ORIGINAL ARTICLE

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Comparison of the Efficacies of Parenteral Iron Sucrose and Oral Iron Sulfate for Anemic Patients with Inflammatory Bowel Disease in Korea

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Background/Aims: The optimal route for iron administration in anemic patients with inflammatory bowel disease (IBD) has not been determined. The aim of this study was to compare the efficacies of parenteral and oral iron therapy in IBD patients in Korea. **Methods:** A retrospective multicenter study was performed. Patients who had been administered parenteral iron were matched to the controls with oral iron at a 1:1 ratio according to age, sex, and type of IBD. **Results:** Patients that received parenteral iron exhibited increases in hemoglobin levels of ≥20% from the baseline at lower doses and in shorter durations (p=0.034 and p=0.046, respectively). In the multivariate analysis, parenteral iron therapy appeared to be more efficient than oral iron therapy, but this difference was not statistically significant (hazard ratio [HR], 1.552; 95% confidence interval [CI], 0.844 to 2.851; p=0.157). Patients with ulcerative colitis responded better to iron therapy than those with Crohn's disease (HR, 3.415; 95% CI, 1.808 to 6.450; p<0.001). Patients with an initial hemoglobin level of 10 g/dL or higher responded poorly to iron therapy (HR, 0.345; 95% CI, 0.177 to 0.671; p=0.002). **Conclusions:** Parenteral iron therapy appears to be more efficient than oral iron therapy. Physicians should focus on the iron deficiency of IBD patients and consider parenteral iron supplements in appropriate patient groups. **(Gut Liver 2016;10:562-568)**

Key Words: Crohn disease; Inflammatory bowel diseases; Anemia, iron-deficiency; Parenteral iron; Colitis, ulcerative

INTRODUCTION

Anemia is common in patients with inflammatory bowel disease (IBD). Previous study reported that 26% of patients with Crohn's disease (CD) and 37% of patients with ulcerative colitis (UC) had anemia,[1] and anemia is associated with significant morbidity and mortality.[2-4] Many factors contributed to the development of anemia, for instance, iron, vitamin B_{12} and folic acid deficiencies, effect of proinflammatory cytokines, hemolysis, and myelosuppression due to drug therapy. Among them, iron deficiency anemia (IDA) is the most common cause of anemia in IBD patients. Chronic blood loss through gastrointestinal tract and malabsorption of iron when the proximal digestive tract is affected by IBD caused iron deficiency.[5,6] However, IDA was underdiagnosed so that only one third of patients with anemia undertook further diagnostic tests.[7] Furthermore, treatment of anemia was often neglected by physicians, so only 45.7% of patients diagnosed with IDA received iron supplements.[7]

Oral administration of iron was the conventional approach in the treatment of IDA. However, bioavailability of oral iron is low and intestinal absorption is compromised in IBD patients due to bowel inflammation and increased hepcidin level. Therapeutic effect of oral iron supplement is relatively slow so it took at least six months to replenish iron stores completely.[8] Also, oral iron induced gastrointestinal discomfort and due to poor tolerability, 66% patients who took oral supplements were dissatisfied with their treatment.[9] Recent meta-analysis showed that parenteral iron therapy is more efficient and better tolerated by patients.[10,11] American and European guideline recommended parenteral iron in patients with severe anemia (hemoglobin [Hb] <10 g/dL), with intolerance or inadequate response to oral iron, or with concomitant erythropoietin (Epo) treatment and/or

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presence of active IBD.[12,13] However, parenteral iron therapy in Korea is restricted to the patients with Hb <8 g/dL and intolerance to oral iron, needs for urgent iron therapy with bleeding and serum ferritin <12 ng/mL or transferrin saturation <15%. This criteria for parenteral iron administration was compelled by national health insurance service. Therefore, numerous IDA patients with IBD could not receive active treatment with parenteral iron supplements.

All the current studies which compare the effect of oral and parenteral iron therapy were performed in America and Europe.[14-17] Little information is available for IBD patients with Asian ethnicity.[18] The aim of this study was to compare the efficacy of parenteral and oral iron therapy in IBD patients in Korea. We planned to verify whether parenteral iron therapy was superior to oral iron therapy in terms of required time and dose to the response. Furthermore, we tried to figure out the factors that affect the treatment outcome of iron therapy by multivariate analysis.

MATERIALS AND METHODS

1. Patients

Patients who were diagnosed as IBD between 2005 and 2012 at Seoul National University Hospital, Seoul National University Bundang Hospital, and Seoul National University Boramae Medical Center were screened. IBD was diagnosed according to clinical, endoscopic, radiological, and histological criteria.[19,20] We reviewed electronic medical records of these patients. Among them, patients with anemia (Hb lower than 13.0 g/dL in men, 12.0 g/dL in women) were identified. We included the patients with microcytic hypochromic anemia (mean corpuscular volume <80 fL and mean corpuscular Hb <27 pg). Eligible patients had to be 16 years of age or older. Exclusion criteria comprised pregnancy or lactation, clinically significant overt bleeding, surgery with relevant blood loss (Hb decrease >2 g/dL), myelodysplastic syndrome, active malignancy or chronic renal failure.

Patients who had been administered over 400 mg of parenteral element iron were selected. The available parenteral iron prescription in these hospitals was ferric hydroxide sucrose complex (Venoferrum; Nycomed, Zurich, Switzerland) which contained 100 mg of elemental iron per ample. Treatment schedules were not consistent among the patients, some treated as daily injection for several days, and others treated as weekly or monthly injection schedule.

2. Controls

Among the patients with IBD and IDA, those who had been administered over 4,000 mg oral iron were selected. Bioavailability of oral iron is esteemed as 10%,[21] therefore, we considered that parenteral injection of 1 mg elemental iron were equivalent to the orally administered 10 mg of elemental iron. The available oral iron prescription in our hospitals was ferrous sulfate complex (Feroba; Bukwang, Seoul, Korea) which contained 80 mg of elemental iron per tablet. Ferrous sulfate tablet was prescribed to be taken twice a day before meal. The controls were matched at a fixed 1:1 ratio according to age, sex, and type of IBD.

3. Efficacy measures

Age, sex, extent and behavior of disease, presence of perianal lesions, operation history, and concurrent medication were reviewed. Baseline Hb level were also reviewed.

The primary efficacy measure was the rise in Hb ≥2 g/dL from the baseline. The secondary efficacy measure was the rise in Hb ≥20% from the baseline. The total dose of iron and time required to accomplish the end points were also evaluated.

4. Statistical analysis

The data were analyzed using IBM SPSS version 20.0 (IBM Corp., Armonk, NY, USA). Continuous variables were analyzed using the Student t-tests or Mann-Whitney U tests and categorical variables were analyzed using chi-squared tests or Fisher exact tests.

The life table method was used to compare the efficacy between the parenteral and oral iron therapy groups. Efficacy was assessed from two points of view, total dose of iron required and time spent to achieve the end point.

Covariates evaluated included age, gender, type of IBD, route of iron treatment, and baseline Hb. Multivariate Cox regression analysis were used to verify the factors that affect the treatment response. Patients were censored when they discontinued iron therapy due to follow-up loss, ineffectiveness, or adverse event to iron therapy, even though treatment outcomes were not accomplished. Variables with p-values less than 0.20 in the univariate analysis were included to estimate the overall treatment effect. Because demographic data of age and sex were considered clinically fundamental and important, we included these variables in multivariate analysis irrespective of p-value. The p-values less than 0.05 were considered statistically significant in the multivariate analysis.

5. Ethical considerations

The study was approved by the International Review Board of Seoul National University Hospital (IRB number: J-1406-001-580) and was conducted in accordance with the Declaration of Helsinki.

RESULTS

1. Baseline characteristics

Among IBD patients diagnosed with IDA, 41 patients were treated with more than 400 mg of parenteral iron. Indications for parenteral iron prescription were listed in Table 1. Main

Table 1. Indication of Parenteral Iron Therapy

Cause of parenteral administration	No. (%)
Intolerance to oral iron	10 (24)
Nonresponse to oral iron	9 (22)
Severe anemia	9 (22)
Severe intestinal disease activity	9 (22)
Patient's requests	1 (3)
Others	3 (7)

reason was intolerance to oral iron therapy (24%), and others were non-response to oral iron (22%), severe anemia (22%), and severe intestinal disease activity (22%).

Controls were matched with a 1:1 ratio according to age, sex, and type of IBD. Twenty-seven patients (66%) were diagnosed as CD, and 14 (34%) were UC in each group. Between the two groups, there was no significant difference in baseline characteristics (Table 2).

Initial Hb was significantly lower in parenteral iron group than oral iron group (8.4 g/dL vs 9.8 g/dL, p<0.001). Treatment duration was shorter in parenteral iron group but it was not statistically significant (4 weeks vs 12 weeks, p=0.251). Total dose of oral iron was converted to parenteral dose as 1/10 ratio, in other words, 10 mg of oral iron was considered equivalent to 1 mg parenteral iron. Total dose of iron administered was significant lower in parenteral iron group (600 mg vs 1,120 mg, p=0.001), however, there was no significant difference in weekly dose of iron (125 mg vs 112 mg, p=0.162) (Table 3).

2. Efficacy of iron therapy

The life table method was used to compare the efficacy of parenteral and oral iron. The primary efficacy measure was the rise in Hb ≥2 g/dL from the baseline. Among 41 patients in each group, 25 patients (61.0%) in the parenteral iron group achieved the primary end point, meanwhile, 34 patients (82.9%) out in the oral iron group accomplished the goal. Patients in parenteral iron group had tendency to acquire the primary end point in the lower iron dose, but it was not statistically significant (p=0.060) (Fig. 1). Patients in parenteral iron group tended to achieve the primary end point in shorter treatment duration, however, it was also not statistically significant (p=0.087) (Fig. 2).

The secondary efficacy measure was the rise in Hb ≥20% from the baseline. Among the 41 patients in each group, 25 patients (61.0%) in parenteral iron group and 34 patients (82.9%) out in oral iron group achieved the secondary end point. Total iron required to acquire primary end point was much lower in parenteral iron group (p=0.034) (Fig. 3). Parenteral iron group achieved the secondary end point more quickly than oral iron group (p=0.046) (Fig. 4).

Table 2. Baseline Characteristics

Characteristic	Parenteral iron (n=41)	Oral iron (n=41)	p-value
Crohn's disease (n=54)			
Female sex	14 (52)	14 (52)	>0.999*
Age, yr	35.0±11.7	33.7±11.9	0.694†
Age at diagnosis, yr			0.108*
A1 ≤16	6 (22)	1 (4)	
A2 17–40	19 (70)	22 (81)	
A3 >40	2 (8)	4 (15)	
Disease location			0.741*
L1 Terminal ileum	8 (30)	7 (26)	
L2 Colon	3 (11)	5 (18)	
L3 Ileocolon	16 (59)	15 (56)	
Upper gastrointestinal tract	1 (4)	1 (4)	>0.999‡
Disease behavior			0.188*
B1 (NS-NP)	5 (18)	11 (41)	
B2 (structuring)	11 (41)	9 (33)	
B3 (penetrating)	11 (41)	7 (26)	
Perianal disease	6 (22)	11 (41)	0.143*
Operation history	10 (37)	10 (37)	>0.999*
Medication			
5-Aminosalicylic acid	20 (74)	20 (74)	1.000*
Thiopurines	12 (44)	15 (56)	0.414*
Steroid	13 (48)	9 (33)	0.268*
Anti-TNF-α	1 (3.7)	5 (18.5)	0.192‡
Ulcerative colitis (n=28)			
Female sex	7 (50)	7 (50)	>0.999*
Age, yr	39.7±13.4	40.0±14.6	0.963
Age at diagnosis, yr			0.574*
A1 ≤16	0	1 (7)	
A2 17–40	9 (64)	9 (64)	
A3 >40	5 (36)	4 (29)	
Disease location			0.482*
E1 Proctitis	0	1 (7)	
E2 Left side colitis	6 (43)	4 (29)	
E3 Pancolitis	8 (57)	9 (64)	
Operation history	4 (29)	4 (29)	>0.999‡
Medication			
5-Aminosalicylic acid	10 (71)	6 (43)	0.127*
Thiopurines	4 (29)	2 (14)	0.648‡
Steroid	5 (36)	8 (57)	0.256*
Anti-TNF-α	0	0	NA

Data are presented as number (%) or mean±SD.
NS-NP, nonstricturing-nonpenentrating; Anti-TNF-α, anti-tumor necrosis factor α; NA, not applicable.
*Chi-square test; †Student t-test; ‡Fisher exact test.

Table 3. Initial Hemoglobin and Treatment Profile

	Parenteral iron (n=41)	Oral iron (n=41)	p-value
Total dose of iron, mg	600 (400–1,000)	1,120 (560–1,848)	0.001*
Weekly dose of iron, mg	125 (46–200)	112 (112–112)	0.162*
Treatment duration, wk	4 (4–12)	12 (7–17)	0.251*
Initial hemoglobin, g/dL	8.4 (7.5–9.8)	9.8 (8.7–10.6)	<0.001*

Data are presented as median (interquartile range).
*Mann-Whitney U test.

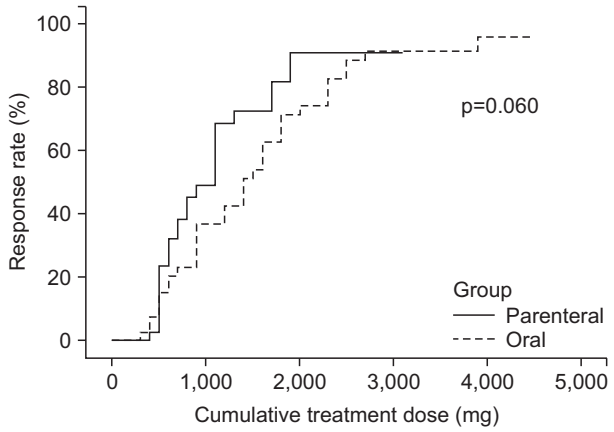

Fig. 1. Comparison of the efficacies of parenteral and oral iron treatment according to the total dose required to achieve a ≥2 g/dL increase in hemoglobin from the baseline. The data were analyzed using the life table method.

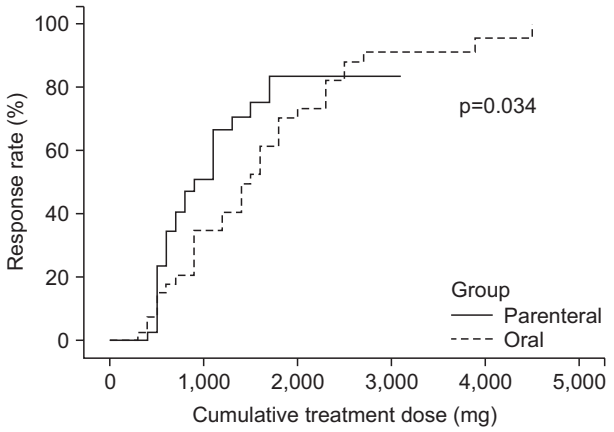

Fig. 3. Comparison of the efficacies of parenteral and oral iron treatment according to the total dose required to achieve a ≥20% increase in hemoglobin from the baseline. The data were analyzed using the life table method.

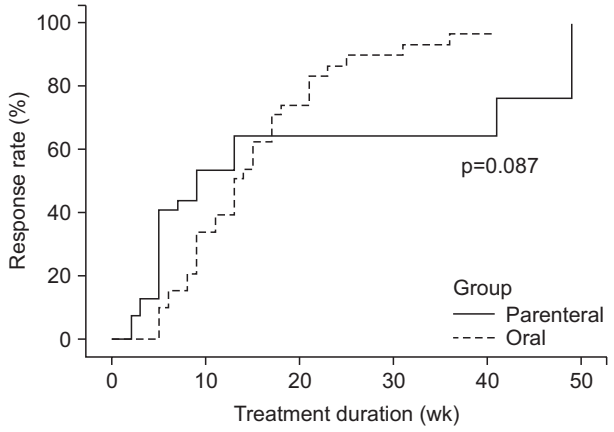

Fig. 2. Comparison of the efficacies of parenteral and oral iron treatment according to the time spent to achieve a ≥2 g/dL increase in hemoglobin from the baseline. The data were analyzed using the life table method.

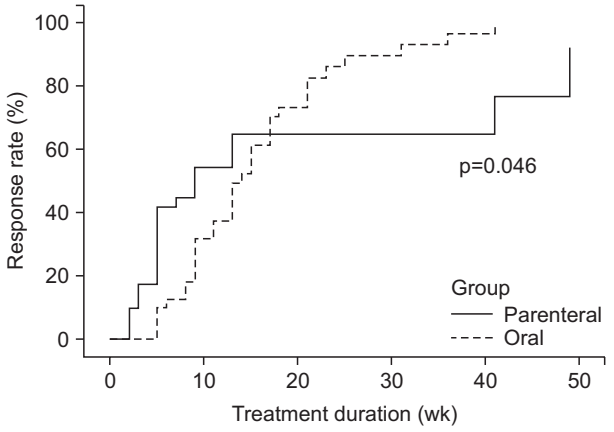

Fig. 4. Comparison of the efficacies of parenteral and oral iron treatment according to the time spent to achieve a ≥20% increase in hemoglobin from the baseline. The data were analyzed using the life table method.

3. Multivariate assessment

Covariates evaluated were age, gender, type of IBD, route of iron treatment, and baseline Hb, and all statistically significant covariates were used to estimate the overall treatment effect.

First, we evaluated the factors associated with the primary outcome, the rise in Hb ≥2 g/dL from the baseline (Table 4). When the same equivalent doses of iron were administered, parenteral iron therapy seemed to be more efficient that oral iron therapy, but it was not statistically significant (hazard ratio [HR], 1.565; 95% confidence interval [CI], 0.855 to 2.864; p=0.146). Patients with UC were good responder to iron therapy (HR, 3.009;

Table 4. Analysis of the Factors That Affect the Increase in Hemoglobin of ≥2 g/dL from the Baseline

Variable	No.	No. of responder (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Age			1.011 (0.992–1.031)	0.256*	0.988 (0.966–1.010)	0.273†
Sex						
Male	40	32 (80.0)	1.000	-	1.000	-
Female	42	27 (64.3)	0.827 (0.494–1.385)	0.471*	0.960 (0.561–1.644)	0.882†
Route of administration						
Oral	41	34 (82.9)	1.000	-	1.000	-
Parenteral	41	25 (61.0)	1.576 (0.911–2.725)	0.103*	1.565 (0.855–2.864)	0.146†
Type of IBD						
Crohn's disease	54	35 (64.8)	1.000	-	1.000	-
Ulcerative colitis	28	24 (85.7)	2.431 (1.432–4.127)	0.001*	3.099 (1.659–5.789)	<0.001†
Initial hemoglobin, g/dL						
Hemoglobin <10	54	41 (75.9)	1.000	-	1.000	-
Hemoglobin ≥10	28	18 (64.3)	0.580 (0.332–1.012)	0.055*	0.449 (0.240–0.841)	0.012†
Anti-TNF-α						
No	76	55 (72.4)	1.000	-	1.000	-
Yes	6	4 (66.7)	0.316 (0.098–1.021)	0.054*	0.416 (0.121–1.425)	0.163†

HR, hazard ratio; CI, confidence interval; IBD, inflammatory bowel disease; Anti-TNF-α, anti-tumor necrosis factor α.
*Univariate Cox regression analysis; †Multivariate Cox regression analysis.

Table 5. Analysis of the Factors That Affect the Increase in Hemoglobin of ≥20% from the Baseline

Variable	No.	No. of responder (%)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	p-value	HR (95% CI)	p-value
Age			1.013 (0.993-1.033)	0.197*	0.986 (0.965-1.008)	0.224†
Sex						
Male	40	32 (80.0)	1.000	-	1.000	-
Female	42	27 (64.3)	0.794 (0.472-1.335)	0.384*	0.910 (0.527-1.571)	0.735†
Route of administration						
Oral	41	34 (82.9)	1.000	-	1.000	-
Parenteral	41	25 (61.0)	1.613 (0.929-2.798)	0.089*	1.552 (0.844-2.851)	0.157†
Type of IBD						
Crohn's disease	54	35 (64.8)	1.000	-	1.000	-
Ulcerative colitis	28	24 (85.7)	2.522 (1.480-4.298)	0.001*	3.415 (1.808-6.450)	<0.001†
Initial hemoglobin, g/dL						
Hemoglobin <10	54	44 (81.5)	1.000	-	1.000	-
Hemoglobin ≥10	28	15 (53.6)	0.464 (0.257-0.838)	0.011*	0.345 (0.177-0.671)	0.002†
Anti-TNF-α						
No	76	54 (71.1)	1.000	-	1.000	-
Yes	6	5 (83.3)	0.327 (0.101-1.058)	0.062*	0.427 (0.125-1.472)	0.178†

HR, hazard ratio; CI, confidence interval; IBD, inflammatory bowel disease; Anti-TNF-α, anti-tumor necrosis factor α.
*Univariate Cox regression analysis; †Multivariate Cox regression analysis.

95% CI, 1.659 to 5.789; p<0.001) and response to iron therapy were poorer when patients' initial Hb was 10 g/dL or higher (HR, 0.449; 95% CI, 0.240 to 0.841; p=0.012).

Moreover, factors associated with secondary outcome, the rise in Hb ≥20% from the baseline, were evaluated (Table 5). When the same equivalent doses of iron were administered, patients treated with parenteral iron achieved the secondary outcome more effectively than those with oral iron, but it was not statis-

tically significant (HR, 1.552; 95% CI, 0.844 to 2.851; p=0.157). Patients with UC responded better to the iron therapy than those with CD (HR, 3.415; 95% CI, 1.808 to 6.450; p<0.001). Patients with initial Hb 10 g/dL or higher responded poorly to iron therapy (HR, 0.345; 95% CI, 0.177 to 0.671; p=0.002).

DISCUSSION

In this study, we showed that parenteral iron is more efficient than oral iron in IBD patient. When evaluating the response rate of Hb rising over 20% from the baseline, it was higher in oral iron group than parenteral iron group (82.9% vs 61.0%). However, patients in parenteral iron group achieved the treatment outcome at the lower total dose and in the shorter duration (p=0.034 and p=0.046, respectively). Considering the influence of confounding factors, multivariate analysis was performed to evaluate the overall treatment effect. Parenteral iron therapy seemed to be more efficient than oral iron therapy, but it was not statistically significant (HR, 1.552; 95% CI, 0.844 to 2.851; p=0.157). Other factors affected the treatment outcome were type of IBD and Initial Hb (HR, 3.415, 95% CI, 1.808 to 6.450, p<0.001; and HR, 0.345, 95% CI, 0.177 to 0.671, p=0.002, respectively).

We established the primary outcome measure as the rise in Hb ≥2 g/dL from the baseline. It was the most widely used criteria in the previous studies to evaluate the treatment response of anemia. However, there was a discrepancy in baseline Hb between parenteral and oral iron groups in our study. Therefore, it seemed unfair to compare the treatment outcome with the absolute rise in the Hb. Thus, we set the secondary outcome as the rise in Hb ≥20% from the baseline. As we expected, in the life table method, only the secondary outcome showed the positive results that meant the superiority of parental iron over oral iron.

Interestingly, in this study the patients with UC responded better to the iron therapy than those with CD. Although we performed extensive literature search to find evidence based explanations for our findings, we couldn't find satisfactory explanations. A possible explanation is that CD patients might have chance that other type of anemia, such as megaloblastic anemia due to vitamin B_{12} deficiency, was combined, because involvement of terminal ileum was observed in 56% of CD patients in this study.

Also, our study showed that patients with initial Hb 10 g/dL or higher responded poorly to iron administration. It is well known that Epo levels are elevated in patients with IDA.[22] We can infer that serum Epo concentration progressively increased as serum iron concentration decreased.[23] Therefore, we can erect a hypothesis that patients with severe IDA (initial Hb <10 g/dL), might have higher Epo level, and responded better when iron was supplied.

Several randomized controlled trials compared the efficacy of parenteral and oral iron therapy.[14-17,24] These studies suggested that intravenous iron is safe, effective and well tolerated in patients with IBD. In the study by Erichsen *et al*.,[17] patients in parenteral iron group received 600 mg of elemental iron, on the other hand, patients in oral iron group received 1,680 mg of elemental iron. Considering low bioavailability of oral iron, there would be discrepancy of total dose of iron absorbed. These discrepancy was also observed in the study of Schröder *et al*.,[16] 1,000 mg to 2,000 mg of parenteral iron versus 8,400 mg to 16,800 mg of oral iron. In the other three studies,[14,15,24] oral iron was administered in the fixed dose, but parenteral iron was adjusted according to the Ganzoni formula.[25] These differences in the treated dose of iron, the efficacy of parenteral iron might be misread. So we adopted the concept of equivalent dose, considering the bioavailability of iron, to measure dose-effect relationship according to the route of administration.

Our study provided the valuable information that the efficacy of parenteral iron was superior to oral iron in Asian population, however, present study had several limitations. First, the number of patients involved in this study was relatively small. It reduced the statistical power, thus, we could only observed the trend of better response of parenteral iron but failed to prove this theory statistically in multivariate analysis. Second, inclusion criteria of IDA patients were ambiguous. We included patients with microcytic hypochromic anemia in complete blood count, because many patients did not undergo further diagnostic test like ferritin, transferrin saturation, vitamin B_{12}, folate, and C-reactive protein. Third, as this was a retrospective design, there was no standardized treatment protocol for oral and parenteral iron therapy. Treatment dose, interval and duration of iron therapy were not uniform. Furthermore, follow up interval in the treated patients were not consistent. Forth, the disease activity at the time of iron administration is one of the important factors which attribute to the efficacy of iron therapy; however, we failed to acquire the data about baseline disease activity such as Crohn's disease activity index or Mayo score at the time of iron administration. However, to overcome this limitation, we analyzed the data about concurrent medication at the time of iron administration, because concurrent medications reflect disease activity. At last, we failed to exactly monitor the safety profile of parenteral and oral iron therapy. When we reviewed the medical records, we could not find any description regarding significant adverse events causing morbidity or mortality. However, minor adverse events might be missed.

In conclusion, our study showed that the efficacy of parenteral iron was better than oral iron group in terms of required iron amount and treatment duration. This study suggested the potential advantage of parenteral iron therapy in IBD patients. Physicians should pay attention to the IDA of IBD patients and consider parenteral iron supplement in appropriate patient group.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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