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Effect of intraoperative intravenous ferric derisomaltose supplementation on reduction of postoperative anemia and transfusion in chronic kidney disease patients after total knee replacement

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Abstract

Total knee replacement (TKR) is associated with a large amount of bleeding; therefore, the prevalence of postoperative anemia is high. In particular, patients with chronic kidney disease (CKD) are more vulnerable to postoperative anemia than are healthy individuals. Accordingly, the effect of intraoperative intravenous ferric derisomaltose (FDI) supplementation on postoperative anemia and blood transfusion volume reduction in patients with CKD was studied. Patients who underwent unilateral TKR between January 2019 and December 2020 were retrospectively reviewed. In analyzing the data, the patients fell into the CKD group (n = 85) and the non-CKD group (n = 106). Each group was divided into a group using FDI and a non-FDI group, and classified into 4 groups. The postoperative hemoglobin level for each postoperative day (POD) was determined as the primary outcome. In addition, the patient transfusion rate, volume of transfusion, and length of hospital stay were set as secondary study outcomes during the period from surgery to discharge. There was no statistically significant difference in hemoglobin levels on PODs 0, 1, 2, 7, and 14 in the CKD group. In the CKD group, the transfusion volume of the FDI group was 0.58 ± 0.91 units per person, which was statistically significantly lower than 1.28 ± 1.28 units of the non-FDI group (*P* = .01). In the CKD group, the transfusion rate of the FDI group was 30.2%, which was statistically significantly lower than that of the non-FDI group, which was 56.3% (*P* = .02). This study showed that intravenous FDI supplementation after TKR in CKD patients did not reduce postoperative anemia but was an effective and safe treatment to reduce transfusion volume and transfusion rate. There was no statistically significant difference in hemoglobin levels on POD 0, 1, 2, 7, and 14 in the non-CKD group. In the non-CKD group, the transfusion volume of the FDI group was 0.46 ± 0.88 units per person, which was lower than the 0.56 ± 0.91 units of the non-FDI group, but it was not statistically significant (*P* = .59). In the non-CKD group, the transfusion rate of the FDI group was 23.0%, which was lower than that of the non-FDI group, which was 31.3%, but it was not statistically significant (*P* = .37).

Abbreviations: CKD = chronic kidney disease, FDI = ferric derisomaltose, GFR = glomerular filtration rate, POD = postoperative day, TKR = total knee replacement.

Keywords: chronic kidney disease, ferric derisomaltose, intravenous iron supplement, postoperative anemia, retrospective observational study, total knee replacement

1. Introduction

Total knee replacement (TKR) is an effective treatment for osteoarthritis of the knee.[1] TKR is associated with a large amount of bleeding after surgery, which leads to a high prevalence of postoperative anemia.[2,3] The World Health Organization defines anemia as a hemoglobin level of <13 g/dL in men and <12 g/dL in women.[4] Postoperative anemia reduces the quality of life after surgery and improves physiological function.[5] In addition, postoperative anemia increases nosocomial infections, mortality, length of hospital stay, and blood transfusion requirements.[3] The increase in blood transfusions after surgery causes negative problems such as transfusion side effects, infection, and increased medical costs.[2]

Therefore, to improve postoperative anemia, patient blood management is attempted using various methods such as erythropoietin-stimulating agents, iron supplementation, intra- or

postoperative cell salvage, and preoperative autologous blood donation.[3] Among these treatments, iron supplementation has been reported to be helpful in treating postoperative anemia and reducing the transfusion rate, especially in patients with preoperative anemia.[6] Iron supplementation can be used easily with few adverse effects and is also cost-effective. Iron can be administered orally or intravenously and is also available at high and low doses, as required. However, there is little consensus regarding the optimal method and dose of iron supplementation.[7]

In several studies, intravenous iron supplementation for postoperative anemia was found to be more effective than oral administration.[6] In addition, oral iron supplementation causes side effects, such as constipation, if taken for a long time, resulting in low drug compliance.[8] Therefore, intravenous iron supplementation can be considered a good treatment for postoperative anemia.[6]

The TKR prevalence was higher among women than among men and increased with age. The main age group receiving TKR was those in their 60s and 80s.[9] Likewise, the prevalence of chronic kidney disease (CKD) is high among the elderly.[10] CKD is defined as a glomerular filtration rate (GFR) of <60 mL/min/1.73 m², albuminuria of at least 30 mg per 24 hours, or markers of kidney damage (e.g., hematuria or structural abnormalities such as polycystic or dysplastic kidneys) persisting for >3 months.[11] CKD have a high prevalence of anemia due to impaired hematopoietic function.[12,13] Therefore, CKD patients are thought to be more susceptible to anemia after major orthopedic surgeries such as TKR.

Iron supplementation has been shown to be effective in treating anemia in patients with non-surgical CKD.[14] In addition, studies related to the effects of intravenous iron supplementation on postoperative anemia in healthy people have been conducted several times and are known to be effective.[15–18] But studies on intravenous iron supplementation for postoperative anemia in patients with CKD have not been conducted.

Therefore, in this study, the effects and safety of intraoperative intravenous iron on postoperative anemia and blood transfusion reduction in patients with CKD were studied.

2. Method

We retrospectively reviewed the medical records of patients who underwent unilateral TKR at the Seoul Sungsim General Hospital in South Korea from January 2019 to December 2020. This study was conducted in accordance with good clinical practice and the Declaration of Helsinki.

This study was approved by the institutional review board (P01-202201-01-014). The requirement for informed consent was waived by the ethics committee because this retrospective study was limited to pre-existing data from medical records. The identified data were anonymized, and privacy issues were kept confidential.

In the process of selecting study subjects, the following patients were excluded: patients <19 years of age, poor or insufficient medical records, patients undergoing revision surgery, patients under general anesthesia, patients undergoing dialysis, patients with an initial hemoglobin level <10 mg/dL on preoperative examination, patients who received blood transfusion within the month prior to surgery, patients with liver cirrhosis, patients with American Society of Anesthesiologist (ASA) classification IV or higher, patients who underwent reoperation after surgery, and patients with a history of drug allergy.

In all patients, creatinine and hemoglobin levels were measured preoperatively. All patients underwent kidney ultrasonography before surgery. All patients were anesthetized under spinal anesthesia, and all surgeries were performed in the same manner by a team of experienced orthopedic surgeons. After surgery, the patient's hemoglobin level was measured on

operative days (PODs) 0, 1, 2, 7, and 14. A blood transfusion protocol was implemented when the hemoglobin was <8 mg/dL as a result of the measurement. And, no patients underwent autotransfusion. In the group that gave the ferric derisomaltose (FDI) (Monofer®, Pharmacosmos, Denmark), from the time skin was sutured at the end of the operation, 400 mg of FDI was mixed with 100 mL of 0.9% normal saline and injected intravenously for 20 minutes. No additional measures were taken in the non-FDI group. We defined the CKD group as patients with CKD stage 3 or lower with a GFR of 60 mL/min/1.73 m² or less.[19] Non-CKD group was defined as the group with normal renal function of GFR 90 mL/min/1.73 m² or higher. GFR was calculated using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

We analyzed the medical records of 191 patients who underwent unilateral TKR at Seoul Sungsim General Hospital in South Korea between January 2019 and December 2020, excluding those who met the exclusion criteria. In analyzing the data, the patients fell into the CKD group (n = 85) and the non-CKD group (n = 106). Each group was divided into a group using FDI and a non-FDI group, and classified into 4 groups. In the CKD group, 53 and 32 patients were classified into FDI and non-FDI groups, respectively. In the non-CKD group, 74 patients were classified into the FDI group and 32 patients were classified into the non-FDI group.

2.1. Statistical analysis

Patient characteristics and clinical outcome data are presented as the number of patients and the mean ± standard deviation. For continuous variables, the independent t test was used to compare parametric data, and the Mann–Whitney U test was used for nonparametric data. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Statistical significance was set at $P < .05$. Statistical analyses were conducted using SPSS (IBM SPSS Statistics for Windows, Version 26.0, IBM Corp., Armonk, NY, USA). Missing data were excluded from the analyses.

2.2. Objectives and outcome

The postoperative hemoglobin level for each POD was determined as the primary outcome. In addition, the patient transfusion rate, volume of transfusion, and length of hospital stay were set as secondary study outcomes during the period from surgery to discharge. Safety was evaluated by reviewing the medical records related to the side effects of FDI.

3. Results

The CKD and non-CKD groups were first divided, and each group was further divided into the FDI and non-FDI groups. Within the CKD group, there was no statistically significant difference in the demographic characteristics between the FDI and non-FDI groups. Similarly, within the non-CKD group, there was no statistically significant difference in the baseline characteristics between the FDI and non-FDI groups. The baseline characteristics of the patients are presented in Table 1.

There was no statistically significant difference in hemoglobin levels on POD 0, POD 1, POD 2, POD 7, and POD 14 in the CKD group after surgery. Similarly, there was no statistically significant difference in hemoglobin levels on POD 0, POD 1, POD 2, POD 7, and POD 14 in the non-CKD group after surgery (Figs. 1 and 2).

In the CKD group, the transfusion volume of the FDI group was 0.58 ± 0.91 units per person, which was statistically significantly lower than 1.28 ± 1.28 units of the non-FDI group ($P = .01$). In the non-CKD group, the transfusion volume of the FDI group was 0.46 ± 0.88 units per person, which was lower

Baseline characteristics.

Variable	CKD* group (n = 85)			Non-CKD group (n = 106)		
	FDI† group (n = 53)	Non-FDI group (n = 32)	P value	FDI group (n = 74)	Non-FDI group (n = 32)	P value
Age	72.85 ± 6.00	73.94 ± 5.97	.42	67.30 ± 4.82	67.25 ± 5.48	.97
Sex (M/F)‡	6/47	5/27	.57	10/64	5/27	.78
Height (cm)	153.60 ± 6.78	154.91 ± 7.02	.40	154.54 ± 6.20	155.16 ± 7.57	.66
Body weight (kg)	62.47 ± 11.52	62.09 ± 10.12	.88	63.39 ± 14.18	62.66 ± 8.07	.78
Preoperative Hb§ (mg/dL)	13.23 ± 1.10	13.05 ± 1.28	.49	13.72 ± 1.14	13.76 ± 1.09	.87
GFRǁ (mL/min/1.73 m^2)	52.08 ± 7.93	51.43 ± 10.48	.75	96.23 ± 5.52	96.36 ± 5.04	.91
CKD stage (3/4/5)	53/0/0	30/1/1	.07			
ASA PS¶ (I/II/III)	0/44/9	0/24/8	.37	6/57/11	1/26/5	.58
Hypertension	36 (67.9%)	23 (71.9%)	.70	44 (59.5%)	18 (56.3%)	.76
Diabetes mellitus	15 (28.3%)	9 (28.1%)	.99	24 (32.4%)	7 (21.9%)	.27

*Chronic kidney disease.
†Ferric derisomaltose.
‡Male/female.
§Hemoglobin.
ǁGlomerular filtration rate.
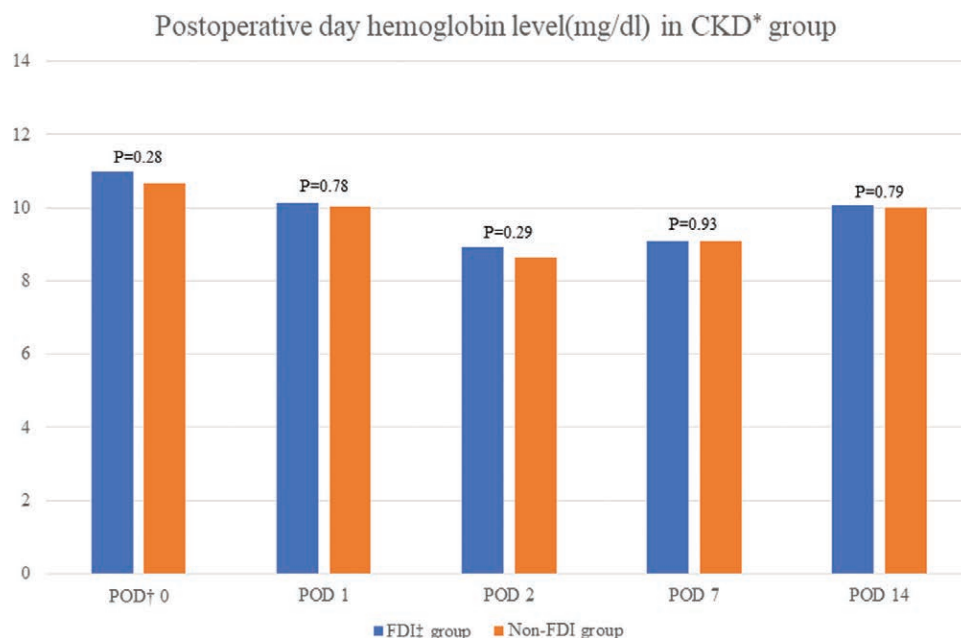¶The American Society of Anesthesiologist physical status.

Figure 1. Within the CKD group, there was no statistically significant difference in postoperative hemoglobin levels between the FDI group and the non-FDI group. *CKD = chronic kidney disease, ‡ FDI = ferric derisomaltose, †POD = postoperative day.

than the 0.56 ± 0.91 units of the non-FDI group, but it was not statistically significant (P = .59), respectively (Fig. 3).

In the CKD group, the transfusion rate of the FDI group was 30.2%, which was statistically significantly lower than that of the non-FDI group, which was 56.3% (P = .02). In the non-CKD group, the transfusion rate of the FDI group was 23.0%, which was lower than that of the non-FDI group, which was 31.3%, but it was not statistically significant (P = .37), respectively (Fig. 4).

In the CKD group, the length of hospital stay was 27.91 ± 7.76 days in the FDI group, which was shorter than the 29.94 ± 8.84 days in the non-FDI group, but it was not statistically significant (P = .27). In the non-CKD group, the length of hospital stay was 25.96 ± 9.32 days in the FDI group, which was shorter than the 26.63 ± 13.93 days in the non-FDI group, but the difference was not statistically significant (P = .77). The above results are detailed in Table 2.

In the CKD group (n = 85), the decrease in the hemoglobin level of POD0 compared to the preoperative hemoglobin level was 2.31 ± 0.77 mg/dL. In the non-CKD group (n = 106), the

decrease in the hemoglobin level of POD0 compared to the preoperative hemoglobin level was 1.90 ± 0.70 mg/dL, which was smaller than that of the CKD group, but there was no statistically significant difference (P = .567).

Regarding the safety evaluation, FDI-related adverse drug events were not reported in any of the patients.

4. Discussion

Major orthopedic surgeries, such as TKR, involve a large amount of bleeding during and after surgery.[2,3] TKR patients are susceptible to postoperative anemia. Postoperative anemia has negative effects such as increased infection, decreased physiological function, and extended length of hospital stay. This can lead to blood transfusion.[3] Therefore, medical efforts, such as patient blood management, are being made to prevent postoperative anemia, but the protocol has not been fully established, and the prevalence of postoperative anemia is still high.[3] Various methods for patient blood management are being implemented
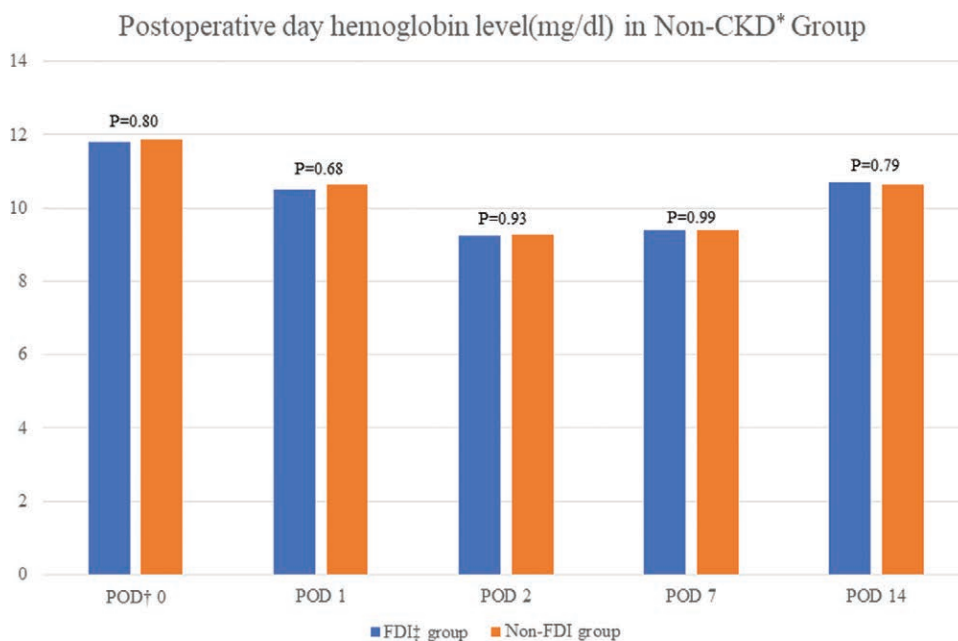
Postoperative day hemoglobin level(mg/dl) in Non-CKD* Group

Figure 2. Within the non-CKD group, there was no statistically significant difference in postoperative hemoglobin levels between the FDI group and the non-FDI group. *CKD = chronic kidney disease, ‡ FDI = ferric derisomaltose, †POD = postoperative day.
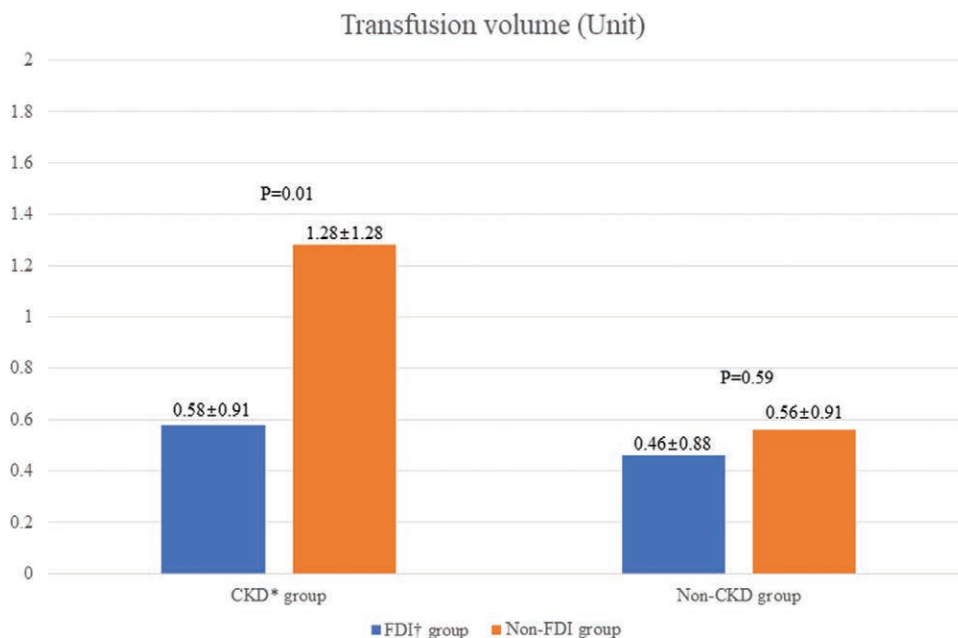
Transfusion volume (Unit)

Figure 3. Blood transfusion volume for each group. *CKD = chronic kidney disease, †FDI = ferric derisomaltose.

in clinical practice, including measurement of anemia before surgery, use of erythropoietin-stimulating agents, cell salvage during or after surgery, preoperative autologous blood transfusion, and iron supplementation.[3,20]

FDI is composed of iron and chemically modified iso-malto-oligosaccharides that have a mean molecular weight of 1000 Da and predominantly consist of 3–5 glucose units. Unlike conventional dextran, dextran has low immunological potential as a linear unbranched structure.[21] The strong binding of iron in the FDI state enables the release of iron at a slower rate, lowering the risk of iron toxicity, thus eliminating the need for a preinjection test dose.[22] This allows flexible dosing, including high and rapid dosing, securing convenient iron therapy for a wide range of patients, including CKD patients.

Several studies on the effects of FDI on postoperative anemia in healthy subjects have been conducted in various surgeries and situations. Existing studies on the effects of FDI on postoperative anemia have mainly been conducted in healthy individuals.[15–18] Studies have shown that iron supplementation in CKD patients is effective in non-surgical situations,[14] but to our knowledge, there are no studies on the effect of iron supplementation on postoperative anemia in patients with CKD.

Patients with CKD have a higher prevalence of anemia than healthy individuals.[23] This is because the kidney is responsible for producing erythropoietin, which stimulates the production of red blood cells. Chronic inflammation, iron deficiency, and the accumulation of uremic toxins may contribute to the development of anemia in patients with CKD.[24] When
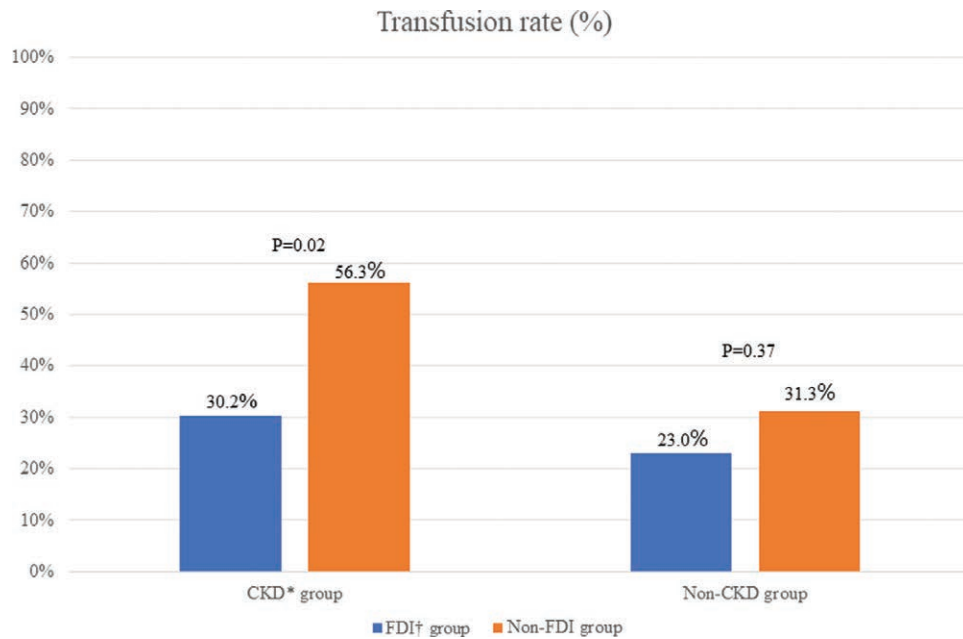
Figure 4. Blood transfusion rate for each group. *CKD = chronic kidney disease, †FDI = ferric derisomaltose.

Table 2

Clinical outcomes.

Variable	CKD* group (n = 85)			Non-CKD group (n = 106)		
	FDI† group (n = 53)	Non-FDI group (n = 32)	P value	FDI group (n = 74)	Non-FDI group (n = 32)	P value
POD‡0 Hb§ (mg/dL)	10.98 ± 1.27	10.66 ± 1.33	.28	11.82 ± 1.23	11.88 ± 1.27	.80
POD 1 Hb (mg/dL)	10.12 ± 1.26	10.04 ± 1.41	.78	10.52 ± 1.26	10.63 ± 1.17	.68
POD 2 Hb (mg/dL)	8.93 ± 1.09	8.66 ± 1.25	.29	9.26 ± 1.45	9.28 ± 1.29	.93
POD 7 Hb (mg/dL)	9.09 ± 1.20	9.08 ± 1.18	.93	9.40 ± 1.24	9.40 ± 1.20	.99
POD 14 Hb (mg/dL)	10.08 ± 1.01	10.02 ± 1.07	.79	10.70 ± 0.99	10.64 ± 1.03	.79
Transfusion rate	16 (30.2%)	18 (56.3%)	.02	17 (23.0%)	10 (31.3%)	.37
Transfusion volume (unit)	0.58 ± 0.91	1.28 ± 1.28	.01	0.46 ± 0.88	0.56 ± 0.91	.59
Length of hospital stays (days)	27.91 ± 7.76	29.94 ± 8.84	.27	25.96 ± 9.32	26.63 ± 13.93	.77

*Chronic kidney disease.
†Ferric derisomaltose.
‡Postoperative day.
§Hemoglobin.

surgical bleeding occurs, hematopoietic function is activated as a compensatory mechanism. With intravenous iron supplementation, hematopoietic function was further activated within 1 week. This may reduce the incidence of postoperative anemia.[25]

In patients with CKD, platelet function is insufficient and platelet-vascular interaction related to coagulation is decreased, so the risk of bleeding is increased in patients with CKD. Patients with CKD are vulnerable to postoperative anemia.[26] In this result, the decrease in hemoglobin level between the preoperative day and POD0 was also greater. However, it was not statistically significant. We studied the efficacy and safety of FDI for postoperative anemia by retrospectively analyzing medical records. In this study, we found that intravenous FDI administration during surgery had no effect on changes in hemoglobin levels in CKD and non-CKD patients. In the non-CKD group, intraoperative intravenous FDI supplementation resulted in lower transfusion volume and transfusion rate, but the difference was not statistically significant. However, in the CKD group, intraoperative intravenous FDI supplementation was significantly effective in reducing the transfusion volume and transfusion rate.

There were no significant differences in hemoglobin levels according to FDI use in patients with CKD. However, there was

a significant effect in terms of the blood transfusion volume and transfusion rate. There was no significant difference in hemoglobin levels between the FDI and non-FDI groups despite fewer transfusions, indicating that FDI is effective for postoperative anemia. Regarding the safety evaluation, FDI-related adverse drug events were not reported in any of the patients.

However, this study has several limitations. First, this study was a retrospective study and the number of subjects was small. And the lack of data on the iron status of the subjects has insufficient adequacy of IV iron supplement. In this regard, we believe that a prospective study with a larger sample size including data on iron status is needed.

Second, erythropoietin-stimulating agents would activate the production of hemoglobin so indirectly increase the hemoglobin level after surgery.[27] However, it was not possible to accurately evaluate the use of erythropoietin-stimulating agents in medical records because of insufficient records. Therefore, there is a limitation to whether the use of erythropoietin-stimulating agents affects the research results.

Third, in patients with CKD, FDI at 1000 mg was more effective than at 400 mg.[28] However, all patients in this study who received FDI were administered 400 mg of FDI. Therefore, more research is needed to determine the optimal injection dose.

Fourth, transfusion itself has the effect of increasing hemoglobin levels.[29] In this study, the effects of differences in transfusion rate and transfusion volume on hemoglobin levels were not considered. In the CKD group, transfusion volume was significantly higher in the non-FDI group (1.28 ± 1.28 units) than in the FDI group (0.58 ± 0.91 units). This may have affected the hemoglobin levels. Therefore, the hemoglobin levels in the CKD group may have been overestimated compared to those in the non-CKD group.

5. Conclusion

In conclusion, this study showed that intraoperative intravenous FDI supplementation is an effective and safe treatment method for reducing the transfusion volume and transfusion rate after TKR in patients with CKD.

Author contributions

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Writing – review & editing: Jae Hyun Kwon.

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