Systematic Review and Meta-Analysis

Medicine

OPEN

Effects of intraoperative or postoperative administration of intravenous iron supplements on hemoglobin recovery in patients with total knee arthroplasty

A systematic review and meta-analysis

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Abstracts

Background: The objectives of the researchers are as follows: First, to investigate whether intraoperative or postoperative administration of Intravenous (IV) iron supplements in patients undergoing primary total knee arthroplasty (TKA) can contribute to the hemoglobin recovery during the postoperative period (between 4 and 8 weeks after surgery). Second, to examine whether the administration of IV iron supplements during or immediately after TKA in patients undergoing primary TKA can reduce the need for allogenic blood transfusion during hospitalization.

Methods: Articles published between January 1, 1990, and June 30, 2023 were searched in PubMed, Cochrane, and Embase. The population, intervention, comparison, and outcome of this study are as follows; Population: Patients undergoing primary total knee arthroplasty; Intervention: Administration of IV iron supplements during or immediately after surgery; Comparison: Non-administration of IV iron supplements; Outcome: Degree of hemoglobin recovery (between 4 and 8 weeks after surgery) and the need for blood transfusion during hospitalization.

Results: There was a statistically significant difference in the amount of change in hemoglobin between iron supplementation group and non-iron supplementation group. The effect size were –0.44 (95% confidence interval: –0.69 to –0.19, *P* value < .001) in all patients. This means that the amount of change in hemoglobin were significantly reduced in the iron supplementation group than in the non-iron supplementation group. There was a statistically significant difference for post-operative transfusion rate between 2 groups. The effect size were 0.28 (95% confidence interval: 0.10–0.81, *P* value = .02) in all patients. This means that the post-operative transfusion rate was significantly less in the iron supplementation group than in the non-iron supplementation group

Conclusion: The administration of IV iron supplements during or after TKA surgery increases hemoglobin recovery between 4 and 8 weeks after surgery and reduces the need for allogeneic blood transfusion during hospitalization.

Abbreviations: CI = confidence interval, IV = Intravenous, TKA = total knee arthroplasty.

Keywords: total knee arthroplasty, iron, hemoglobin, transfusion

1. Introduction

Total knee arthroplasty (TKA) is one of the surgeries associated with high blood loss.[1] The frequency of allogeneic blood transfusion after surgery among different institutions varies from 3% to 69%.[2,3] Surgeons performing TKA make various efforts to reduce blood transfusions and minimize their associated complications.[4] One method of reducing allogenic blood transfusions is by promoting the recovery of hemoglobin levels in patients. The administration of intravenous (IV) iron supplements is one of the commonly used approaches to enhance hemoglobin recovery.[5,6] Traditionally, IV iron

This research was supported by a grant of Daegu Catholic Medical University Student Research Program (2023).

The authors have no funding and conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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How to cite this article: Kwak SG, Kwon JB, Bae JW, Bae DJ, Kim DK, Choi W-K. Effects of intraoperative or postoperative administration of intravenous iron supplements on hemoglobin recovery in patients with total knee arthroplasty: A systematic review and meta-analysis. Medicine 2023;102:43(e35744).

Received: 30 July 2023 / Received in final form: 20 September 2023 / Accepted: 29 September 2023

http://dx.doi.org/10.1097/MD.0000000000035744

supplements are administered in the outpatient setting before surgery, as it takes approximately 2 weeks for hemoglobin levels to recover.[7–9] Previous studies have investigated the effects of preoperative IV iron supplementation on hemoglobin recovery.[10] However, due to the difficulty of additional outpatient visits for IV iron supplementation, there has been an increasing trend in administering IV iron supplements during or immediately after TKA, and research results on this approach have also been reported.

Therefore, the authors aim to analyze the existing research on whether intraoperative or postoperative administration of IV iron supplements can facilitate hemoglobin recovery and reduce the need for blood transfusion in patients undergoing primary TKA.

The objectives of the researchers are as follows: First, to investigate whether intraoperative or postoperative administration of IV iron supplements in patients undergoing primary TKA can contribute to the hemoglobin recovery during the postoperative period (between 4 and 8 weeks after surgery). Second, to examine whether the administration of IV iron supplements during or immediately after TKA in patients undergoing primary TKA can reduce the need for allogenic blood transfusion during hospitalization.

2. Methods

This study is not a clinical study for humans, a protocol for obtaining IRB approval has not been written. However, the protocol necessary to carry out this study was written, and the contents of the protocol were described throughout the paper. We have registered on the International prospective register of systematic reviews site (https://www.crd.york.ac.uk/PROSPERO/) and the ID is 448010.

2.1. Search strategy

The population, intervention, comparison, and outcome of this study are as follows.

(1) Population: Patients undergoing primary total knee arthroplasty.
(2) Intervention: Administration of IV iron supplements during or immediately after surgery.
(3) Comparison: Non-administration of IV iron supplements.
(4) Outcome: Degree of hemoglobin recovery (between 4 and 8 weeks after surgery) and the need for blood transfusion during hospitalization.

Articles published between January 1, 1990, and June 30, 2023 were searched in PubMed, Cochrane, and Embase using the following key phrases (Table 1).

2.2. Inclusion and exclusion criteria

The following studies were included in this study:

(1) Studies involving patients undergoing primary total knee arthroplasty and receiving intraoperative or postoperative administration of IV iron supplements.
(2) Studies comparing the intervention group (administration of IV iron supplements during or immediately after surgery) with a control group (no administration of IV iron supplements).
(3) Studies written in English.

The exclusion criteria were as follows:

(1) Review articles, case reports, protocols, and conference presentations.
(2) Studies involving patients undergoing primary total knee arthroplasty who received preoperative administration of IV iron supplements.

Table 1

Articles were searched in PubMed using the following key phrases.

Pubmed; search on July 1, 2023	
Search	**Query**
#1	"Total knee arthroplasty" [Ti/Ab] or "Total knee replacement" [Ti/Ab] or "Arthroplasty" [Ti/Ab]
#2	"Ferrous" [Ti/Ab] or "Ferric" [Ti/Ab] or "Iron" [Ti/Ab]
#3	#1 and # 2

2.3. Data extraction

Data for meta-analysis were independently investigated by 2 researchers (W.K.C. and S.G.K.). Duplicate studies were excluded, and studies that met the eligibility criteria were selected. Studies were evaluated for eligibility by reviewing the title and abstract. After reading the full-text, studies were finally selected for inclusion in the meta-analysis, and discrepancies were resolved through discussion. Study design, intervention, treatment timing, number of patients (intervention and control groups), operation, outcome measurements and time of hemoglobin measurements were investigated.

Outcome variables were the degree of hemoglobin recovery after surgery (between 4 and 8 weeks after surgery) and the presence or absence of blood transfusion during hospitalization. We collected the values of the evaluation variables such as the degree of hemoglobin recovery after surgery (4–8 weeks after surgery) and the presence or absence of blood transfusion presented in the paper according to the evaluation time points. Then, the amount of change from pre-operation to 4 to 8 weeks after surgery calculated. Since this corresponds to the amount of change in the dependent group, the mean value and standard deviation for change between pre-operation and post-operation were calculated using the following formulas and the correlation was derived from different study which presented the standard deviation for change.

$$Mean_{change} = Mean_{pre-op} - Mean_{post-op}.$$

$$SD_{change} = \sqrt{SD^2_{pre-op} + SD^2_{post-op} - 2 \times Correlation \times SD_{pre-op} \times SD_{post-op}}.$$

In some papers, while presenting an analysis using the data of the entire subject, at the same time, the results of the analysis using the data of patients with anemia and patients without anemia as a subgroup analysis were presented. Subgroup analysis results according to anemia were also collected.

2.4. Quality assessment

The quality assessment of risk of bias for the included studies was assessed using the Cochrane Collaboration's Handbook for randomized controlled trials. It was consisted of random sequence generation, allocation concealment, blinding of participants, incomplete outcome data, selective reporting, and other potential sources of bias. The judgments of bias were expressed as "low risk," "high risk," or "unclear risk." Quality assessment for retrospective studies was performed using the Newcastle–Ottawa quality assessment scale.[11] It was consisted of selection, comparability and exposure. The questions in the selection part are composed of; Is case definition adequate; Representativeness of the cases; Selection of controls, and; Definition of controls, and each item can be evaluated with 1 star. The question in the comparability section is; Comparability of cases and controls on

the basis of the design or analysis and can be rated up to 2 stars. The questions in the exposure part consist of; Ascertainment of exposure; Same method of ascertainment for cases and controls, and; Nonresponse rate, and each question can be evaluated with 1 star. The Newcastle–Ottawa quality assessment scale can be evaluated by a total of 8 items and up to 9 stars.

2.5. Statistical analysis

RevMan v.5.3 software (http://tech.cochrane.org/revman) was used for statistical analysis of the pooled data. For each analysis, a heterogeneity test was performed using I^2 statistics, which measures the extent of inconsistency among results. P values of < .05 were considered as having substantial heterogeneity, and the random-effects model was used for analysis of the data. In contrast, when P values were ≥ .05, pooled data was homogenous, and the fixed effects model was applied. We analyzed the mean difference between iron supplementation and non-iron supplementation. Further, the 95% confidence interval (CI) was used in the analysis. The effect size was calculated using mean difference for hemoglobin recovery and odds ratio for blood transfusion. For the evaluation of publication bias, the funnel plot and the egger test were used. P value < .05 was considered statistically significant. For sensitivity analysis, RMSE (Root Mean Square Error) was calculated by using the effect size and total effect size calculated for each evaluation variable except for the I-th study. For RMSE calculation, the following formula was used.

$$RMSE = \sqrt{\frac{1}{k}\sum_{i=1}^{k}\left(Total\ effect\ size - \quad Total\ effect\ size_{(i)}\right)^2}$$

For RMSE, closer to 0 means that the overall effect size is not sensitive to the study, and larger value means that the overall effect size is sensitive to the study.

3. Results

In the databases, 526 articles were searched, and 187 duplicated articles were removed (Fig. 1). After screening for

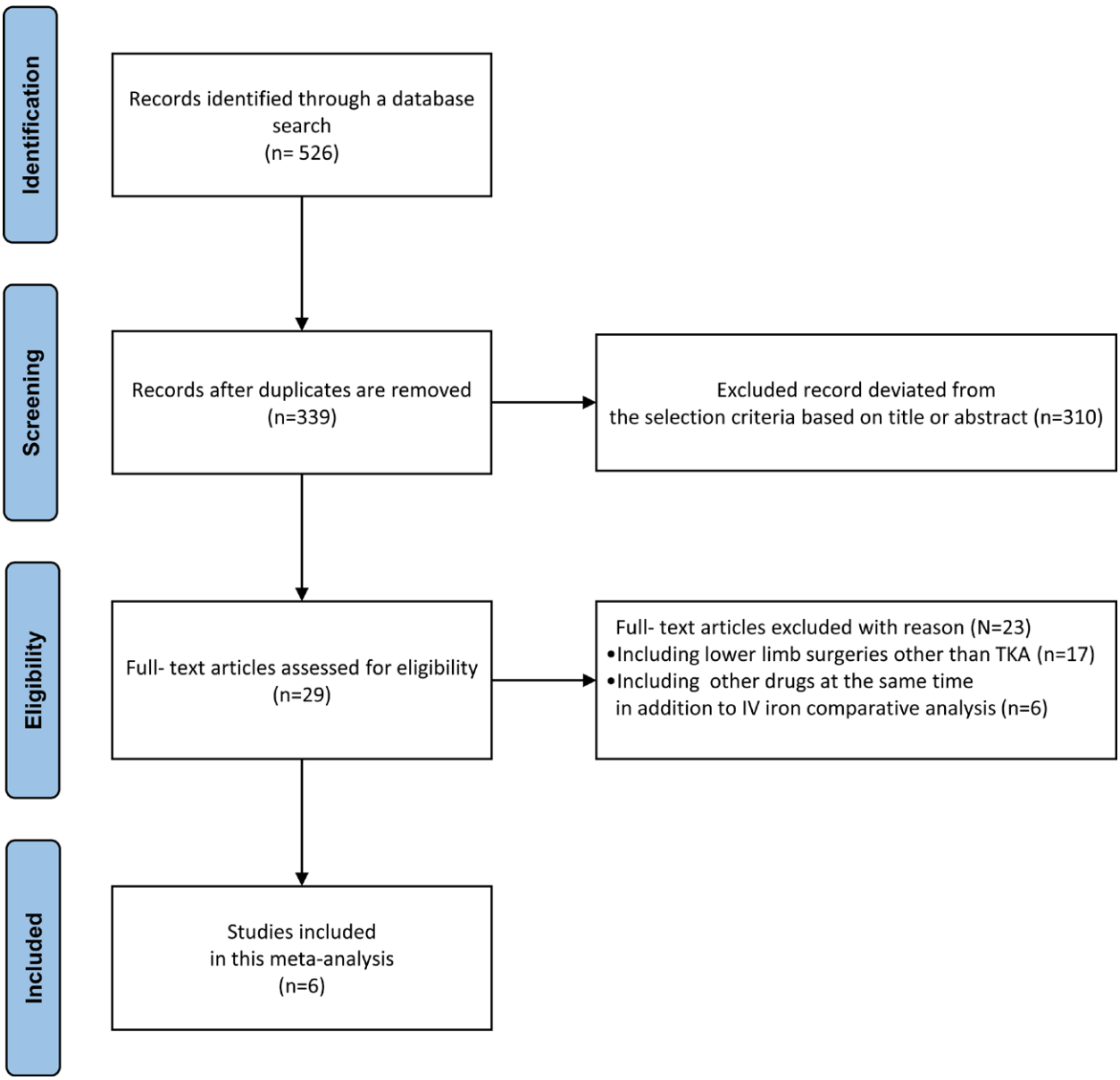

Figure 1. Flowchart showing the search results.

eligibility based on a review of the title and abstract, 29 articles were included for full-text reading. After a detailed assessment, 23 articles were excluded: 17 articles Included lower limb surgery other than TKA, and 6 articles included studies that used other drugs at the same time in addition to IV iron in the comparative analysis. Accordingly, 6 studies were finally included in our meta-analysis.[5,6,12–15] The characteristics of the studies included in the research also described in Table 2.

3.1. Study characteristics

As a result of reviewing title and abstracts, 2 RCT studies and 4 retrospective case-control studies were included. In the 6 studies, 784 participants for iron supplementation and 688 participants for non-iron supplementation. In all 6 studies, measurement of treatment effect was performed at 4 to 8 weeks after surgery. There were 6 studies measuring Hgb and 5 studies measuring the post-operative transfusion rate.

3.2. Quality assessment

The results of a quality assessment using Newcastle–Ottawa quality assessment scale and Cochrane collaboration's handbook were presented in Table 3. Park et al (2021), Park et al (2022), Mamiar et al (2022), and Lee et al (2023) were case-control studies. Therefore, 4 studies were assessed using NOS. All then were rated 8 stars, which is considered as relatively high quality (selection: 4 stars; comparability: 2 stars; exposure: 2 stars). However, none of them mentioned a "nonresponse rate". Yoo et al (2021) and Choi et al (2022) were randomized controlled trials. Therefore, 2 studies were assessed the risk of bias based on the using and Cochrane collaboration's handbook. These studies had low-risk of bias for random sequence generation,

Table 2

Six studies were finally included in our meta-analysis.

Reference	Study design	Intervention	Treatment timing	Number of patients (Intervention/control)	OP	Outcome measurements	Transfusion indication	Time and number of Hgb measurements
Park et al (2021)[14]	Retrospective (propensity score matching)	FCM 1000mg	1 h after OP	231/231	Primary unilateral TKA	Hgb Post OP transfusion rate	Hgb < 8 g/dL or acute anemia symptoms	Pre OP POW 5
Yoo et al (2021)[15]	RCT	Iron isomaltoside	Intra OP	44/45	Primary unilateral TKA	Hgb Post OP transfusion rate	Hgb < 8 g/dL or acute anemia symptoms	Pre OP POD 30
Park et al (2022)[6]	Retrospective	FCM 1000mg	1 h after OP	78/53	Staged bilateral TKA (1 week interval)	Hgb Post OP transfusion rate	Hgb < 8 g/dL or acute anemia symptoms	Pre OP POW 5
Maniar et al (2022)[13]	Retrospective	FCM 500mg	1 d after OP	157/106	Primary unilateral TKA	Hgb		Pre OP POW 5 (+1)
Choi et al (2022)[5]	RCT	FCM 1000mg (body weight ≥ 50 kg) FCM 500mg (body weight < 50 kg)	3 d after OP	54/55	Primary unilateral TKA	Hgb Post OP transfusion rate	Hgb < 7g/dL or acute anemia symptoms	Pre OP POW 4 POW 8
Lee et al (2023)[12]	Retrospective	Iron isomaltoside 400 mg	2 h after OP	220/198	Staged bilateral TKA (1 week interval)	Hgb Post OP transfusion rate	Iron group: Abnormal vital signs Non-Iron group: Low Hgb	Pre OP POW 6

FCM = ferric carboxymaltose, Hgb = hemoglobin, OP = operation, POD = post operative day, POW = post operative week, TKA = total knee arthroplasty.

Table 3

Quality assessment using Newcastle–Ottawa quality assessment scale and Cochrane collaboration's handbook.

		Selection				Comparability	Exposure			
	Quality criteria	Is case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability on basis of design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate	Total
Case-Control Studies	Park et al (2021)[14]	★	★	★	★	★★	★	★	☆	8
	Park et al (2022)[6]	★	★	★	★	★★	★	★	☆	8
	Maniar et al (2022)[13]	★	★	★	★	★★	★	★	☆	8
	Lee et al (2023)[12]	★	★	★	★	★★	★	★	☆	8
RCT	Quality criteria	Random sequence generation		Allocation concealment		Blinding of participants	Incomplete outcome data		Selective reporting	
	Yoo et al (2021)[15]	Low-risk		low-risk		Low-risk	Low-risk		Low-risk	
	Choi et al (2022)[5]	Low-risk		Unclear risk		Low-risk	Low-risk		Low-risk	

allocation concealment, blinding of participants, incomplete outcome data and selective reporting.

3.3. Meta-analysis results

In performing meta-analysis, a fixed effect model was used when the *P* value was > .05 as a result of the homogeneity test, and a random effect model was used when the *P* value was < .05.

Mean difference and 95% confidence interval were presented in the forest plot for change in hemoglobin from pre-operation to 4 to 8 week between iron supplementation group and non-iron supplementation group (Fig. 2). There was a statistically significant difference in the amount of change in hemoglobin between iron supplementation group and non-iron supplementation group. The effect size were –0.44 (95% CI: –0.69 to –0.19, *P* value < .001) in all patients. This means that the amount of change in hemoglobin were significantly reduced in the iron supplementation group than in the non-iron supplementation group. However, in the subgroup analysis, there was no statistically significant difference in the amount of change in hemoglobin between iron supplementation group and non-iron supplementation group. The effect size were –0.33 (95% CI: –1.23 to 0.56, *P* value = .46) in patients with preoperative anemia and -0.30 (95% CI: –0.90 to 0.30, *P* value = 0.32) in patients without preoperative anemia.

Odd ratio and 95% confidence interval were presented in the forest plot for post-operation transfusion between iron supplementation group and non-iron supplementation group (Fig. 3). There was a statistically significant difference for post-operative transfusion rate between 2 groups. The effect size were 0.28 (95% CI: 0.10–0.81, *P* value = .02) in all patients. This means that the post-operative transfusion rate was significantly less in the iron supplementation group than in the non-iron supplementation group. In the subgroup analysis, there was statistically significant difference for post-operative transfusion rate between 2 groups. The effect size were 0.34 (95% CI: 0.16–0.71, *P* value = .004) in patients with preoperative anemia, 0.06 (95% CI: 0.03–0.13, *P* value < .001) in patients without preoperative anemia and 0.13 (95% CI: 0.08–0.21, *P* value < .001) in patients with staged bilateral TKA operation.

3.4. Sensitivity analysis

For change in hemoglobin from pre-operation to 4 to 8 week, the RMSE were calculated as 0.055 in all patients, 0.471 in patients with preoperative anemia and 0.139 in patients without preoperative anemia. For post-operation transfusion, the RMSE were calculated as 0.076 in all patients, 0.077 in patients with preoperative anemia, 0.058 in patients without preoperative anemia. RMSE were not calculated when there were only 2 studies. RMSE values in all cases were calculated to be < 0.5. It can be seen that the overall effect size is not sensitive depending on the study.

3.5. Publication bias

On the basis of a few distinct methods, 2 of the authors (W.K.C. and S.G.K.) individually assessed the publication bias. The publication bias was determined using a funnel plot and the Egger test. A funnel plot was produced to investigate the risk of publication bias. All funnel plots seemed to be symmetrical (Fig. 4). In addition, the publication bias was quantified using Egger test. The *P* value of Egger test were .774 for change in hemoglobin from pre-operation

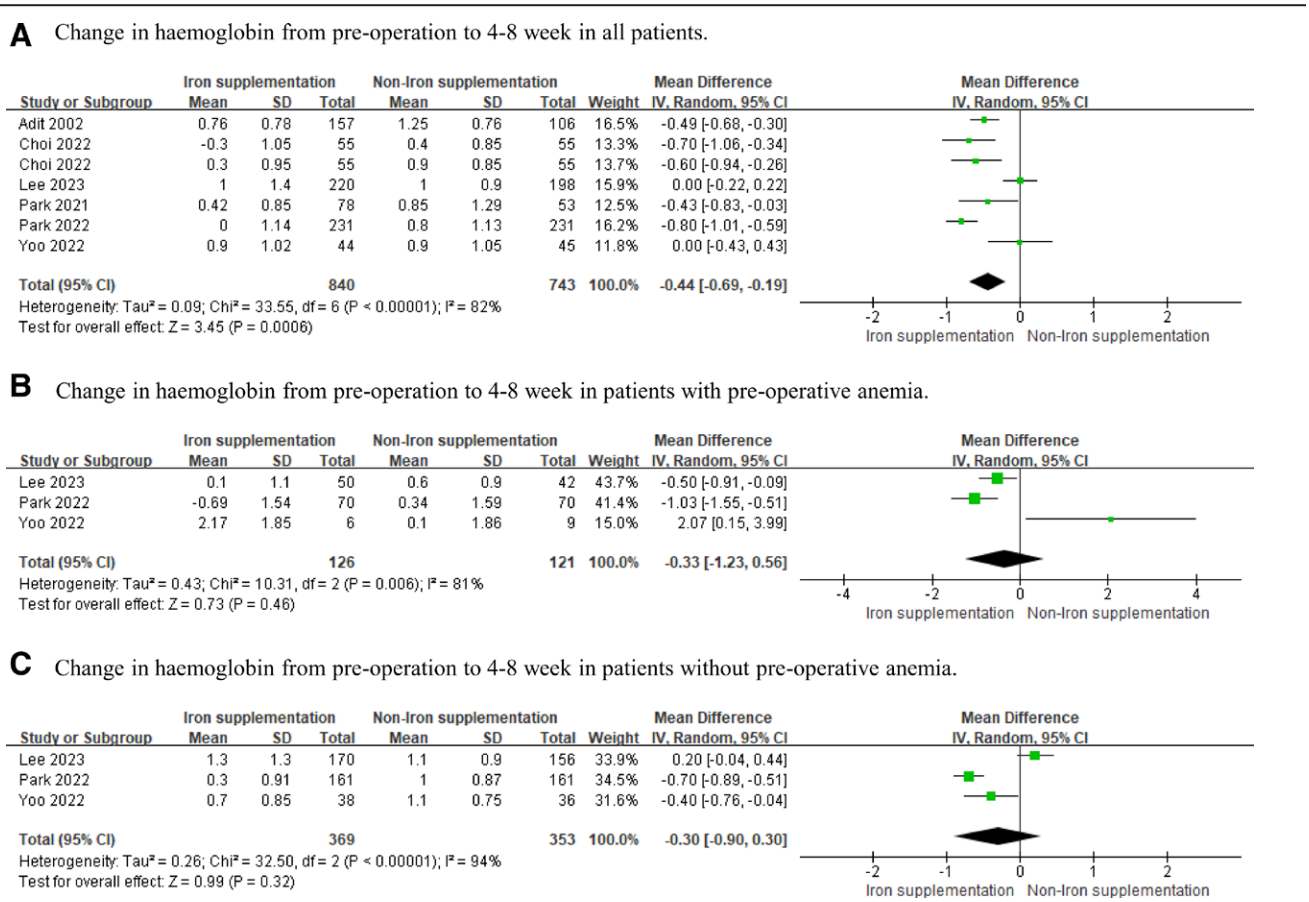

Figure 2. Forest plots for change in hemoglobin from pre-operation to 4–8 week between iron supplementation group and non-iron supplementation group (A) in all patients, (B) in patients with anemia, and (C) in patients without anemia.

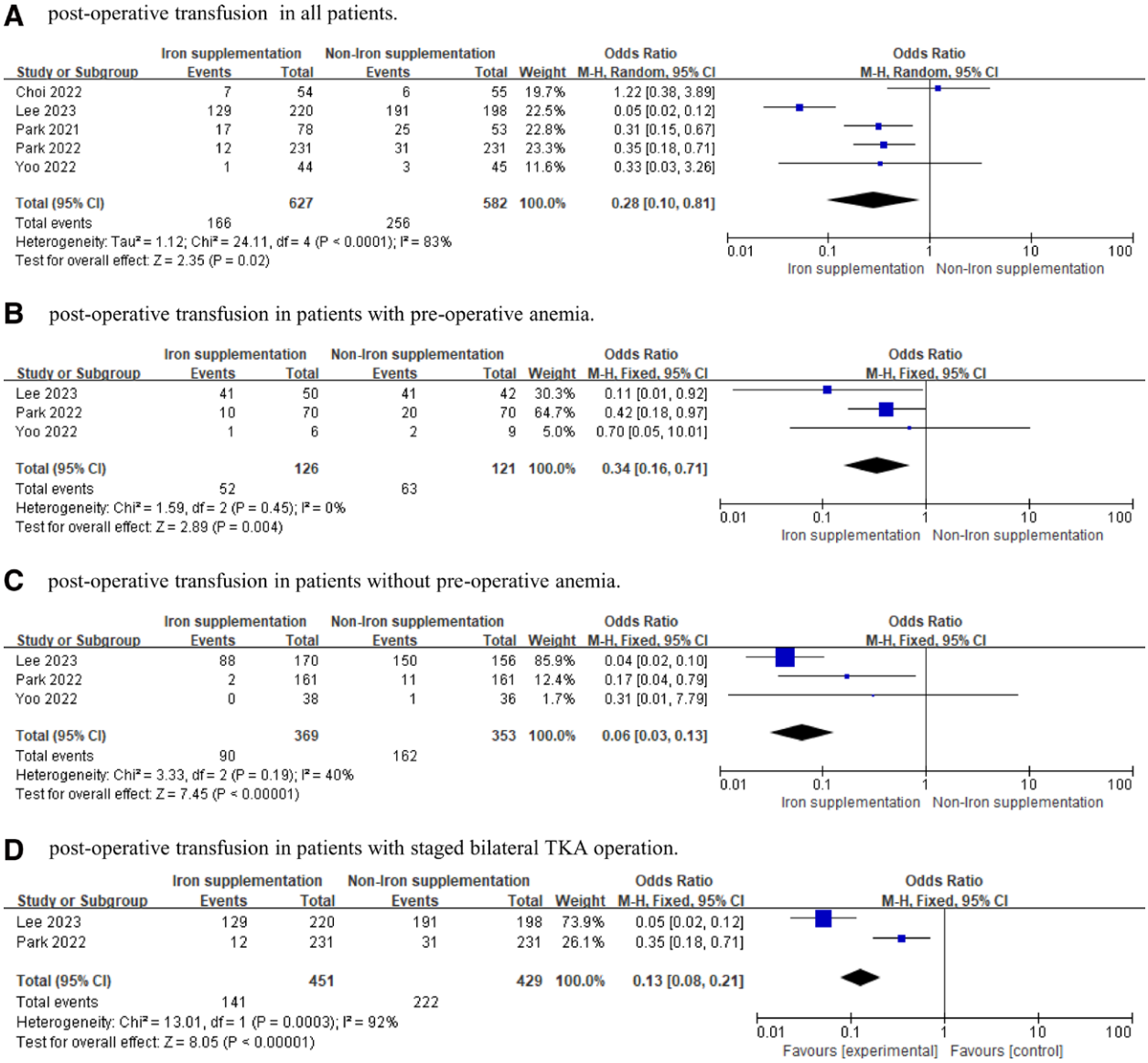

Figure 3. Forest plots for post-operative transfusion between iron supplementation group and non-iron supplementation group (A) in all patients, (B) in patients with anemia, (C) in patients without anemia, and (D) in patients with staged bilateral TKA operation. TKA = total knee arthroplasty.

to 4 to 8 week and 0.192 for post-operative transfusion. Therefore, statistically significant publication bias was unlikely to occur.

4. Discussion

Meta-analyses on the effects of intraoperative or postoperative administration of IV iron supplements during orthopedic surgery, including TKA, have been previously published.[16–18] However, most of these studies included not only TKA but also other hip joint surgeries, such as hip arthroplasty or hip fracture.[19] Additionally, previous meta-analyses analyzed studies that included various time points for IV iron supplementation, including preoperative, intraoperative, and postoperative administration.[16,17] Generally, it is known that hemoglobin recovery takes about 2 weeks after IV iron supplementation, therefore preoperative administration of IV iron supplements in outpatient setting is commonly considered effective.[9] However, due to practical limitations in additional outpatient visits for IV iron supplementation, recent practice has seen an increase in intraoperative or postoperative administration of IV iron supplements in patients undergoing TKA. For this reason, the authors of this study aimed to analyze the effects of intraoperative or postoperative IV iron supplementation, excluding preoperative administration, in patients undergoing primary TKA.

The following are the findings revealed through the analysis:

First, in patients undergoing primary TKA, the administration of IV iron supplements during or after surgery showed faster hemoglobin recovery between 4 and 8 weeks after surgery compared to the group without IV iron supplementation. This period, 4 and 8 weeks after surgery, is characterized by rehabilitation for improved knee movement and recovery of decreased muscle strength. Rapid hemoglobin recovery after surgery is known to aid in functional recovery and reduce the length of hospital stay.[20,21] Additionally, rapid hemoglobin recovery after surgery promotes general well-being, facilitating wound healing and early rehabilitation.[18]

Second, in patients undergoing primary TKA, the group receiving intraoperative or postoperative IV iron supplementation showed a lower frequency of allogeneic blood transfusion after surgery compared to the control group. Previous studies have reported adverse effects associated with allogeneic blood transfusion after TKA, including impaired functional recovery

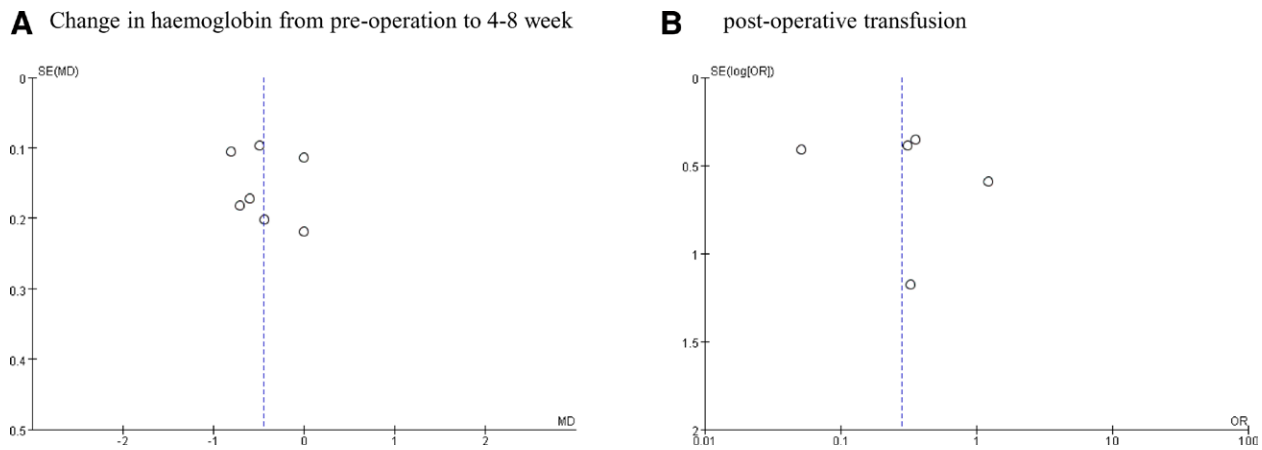

Figure 4. Funnel plots for (A) change in hemoglobin from pre-operation to 4–8 week and (B) post-operative transfusion between iron supplementation group and non-iron supplementation group.

and increased risk of infection.[22,23] Ryan et al[24] found that a hemoglobin level below 12.5 g/dL has increased the risk of allogeneic blood transfusion after TKA. Pierson et al[25] reported an average decrease of 3.8 g/dL in hemoglobin levels after TKA. In this study, the analysis was based on a transfusion threshold of hemoglobin levels below 8 g/dL or 7 g/dL. Therefore, patients with hemoglobin levels below 12.5 g/dL, as suggested by Ryan et al, would require allogeneic blood transfusion in the absence of specific measures to improve hemoglobin recovery. The subjects of the 6 studies included in the analysis were all patients undergoing total knee arthroplasty, regardless of the presence or absence of anemia. Considering that surgical inflammation caused by TKA induces functional iron deficiency,[26] which is mediated by increased hepcidin during the postoperative period,[27] even patients without preoperative anemia may experience a decrease in hemoglobin levels due to the substantial blood loss and increased hepcidin levels after TKA. Therefore, analyzing the decrease in hemoglobin levels in all patients, regardless of preoperative anemia, is appropriate.

Among the 6 studies included in the analysis, 2 studies investigated staged TKA instead of unilateral TKA. In both studies, bilateral TKA was performed sequentially with a 1-week interval. Considering the time required for hemoglobin recovery after surgery, sequential bilateral TKA with a 1-week interval carries a higher risk of blood transfusion during the hospital stay compared to unilateral TKA. The analysis of the 2 studies on sequential bilateral TKA demonstrated a statistically significant lower frequency of allogeneic blood transfusion in the group receiving intraoperative or postoperative IV iron supplementation.

The limitations of this study are as follows: First, there were variations in the composition and dosage of IV iron supplements used in the studies. Secondly, different indications for blood transfusion were applied in each facilities. Thirdly, 2 out of the 6 studies included in the analysis involved sequential bilateral TKA with a 1-week interval.

5. Conclusion

The administration of IV iron supplements during or after TKA surgery increases hemoglobin recovery between 4 and 8 weeks after surgery and reduces the need for allogeneic blood transfusion during hospitalization.

Author contributions

Conceptualization: Jin Woo Bae, Dong Jin Bae, Dong Kun Kim, Won Kee Choi.
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Investigation: Jae Bum Kwon, Dong Jin Bae, Dong Kun Kim, Won Kee Choi.
Methodology: Jin Woo Bae, Won Kee Choi.
Project administration: Won Kee Choi.
Resources: Won Kee Choi.
Software: Won Kee Choi.
Supervision: Sang Gyu Kwak, Won Kee Choi.
Validation: Jin Woo Bae, Won Kee Choi.
Visualization: Jin Woo Bae, Dong Kun Kim, Won Kee Choi.
Writing – original draft: Sang Gyu Kwak, Jae Bum Kwon, Dong Jin Bae, Dong Kun Kim, Won Kee Choi
Writing – review & editing: Won Kee Choi.

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