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Oral Ferric Citrate Hydrate Associated With Less Oxidative Stress Than Intravenous Saccharated Ferric Oxide

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Introduction: A recent study suggested that orally dosed ferric citrate hydrate (FC) corrects renal anemia in patients on hemodialysis (HD), suggesting biological differences in effects of iron supplementation using different routes of administration. To address this issue, the present study compared oral FC with i.v. saccharated ferric oxide (FO) in stable HD patients.

Methods: Participants comprised 6 patients administered 3 consecutive protocols in the first HD session of the week in a fasting state: nothing given, as control (C); oral load of FC (480 mg iron), and 5 minutes of i.v. FO (40 mg iron). Iron dynamics in the body and biological impact on redox-inflammation status during the study (6 hours) were examined.

Results: Significant increases in serum iron and transferrin saturation were seen with both FC and FO. Regarding total iron-binding capacity as the sum of serum iron and unsaturated iron-binding capacity, no changes were found in FC, whereas significant increases were seen in FO (appearance of non–transferrin-binding iron [NTBI]), despite the lower serum iron levels in FO. Compared with C, increases were seen in serum myeloperoxidase (oxidative marker) with accompanying significant decreases in thioredoxin (antioxidant) in FO, whereas no changes were found in FC.

Conclusion: Oral FC differs from i.v. FO in areas such as less NTBI generation and less induction of oxidative stress. The result indicates potential clinical benefits of oral FC in terms of iron supplementation for renal anemia in HD patients.

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Renal anemia in patients with chronic kidney disease (CKD) and those on chronic dialysis treatment increases the risks of cardiovascular events, progression of CKD, and mortality, and decreases quality of life, mental health, and cognitive function.[1] Adequate management of renal anemia is thus important for these patients.

Primary pathologic mechanisms of renal anemia include relatively suppressed production of erythropoietin and impaired utilization of iron in the body. And enhanced oxidative stress, and micro-inflammation by uremia could be involved with the pathology of poor response to erythropoietin-stimulating agent, and underutilization of iron in the body.[2,3] In addition, iron loss associated with blood loss in patients on hemodialysis (HD) reportedly reaches up to 2000 to 6000 mg annually.[4] Given this pathologic background, adequate iron supplementation should be a mainstay for renal anemia management in HD patients.

At present, i.v. iron administration is a common practice in HD treatment, because the superior

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effectiveness of i.v. iron has been confirmed as compared with oral iron intake, as recently reviewed by Albaramki *et al.*[5] and Shepshelovich *et al.*[6] However, meta-analysis of randomized clinical trials in a wide range of clinical backgrounds (a total of 75 studies including 19 of renal anemia) have revealed that i.v. iron administration increases the risks of infectious diseases, as compared with oral iron and no iron intake.[7] Furthermore, a recent randomized clinical trial conducted in patients with pre-dialysis CKD have suggested increased risks for cardiovascular disease and infection[8] with i.v. iron administration, suggesting that i.v. iron may damage endothelial and immune cells to disturb those functions.

Ferric citrate hydrate (FC) is used as a phosphate binder for patients with CKD,[9–13] and has recently gained attention with respect to iron supplementation for CKD.[11,14,15] Patients who have been receiving FC as a phosphate binder have recently been reported to show significantly decreased prevalences of i.v. iron administration, decreased dose of erythropoietin-stimulating agents, and increased level of hemoglobin during a 12-month observation period,[15] suggesting that FC benefits patients with renal anemia. Notably, a recent randomized clinical trial of renal anemia revealed the effectiveness of FC for increasing hemoglobin in patients with pre-dialysis CKD.[16] Taking these findings together, orally administered FC may offer clinical advantages with respect to the iron load to patients with CKD. The biological characteristics of this agent thus need to be clarified.

The present study examined differences between orally administered FC and i.v.-administered saccharated ferric oxide (FO), in terms of iron kinetics and biological impact on redox-inflammation status in the body during the acute phase of iron loading.

PATIENTS AND METHODS

Patients

Six patients on maintenance HD were recruited for the study from Jikyukai Tani Hospital (Motomiya, Japan). They had been receiving HD 3 times a week at 4 hours per session. Patient characteristics are shown in Table 1. Patients who had acute infection, malignancy or gastrointestinal disease, or who were current smokers were excluded from the study. Informed consent was obtained from all participants, and the study protocol was fully approved by the ethics committee at Fukushima Medical University (No. 2605).

Table 1. Patient demographics

n	6
Age, yr	70.3 ± 6.2
Sex, male	3
Dialysis vintage, yr	2.4 (1.6 to 12.0)
Body weight, kg	58.1 ± 7.4
Height, cm	155 ± 5
Underlying kidney disease	
Nephrosclerosis	3
Diabetic nephropathy	3
ESA	
Darbepoetin (15–40)/wk	5
None	1
WBC ($\times 10^2/\mu l$)	5117 ± 1060
Neutrophils, %	70.5 ± 9.5
Hemoglobin, g/dl	11.4 ± 1.6
Total protein, g/dl	6.5 ± 0.1
Albumin, g/dl	3.7 ± 0.3
Creatinine, mg/dl	7.7 ± 1.0
CRP, mg/dl	0.12 ± 0.18
Iron, μg/ml	56 ± 23
Ferritin, ng/ml	27.0 (17.1 to 244.0)
TIBC, μg/dl	293 ± 28
Transferrin saturation, %	19.2 ± 7.6

CRP, C-reactive protein; ESA, erythropoiesis-stimulating agents; TIBC, total iron-binding capacity; WBC, white blood cells.
Values are mean ± SD or median (minimum to maximum).

Patients participating in the study received 3 consecutive protocols. Under the first protocol (phase I), nothing was given. Second (phase II), 8 tablets of FC (Riona 250 mg; Japan Tobacco Inc., and Torii Pharmaceutical Company, Ltd., Tokyo, Japan) containing a total of 480 mg of iron were given orally. In the study, the dose of FC was decided according to the allowance of the Japanese medical insurance system. Permissible daily maximum dose of FC (Riona 250 mg) is 6 g (24 tablets: oral 3 times a day) in Japan. Based on this, we designed to give the maximum amount of 1 time of FC to patients (e.g., 8 tablets at once). Third (phase III), saccharated FO (Fesin; Nichi-Iko Pharmaceutical Co., Ltd., Toyama, Japan) containing 40 mg of iron was infused during the first 5 minutes of HD. The dose of infused FO was decided according to the standard clinical practice in Japan. Fesin is the only injectable iron drug commercially available in Japan, and it is recommended to inject once a week if needed from Japanese Society Dialysis Treatment (Guideline for Renal Anemia in Chronic Kidney Disease, J Jpn Soc Dial Ther 2016; 49(2):89–158, in Japanese).

The study was performed in all patients during the first HD session of the week in a fasting state in the morning over the course of 3 weeks. Blood samples were taken from an arterial access site at 0 hour (T0) just before starting HD, and at 0.5, 1, 2, and 4 hours (at the end of HD), and 6 hours (2 hours after the end of HD), respectively.