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Perioperative intravenous ferric carboxymaltose improves anemia in patients with colorectal cancer: a propensity score–matched analysis

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Abstract

Background:

Iron deficiency anemia (IDA) is common in patients with colorectal cancer and may negatively affect perioperative management. Although intravenous ferric carboxymaltose (FCM) has been shown to be effective for anemia correction, evidence regarding its perioperative clinical utility remains limited, particularly in Japan.

Methods:

We retrospectively analyzed patients with IDA who underwent elective colorectal cancer surgery between January 2020 and August 2023 at a single institution. Patients receiving a single preoperative dose of FCM (500 mg) were compared with those who did not receive FCM. Propensity score matching was applied to adjust for baseline differences. Hemoglobin (Hb) and mean corpuscular volume (MCV) were evaluated before surgery and postoperatively, along with perioperative transfusion, complications, and hospital stay.

Results:

After matching, 24 patients were included in each group. Hb levels were significantly higher in the FCM group immediately before surgery and 21 days postoperatively ($p < 0.05$). MCV levels were consistently higher in the FCM group at all postoperative time points. No significant differences were observed in perioperative transfusion rates, postoperative complications, or length of hospital stay. No FCM-related adverse events were reported.

Conclusions:

Preoperative intravenous FCM administration effectively improved perioperative hematological parameters in patients with colorectal cancer and IDA. Although short-term surgical outcomes were not significantly affected, intravenous iron supplementation represents a feasible strategy for optimizing perioperative anemia management in routine clinical practice.

Introduction

The World Health Organization defines anemia as a hemoglobin (Hb) level below 13 g/dL for men and below 12 g/dL for women. Iron deficiency anemia (IDA) accounts for over half of all anemia cases, and 38.9% of patients with colorectal cancer have IDA with Hb levels below 12 g/dL [7]. Additionally, patients with colorectal cancer and anemia experience increased postoperative complications and longer hospital stays [6]. Blood transfusions during general surgery are linked to higher mortality rates, surgical

site infections, pneumonia, and sepsis. In colorectal cancer surgery, blood transfusions increase mortality risk, recurrence rate, postoperative infection, and reoperation [1, 2]. Therefore, correcting IDA before colorectal cancer surgery is crucial.

The preoperative management of patients with IDA and malignant disease is described in the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. ESMO recommends intravenous iron supplements for patients with iron deficiency, Hb levels < 11 g/dL, serum ferritin levels < 100 ng/mL, and transferrin saturation (TSAT) < 20%. NCCN recommends considering the intravenous administration of iron supplements if ferritin levels are < 500 ng/mL. However, erythropoiesis-stimulating agents mentioned in these guidelines have not been approved for use in Japan.

Studies have shown that iron therapy for patients with colorectal cancer and anemia before surgery improves blood transfusion volume, reduces complication rates, and shortens hospital stays [3, 12]. Additionally, a study comparing oral and intravenous iron supplements showed that intravenous iron supplements more effectively improved anemia [5, 11].

Iron supplementation can be orally or intravenously administered. Oral administration is simple but may be problematic owing to patient forgetfulness and side effects such as nausea, abdominal pain, constipation, and diarrhea. In Japan, only saccharated ferric oxide has been approved for intravenous administration; however, it requires daily administration, making it difficult for outpatient use. Ferric carboxymaltose (FCM) (Ferinject®; Zeria Pharmaceutical Co., LTD. Japan), which has been recently released, provides sufficient iron supplementation with two or three administrations per week, making it suitable for iron administration in outpatient settings. However, evidence regarding preoperative FCM administration for colorectal treatment in Japan remains limited.

The waiting time from diagnosis to surgery for patients with colorectal cancer varies by country: approximately 21 days in Norway and 27–80 days in Sweden [9, 10]. Although no reports regarding the waiting time exist in Japan, surgery is often performed approximately 4 weeks after the initial consultation. This timing for medication administration can be challenging owing to multiple tests and procedures at the first visit. In clinical practice, there is an opportunity to administer medication when explaining test results and treatment plans, and surgery is often performed about two weeks later. We considered having patients visit the hospital one week before surgery to administer the medication, but decided not to do so because the time from administration was too short and we felt it would not contribute to improving anemia at the time of surgery. This study investigates the efficacy of a single dose of FCM (500 mg) administered preoperatively to patients with colorectal cancer and anemia and its impact on the perioperative period.

Patients and methods

This retrospective cohort study was conducted at a single institution. At our facility, FCM was administered to patients with IDA during an initial consultation between April 2022 and August 2023. We

targeted 137 patients diagnosed with IDA at the initial consultation of 409 patients who underwent elective surgery for colorectal cancer in our department between January 2020 and August 2023. We enrolled 102 patients who did not receive FCM and 35 patients who received FCM in the non-FCM and FCM groups, respectively (Fig. 1). Patients who underwent chemotherapy or radiation therapy before surgery and those who lacked sufficient follow-up after surgery were excluded.

Clinical records were collected from patients‘ medical records, including sex, age, body mass index (BMI), tumor location, tumor size, tumor, node, metastasis (TNM) stage, Hb level, mean corpuscular volume (MCV), antithrombotic drugs, and oral iron supplements. Additionally, treatment details included surgical method, surgical time, intraoperative blood loss, perioperative transfusion, postoperative complications, postoperative course, and adjuvant therapy. Surgery was performed approximately 14 days after FCM administration. Hb and MCV values were extracted from blood samples collected the day before surgery, approximately 21 days after, and approximately 90 days after surgery as part of routine management.

In the FCM group, a single dose of 500 mg FCM was administered based on blood tests at the first visit: IDA was defined as Hb levels below 12 g/dL and TSAT below 20%, or serum ferritin below 100 ng/mL, according to the ESMO 2018 guidelines.

Propensity score matching was used to adjust for baseline differences between the non-FCM and FCM groups. The propensity score was estimated using logistic regression analysis incorporating clinically relevant baseline variables associated with anemia. Based on previous reports on anemia, the following variables were defined as potential confounders: sex, age, BMI, tumor location and size, tumor, node, metastasis (TNM) stage, Hb level at the initial visit, MCV at the initial visit, and intraoperative blood loss. One-to-one propensity score matching was performed between the non-FCM and FCM groups, with a caliper of 0.05. Patient characteristics were examined before and after propensity score matching. Continuous variables were compared using the Mann–Whitney U test, and categorical variables were compared using Fisher’s exact test or the chi-square test. Significance was set at $p < 0.05$. Statistical analyses were performed using JMP Pro version 18 (SAS Institute Inc., Cary, NC, USA).

Results

The characteristics of the non-FCM iron group (102 patients) and FCM group (35 patients) are presented in Table 1. No significant differences were observed in sex or age between groups. Although BMI showed no significant difference, it was slightly higher in the FCM group (22.5 vs. 23.8, p=0.07). We compared the right side of the colon (from the cecum to the transverse colon) and the left side (from the descending colon to the rectum); however, no differences were observed. Tumor diameter showed no significant difference; however, it tended to be larger in the non-FCM iron group (46.9 mm vs. 39.2 mm, p=0.07). Although the T factor was similar between the groups, significant differences were observed in the N factor (N0:N1/2/3) (49:53 vs. 25:10, p<0.05), M factor (M0:M1) (77:24 vs. 32:3, p<0.05), and clinical stage (Stage I/II:III/IV) (42:60 vs. 25:10, p<0.01). Additionally, no differences were noted in baseline Hb or

MCV, and when the degree of anemia was divided into two groups: Hb <10 and 10.1–11.9. Notably, no differences were observed in antithrombotic drug or oral iron supplement use at the initial consultation, surgical approach, operative time, intraoperative blood loss, or postoperative adjuvant usage. Propensity score matching yielded 24 pairs of patients in each group. Subsequently, the characteristics of both groups were well-balanced.

When comparing the two groups, no significant differences were found in perioperative blood transfusion, postoperative complications, length of postoperative hospital stay, reoperation, or readmission, with no adverse effects associated with the administration of FCM (Table 2).

Hb levels at each blood sampling point were significantly higher in the FCM group before surgery (10.1 g/dL vs. 10.9 g/dL, $p<0.05$) and 21 days after surgery (10.2 g/dL vs. 11.0 g/dL, $p<0.05$). However, no significant difference was observed 90 days after surgery (Fig. 2). Mean corpuscular volume was significantly higher in the FCM group just before surgery (86.2 fl vs. 90.2 fl, $p<0.05$), 21 days (87.1 fl vs. 91.9 fl, $p<0.05$), and 90 days after surgery (88.8 fl vs. 94.2 fl, $p<0.05$) (Fig. 3).

Discussion

In this propensity score–matched analysis, we demonstrated that a single preoperative administration of ferric carboxymaltose (FCM) was associated with significant improvement in hemoglobin and mean corpuscular volume (MCV) levels in patients with colorectal cancer and iron deficiency anemia (IDA). These hematological improvements were observed both before surgery and during the postoperative period, indicating a sustained effect of intravenous iron supplementation. To our knowledge, this is the first Japanese study using propensity score matching to evaluate the perioperative clinical impact of FCM in colorectal cancer surgery.

Importantly, although correction of anemia did not translate into measurable improvements in short-term surgical outcomes such as transfusion rate or postoperative complications, our findings support the clinical feasibility and safety of incorporating intravenous iron into perioperative management. In contemporary colorectal surgery, where blood loss and transfusion rates are already low, optimization of hematological status itself may represent a meaningful clinical goal rather than a surrogate for surgical outcomes.

Our findings are consistent with previous international studies reporting superior hematological improvement with intravenous iron supplementation compared to oral iron therapy [5, 11]. However, in contrast to reports from European cohorts, our study did not demonstrate reductions in perioperative transfusion rates, postoperative complications, or hospital stay[3, 12]. Several factors may explain this discrepancy. First, the invasiveness of colorectal surgery in Japan has markedly decreased, with median intraoperative blood loss as low as 15–20 mL and transfusion rates ranging from 1.3% to 2.0% in national databases[8]. This background may have attenuated the clinical impact of correcting preoperative anemia, even though hematological parameters improved significantly. Second, the FCM dosage in our cohort (500 mg single administration) was lower than the standard regimen of 1000–1500

mg, and the short interval of approximately two weeks between administration and surgery may not have allowed sufficient time for maximal hematopoietic effect. Previous reports suggest that hemoglobin increases peak at 4–6 weeks following FCM infusion[4]. Administering FCM at the initial consultation, rather than one or two weeks later, may have enhanced perioperative outcomes.

Another important consideration is patient selection. Although our study included all patients with IDA undergoing elective colorectal resection, the magnitude of benefit from FCM may differ according to baseline anemia severity, tumor location, or comorbidities. Subgroup analyses focusing on patients with severe anemia or rectal cancer requiring prolonged preoperative treatment might reveal more pronounced clinical benefits. Furthermore, in the context of total neoadjuvant therapy, which often involves longer intervals before surgery, earlier or repeated administration of FCM could be particularly advantageous.

In conclusion, preoperative FCM administration significantly improved anemia in Japanese patients with colorectal cancer, although its impact on short-term perioperative outcomes such as transfusion, complications, or hospital stay was limited in this cohort. Nevertheless, correction of anemia may contribute to improved physiological reserve and perioperative readiness, supporting safer surgical management even in the absence of measurable differences in short-term outcomes. Therefore, intravenous iron supplementation should be considered not only as a hematological intervention but also as an integral component of perioperative clinical management.

This study has several limitations. First, it was a single-center, nonrandomized, retrospective study, and although propensity score matching was used to reduce confounding, unmeasured bias may still exist. Second, the FCM dosage (500 mg single administration) was lower than the standard regimen, and the short interval between administration and surgery may have limited its full hematopoietic effect. Third, the sample size was relatively small, which restricts the generalizability of our findings. Future multicenter, prospective studies with optimized timing and dosage are warranted to validate the role of preoperative intravenous iron supplementation in improving not only hematological outcomes but also broader aspects of perioperative supportive care, including patient-reported outcomes and long-term oncological results.

Conclusion

Preoperative administration of intravenous ferric carboxymaltose significantly improved hemoglobin and mean corpuscular volume in patients with colorectal cancer and iron deficiency anemia. While no significant differences were observed in short-term surgical outcomes, intravenous iron supplementation represents a safe and practical approach to optimizing perioperative anemia management. Further prospective studies are warranted to define optimal timing, dosage, and patient selection.

Declarations

Funding

This research received no external funding.

Conflicts of interest / Competing interests

The authors declare that they have no competing interests.

Ethics approval

This study was approved by the Ethics Review Committee of Chiba University School of Medicine. All procedures involving human participants were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Consent to participate

The requirement for informed consent was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

Not applicable.

Authors' contributions

Tetsuro Maruyama conceived the study and drafted the manuscript. Gaku Ohira, Toru Tochigi, Koichiro Okada, and Atsushi Hirata reviewed the manuscript. Michihiro Maruyama supervised the study. All authors approved the final manuscript.

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Tables

Table 1. Characteristics of Patients before and after Propensity Score Matching.

	Total study cohort			Propensity-matched cohort		
	Non-IV (n=102)	FCM (n=35)	P-value	Non-IV (n=24)	FCM (n=24)	P-value
Sex, cases						
Male	54	17	0.66	10	11	0.77
Female	48	18		14	13	
Age, years	71.9±11.7	73.2±11.8	0.58	73.9±12.3	73.2±13.2	0.86
BMI, kg/m2	22.5±3.5	23.8±4.3	**0.07**	23.5±3.9	23.2±4.1	0.83
Tumor location, cases						
Right side	43	12	0.41	9	8	0.76
Left side	59	23		15	16	
Tumor size, mm	46.9±22.4	39.2±14.6	**0.07**	42.0±25.1	39.1±12.6	0.61
Tumor stage, cases						
T1 / T2	9/16	3/8	0.36	4/8	1/6	0.14
T3 / T4	29/48	14/10		8/4	10/7	
Node stage, cases						
N0	49	25	**<0.05**	20	16	0.18
N1 / N2 / N3	38/13/2	8/1/1		2/1/1	7/1/0	
Metastasis stage, cases						
M0	77	32	**<0.05**	23	22	0.54
M1	24	3		1	2	
Stage, cases						
1 / 2	22/20	11/14	**<0.01**	9/10	0/7/9	0.69
3 / 4	36/24	7/3		4/1	6/2	
Baseline Hb, g/dl	10.3±1.4	10.4±1.3	0.62	10.7±1.1	10.5±1.3	0.57
10-11.9	65	23	0.83	26	23	0.43
<10	37	12		9	12	

Baseline MCV, fl	85.8±9.1	87.8±6.8	0.24	86.9±9.6	88.9±6.4	0.40
Anticoagulant medication use, cases	26	13	0.19	7	8	0.76
Oral Iron treatment at diagnosis, cases	21	8	0.78	5	4	0.71
Surgical approach, cases						
Open	32	3	0.52	7	5	0.48
Laparoscopic	70	32		17	19	
Operation time, minute	236±101	244±92	0.70	231±95	242±98	0.67
Intraoperative blood losses, ml	179±304	65±162	**<0.05**	126±241	92±188	0.37
Adjuvant chemotherapy, cases	37	10	0.40	6	6	1.00

Table 2. Postoperative outcome in non-IV group versus FCM group

	Non-IV (N=24)	FCM (N=24)	P-value
Need for RBC transfusion, cases	1	1	1.00
Complication			
>CD grade 2	4	6	0.25
Intestinal obstruction	2	3	
Anastomotic leakage	1	1	
Urinary dysfunction	1	1	
Pneumonia	0	1	
>CD grade 3	1	1	0.29
Anastomotic leakage	1	1	
Postoperative hospital stay, day	8 (5 – 39)	8 (6 – 42)	0.83
Surgical reintervention, cases	0	0	-
Hospital readmission (surgical-related cause), cases	0	0	-
Side effects related to FCM administration	-	0	-

Figures

*FCM: Ferric carboxymaltose

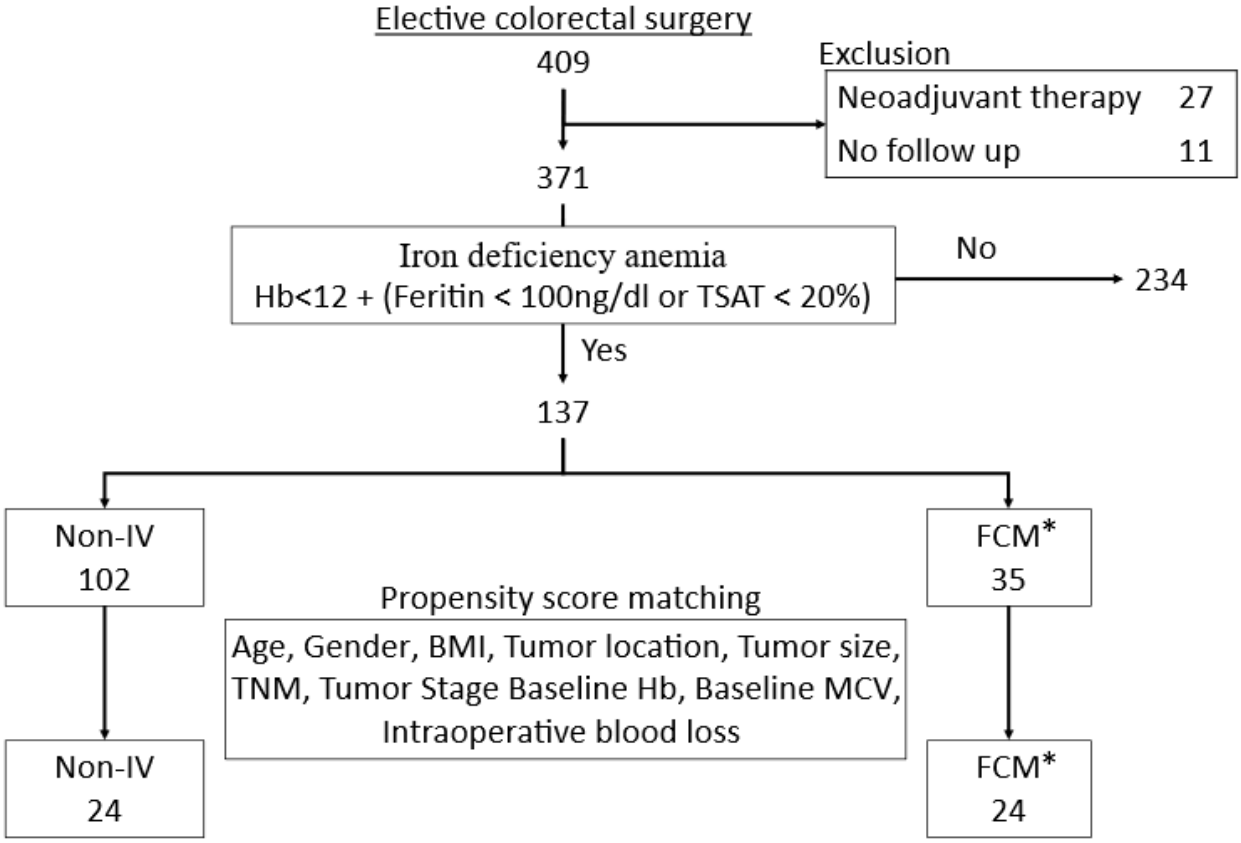


Figure 1

Study flow

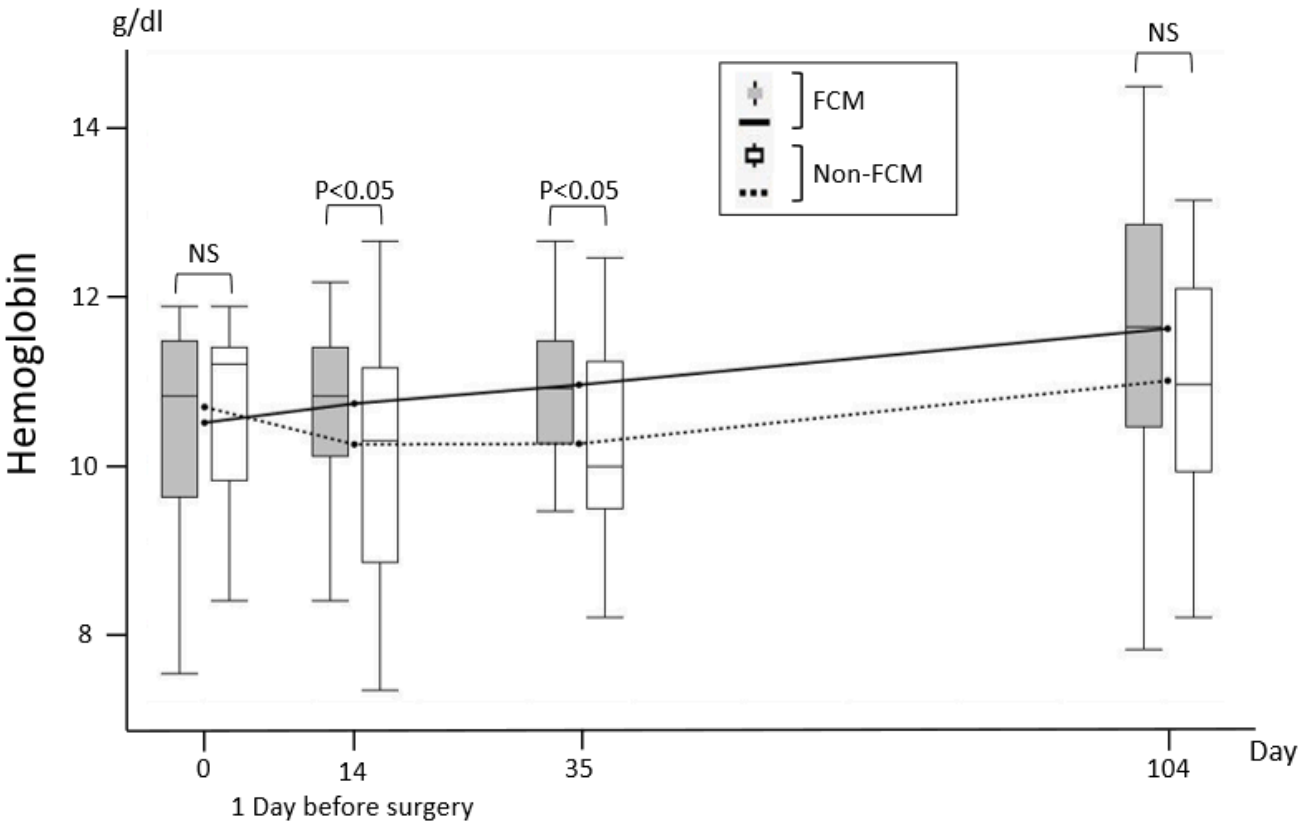


Figure 2

Hemoglobin levels at each blood sampling point in the FCM and non-FCM groups. FCM: ferric carboxymaltose, NS: not significant.

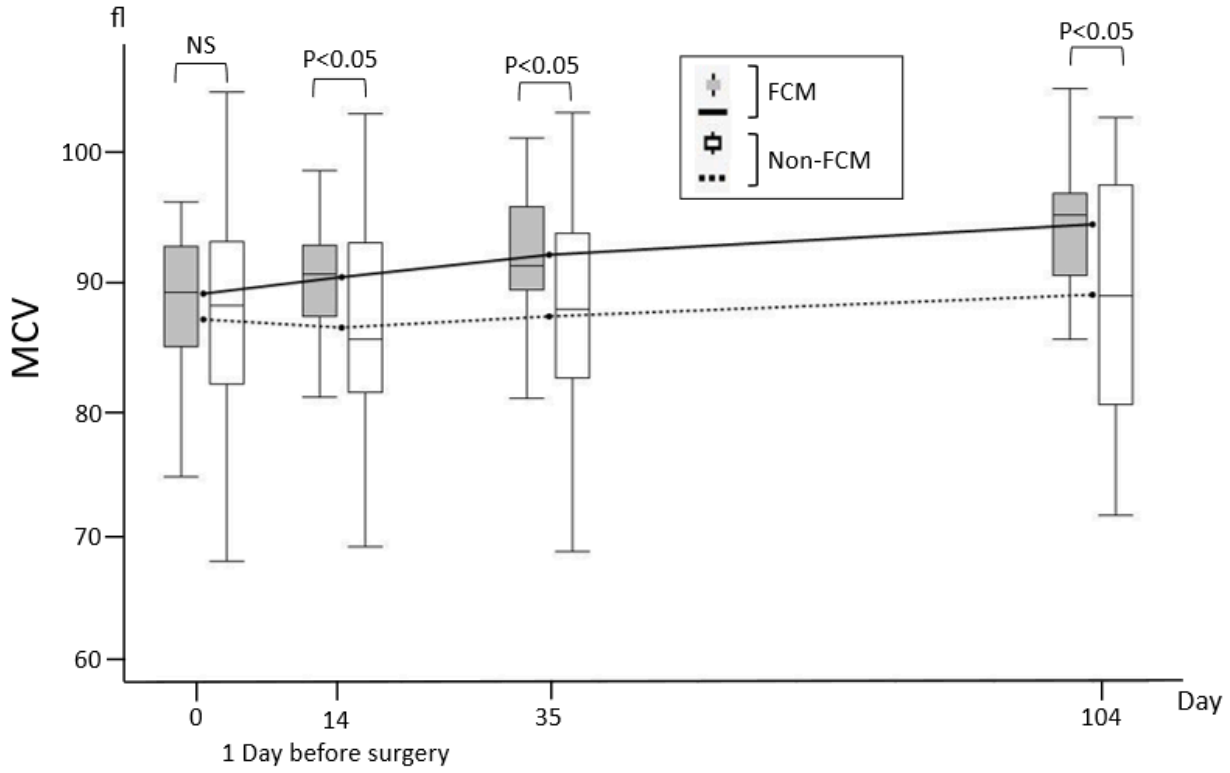


Figure 3

Mean corpuscular volume (MCV) levels at each blood sampling point in the FCM and non-FCM groups. FCM: ferric carboxymaltose.