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ORIGINAL ARTICLE

Low-dose ferrous bisglycinate chelate supplementation in chronic kidney disease and hemodialysis patients

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Abstract

Background: Provision of parenteral or oral iron supplementation can restore iron stores and maintain stable hemoglobin levels in chronic kidney disease (CKD) and hemodialysis (HD) patients. The route for oral or intravenous (IV) administration of iron depends on the acuity of anemia, costs, and patient tolerance. IV iron can restore iron stores rapidly but also carries higher risks for allergy and infection. Oral iron supplementation is limited by high gastrointestinal adverse effects.

Methods: We conducted an open-label trial to study the efficiency of a film-coated iron supplementation tablet, which contains ferrous bisglycinate chelate, vitamin C, and folic acid, in CKD stage 3b to 4 and HD patients.

Results: Twenty-seven HD patients and 20 CKD patients participated this study. After a 16-week intervention, low-dose ferrous bisglycinate chelate improved serum iron concentration (67.8 vs 87.2 mg/dL, $p = 0.04$) and transferrin saturation (24.7% vs 31.3%, $p = 0.03$) in stage 3 to 4 CKD patients, restored iron loss, and maintained stable hemoglobin levels in HD patients. No GI upset events were reported.

Conclusion: Ferrous bisglycinate chelate is a well-tolerated oral iron supplementation for CKD and HD patients.

Keywords: Chronic kidney disease; Ferrous bisglycinate; Hemodialysis; Iron deficiency anemia

1. INTRODUCTION

Anemia occurs commonly among patients with advanced chronic kidney disease (CKD) and hemodialysis (HD) or peritoneal dialysis. The main pathophysiological mechanism of anemia in this population is the deficiency of kidney-derived erythropoietin. Even 30 years after the introduction of erythropoiesis-stimulating agents (ESAs), 50% or more of CKD patients are suffering from anemia. Iron deficiency is another major factor contributing to the impaired erythropoiesis in CKD patients. Iron deficiency is highly common in CKD patients with anemia. Iron deficiency includes absolute iron deficiency (paucity of iron stores) and functional (relative) iron deficiency. The latter is usually caused by chronic inflammation and upregulated expression of hepcidin, which inhibits iron availability. An adequate repletion of iron is necessary to improve or even maximize the efficacy of ESA therapy.

There are a few different options to choose from when providing iron. There are advantages and drawbacks of each option. For rapid correction of iron deficiency, parenteral iron is often used for CKD patients. It is a more common route taken for HD patients. The drawbacks of intravenous (IV) iron include endothelial dysfunction, systemic inflammation, risk of bacterial infection, and anaphylaxis.[1,2] Hemosiderosis may even increase risk of cardiovascular complications.[3] On the other hand, the oral iron supplement is limited by the gastrointestinal (GI) side effects and bioavailability.[4] Cochrane Kidney and Transplant Group reviewed all registered randomized controlled trial and compared the parenteral versus oral iron therapy for CKD patients up to 2018.[5] The analysis showed that there is no difference in the total patient mortality rate, death due to cardiovascular complications, renal function decline, or blood transfusion rate in the two options for iron supply. In addition to the rate of goal achievement time, the main difference between the two options is that allergic reactions and hypotension (relative risk [RR], 3.56; 95% confidence interval [CI], 1.88-6.74) are seen more often with use of IV iron, but there are less GI adverse effects (RR, 0.47; 95% CI, 0.33-0.66).[5] The best way to improve iron supplementation is either by reducing inflammatory and allergic reactions of IV iron or diminishing GI side effects of oral iron supplements.

Three common oral iron supplements are ferrous sulfate, ferrous gluconate, and ferrous fumarate. Increasing the dose of these iron salts theoretically increases the total iron absorption, but it also increases the risks of GI side effects. Of the side effects, nausea, constipation, and flatulence are especially common to see. In addition, the bioavailability of these oral ferrous supplements is decreased by foods and chelating drugs. Ferrous bisglycinate chelate is an iron amino acid chelate. It is formed by chelating a ferrous iron to two molecules of amino acid glycine with a covalent bond. Therefore, ferrous bisglycinate chelate has fewer GI tract side effects, better absorption, and better storage of iron. It also has a higher margin of increase in hemoglobin levels than conventional iron salts.[6–8] Preclinical studies illustrate that ferrous bisglycinate chelate, when compared with other iron elements, exhibits

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a different enterocyte mechanism in intestine cells.[9,10] In an anemic animal model, ferrous bisglycinate chelate normalized microbiota and prevented colitis. Other iron supplements had higher detrimental effects.[11] The safety margin of ferrous bisglycinate chelate was up to 500 mg/kg higher than other oral iron forms.[12] Several clinical studies showed that when compared with ferrous citrate or ferrous phosphate, ferrous bisglycinate chelate increased the iron absorption by 2 to 4 times. It also cut the GI side effects in half.[7,8,13–15] The "Er Yue Hong" is an oral iron supplement in tablet form with film coating. Each tablet contains 10.35 mg iron from ferrous bisglycinate chelate, 36.45 mg vitamin C, and 0.122 mg folic acid. On the basis of the significant improvement in hemoglobin level and the iron structure difference, it was inferred that CKD patients with iron deficiency may have better response to the ferrous bisglycinate chelate than other iron supplements. Until now, there have not been any studies on ferrous bisglycinate chelate supplement in the CKD and HD population. Therefore, to study the safety and potential benefits of ferrous bisglycinate chelate as iron supplementation in CKD and HD patients, we conducted a 16-week open-label intervention study in nondialysis dependent (NDD) CKD and HD patients, respectively.

2. METHODS

2.1. Patient enrollment and study design

This is an open-label interventional study. CKD stage 3b to 4 (expected glomerular filtration rate [eGFR]15–45 mL/min) and HD patients from ages 20 to 80 years old were enrolled from the Wei-Gong Memorial Hospital Outpatient Department. The inclusion criteria was hemoglobin less than 12 g/dL and ferritin <500 mg/L. Individuals with recent GI bleeding, active infections, red blood cell transfusions, or those under current iron replacement treatment were excluded. After getting informed of the process and giving consent, patients stopped all their IV or oral form iron supplements. Folic acid and vitamin supplements were also discontinued. The participants took 10.35 mg iron daily for 16 weeks. Hemoglobin, serum iron, ferritin, transferrin saturation, total iron binding capacity, and serum creatinine were measured at baseline and monthly. The total intervention time was 16 weeks. The primary outcome was the changes of hemoglobin, ferritin, serum iron, and transferrin saturation. This study was approved by the Institute Review Board, and all participants have signed the informed consent form.

2.2. Ferrous bisglycinate chelate supplement

Er Yue Hong, an iron supplement in film-coated tablet form containing iron 10.35 mg from ferrous bisglycinate chelate, vitamin C 36.45 mg, and folic acid 0.122 mg was provided by Microbio Co., Ltd., Taiwan.

2.3. Statistical analysis

Normally distributed continuous data were expressed as mean ± standard deviation. Numeric data not normally distributed was expressed as median and interquartile range. Statistical analysis was performed with SPSS 19.0 software. Chi-square and student *t* tests were used to compare data between different groups. Comparisons of continuous variables before and after iron supplement were performed by paired *t* tests or the Mann-Whitney *U* test. One-way analysis of variance with linear term and unweighted descriptive was used for trend analysis. All probabilities were two tailed, and significance was determined as p value <0.05.

3. RESULTS

3.1. Baseline demographic data

Fifty patients signed informed consent and were enrolled in this study, three patients drop out (one patient immigrated, another patient received blood transfusion in bone fracture surgery, the other withdraw because she want to continue other vitamin supplements). Twenty NDD CKD stage 3b to 4 patients and 27 HD patients participated in and completed the study. The baseline demographic data is listed in Table 1. The serum creatinine levels in the NDD CKD group were 2.47 ± 0.68 mg/dL. Our patients had multiple comorbid conditions. More than half of the patients had diabetes and hypertension. Baseline hemoglobin levels were 9.6 and 10.8 g/dL in NDD CKD and HD patients. Ferritin levels were 206.5 ± 137 ng/mL in NDD CKD patients and 235.9 ± 156 ng/L in HD patients. Transferrin saturation was above 20% in both groups. The baseline data showed that iron status of these patients was controlled within KDOQI anemia treatment guideline recommendations, that is, serum ferritin >200 ng/mL and transferrin saturation >20%.

3.2. Low-dose ferrous bisglycinate chelate improved serum iron and transferrin saturation in NDD CKD patients

Under the Taiwan National Health Insurance Reimbursement Policy, CKD patients with eGFR <15 mL/min are eligible to ESA treatment as long as hemoglobin <9 gm/dL. To avoid possible bias caused by ESA, we did not include CKD patients with eGFR <15 mL/min who had not yet received dialysis. After the 4-month intervention, the fixed-dose ferrous bisglycinate chelate supplement showed an improved serum iron level from 67.8 to 82.2 μg/mL (p for trend = 0.04) and transferrin saturation from 24.7% to 31.3% (p for trend = 0.03). There were no significant changes in hemoglobin concentration or serum ferritin level after intervention. The fixed-dose ferrous bisglycinate chelate supplement did not alter the renal function of NDD CKD patients (Fig. 1).

3.3. Low-dose ferrous bisglycinate chelate maintained hemoglobin and iron status in HD patients

Under the Taiwan National Health Insurance System, the HD reimbursement bundle payment policy for indication of ESA treatment if hemoglobin level was less than 11 g/dL. All patients on HD have to take a hemoglobin test every week and receive a corresponding dose of ESA to maintain a hemoglobin value of 10–11 g/dL. We followed the National Health Insurance Reimbursement Policy and did not restrict ESA dosage for the moral issue in this study. In the study period, the average monthly ESA doses were around 25,000 to 32,000 units per week. Hemoglobin levels ranged from 9.0 to 10.2 g/dL. The paired *t* analysis revealed that a low-dose ferrous bisglycinate chelate supplement has no change in hemoglobin, serum ferritin, TIBC, and transferrin saturation. In addition, no patients

Table 1

Baseline demographic data of study populations

Characteristics	HD (n = 27)	NDD CKD (n = 20)	*p*
Age, y	64 ± 11.2	58 ± 8.2	0.573
Male gender, n (%)	20 (74%)	10 (50%)	0.218
Hypertension, n (%)	22 (81%)	19 (95%)	0.178
Diabetes mellitus, n (%)	18 (67%)	17 (85%)	0.138
Coronary artery disease, n (%)	1 (4%)	10 (50%)	0.014
Peptic ulcer, n (%)	0	1	1.000
Albumin, g/dL	3.2 ± 0.3	3.5 ± 0.4	0.102
Hemoglobin, mg/dL	9.6 ± 1.1	10.8 ± 1.2	<0.001
Ferritin, ng/mL	235.9 ± 156	206.5 ± 137	0.253
TIBC, μg/dL	255.1 ± 49.3	284.4 ± 45.7	0.022
Serum iron, μg/dL	67.8 ± 21.8	65.9 ± 21.8	0.278
Transferrin saturation, %	24.7 ± 10.5	23.8 ± 8.9	0.295

CKD = chronic kidney disease; HD = hemodialysis; NDD = nondialysis dependent; TIBC = total iron-binding capacity.

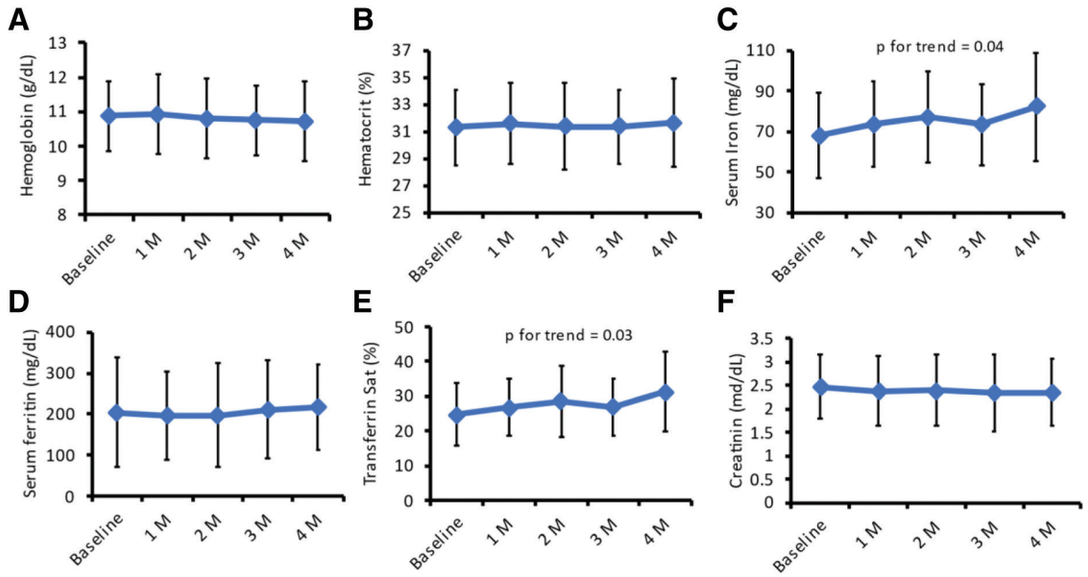

Fig. 1 Low-dose cheated ferrous bisglycinate supplement improves iron storage in CKD stage 3–4 patients. Serial changes of hemoglobin (A), hematocrit (B), serum iron (C), ferritin (D), transferrin saturation (E), and serum creatinine (F) in the 16-week study period. CKD = chronic kidney disease.

needed blood transfusion or parenteral iron supplement during the study period (Fig. 2).

3.4. Safety issues

Nausea, flatulence, abdominal pain, diarrhea, constipation, and black stools were common side effects of oral iron supplementation. The ferrous sulfate supplementation will cause significant GI side effects.[14] In the current study, no GI side effects were reported and no patients required blood transfusion during the study period. In addition, it indicated that ferrous bisglycinate chelate may be a well-tolerated iron supplement.

4.DISCUSSION

In this study, we observed that a fixed-dose supplement containing ferrous bisglycinate chelate was well tolerated and improved iron status in NDD CKD patients. For HD patients, insensible blood clot in the artificial kidney during HD sessions leads to significant iron loss. Although the low-dose ferrous bisglycinate chelate supplement failed to improve iron status or reduce ESA dosage, it maintained a stable hemoglobin level for 16 weeks during the study period. When compared with other oral iron supplementation, GI side effects were not encountered in the low-dose ferrous bisglycinate chelate supplement.[16] Therefore,

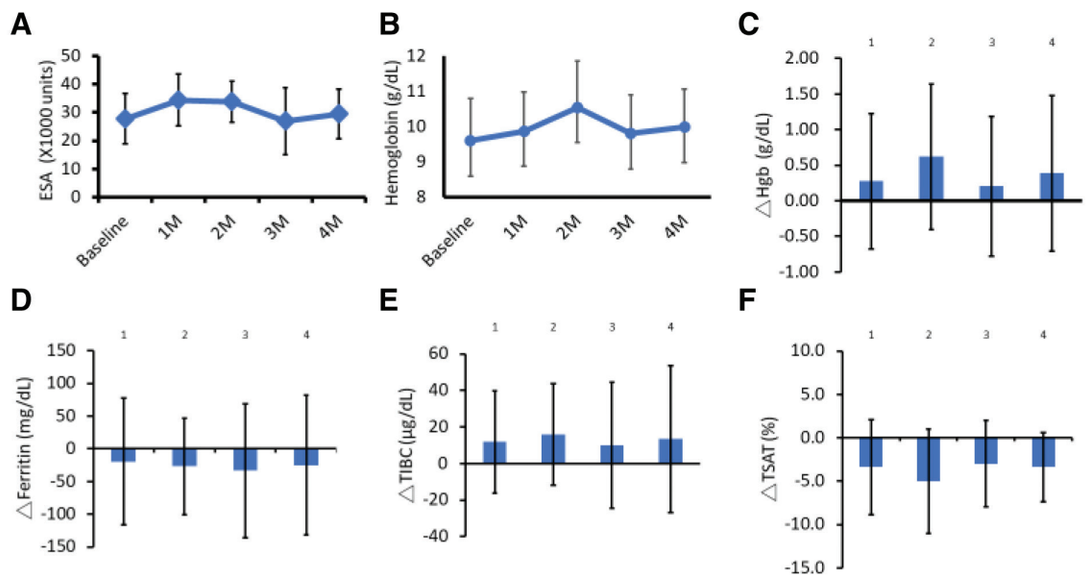

Fig. 2 Low-dose cheated ferrous bisglycinate supplement compensates blood loss and maintains iron storage in hemodialysis patients. Serial changes of ESA dosage (A) and hemoglobin (B). Compared with baseline line, there was no significant changes in hemoglobin (C), ferritin (D), TIBC (E), or transferrin saturation (F) in the 16-week study period. ESA = erythropoiesis-stimulating agent.

the ferrous bisglycinate chelate could be an attractive option for an oral iron supplement.

Although deficiency of erythropoietin production is a major issue of anemia for CKD and HD patients, inadequate iron repletion contributing to the impaired erythropoiesis also plays a major role in correction of renal anemia. In the United States, around 30% NDD CKD patients have absolute iron deficiency anemia and 19% have functional iron deficiency anemia.[17] In HD patients, at least 2000 mg of annual iron supplementation is required to maintain iron status.[18] Iron deficiency has detrimental effects on the cardiovascular system. Therefore, iron deficiency increases the risk of death, cardiovascular complications, and hospitalization in CKD and HD patients.[17,19] Unlike high-dose ESA increased cardiovascular and total mortality in CKD patients,[20–23] iron supplementation has been reported to reduce the myocardial infarction rate in HD patients.[24] The traditional oral and IV iron preparations are considered far from ideal. This is primarily because of GI intolerability by oral iron, the potential risk of infusion reactions, and exacerbated endothelial injury by IV iron.[2]

In nondialysis CKD stage 5 patient, oral iron supplementation associated with a low mortality risk and hospitalization rate.[25] Ferrous bisglycinate has been observed to be a well tolerated and efficient treatment for iron deficient anemia in different patient populations. This includes preterm infants,[13] children,[8,26] pregnant women,[7,14] cancer patients,[15] and even inflammatory bowel disease patients.[27–29] As far as we know, this is the first study that uses ferrous bisglycinate chelate as a supplement for NDD CKD and HD patients. Compared with previous studies in adults,[7,15] using 25–28 mg of ferrous bisglycinate per day, we administered a much lower dose in our study. Our data showed although given in a much lower dose, ferrous bisglycinate chelate was shown to improve iron levels and prevent iron deficiency in NDD CKD patients. Data from human and animal studies indicate that ferrous bisglycinate is bioavailable with fewer side effects than other commonly used iron salts. It is possible that a higher dose ferrous bisglycinate would further improve iron storage and correct anemia in NDD CKD and HD patients. Further studies need to be conducted in order to confirm this theory.

Another fundamental difference between Er Yue Hong and other oral supplementation is that Er Yue Hong contains a fixed-dose Vitamin C. Vitamin could enhance iron availability by two different mechanism. First, vitamin C is reducing agent that can mobilize iron from its storage sites; second, Vitamin C could integrate iron into the heme moiety.[30] Many studies have shown that in HD patients, ascorbic acid supplementation improves transferrin saturation,[31] and EPO responsiveness.[32,33]

There are a few limitations in our study. First, this is an open-label one arm intervention trial. We did not have a control group who received placebo or other oral iron supplements for comparisons. However, our results did show that a low-dose oral ferrous bisglycinate chelate supplement maintained or even improved the iron status of NDD CKD patients without any adverse effects in the GI tract. The fixed-dose ferrous bisglycinate chelate in the current study is most likely not enough to treat severe cases of iron deficient CKD patients. However, it is sufficient to maintain iron status and prevent iron deficiency in NDD CKD patients. Second, a small patient number is a limitation we had. Larger studies with a larger patient number are needed to further test our findings. Third, the ESA dosage in HD patients in the current study is higher than most study. In Taiwan, the upper limit ESA dose for "non-dialysis" CKD patient is 20,000 unit. For HD patients, the ESA is included in dialysis reimbursement as long as hemoglobin below 11 g/dL, which means there is no upper limit. Some dialysis patients in this study have well iron status but still have suffered from renal anemia received high ESA dosage to maintain their hemoglobin level and well-being. We cannot be sure whether low-dose ferrous bisglycinate chelate supplement would work in a low ESA treatment HD patients. Finally, a study using higher doses of ferrous bisglycinate chelate in patients with longer follow-up period is required to validate our results.

In conclusion, our study showed that fixed-dose ferrous bisglycinate chelate supplements are well tolerated in NDD CKD and HD patients. The supplement combination is able to improve iron status in NDD CKD patients and compensate for the potential iron loss in HD patients. Oral ferrous bisglycinate chelate may be an alternative for parenteral iron supplementation in CKD stage 3b to 4 and HD patients. Further studies with larger groups of patients and control groups are needed to further confirm and support this theory.

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