 21 days, and monitoring of daily blood results and complications related to iron therapy was conducted. Oral iron therapy was continued for patients with ongoing anemia after discharge from the ICU. Iron therapy was not used in patients with gastrointestinal system absorption disorders or a history of allergy to iron preparations. Treatment was terminated when complications such as allergy, anaphylaxis, severe nausea-vomiting, diarrhea, and melena occurred due to iron treatment. Patients whose treatment was not completed were excluded from the study.

During the hospitalization of the patients included in the study, the total volume of blood drawn daily was recorded via follow-up forms by calculating the amount of blood samples taken in the hospital information system.

Statistical Analysis

The SPSS 21.0 (Version 22.0, SPSS, Inc, Chicago, IL, USA) program was used for statistical analysis. After applying the Shapiro–Wilk test for normality, Student's t-test was used if the distribution was normal for the comparison of continuous variables between groups, and the Mann–Whitney U-test was used if with nonnormal distribution. The chi-square test was used for categorical variables. Statistical significance was set at $p<0.05$.

Results

A total of 66 patients diagnosed with IDA who were hospitalized in the ICU of our hospital for more than 21 days between July 1, 2021 and January 1, 2022 were included in the study. A total of 11 patients were excluded from the study because of missing data, and treatment of seven patients was terminated before the 21-day period because of gastrointestinal system complications during iron supplementation treatment. As a result, data of 48 patients were analyzed, including 25 (18 women, 7 men) with iron therapy and 23 (13 women, 10 men) in group 2 without iron therapy. The female to male ratio was similar in both groups, and there was no statistically significant difference between the groups (p=0,263) (Fig. 1).

The mean age of the patients was 70,17±12,01 years (group 1: 70,96±15,09; group 2: 69,39±8,94). There was no difference in the mean age between the groups (p=0,667) (Table 1).

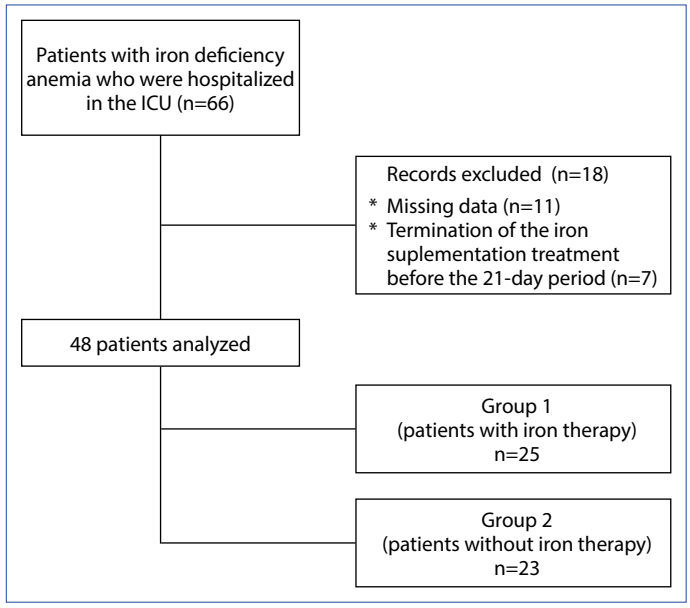

Figure 1. Patient flow chart.

Table 1. Demographic and clinical characteristics

	Group 1 (patients with iron therapy) n=25	Group 2 (patients without iron therapy) n=23	p
Age (year)*	70.96±15.09	69.39±8.94	0.667
Sex (n)			
Female	18	13	0.263
Male	7	10	
Length of ICU stay (day) *	38.20±14.82	37.04±9.23	0.750
APACHE II score *	16.48±6.97	17.65±7.49	0.577
Glasgow coma scale (GCS)*	13.20±2.10	11.78±3.96	0.124
Comorbidity (n)			
COPD	13	14	0.536
CAD	10	10	0.807
Cerebrovascular disease	11	12	0.571
Diabetes mellitus	6	6	0.868
Hypertension	13	8	0.230
Dementia/Alzheimer	4	1	0.187
Renal disease	1	3	0.257
Rheumatological disease	0	2	0.132
Malignancy	1	2	0.502
Mechanical ventilation requirement (n)			
IMV	5	9	0.316
NIMV	4	2	
SP	16	12	
Result (n)			
Exit	2	4	0.274
Discharge	17	17	
Transfer to hospital wards	6	2	

P<0.05 was considered significant. *: Mean±standard deviation. ICU: Intensive care unit; APACHE II score: Acute Physiology and Chronic Health Evaluation II score; COPD: Chronic obstructive pulmonary disease; CAD: Coronary artery disease; IMV: Invasive mechanical ventilation; NIMV: Noninvasive mechanical ventilation; SP: Spontaneous breathing.

Table 2. Comparison of laboratory evaluation and transfusion requirements

	Group 1 (patients with iron therapy) n=25	Group 2 (patients without iron therapy) n=23	p
Hemoglobin values (g/dL)			
0	9.4±1.41	9.28±1.90	0.809
7	9.06±1.13	8.73±1.17	0.323
21	8.79±0.89	8.38±1.27	0.202
Hematocrit values (%)			
0	28.5±4.40	28.38±5.58	0.925
7	28.32±4.06	26.88±3.31	0.188
21	27.17±3.29	25.48±3.39	0.086
Ferritin values (µg/L)			
0	21.73±5.12	22.86±5.35	0.459
7	22.54±4.92	23.60±4.71	0.449
21	23.23±5.34	23.61±4.82	0.797
Total volume of blood drawn (mL)			
0	25.4±13.62	30±9.53	0.186
7	116.8±39.87	127.8±19.76	0.241
21	213.4±77.44	220.87±23.53	0.659
Total volume of blood per patient transfused during the 7-day period (mL)	24±83.06	78.26±134.69	0.097
Total volume of blood per patient transfused during the 21-day period (mL)	60±150	247.82±195.09	<0.001*

*: p<0.05 was considered significant.

Comparisons between comorbidities in the ICU patients are listed in Table 1. No statistical difference was found between the groups (p>0.05).

Comparisons between Hb/hematocrit/ferritin values in the ICU patients are listed in Table 2. No difference between the groups was found (p>0.05).

The mean of the total volume of blood samples drawn per patient on the first day, during the 7-day period, and during the 21-day period are listed in Table 2. No statistically significant difference was found between the groups (p>0.05).

While the mean volume of blood per patient transfused during the 7-day period and during the 21-day period were 24±83.06 mL/60±150 mL in group 1, respectively, they were 78.26±134.69 mL/247.82±195.09 mL in group 2. While there was no difference between the groups on the 7-day period, a statistically significant difference was found on the 21-day period (p=0.097/ p<0.001) (Table 2).

While the mean length of the ICU stay was 38.20±14.82 days in group 1, it was 37.04±9.23 days in group 2. No difference between was found in both groups (p=0.750) (Table 1).

Six patients (group 1: 2; group 2: 4) died in the ICU, 34 patients (group 1: 17; group 2: 17) were discharged, and eight patients (group 1: 6; group 2: 2) were transferred to the hospital wards. When the ICU mortality rates were compared between the groups, these were similar in both groups (p=0.274) (Table 1).

Discussion

In this study, which includes a retrospective comparison of the ICU patients diagnosed with IDA with and without iron therapy, we found that while the volume of blood per patient transfused during the 21-day period was lower in patients with iron therapy, the volume of blood per patient transfused during the 7-day period, the total volume of blood samples drawn, Hb, hematocrit, ferritin values, length of ICU stay, APACHE II score, GCS, and mortality rates of the patients were similar in both groups.

In an intensive care study, the average volume of blood samples drawn for diagnostic purposes was 40–41 mL during the first 24-h period.[7] In another study, the average volume of blood samples drawn for diagnostic purposes in patients in the ICU is 9.62 mL.[8] Conversely, the total volume of blood samples taken during hospitalization was <196 mL in 95% of hospitalized patients. However, for 5% of the patients in the ICU, it was > 200 mL.[16] In our study, we

found that the mean of the total volume of blood samples drawn during the 21-day hospitalization of the patients in the ICU was 217.13 mL, which was similar to that reported in the literature.

In a study comparing iron treatment with placebo in anemic patients admitted to the ICU, iron therapy did not lead to a significant reduction in the need for red blood cell transfusions throughout the hospital stay. However, patients receiving iron had a significantly higher Hb concentration at the time of hospital discharge.[17] In a different study, patients treated with iron therapy in the postoperative critical ICU had a lower blood transfusion rate.[18] In our study, we noted a significant decrease in blood transfusion requirement at the end of the 21-day period in the patient group with iron therapy. We believe that iron therapy is effective in preventing anemia, which occurs as a result of frequent diagnostic blood sampling.

Higher Hb and ferritin values have been reported in patients receiving intravenous iron treatment compared with the control group.[14] In another study, significant changes in the Hb levels were observed in the patient group receiving iron treatment compared with the control group at the 4th week; however, no difference in the 12th week values was observed.[19] Perioperative intravenous iron administration in major abdominal surgeries results in a 60% reduction in allogeneic blood transfusion. However, no significant difference in Hb levels at discharge was observed compared with the control group.[20] We also noted that Hb values were similar in both groups. We believe that this is attributed to more blood transfusions administered to patients who did not receive iron therapy.

In a meta-analysis, intravenous iron therapy was reported to improve exercise capacity and quality of life in patients with heart failure; however, it did not have an effect on all-cause mortality or cardiovascular mortality. Furthermore, oral iron supplements were reported to not only improve exercise capacity and quality of life but also reduce all-cause mortality and hospitalizations for heart failure. The inefficacy of intravenous iron supplements on all-cause mortality or cardiovascular mortality is thought to be due to potential excessive iron accumulation in tissues, leading to tissue damage induced by free radicals.[21] Conversely, in a study conducted in patients on hemodialysis, there is no relationship between iron treatment and mortality.[22] In our study, we observed that the mortality rates during intensive care hospitalization in both groups were similar. However, owing to the retrospective nature of our study, long-term mortality rates after discharge could not be evaluated.

A study reported that iron treatment did not decrease the length of stay.[23] In a study evaluating the efficacy of intravenous iron supplementation in anemic, critically ill trauma patients, no significant difference among groups was found in terms of length of ICU stay and mortality.[24] In our study, similarly, in both patient groups, we found that the length of the ICU stay was similar. We believe that the possible complications and negative effects of anemia were prevented in both groups through iron treatment and blood transfusion, and as a result, we could not find a difference in the length of stay.

The primary recommendation for the treatment of IDA is oral iron therapy. However, in cases where surgery is scheduled within 6 weeks of iron deficiency diagnosis, in patients with an ineffective response to oral iron therapy, or in those intolerant to oral iron, intravenous iron therapy is recommended. However, intravenous iron has a risk of serious transfusion reactions such as anaphylaxis.[3,25] Because the patients in our study had a long-term stay in the ICU and did not have a surgical plan, intravenous iron therapy was not utilized, which has rapid activity. We preferred oral iron therapy, which is considered safer and more cost-effective than intravenous iron therapy.

In a study, mild gastrointestinal side effects were noted in 20.4% of patients receiving oral iron supplements.[26] In a different study, it was reported that the most commonly reported symptoms in patients receiving oral iron therapy were constipation, diarrhea, and nausea at a rate of 12%, 8%, and 11%, respectively.[27] In our study, because 3 of 28 patients who received iron treatment in the ICU had severe nausea and melena, their treatments were terminated. Gastrointestinal side effects were observed in four of the remaining 25 patients; however, their treatment was continued. We noted that the use of oral iron therapy is associated with frequent gastrointestinal side effects, and this rate was approximately 25% in patients who received iron supplements. This rate was similar to the data in the literature.

This study has limitations. First, we could not evaluate the anemia status and long-term mortality rates of patients after discharge because patient data were obtained from the hospital information system and ICU assessment forms. Second, this was a single-center and retrospective study; therefore, the number of patients included in the study was limited.

Conclusion

Anemia is a common condition among patients in the ICU. Frequent diagnostic blood sampling from patients is one of the most important causes of anemia in hospitalized patients. The frequency of blood transfusion is increasing in patients with prolonged ICU stays. Currently, no consensus exists regarding anemia and transfusion treatment in ICUs. In our study, we noted that oral iron therapy was effective in reducing blood transfusions in patients with prolonged ICU stays. Further studies are warranted to explore the implications in larger patient groups.

Disclosures

Ethics Committee Approval: The study was approved by The Diskapi Yildirim Beyazit Training and Research Hospital Ethics Committee (Date: 10/01/2022, No: 128/17).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

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References

1. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: Evidence for a high rate of unexplained anemia. Blood 2004;104:2263–8.
2. Saraçoğlu A, Gungor Arslan D, Laçin T, Yamansavcı Şirzai E, Batirel H, Fenger-Eriksen C, et al. The effect of preoperative anemia on postoperative morbidity and mortality in patients undergoing thoracic surgery. GKD Anest Yoğ Bak Dern Derg 2020;26:197–203.
3. Ertugay S, Kudsioğlu T, Şen T; Patient Blood Management Study Group Members. Consensus report on patient blood management in cardiac surgery by Turkish Society of Cardiovascular Surgery (TSCVS), Turkish Society of Cardiology (TSC), and Society of Cardio-Vascular-Thoracic Anaesthesia and Intensive Care (SCTAIC). Turk Gogus Kalp Damar Cerrahisi Derg 2019;27:429–50.
4. Lo JO, Benson AE, Martens KL, Hedges MA, McMurry HS, DeLoughery T, et al. The role of oral iron in the treatment of adults with iron deficiency. Eur J Haematol 2023;110:123–30.
5. Stoffel NU, Cercamondi CI, Brittenham G, Zeder C, Geurts-Moespot AJ, Swinkels DW, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: Two open-label, randomised controlled trials. Lancet Haematol 2017;4:e524–33.
6. Brittenham GM. Chapter 36 - Disorders of iron homeostasis: Iron deficiency and overload. In: Hoffman R, Benz EJ, Silberstein LE, Heslop HE, Weitz JI, Anastasi J, et al., editors. Hematology. 7th ed. Amsterdam: Elsevier; 2018. p.478–90.
7. Vincent JL, Baron JF, Reinhart K, Gattinoni L, Thijs L, Webb A, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002;288:1499–507.
8. Kelebek Girgin N, İşçimen R, Hazıroğlu E, Hacıferat N, Özkaya G, Yılmazlar T, et al. Blood loss from diagnostic laboratory tests in critically Ill patients and anemia. J Turk Soc Intens Care 2010;8:61–5.
9. Cankar Dal H, Emir HO, Bayar A, Aysel A, Şirin H, Bayındır Dicle Ç, et al. Analysis of prolonged hospitalizations in tertiary intensive care units. J Cardio-Vasc-Thoracic Anaesth Intens Care Soci 2022;28:269–75.
10. Güler T. Transfusion triggers in cardiac surgery. GKD Anest Yoğ Bak Dern Derg 2012;18:27–45.
11. Leal-Noval SR, Muñoz-Gómez M, Jiménez-Sánchez M, Cayuela A, Leal-Romero M, Puppo-Moreno A, et al. Red blood cell transfusion in non-bleeding critically ill patients with moderate anemia: Is there a benefit? Intensive Care Med 2013;39:445–53.
12. Williams AP, Gettinger A. Transfusion therapy in the intensive care unit. Curr Opin Anaesthesiol 2006;19:127–31.
13. T. C. Sağlık Bakanlığı Sağlık Hizmetleri Genel Müdürlüğü Kan ve Kan Ürünleri Dairesi Başkanlığı. Hasta kan yönetimi rehberi modül 4: Yoğun bakım. In: Cinel İ, Çetin AT, Yenicesu İ, Ertuğrul Örüç N, Tezcan B, editors. Ankara; 2020. Available at: https://dosyamerkez.saglik.gov.tr/Eklenti/44849/0/4-hasta-kan-yonetimi-rehberi-modul-4---yogun-bakimpdf.pdf. Accessed Nov 23, 2023.
14. Shah A, Chester-Jones M, Dutton SJ, Marian IR, Barber VS, Griffith DM, et al. Intravenous iron to treat anaemia following critical care: A multicentre feasibility randomised trial. Br J Anaesth 2022;128:272–82.
15. Powell JJ, Cook WB, Hutchinson C, Tolkien Z, Chatfield M, Pereira DIa, et al. Dietary fortificant iron intake is negatively associated with quality of life in patients with mildly active inflammatory bowel disease. Nutr Metab (Lond) 2013;10:9.
16. Wisser D, van Ackern K, Knoll E, Wisser H, Bertsch T. Blood loss from laboratory tests. Clin Chem 2003;49:1651–5.
17. IRONMAN Investigators; Litton E, Baker S, Erber WN, Farmer S, Ferrier J, et al. Intravenous iron or placebo for anaemia in intensive care: The IRONMAN multicentre randomized blinded trial : A randomized trial of IV iron in critical illness. Intensive Care Med 2016;42:1715–22.
18. Pieracci FM, Henderson P, Rodney JR, Holena DN, Genisca A, Ip I, et al. Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. Surg Infect (Larchmt) 2009;10:9–19.
19. Khalafallah AA, Yan C, Al-Badri R, Robinson E, Kirkby BE, Ingram E, et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: A prospective, open-label, randomised controlled trial. Lancet Haematol 2016;3:e415–25.
20. Froessler B, Palm P, Weber I, Hodyl NA, Singh R, Murphy EM. The important role for intravenous iron in perioperative patient blood management in major abdominal surgery: A randomized controlled trial. Ann Surg 2016;264:41–6.
21. Mei Z, Chen J, Luo S, Jin L, Liu Q, Chen Y. Comparative efficacy of intravenous and oral iron supplements for the treatment of iron deficiency in patients with heart failure: A network meta-analysis of randomized controlled trials. Pharmacol Res 2022;182:106345.
22. Miskulin DC, Tangri N, Bandeen-Roche K, Zhou J, McDermott A, Meyer KB, et al. Intravenous iron exposure and mortality in patients on hemodialysis. Clin J Am Soc Nephrol 2014;9:1930–9.

23. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A. Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Care Med 2000;28:2773–8.
24. Pieracci FM, Stovall RT, Jaouen B, Rodil M, Cappa A, Burlew CC, et al. A multicenter, randomized clinical trial of IV iron supplementation for anemia of traumatic critical illness*. Crit Care Med 2014;42:2048–57.
25. Muñoz M, Acheson AG, Auerbach M, Besser M, Habler O, Kehlet H, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. Anaesthesia 2017;72:233–47.
26. Zdravkovic SC, Nagorni SP, Cojbasic I, Mitic V, Cvetkovic P, Nagorni I, et al. Effects of 6-months of oral ferrous and ferric supplement therapy in patients who were hospitalized for decompensated chronic heart failure. J Int Med Res 2019;47:3179–89.
27. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: A systematic review and meta-analysis. PLoS One 2015;10:e0117383.