【 ORIGINAL ARTICLE 】

Beneficial Effects of Oral Iron in Japanese Patients on Hemodialysis

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Abstract:
Objective Iron deficiency anemia (IDA) has become important with regard to mortality in hemodialysis (HD) patients. Therefore, it is necessary to optimize the treatment of these patients.
Methods IDA in end-stage renal disease patients on HD was observed in 42 (33.6%) of 125 patients. We examined the influence of daily orally iron [sodium ferrous citrate (SFC) iron/tablet 50 mg, 1-2 tablets] on the renal function markers, anemia and iron data for about 6 months.
Results The hematocrit and hemoglobin levels were significantly increased in the patients treated with SFC [hematocrit: before 28.5%±2.1% (mean ± standard deviation), 1st month 30.0%±2.3%, $p<0.05$; 3rd month 32.4%±2.9%, $p<0.05$; 6th month 31.3%±3.4%, $p<0.05$; and hemoglobin: before 9.25±0.70, 1st month 9.72± 0.71, $p<0.05$; 3rd month 10.54±0.96, $p<0.05$; 6th month 10.25±1.21 g/dL, $p<0.05$]. The transferrin saturation (TSAT) and serum ferritin levels were significantly increased in the patients treated with SFC (TSAT: before 21.5%±10.0%, 1st-3rd month, 34.1%±15.1%, $p<0.05$; 6-8th month 34.7%±11.9%, $p<0.05$; and ferritin: before 38.2±37.1, 6-8th month 67.5±44.0 ng/mL, $p<0.05$). The present findings clearly indicate that oral iron is an effective route of iron supplementation in HD patients, and no adverse effects associated with SFC occurred during the treatment and follow-up period.
Conclusion Our results clearly indicate that oral iron delivered via SFC is a well-tolerated and effective form of iron supplementation in long-term HD and IDA patients in Japan.

Key words: ferritin, hemodialysis (HD), iron (Fe), iron deficiency anemia (IDA), oral iron, transferrin saturation (TSAT)

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Introduction

Advances in treating hemodialysis (HD) have enabled patients with end-stage renal disease (ESRD) to survive for long periods (1, 2). However, the progression of cardiovascular disease remains a major clinical problem (3). Consequently, iron deficiency anemia (IDA) is common, and the presence of cardiovascular disease has become an increasingly important factor with regard to mortality due to IDA in HD patients.

Parenteral iron therapy is sometimes required in iron-deficient patents with extensive chronic blood loss and in those who are unable to tolerate or absorb adequate amount of iron by normal oral ingestion (4). However, various side effects of iron preparation have been reported, and thus far no studies have reported the effect of iron supplementation on the metabolism of phosphorus, except for our previous reports and other reports on hypophosphatemia and/or osteomalacia induced by the use of saccharated iron oxide (SIO) [Fesin®, also known as iron sucrose (IS)] (4-9). To investigate the physiologic damage and histologic deterioration of the kidney caused by SIO and iron dextran (ID), we administered these substances intraperitoneally to rats (10). SIO was found to be more toxic than ID. However, only SIO is currently available as an iron preparation, and neither iron chondroitinsulfate (Blutal®) nor cideferron (Ferricon®, also known as iron dextrin) are available in Japan any longer.

Table 1. Patients Profile.

	All	No iron	Oral iron
No	125	83	42
Age (year), male/female	66±13, 86/39	67±13, 56/27	64±14, 24/18
Duration of HD (years)	10±10	10±10	10±8
Original disease*	48/49/10/9/9	34/29/5/7/8	14/20/5/2/1
Hb (g/L)	10.4±1.3	10.9±1.2	9.3±0.7
Fe (µg/dL)	74±33	81±35	58±27
TIBC (µg/dL)	277±54	276±54	278±55
TSAT (%)	28±14	31±15	22±10
Ferritin (ng/mL)	76±127	94±151	38±37
Cr (mg/dL)	9.2±2.3	9.2±2.5	9.3±2.0
BUN (mg/dL)	53±11	54±11	52±12
Ca (mg/dL)	9.2±0.6	9.2±0.7	9.1±0.6
P (mg/dL)	5.1±1.1	5.0±1.0	5.3±1.1
Alb (g/dL)	3.8±0.4	3.8±0.4	3.7±0.4
AST (IU/L)	13±5	13±5	13±5
ALT (IU/L)	10±7	10±4	11±10
ALP (IU/L)	263±88	266±97	253±69
CRP (mg/dL)	0.32±0.47	0.32±0.44	0.32±0.53

The data are expressed as mean ± standard deviation.

Hb: hemoglobin, Fe: iron, TIBC: total iron binding capacity, TSAT: transferrin satura-
tion, Cr: creatinine, BUN: blood urea nitrogen, Ca: calcium, P: phosphate, Alb: albu-
min, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline
phosphatase, CRP: C-reactive protein, HD: hemodialysis, CGN: chronic glomerulone-
phritis, DM: diabetic nephropathy, HTN: hypertensive nephrosclerosis, PCKD: poly-
cystic kidney disease
*: CGN/DM/HTN/PCKD/Other diseases

In this study, we evaluated the treatment of the IDA in ESRD patients on maintenance HD to clarify the beneficial and adverse effects of oral iron in Japanese patients on HD.

Materials and Methods

Patients

A total of 125 patients (Table 1) with ESRD on mainte-
nance HD at Fukumitsu Hospital were examined. IDA with
medication was observed in 42 (33.6%) [men/women 24/18,
64.2±14.2 (mean ± standard deviation) years old] of the 125
patients. We examined the effects of oral iron administration
[sodium ferrous citrate (SFC), Ferromia®, 50 mg iron per
tablet] as 1 tablet/day (one tablet at supper; 39 patients) - 2
tablets/day (one tablet at breakfast and one at supper; 3 pa-
tients) on the renal function markers, anemia and iron pa-
rameters for about 6 months between January 2014 and May
2016. No patients were receiving intravenous iron. All pa-
tients initially took only one tablet at supper.

The present study was performed using a non-randomized
analysis at a single center with a prospective and non-
controlled design and included a small number of patients.
The procedures were carried out in accordance with the
ethical standards of the Human Investigation Committee
(Fukumitsu Hospital No. 2-2014). All patients gave their
oral informed consent.

Dialysis schedule

The patients underwent four- to five- hour sessions of HD
therapy three times per week. We used a standard hollow-
fiber dialyzer and bicarbonate, as follows: sodium (Na⁺) 140
mEq/L, potassium (K⁺) 2.0 mEq/L, calcium (Ca⁺⁺) 2.5 mEq/
L, magnesium (Mg⁺⁺) 1.0 mEq/L, chloride (Cl⁻) 110 mEq/L,
CH_3COO^- 8 mEq/L, HCO_3^- 30 mEq/L and glucose 150 mg/
dL in dialysate. The blood flow rate was 200 mL/min, and
the dialysate flow rate was kept constant at 500 mL/min.

Blood sampling

The hematocrit, hemoglobin, serum creatinine, blood urea
nitrogen, calcium, phosphate, albumin, aspartate aminotrans-
ferase (AST), alanine aminotransferase (ALT), alkaline
phosphatase (ALP), C-reactive protein (CRP), iron, total
iron binding capacity (TIBC), ferritin concentrations, and
transferrin saturation (TSAT = [iron / TIBC] ×100%) were
measured in blood samples drawn immediately before HD
(not fasting).

Statistical analyses

The values are expressed as the mean ± standard devia-
tion. The significance of the differences between the two
groups was calculated using a paired *t*-test. p values of <
0.05 were considered to be statistically significant.

Table 2.   Anemia of the Patients with End - Stage Renal Disease on Maintenance Hemodialysis.

	Before	After		
		1st month	3rd month	6th month
Ht (%)	28.5±2.1	30.0±2.3*	32.4±2.9*	31.3±3.4*
Hb (g/L)	9.25±0.70	9.72±0.71*	10.54±0.96*	10.25±1.21*

The data are expressed as mean ± standard deviation.

*: p<0.05 compared between before and 1st, 3rd or 6th month after treatment.

Ht: hematocrit, Hb: hemoglobin

Table 3.   The Results of the Iron Related Parameters in the Patients with End - Stage Renal Disease on Maintenance Hemodialysis.

	Before	After	
		1st-3rd month	6th-8th month
Fe (µg/dL)	58.4±27.4	86.9±35.3*	85.1±26.9*
TIBC (µg/dL)	278±55	262±42*	249±34*
TSAT (%)	21.5±10.0	34.1±15.1*	34.7±11.9*
Ferritin (ng/mL)	38.2±37.1	41.8±24.7	67.5±44.0*

The data are expressed as the means ± standard deviation.

*: p<0.05 compared between before and 1st-3rd or 6th-8th month after treatment.

Fe: iron, TIBC: total iron binding capacity, TSAT: transferrin saturation

Results

IDA was defined as serum TSAT level <20% or serum ferritin level <100 ng/mL.

As shown in Table 2, the hematocrit and hemoglobin levels were significantly higher after treatment with SFC (hematocrit: before 28.5%±2.1%, 1st month after treatment, 30.0%±2.3%, p<0.05; 3rd month, 32.4%±2.9%, p<0.05; 6th month, 31.3%±3.4%, p<0.05; and hemoglobin: before 9.25± 0.70 g/dL, 1st month after treatment, 9.72±0.71 g/dL, p< 0.05; 3rd month, 10.54±0.96 g/dL, p<0.05; 6th month, 10.25±1.21 g/dL, p<0.05).

As shown Table 3, the serum iron, TIBC, TSAT and serum ferritin levels were significantly higher after treatment with SFC (iron, TIBC or TSAT: before 58.4±27.4 µg/dL, 278±55 µg/dL or 21.5%±10.0%, 1st-3rd month after treatment, 86.9±35.3 µg/dL, 262±42 µg/dL or 34.1%±15.1%, p< 0.05; 6-8th month, 85.1±26.9 µg/dL, 249±34 µg/dL or 34.7%±11.9%, p<0.05; and ferritin: before 38.2±37.1 ng/mL and 6-8th month after treatment, 67.5±44.0 ng/mL, p<0.05).

The blood urea nitrogen and serum albumin levels were significantly lower and higher, respectively, at the 1st, 3rd and 6th month after treatment with SFC (p<0.05; Table 4). The serum phosphate and calcium levels were significantly lower and higher, respectively, at the 6th month after treatment with SFC (p<0.05; Table 4). The serum creatinine, AST, ALT, ALP, and CRP levels were not significantly different between before and after treatment.

Forty of the 42 patients treated with SFC were adminis-

tered erythropoiesis-stimulating agents (ESAs) during the study period. In 17 patients (darbepoetin alfa in 6 patients and epoetin alfa in 11 patients), the ESA dose was reduced (before: 4,941±2,059 IU/week and 3-6th month after treatment: 2,247±1,540 IU/week; p<0.05). The ESA dose was not changed in the other 23 patients.

We investigated the effect of phosphate binders, calcium carbonate, sevelamer hydrochloride, lanthanum carbonate, and bixalomer. The number of patients who used phosphate binders was as follows: calcium carbonate in 22 patients (1.15±0.4 g), sevelamer hydrochloride in 6 patients (1.88± 1.0 g), lanthanum carbonate in 8 patients (1.33±0.80 g), and bixalomer in 15 patients (2.0±1.0 g). The doses of phosphate binders were small and did not differ among the treatment groups during the study period.

No acute or chronic adverse effects associated with SFC occurred during the treatment and follow-up period.

Discussion

The present findings clearly indicate that oral iron (SFC) is a well-tolerated and effective form of iron supplementation in long-term IDA and HD patients.

All of the patients were successfully and safely treated with oral iron alone in our study (Table 2, 3). Although SFC is known to cause nausea, constipation, abdominal pain, diarrhea, and emesis as acute adverse effects, and urticaria, skin eruption and elevation of AST, ALT and ALP as chronic adverse effects, no acute or chronic adverse effects were observed in the patients receiving SFC during the treatment and follow-up period. The lack of any acute or chronic adverse effects may have been because all patients in this study began with one tablet at supper.

Endothelial cell damage is seen *in vivo* with IS but not ID (11). These results support the finding reported that SIO (also known as IS) is more toxic than ID (10). Parenteral iron formulations have potent, but highly variable, cytotoxic potential that appears to correlate with the degree of cell iron uptake (IS >> ID) (12). Agarwal et al. (11) reported that IS administration in chronic kidney diseases patients increased the rate both proteinuria and proximal tubular enzymuria. In Japan, SIO is the only currently available iron preparation, and neither iron chondroitinsulfate nor cideferron are available any longer.

Although it causes oxidative stress, ID does not cause

Table 4.   Clinical Data and Dialysis of the Patients with End - Stage Renal Disease on Maintenance Hemodialysis.

	Before	After		
		1st month	3rd month	6th month
Cr (mg/dL)	9.3±2.0	9.2±2.0	9.3±1.9	9.3±2.2
BUN (mg/dL)	52±12	48±9*	47±8*	48±10*
Ca (mg/dL)	9.1±0.6	9.0±0.5	9.2±0.6	9.3±0.7*
P (mg/dL)	5.3±1.1	5.0±1.1	4.9±1.0	4.8±1.0*
Alb (g/dL)	3.74±0.39	3.85±0.35*	3.87±0.37*	3.87±0.41*
AST (IU/L)	12.7±4.9	12.3±4.3	13.0±5.0	13.6±7.6
ALT (IU/L)	10.9±10.2	10.4±8.3	10.8±7.4	10.6±6.7
ALP (IU/L)	253±69	260±85	249±91	260±87
CRP (mg/dL)	0.32±0.53	0.33±0.43	0.33±0.44	0.42±0.69

The data are expressed as mean ± standard deviation.

*: $p < 0.05$ compared between before and 1st, 3rd or 6th month after treatment.

Cr: creatinine, BUN: blood urea nitrogen, Ca: calcium, P: phosphate, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, CRP: C-reactive protein

kidney injury (13). However, the occurrence of anaphylaxis, which can lead to death, has decreased the use of this drug (14). Anaphylaxis is much rarer in patients administered non-dextran iron (15) but very common in patients administered IS in Japan.

IS and ID induce massive and similar degrees of lipid peroxidation. However, marked differences in the rate of cell death have been noted resulted (IS >> ID). As such, parenteral IS may be a highly potent pro-oxidant capable of inducing tubular and endothelial death (16). These previous findings suggest that IS is the most toxic of parenteral iron supplements.

The serum phosphate level was significantly decreased in the SFC-treated group. It is well known that both oral and intravenous administration of iron cause hypophosphatemia. Kuroda et al. (17) hypothesized that this side effect of iron may be beneficial for the treatment hyperphosphatemia in HD patients. They used the same iron medication as we did in the preset study SFC.

In patients with IDA and moderate-to-advanced chronic kidney disease (non-dialysis dependent), intravenous IS appeared to increase the risk of infections and cardiovascular complications compared with oral iron, so oral iron may be the preferred initial mode of treatment for IDA (18).

In this clinical study, all patients with IDA were given SFC orally, because the intravenous administration of iron to patients with chronic renal failure may cause hemosiderosis (17). The oral administration of iron is not believed to cause hemosiderosis (19).

In general, oral irons may be safer and less expensive, while intravenous irons may be easily utilized and more effective than oral irons. The recent meta-analysis by Shepshelovich et al. (20) showed that intravenous iron was the preferred treatment for dialysis patients with stage 5 chronic kidney disease. However, SFC may have been useful in our study because of its "citric acid" and "ferrous" components.

Kuragano et al. (21) reported that serum hepcidin levels were faithfully reflected in serum ferritin levels (an iron storage parameter) in maintenance HD patients. Consequently, iron administration may be the main cause of the rise in serum hepcidin levels in maintenance HD patients.

Ferroportin is an iron exporter present on the surface of absorptive enterocytes. When hepcidin binds to ferroportin in tissue cell, ferroportin is degraded leading to the reduced export of cellular iron after binding (22).

With the availability of ESAs for HD patients, not only intravenous iron but also oral iron have become effective in treating this population. The present findings indicate that oral or intravenous iron is a well-tolerated and effective form of iron supplementation in long-term IDA and HD patients.

Hypophosphatemia caused by SIO (23) or iron polymaltose (24) is another form of fibroblast growth factor 23-related hypophosphatemia. However, oral iron dose not increase the levels of fibroblast growth factor 23. In this study, the serum phosphate levels were significantly decreased in patients treated with oral iron (SFC) for 6 months (Table 4).

Furthermore, the blood urea nitrogen and serum albumin levels were significantly lower and higher, respectively, at the 1st, 3rd and 6th month after treatment with SFC (Table 4). Although the reason for these changes unclear at present, the reduction in blood urea nitrogen and increase in the serum albumin levels may be good for the quality of life of HD patients with IDA.

Ferric citrate hydrate (FCH) is used to treat hyperphosphatemia in HD/ non-dialysis dependent patients. FCH may also have the ability to replenish iron stores and reduce the ESA dose (25). A long-term trial of FCH will help clarify its relative efficacy and safety as an oral iron supplement. SFC and FCH both contain citric acid which promotes iron absorption.

Several limitations associated with the present study warrant mention. The present study was performed in a single arm using a prospective and non-controlled design with a

small number of patients. Furthermore, a study protocol comparing the effects of oral and intravenous iron (only SIO) is the best. We firmly believe that the potential benefits of oral iron therapy are important for improving the rates of cardiovascular morbidity and mortality in HD and IDA patients.

Conclusion

The present findings clearly indicate that oral iron (SFC) is a well-tolerated and effective form of iron supplementation in long-term HD and IDA patients. These results suggest that oral iron may be an ideal treatment for HD patients with IDA in Japan. Future prospective studies with a larger number of patients are required to confirm our results.

The authors state that they have no Conflict of Interest (COI).

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