Intravenous Iron Administered the Day before Total Knee Arthroplasty Improves Postoperative Anemia Recovery

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Abstract

Background: Total knee arthroplasty (TKA) involves significant blood loss, which increases the risk for postoperative anemia and allogenic blood transfusion. Intravenous (IV) iron supplementation protects against postoperative anemia; however, the effectiveness of IV iron, given one day before TKA, on postoperative anemia and transfusion rates is unknown.

Methods: A retrospective cohort study was conducted using two consecutive groups of patients who underwent TKA. One group received 500 mg iron isomaltoside intravenously one day before TKA (iron group, n=46), whereas the other group did not (non-iron group, n=46). After propensity score matching, transfusion rate, hemoglobin (Hb) level, ferritin and transferrin saturation, and rate of functional iron deficiency anemia (IDA) were compared at postoperative days (PODs) 2, 4, 6, and 14.

Results: Age, sex, body mass index, and the American Society of Anesthesiologists Physical Status score did not differ between the groups. The iron group had higher Hb levels at POD 14 ($p=0.021$) and higher ferritin and transferrin saturation at PODs 2, 4, 6, and 14 than the non-iron group. The rate of functional IDA was significantly higher in the non-iron group than in the iron group at PODs 2 ($p<0.001$), 4 ($p<0.001$), 6 ($p=0.001$), and 14 ($p=0.002$). The rate of transfusion was not different between the groups ($p=0.238$).

Conclusion: IV iron administered one day before TKA improved postoperative anemia recovery, but did not lower the postoperative transfusion rate. Because approximately half of the patients undergoing TKA experience postoperative functional IDA, clinicians should consider IV iron supplementation to improve iron availability.

Introduction

Total knee arthroplasty (TKA) is associated with substantial blood loss and postoperative anemia, which may delay patient recovery, lengthen hospital stays, and eventually lead to poor clinical outcomes [1–4]. Additionally, patients with postoperative anemia may require allogenic red blood cell transfusion, potentially leading to transfusion-related complications [5, 6]. Therefore, a patient blood management program is strongly recommended to optimize hemoglobin (Hb) levels during the perioperative period.

Oral or intravenous (IV) iron supplementation is a key element of patient blood management, with IV iron found to have a faster recovery effect on Hb levels and fewer side effects [7–9]. It is recommended that IV iron be administered for at least two to four weeks before TKA to optimize Hb levels [3]. However, this is not always possible, and it can be inconvenient for a patient to visit the outpatient clinic several times before surgery for IV iron supplementation. Moreover, several studies have reported that IV iron administration during the perioperative period assists postoperative anemia recovery [7, 8]. Recently, Yoo et al. [10] and Park et al. [11] reported that intraoperative IV iron administration helped patients to recover from postoperative anemia after TKA; however, during surgery, the patient is hemodynamically unstable due to active bleeding. In addition, various drugs are administered that may interact and potentially decrease the effectiveness of IV iron administration [12]. Thus, it is prudent to administer IV iron one day prior to surgery when the patient is hemodynamically stable and there is no risk of interactions with other drugs. To the best of our knowledge, no study has analyzed recovery from postoperative anemia and blood transfusion rates following IV iron administration one day before TKA.

Several factors affect recovery from postoperative anemia, such as the total amount of iron as well as circulating iron levels [13–15]. However, the total amount of iron and circulating iron levels are not always proportional. Jeong et al. [16] analyzed changes in iron profiles after TKA and demonstrated that transferrin saturation levels can be low despite sufficient ferritin levels. After surgery, hepcidin quantities increase due to inflammation, resulting in decreased iron mobilization, which may lead to functional iron deficiency anemia (IDA) [17]. Indeed, Park et al. reported that functional IDA reached almost 50% on the fifth day after TKA [11]. Therefore, it is important to understand the incidence of functional IDA after TKA and evaluate whether the use of IV iron supplementation can reduce the occurrence of functional IDA. To date, no study has evaluated the difference in the occurrence of functional IDA after TKA depending on the perioperative use of IV iron.

This study aimed to analyze the effect of IV iron administration one day before TKA on recovery from postoperative anemia and transfusion rate, and determine whether IV iron administration can reduce the occurrence of functional IDA. We hypothesized that IV iron administration one day before surgery would facilitate postoperative anemia recovery and could reduce the occurrence of functional iron deficiency after TKA.

Materials And Methods

Patients

Following Institutional Review Board approval (**IRB No. 2021-04-021)**, we declare that all methods were carried out in accordance with relevant guidelines and regulations. We performed a retrospective cohort study of 158 consecutive patients who (1) underwent primary unilateral TKA for degenerative arthritis with Kellgren–Lawrence grade 3 or 4 and (2) either did or did not receive preoperative IV iron administration between April 2019 and November 2020. From February 2020, we administered preoperative IV iron to all patients undergoing TKA to improve Hb recovery. To avoid selection bias, consecutive patients received the same perioperative protocol with or without preoperative IV iron supplementation, depending upon when the surgery was performed. The exclusion criteria were as follows: (1) presence of inflammatory arthritis, such as rheumatoid arthritis; (2) history of open knee surgery; (3) presence of other secondary arthritis conditions, such as infectious arthritis or traumatic destructive arthritis; and (4) incomplete medical records regarding iron panels and patient’s quality of life index. After the exclusion of 25 patients, a total of 87 patients were included in the non-iron group, and 46 patients were included in the iron group.

Surgical Intervention and Perioperative Management

In the iron group, one day before surgery, 500 mg iron isomaltoside (Monofer®, Pharmacosmos A/S, Holbæk, Denmark) diluted with 200 mL of normal saline was administered intravenously over 2 hours. Except the IV iron administration, all patients underwent primary unilateral TKA according to the same surgical protocol. In both groups, a standard medial parapatellar approach was followed, with a tourniquet inflated to 300 mmHg. The surgical implant was a cemented, posterior stabilized prosthesis, and patellar resurfacing was performed in all patients. The tourniquet was deflated after the cement was completely set, and the prosthesis was firmly fixed. A suction drain was clamped and inserted, before the capsule was closed, and a solution of 1 g tranexamic acid in 50 mL normal saline was injected into the articular space. The drain remained clamped for two hours after the operation before being released.

Patients in both groups had the drain removed 48 hours postoperatively. From postoperative day (POD) 2 to POD 14, patients were administered aspirin as an anticoagulant. Range of motion exercises were started on POD 1, and walker ambulation began on POD 2. Transfusion of allogeneic blood was only indicated when the Hb concentration decreased below 8 g/dL with abnormal symptoms such as tachycardia and hypotension. Patients were discharged on POD 7 and were scheduled for a follow-up on POD 14.

Clinical Evaluations

We retrospectively collected the following preoperative data from medical records, including age, sex, body mass index (BMI), and American Society of Anesthesiologists Physical Status (ASA-PS) classification. The primary outcome variables were serial values of Hb and iron panels, including serum ferritin and transferrin saturation (TSAT), measured preoperatively and on POD 2, 4, 6, and 14. Using the values of iron panels and C-reactive protein (mg/L), the rate of absolute and functional IDA were calculated preoperatively and on POD 2, 4, 6, and 14. Absolute IDA was defined as low Hb (men < 13 g/dL, women < 12 g/dL) with TSAT < 20%, ferritin < 30 ng/mL, and no sign of inflammation; conversely, functional IDA was defined as low Hb (men < 13 g/dL, women < 12 g/dL) with TSAT < 20%, ferritin > 30 ng/mL, and CRP > 5 mg/dL. The secondary outcome variables were transfusion rate and European Quality of Life 5-Dimensional-5 Levels (EQ-5D-5L) index, recorded preoperatively and on POD 7 and 14. The EQ-5D-5L is a generic five-item questionnaire for the assessment of self-reported general health. EQ-5D is derived from five categories: mobility (walking about), self-care (washing and dressing), usual activities (e.g., work, study, housework, family, or leisure activities), pain or discomfort, and anxiety or depression. The five levels in each dimension are as follows: (1) “no problems,” (2) “slight problems,” (3) “moderate problems,” (4) “severe problems,” and (5) “extreme problems.” The EQ-5D index is calculated by weighting each response based on assessments obtained from a population survey [18–20].

Statistical Analysis

Prior to analysis, propensity score matching was performed using age, sex, BMI, and ASA-PS classification as variables. Propensity scores were generated using SPSS version 24 (IBM Corp., Armonk, NY, USA). Each patient in the iron group (n = 46) was assigned a matching patient in the non-iron group (n = 87), with a match tolerance (maximum difference between propensity scores) of 0.1. Therefore, 46 patients were ultimately included in each group (Fig. 1). After matching, we performed independent t-tests for continuous data to compare the means and standard deviations. For binary data, percentages were compared using Pearson's chi-square test and Fisher's exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS version 24 (IBM Corp.).

Results

Age, sex, BMI, and ASA-PS score did not differ between the groups (Table 1). The iron group had significantly higher Hb levels on POD 14 than the non-iron group (11.3 ± 1.2 vs. 10.4 ± 1.1 g/dL, $P = 0.021$) (Fig. 2). The iron group also had higher ferritin level and TSAT on PODs 2, 4, 6, and 14 than the non-iron group (Figs. 3 and 4). The rate of absolute iron deficiency was not different between the two groups, both preoperatively and postoperatively (Fig. 5). However, the rate of functional iron deficiency was significantly higher in the non-iron group than in the iron group on POD 2 (54.3% vs. 0%, $P < 0.001$), POD 4 (58.5% vs. 8.6%, $P < 0.001$), POD 6 (56.5% vs. 21.7%, $P = 0.001$), and POD 14 (47.8% vs. 17.3%, $P = 0.002$) (Fig. 6). The rate of transfusion did not differ between the two groups (non-iron vs iron group: 10.8% vs. 6.5%, $P = 0.238$). EQ-5D index also showed no significant difference between the two groups, preoperatively, or on PODs 7 and 14 (Table 2).

Table 1
Preoperative data after propensity score matching

	Non-iron group (n = 46)	**Iron group (n = 46)**	***P*-value**
Age (years)	68.2 ± 6.5	69.1 ± 5.5	0.720
Males:females	8:38	6:40	0.562
BMI (kg/m^2)	25.2 ± 3.2	25.4 ± 3.5	0.716
ASA-PS classification	2.2 ± 0.4	2.1 ± 0.3	0.587
ASA-PS, American Society of Anesthesiologists Physical Status; BMI, body mass index			

Table 2
Patient QOL (EQ-5D-5L index score)

	Non-iron group (n = 46)	**Iron group (n = 46)**	***P*-value**
Preoperative	0.55 ± 0.16	0.56 ± 0.15	0.842
POD 1 week	0.59 ± 0.18	0.58 ± 0.19	0.656
POD 2 weeks	0.61 ± 0.19	0.60 ± 0.19	0.765
QOL, quality of life; EQ-5D-5L, European Quality of Life Five Dimension 5 Levels; POD, postoperative day			

Discussion

The results showed that the iron group had faster Hb recovery at POD 14 and significantly higher rate of functional IDA during the study period and that the rate of transfusion and EQ-5D index were not different between the iron and non-iron groups. To the best of our knowledge, this is the first clinical study to analyze postoperative anemia recovery and rate of functional iron deficiency following IV iron administration one day before TKA.

Conventionally, oral iron has been used to treat IDA [21]. However, the efficacy of oral iron is compromised due to poor absorption, poor compliance, and gastrointestinal side effects [7, 22, 23]. Das et al. [7] found that IV iron sucrose administration had a better safety profile and efficacy in the treatment of IDA than conventional oral iron supplements. In addition, Macdougall et al. [8] found that among the oral, intramuscular, and IV iron administration methods, IV was the most reliable method for reducing adverse risks and optimizing erythropoietin response. Deloughery et al. [24]found that oral iron administration was often poorly tolerated and that up to 70% of patients in their study complained of gastrointestinal issues. According to a recent meta-analysis of 20,000 patients from 103 studies, IV iron administration can effectively treat anemia without increasing adverse events or the incidence of infection when compared to oral or intramuscular iron administration [25]. Therefore, IV administration is considered more effective than oral or intramuscular administration.

Currently, three IV iron formulations (iron sucrose, ferric carboxymaltose, and iron isomaltoside) are most commonly used because they do not have serious side effects [26]. Many studies have compared the efficacy and safety of different IV iron formulations [27–30]. Derman et al. [28] analyzed IV iron isomaltoside and IV iron sucrose administration and found that iron isomaltoside required fewer administrations and showed a higher and faster Hb response than iron sucrose administration. Wolf et al. [29] compared IV iron carboxymaltose and IV iron isomaltoside and found that IV iron isomaltoside administration led to a lower incidence of hypophosphatemia over 35 days and that it was a safer treatment for anemia than IV iron carboxymaltose administration. In addition, Pollock et al. [30] found that IV iron isomaltoside was more effective even when used less frequently than IV iron carboxymaltose and thus was more cost-effective. Therefore, when comparing several studies, IV iron isomaltoside has been regarded as the most effective and safest of the currently utilized IV formulations.

The current protocol states that IV iron should be administered to IDA patients four weeks before surgery; although this is the ideal treatment, it is not always possible in the field of orthopedic surgery [16, 31]. Jeong et al. [16] indicated that this lack of feasibility was due to time constraints, requiring frequent outpatient visits and multiple blood sampling tests. Moreover, several reports indicate that IV iron administration used in the perioperative period was effective for treating postoperative anemia after TKA [10, 32, 33]. Yoo et al. [10] found that intraoperative IV iron isomaltoside administration was an effective method to recover from postoperative anemia after TKA. Similarly, Park et al. [11] found that intraoperative IV iron carboxymaltose administration was effective in the treatment of postoperative anemia in patients who had undergone TKA. However, to date, no study has analyzed the effect of preoperative administration of IV iron one day before TKA. IV iron administration one day before TKA may have several advantages when compared to intraoperative administration, considering that it can be administered in a hemodynamically stable state and since there is no contraindication with other drugs [34–36].

In this study, serum ferritin and TSAT were higher and the rate of functional IDA was lower during the study period in the iron group when compared to those in the non-iron group, which resulted in faster Hb recovery of patients in the iron group. Serum ferritin levels reflect the total amount of iron stored in the body, and TSAT reflects the amount of circulating iron which can be directly used in erythropoiesis [37–39]. Several studies have shown that circulating iron levels were more crucial to postoperative anemia recovery than total iron levels [40–42]. Functional IDA can be caused by the TKA-induced inflammatory response in which the available quantities of total iron are sufficient but iron mobilization is decreased due to an increase in hepcidin synthesis. Hepcidin inhibits ferroportin (an iron transporter), which regulates iron excretion from the body's storage reserves to the bloodstream for erythropoiesis. Considering that the circulating iron is insufficient for anemia recovery, owing to acute blood loss during TKA and decreased iron mobilization due to TKA-induced inflammation, IV iron administration quickly restores iron utilization to prevent the development of functional iron deficiency and promotes the erythropoietic response to quickly recover from anemia [23, 43–45].

In our study, despite faster Hb recovery in the iron group, transfusion rate and EQ-5D index were not different between the two groups. Regarding QOL, several studies have shown that postoperative anemia was associated with patient function and postoperative recovery, which consequently affects QOL [46–51]. Foss et al. [50] found that the degree of anemia was associated with functional mobility in the early postoperative period. Moreover, Lawrence et al. [51] found that patients with higher postoperative Hb levels had higher functional recovery. However, in this study, the EQ-5D index was only evaluated for 2 weeks after TKA. During this postoperative period, the EQ-5D index is greatly influenced by other factors such as various comorbidities [52–54]. We assumed that the recovery from anemia may be related to both functional recovery and improvement in patients' quality of life—from a long-term perspective—and subsequent investigations focusing on long-term outcomes are warranted. Regarding transfusion rate, several reports state that IV iron administration could lower the risk of transfusion [55–57]. However, postoperative transfusion is determined by the amount of acute blood loss that occurs during surgery; therefore, most transfusions occur within 1–2 days (hyper-acute phase) after surgery. We assumed that the effect of IV iron administration one day before surgery has not been demonstrated yet within the hyper-acute phase. In addition, it is possible that our IV iron dose and administration timing was not optimal to obtain a low transfusion rate. Considering that several authors have reported that the transfusion rate was different according to IV iron dose and administration timing [58–60], the optimal dose and timing of iron supplementation to reduce transfusion rates in TKA should also be investigated in the future.

Our study has several limitations. First, this study had a relatively short-term follow-up period. Further study is warranted to evaluate the changes in Hb, ferritin and TSAT levels through long-term follow-up, and to identify whether the difference in Hb and iron profile levels between the two groups can lead to differences in patient-reported outcomes in the long term. Second, due to the retrospective study design, there may be concern of possible selection bias. To overcome this limitation, special efforts were made by deciding to administer IV iron based only on the date of surgery. Furthermore, patients in both groups were treated with the same surgical procedure with identical perioperative management. Moreover, propensity score matching was also performed to appropriately set the usage of IV iron as the only independent variable. Lastly, the number of subjects used in this study was determined by the number of eligible patients by retrospective review. Prospective studies with a sufficient power analysis are warranted to confirm our findings.

In conclusion, intravenous iron administered one day before TKA improved postoperative anemia recovery but did not lower the postoperative transfusion rate. Because approximately half of the patients undergoing TKA experience postoperative functional IDA, clinicians should consider the use of IV iron to improve iron availability.

Abbreviations

BMI: Body mass index; IDA: Iron deficiency anemia; POD: Postoperative day; QOL: Quality of life; TKA: Total knee arthroplasty; TSAT: Transferrin saturation

Declarations

Ethics approval and consent to participate

The study was approved by the Hallym University Gangnam Hospital Institutional Review Board (IRB No. 2021-04-021), and follows the ethics principles of the Declaration of Helsinki 1964. The Hallym university Gangnam Hospital's institutional waived the requirement for written informed consent for Dr. Kim to review the data of enrolled patients.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declared that they had no competing interests.

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Authors' contributions

MWK collected the data, performed the measurement and analysis, participated in the study design and drafted the manuscript. JIK and JHJ participated in the study design, supervised the analysis and helped to draft the manuscript. JIK collected the data, performed the measurement. MWK helped to draft the manuscript and review the manuscript. JIK designed the study, supervised the whole study process and helped to draft and review the manuscript. All authors read and approved the final manuscript.

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Figures

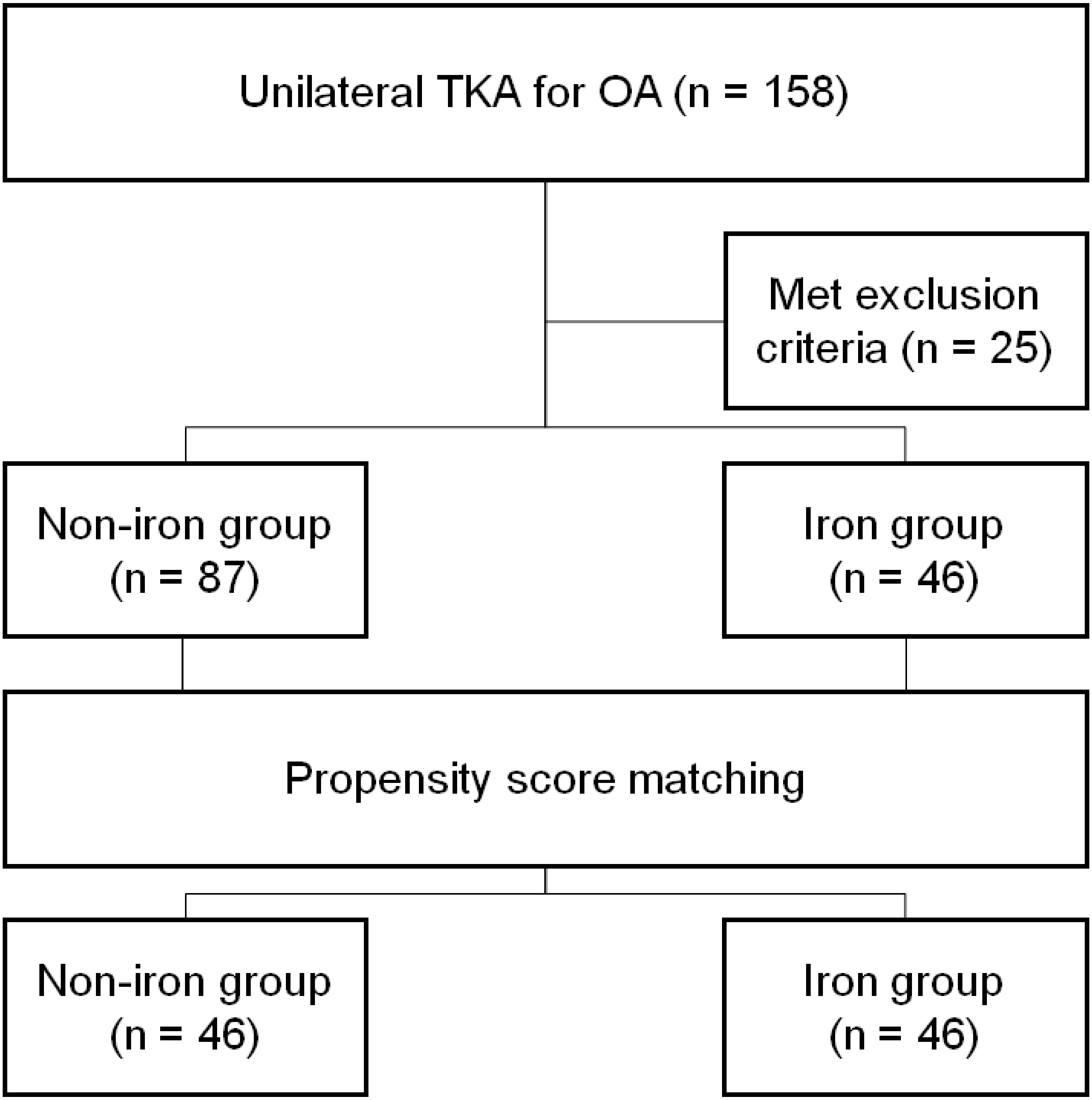

Figure 1

Flow diagram of the study. After propensity score matching, both groups comprised 46 patients. OA, osteoarthritis; TKA, total knee arthroplasty

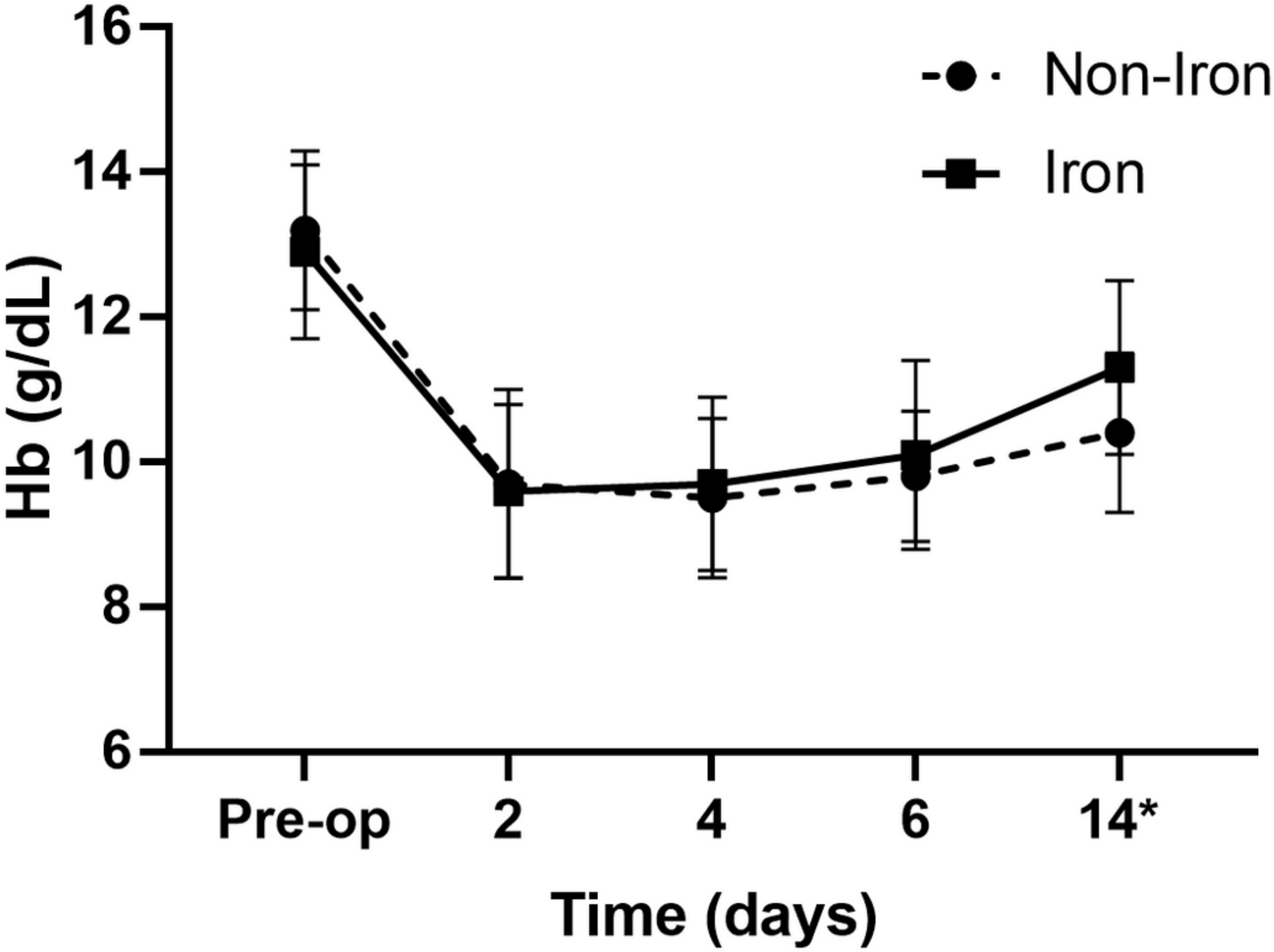

Figure 2

Serial changes in Hb. Hb values on postoperative day 14 were significantly higher in the iron group than in the non-iron group. *P=0.021. Hb, hemoglobin

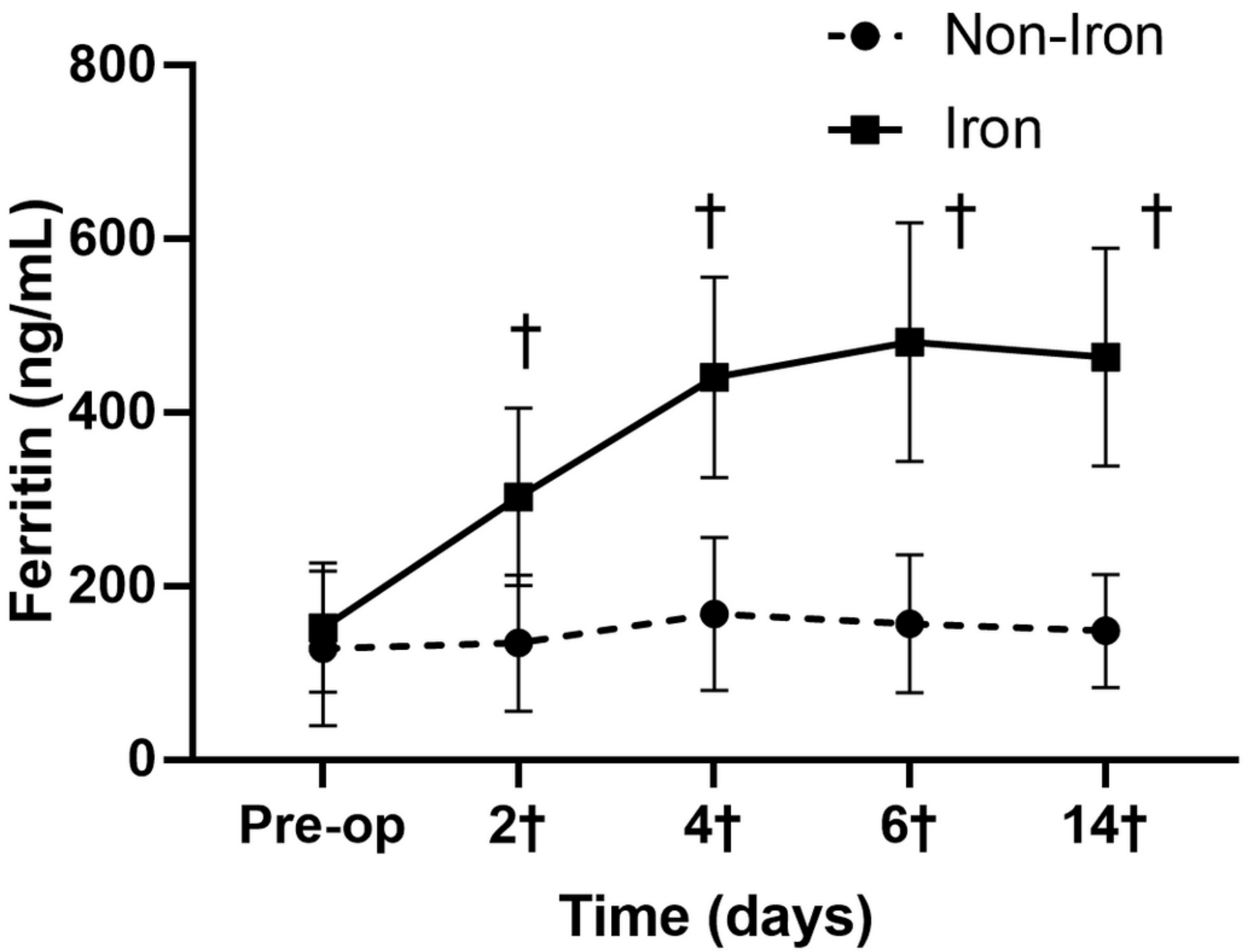

Figure 3

Serial changes in ferritin. Ferritin values on postoperative days 2, 4, 6, and 14 were significantly higher in the iron group than in the non-iron group. †P<0.001

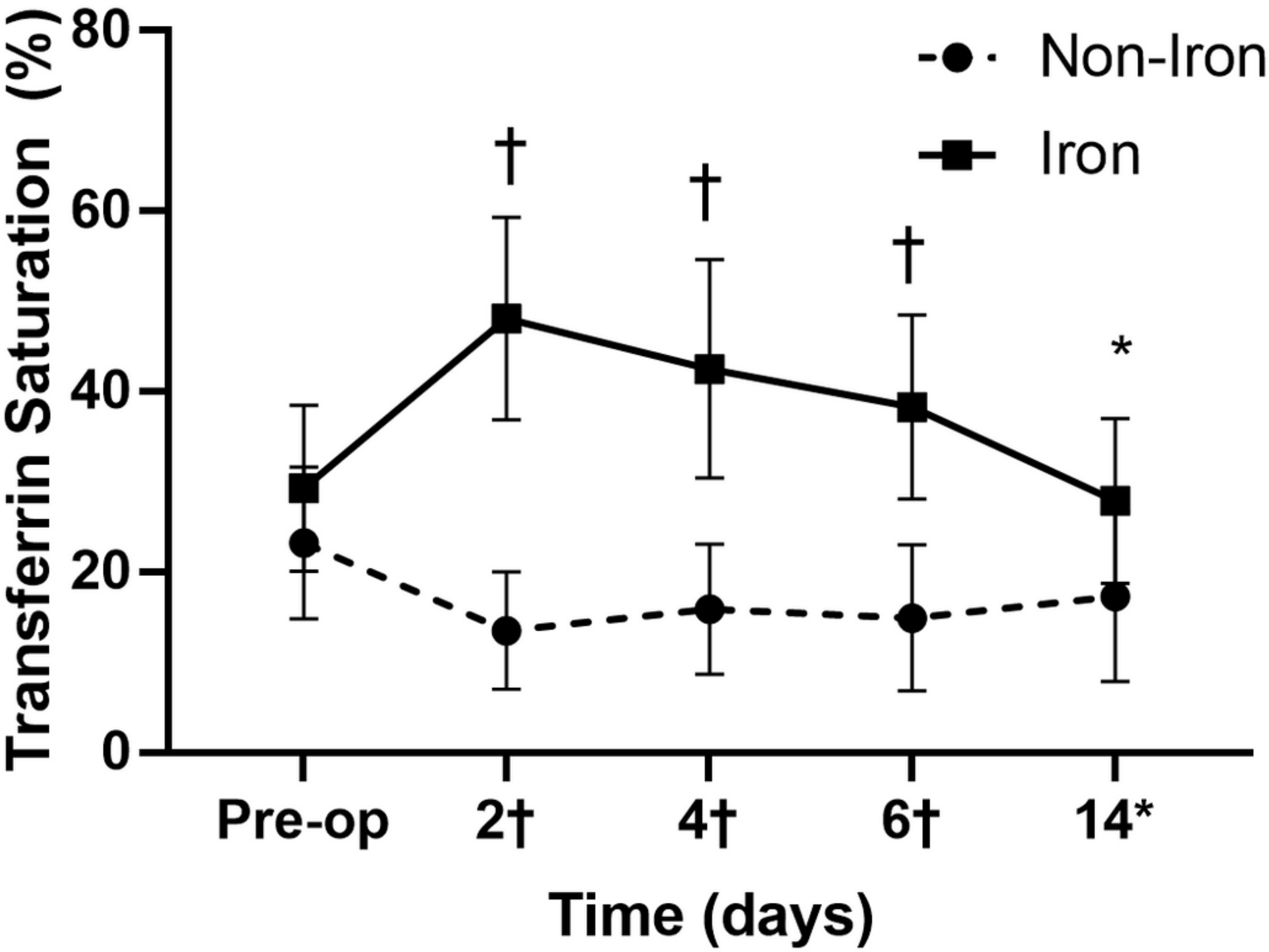

Figure 4

Serial changes in transferrin saturation. Transferrin values were significantly higher in the iron group than in the non-iron group on postoperative days 2, 4, 6, and 14. †P<0.001. *P=0.012

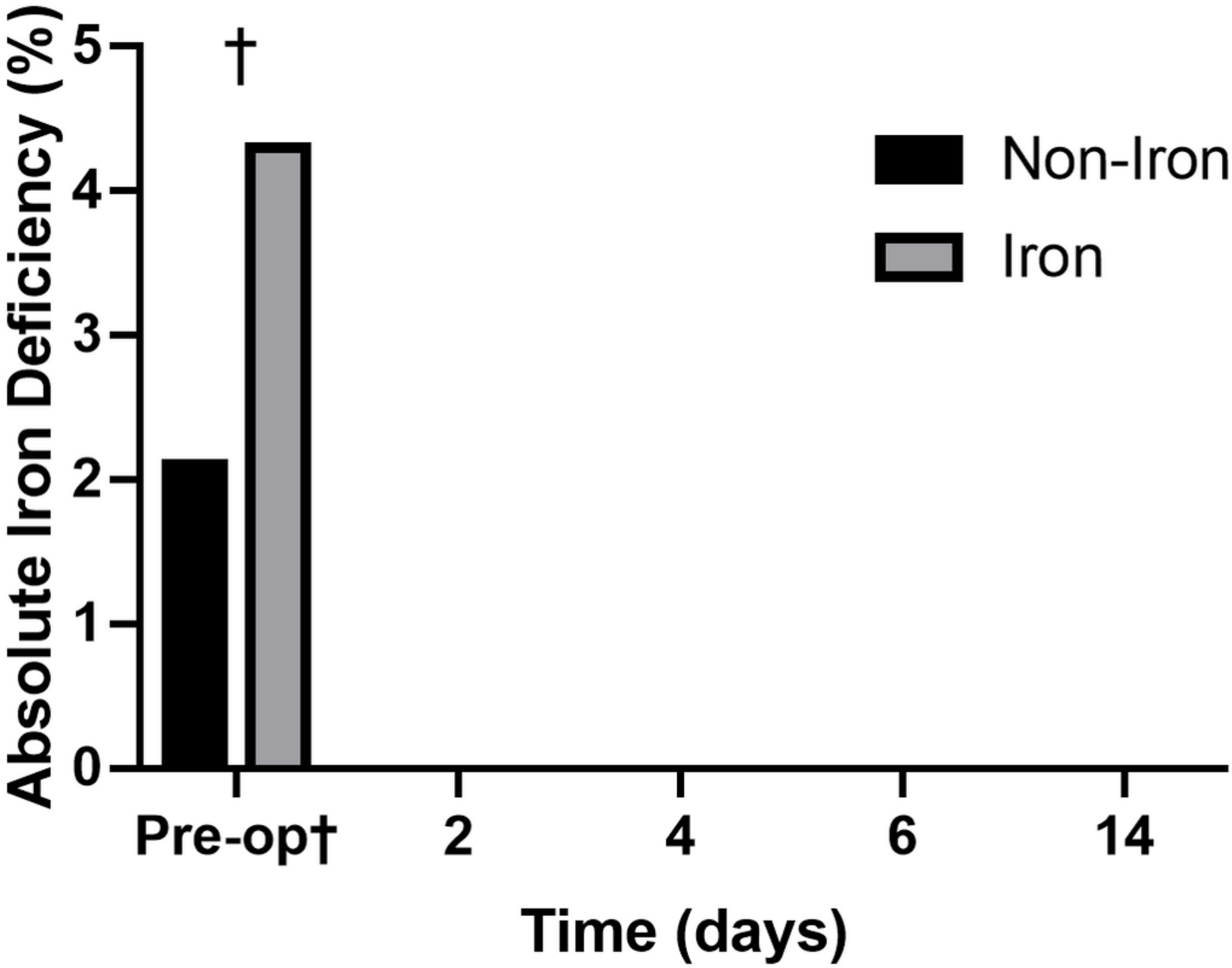

Figure 5

Serial changes in absolute iron deficiency (%). There was no significant difference between the groups preoperatively or on postoperative days 2, 4, 6, or 14. †P=0.21

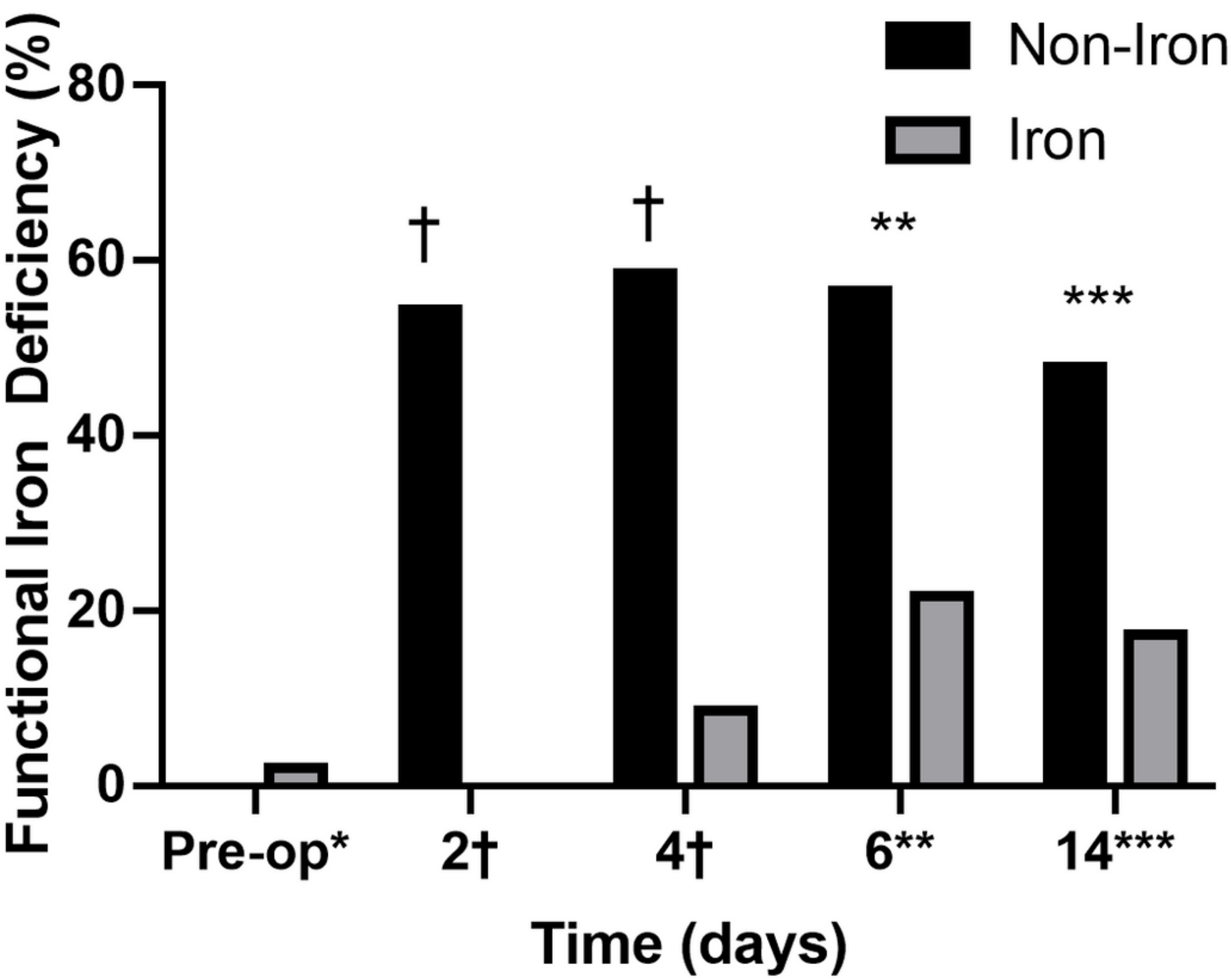

Figure 6

Serial changes in functional iron deficiency (%). Functional iron deficiency values were significantly lower in the iron group than in the non-iron group on postoperative days 2, 4, 6, and 14. †P<0.001, *P=0.021, **P=0.001, ***P=0.002