Original Article

The Effect of Ferric Citrate in Controlling Iron Deficiency Anemia and its Tolerability in a Sample of Iraqi Hemodialysis Patients: Randomized Controlled Clinical Trial

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ABSTRACT

Background: The iron deficiency anemia along with hyperphosphatemia are the main complications of dialysis patients. Traditional iron supplement has been failed to correct iron deficiency anemia, therefore, the current study aimed to investigate the efficacy and tolerability of new phosphate binder, ferric citrate, in a sample of Iraqi patients with end stage renal disease on maintenance hemodialysis.

Method: Prospective, randomized, open label, active controlled trial was conducted in one center for dialysis in Babylon governance. Patients were randomized to receive ferric citrate with dose of 6 g/d and calcium carbonate with dose of 3 g/d for eight weeks. Hemoglobin concentration, mean corpuscular hemoglobin concentration and count of RBCs along with iron store parameters were measured. The adherence and gastrointestinal side effects were reported at the end of study.

Results: A total of 50 patients were completed the study. Ferric citrate group showed elevation in count of RBCs, hemoglobin concentration, MCH-C and reduction in use of IV iron and erythropoietin as well as increased iron store which evidenced by elevation of ferritin level in the participants. There were similar adverse effects in both groups, with good adherence seen in ferric citrate group.

Conclusion: A treatment with ferric citrate for 8 weeks was observed to effectively improve anemia in a sample of Iraqi patients with end stage renal disease on maintenance hemodialysis. In addition, the use of intravenous iron and erythropoietin was reduced in ferric citrate group with well tolerability throughout the study period. Ferric citrate may be useful alternative for restoring iron level in hemodialysis patients.

Keywords: .

Introduction

End stage renal disease (ESRD) is defined as kidney with glomerular filtration rate less than 15 ml/min, in which both kidneys are unable to excrete waste products sufficiently. The permanent loss of kidneys function urges the use of dialysis (either hemodialysis or peritoneal dialysis) to sustain patient's life. There are multiple complications of ESRD from which, hematopoietic imbalance and bone disease are the main ones due to phosphate accumulation and iron deficiency. Furthermore, they are recognized as independent factors for cardiovascular diseases.[1,2] diagnosis, and management

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by primary care clinicians are necessary to prevent adverse CKD-associated outcomes, including cardiovascular disease, end-stage kidney disease, and death. Observations: Defined as a persistent abnormality in kidney structure or function (eg, glomerular filtration rate [GFR] <60 mL/min/1.73 m^2 or albuminuria ≥30 mg per 24 hours

Most patients on dialysis manifested with hyperphosphatemia and iron deficiency anemia that need phosphate binder and iron supplement. Erythropoietin has been shown to increase the demand of iron thus aggravate iron deficiency anemia.[3] Iron supplementation is believed to overcome iron deficiency anemia in dialysis patients however, oral iron preparations are less commonly use nowadays as a result of being less absorbed through gastrointestinal tract and less tolerable.[4] For this reason, intermittent use of intravenous iron has become inevitable as it is more efficient in increasing iron store as compared to traditional oral iron preparations, but it has many disadvantages such as infection, risk of anaphylaxis and expensive.[5] Ferric citrate is a new oral phosphate binder, which has combined functions in declining the phosphate level and elevating iron store. It is dissociated to eliminate ferric ion 220mg per 1g, some of ferric ion bind to phosphorus to form a complex to be excreted with feces and the remaining reduced to ferrous iron to be absorbed, thus improves iron store parameters.[6] Thereby reducing medical costs. Oral and intravenous (IV

Several studies have proven the efficacy and safety of ferric citrate in improving anemia indices, reducing the use of intravenous iron and reducing erythropoietin use. These studies were limited to Japanese and Taiwan populations, so its efficacy and safety in the real world was not well established.[7,8] In the present study, we assessed the efficacy and tolerability of ferric citrate in a sample of Iraqi patients on maintenance hemodialysis.

Method

Study Design and Patients Allocation

A prospective, randomized, open label, parallel group study was conducted during six months from 24/4/2021 to 24/10/2021 in a single center (dialysis unit), at Immam- Al Sadiq hospital in Babylon 'governance. Randomization was done in 1:1 to receive ferric citrate or calcium carbonate for 8 weeks. Patients were allocated in two groups as follow:

Group A: After washing out period (one week) from previous phosphate binder use, patients were received six grams of ferric citrate (FC) (six tablets) in three divided doses immediately after each meal for two months(follow up for each patient).(2)leading the US Food and Drug Administration in 2014 to approve its use for that indication. A concurrent beneficial effect, while using ferric citrate as a phosphate binder, is its salutary effect in HD patients with iron deficiency being treated with an erythropoietin-stimulating agent (ESA

Group B: After washing period (one week) from previous binder, patients were received 1500 mg of elemental calcium per day in three divided doses immediately after each meal. Sometime, when calcium level was decreased, part of calcium carbonate dose was given before food by one hour or after food by two hours to increase the absorption of elemental calcium (according to discretion of the attending physician). Figure 1 displays the patients' distribution throughout the study.

Ethical Approval was obtained from the Ethical Committee of the College of Pharmacy at the University of Baghdad and from the training and human development department-research management unit in the Babylon health directorate. Patients were provided with a written informed consent prior to the study. Before signing the consent, the benefits and risks of treatment were explained to the patients.

Patient Eligibility:

Inclusion criteria: eligible patients were aged 18 years and above with ESRD on maintenance hemodialysis twice weekly for at least 6 months before starting the current study, had serum ferritin less than 500ng /dl at screening time, with calcium level >8.5 mg/dl for ferric citrate group and >7.5 mg/dl for calcium carbonate group while exclusion criteria include: gastrointestinal disease including acute peptic ulcers, chronic ulcerative colitis, regional enteritis, intestinal obstruction or dysphagia; serum ferritin concentrations >500 ng/mL on the initial screening date; corrected serum calcium concentrations (11.0 mg/dL) at 1 week after the initial screening date; patients who had undergone parathyroidectomy.

The discontinuation criteria in the current study were as follows: ferritin ≥1000 ng/mL; for ferric citrate group, two consecutive serum phosphate concentrations (3.0 mg/dL) or

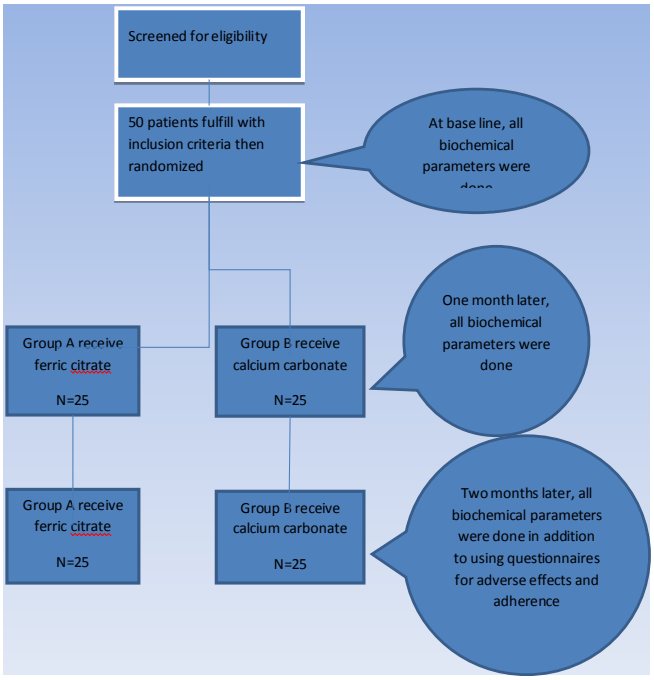

Fig.1: Patients distribution in the study, N= represent the number of patients

≥ (10.0 mg/dL) for two groups; two consecutive corrected serum calcium concentrations < (7.5 mg/dL) for ferric citrate group; two consecutive corrected serum calcium concentrations > (11.0 mg/dL) for calcium carbonate group, sever GIT symptoms for the two groups.

Variables Measurement

Efficacy variables: The efficacy variables measured in this study were related to anemia parameters which included hemoglobin, red blood cell count(RBC), mean corpuscular hemoglobin concentration(MCH-C) (g/dl), serum ferritin (ng/ml), and the cumulative doses of intravenous iron and erythropoietin used by each patient throughout two months.

These variables were measured at baseline (after the washing period), at 4 weeks and at 8 weeks. Whereas the cumulative doses of intravenous iron and erythropoietin were recorded at the end of the study.

Tolerability variables: The tolerability variables were evaluated by measuring the adherence of patients to both treatments, in addition to gastrointestinal side effects. Adherence was measured by using the Morsky questionnaire on all 50 patients who participated in the current study (after two months) at the end of the study**.**

The questionnaire was translated to Arabic version and validated by expert panel from the college of pharmacy/ university of Baghdad. It contains four questions where the patients should answer by either Yes or No.

Score 1 point for every Yes answered.[9]

- 0 points = high adherence
- 1-2 points = intermediate
- 3-4 points = low adherence

While the gastrointestinal adverse effects were recorded in both groups through using Gastrointestinal Symptom Rating Score (GSRS)' questionnaires which is specialized for reporting gastrointestinal side effect at the end of study. The questions were designed as open ended questions that answered in either No discomfort at all, Mild discomfort, Moderate discomfort, Severe discomfort or Very severe discomfort. These answers were encoded from 0-4 score for statistical analysis. The GSRS(10) were translated into Arabic language and then validated by expert panel from the college of pharmacy/ university of Baghdad.

Concomitant Medicine Used

One-alfa cholecalciferol, cinacalcet and erythropoietin were allowed during study period as indicated by the treating physician. The intravenous iron was not permitted if the patient had high ferritin level (1000ng/ml) except when ferritin was less than 1000. Antihypertensive medications, intravenous albumin and vitamins supplement that prescribed by the physician were also allowed during the time of the study.

Sample size and Statistical Analysis

The anticipated 40% of the total population present in the Al-Immam Al-Sadiq-dialysis center fit with inclusion criteria and thus participated in the current study where the total number of patients on maintenance hemodialysis in the hospital was 115. The participants were randomized into 50% receiving ferric citrate and 50% receiving calcium carbonate. The present trial was expected to achieve more than 80% power to detect the hypothesized difference between the two groups of treatments. (Two sided α =0.05)

Statistical analysis was carried out using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). A student t-test was used to compare the means between the two groups. A paired t-test was used to compare the means of two paired readings. Pearson's chi square (X^2) test and Fisher's Exact Test were used to find the association between categorical variables. A *p*-value of ≤ 0.05 was considered as significant.

Results

Fifty patients were included in the current study, then patients were similarly divided into two groups; twenty-five patients were received ferric citrate and twenty-five patients were received calcium carbonate which considered as an active control group.

Demographic Characteristics of Patients

There were 52% males and 48% females with a mean age of (54.42±10.63) years. In general, demographic data was similar (p>0.05) in both groups as shown in tables 1, 2 and figure 2. T-test was used to compare the means of readings of age and Pearson's chi square (X2) test was used to find the association between both gender (categorical variables).

Distribution of Patients According to Primary Cause of CKD

In the current study, the prevalence of DM with hypertension in ferric citrate group was 40% whereas hypertension and DM alone were responsible for 28% and 16% of cases respectively. In contrast, in calcium carbonate group, hypertension was the primary cause in less than half (48%) of

Table 1: The mean of age of patients in both groups

Study variables	*Study group*	*N*	*Mean*	*SD*	*t-test*	*P-value*
Age (years)	Ferric citrate group	25	53.24	11.85	-0.781	0.439
	Calcium carbonate group	25	55.60	9.36		

*P value ≤ 0.05 was significant

CKD patients, whereas DM with hypertension and DM alone were responsible for 36% and 12% of cases respectively. Over all, there were insignificant (p>0.05) differences between both treatment groups in respect to primary cause of CKD as shown in table 3 and figure 3. Pearson's chi square (X^2) test and Fisher's Exact Test were used to find the association between primary causes (categorical variables).

Effect of Treatment on Anemia

In regards to the RBCs count during the treatment period, the means of RBC count were statistically elevated (p<0.05) after two months compared to the base line in the ferric citrate group, while in the calcium carbonate group, there was a significant decline (p<0.05) within the same time frame. A Paired t-test was used to compare the means of two readings, as seen in table 4.

The RBC count was similar (p > 0.05) between the two treatment groups at baseline, with 2.75*10/12/L for the ferric citrate group and 2.79*10/12/L for the calcium carbonate group. However, after one month, RBC count increased in the ferric citrate group to $3.03*10^{12}$/L and decreased in the calcium carbonate group to $2.68*10^{12}$/L, indicating a

Table 2: Comparison of gender

	Study group				
Study variables	*Ferric citrate group*	*Calcium carbonate group*	*Total*	*X2*	*P-value*
Gender					
Male	10 (40.0)	16 (64.0)	26 (52.0)	2.88	0.089
Female	15 (60.0)	9 (36.0)	24 (48.0)		
Total	25 (100.0)	25 (100.0)	50 (100.0)		

*P value ≤ 0.05 was significant

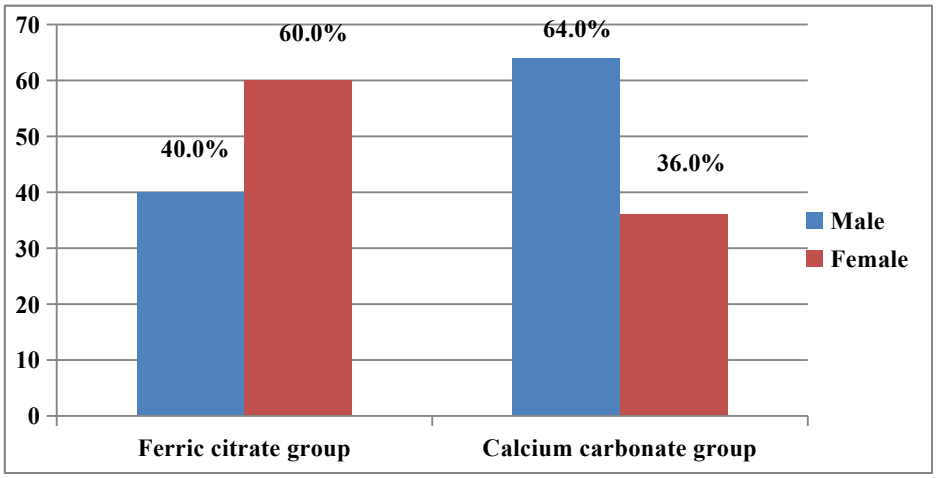

Fig. 2: Distribution of gender between two group

Table 3: Distribution of primary cause of CKD in study groups

	Study group				
Study variables	*Ferric citrate group*	*Calcium carbonate group*	*Total*	*X^2*	*P-value*
Cause				-	0.366 f
Diabetes mellitus	4 (16.0)	3 (12.0)	7 (14.0)		
Hypertension	7 (28.0)	12 (48.0)	19 (38.0)		
DM and hypertension	10 (40.0)	9 (36.0)	19 (38.0)		
Others©	4 (16.0)	1 (4.0)	5 (10.0)		
Total	25 (100.0)	25 (100.0)	50 (100.0)		

*P value ≤ 0.05 was significant. f: Fisher's Exact Test.© others include polycystic kidney (two patients, anemia one patient, drug induce one patient and birth with small kidney one patient).

statistically significant (p 0.05) difference between the two groups. At the end of treatment, the count of RBCs was further increased in the ferric citrate group versus the calcium carbonate group, in which there was a further significant decrease (p<0.05) in RBC count. The study has identified that ferric citrate was associated with an increasing RBC count. A T-test was used to compare the means of readings, as seen in table 5 and figure 4.

With respect to the mean of hemoglobin, in Table 6, the following results were summarized. The changes in hemoglobin levels in both groups during the study period were different, where they were significantly raised (p<0.05) in the ferric citrate group and decreased (p<0.05) in the calcium carbonate group when compared to the base line. A paired t-test was used to compare the means of two rea dings.

The level of hemoglobin was significantly lower (p<0.05) in the ferric citrate group at base line in comparison to the active control group (7.41 g/dl versus 8.16 g/dl). However, after one month, there was an increment in the hemoglobin level in the ferric citrate group and it was significantly indifferent (p>0.05) between treatment groups (8.08g/dl versus 7.79g/dl). Finally, at the end of the intervention, the level of hemoglobin in the ferric citrate group was further raised to be significantly higher (p<0.05) than the calcium carbonate group (8.98g/dl versus 7.66g/dl). Ferric citrate has shown an improvement in hemoglobin levels. A T-test was used to compare the means of readings, as seen in table 5 and figure 5.

Concerning mean corpuscular hemoglobin concentration (MCH-C) (g/dl), this trial displayed that ferric citrate was associated with a statistically elevated (p<0.05) level of MCH-C after two months of treatment, while, in the calcium carbonate group, the level of MCH-C at the end of treatment was insignificantly different when compared to the base line. A paired t-test was used to compare the means of two readings (Table 7, Figure 6).

The MCH-C level was similar (p>0.05) at base line in both treatment groups and there was a minor change (p>0.05) after one month, while after two months of treatment, there was a significant improvement in the level of MCH-C (p<0.05) in the ferric citrate group when compared to the active control group (30.98g/dl versus 29.70g/dl). A T-test was used to compare the means of readings (Table 5).

With respect to ferritin level, after two months of treatment, the ferritin level demonstrated significant elevation (p<0.05) in the ferric citrate group, while in the calcium carbonate group, the decrease was less (p>0.05) (see table 3.8). The level of ferritin from base line to the end of the study period was significantly larger (p<0.05) in the calcium carbonate group (401.76ng/ml–347.6ng/ml versus 118.6 ng/ml–209.36 ng/ml)

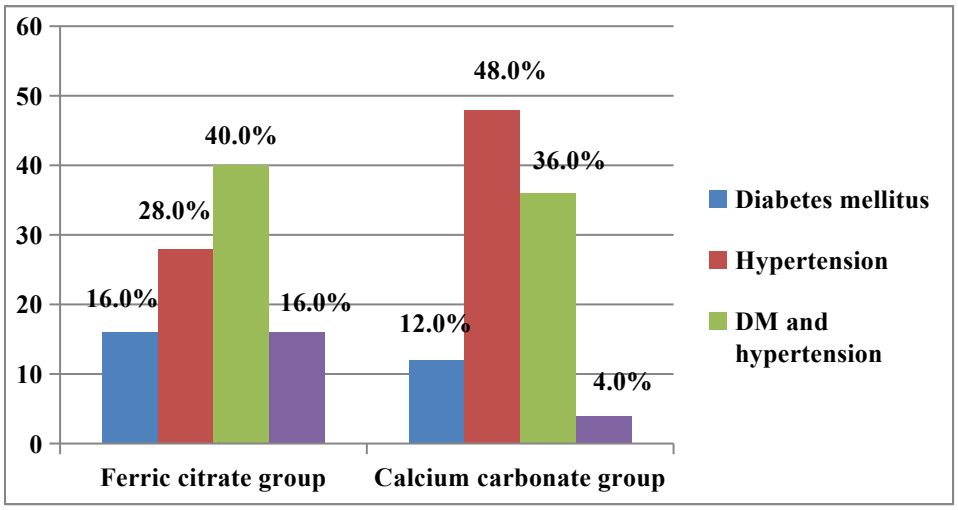

Fig. 3: Distribution of primary cause between two groups

Table 4: Comparison the effect of treatment on RBCs count between two groups

Study markers	*Study groups*	*N*	*Mean*	*SD*	*t-test*	*P-value*
RBC * 10 12/ L baseline	Ferric citrate group	25	2.75	0.41	-0.312	0.757
	Calcium carbonate group	25	2.79	0.35		
RBC * 10 12/ L after one month	Ferric citrate group	25	3.03	0.54	2.701	0.01*
	Calcium carbonate group	25	2.68	0.33		
RBC * 10 12/ L after two months	Ferric citrate group	25	3.33	0.51	5.042	<0.001*
	Calcium carbonate group	25	2.65	0.42		

*P value ≤ 0.05 was significant

(see Table 5 and Figure 7). A paired t-test and a T-test were used to compare the means of two readings in the same group and the means of readings in different groups, respectively.

Effect of treatment on IV iron and erythropoietin use

Patients allocated to ferric citrate group required less cumulative elemental IV iron (milligrams per two month)

Table 5: Effect of treatment on anemia in both group

Study markers and groups	*Time*	*N*	*Mean*	*SD*	*Paired t-test*	*P-value*
RBC * 10 12/ L in ferric citrate	Baseline	25	2.75	0.41	-8.287	<0.001*
	After two months	25	3.33	0.51		
RBC * 10 12/ L in calcium carbonate	Baseline	25	2.79	0.35	3.709	0.001*
	After two months	25	2.65	0.42		
Haemoglobin (g/dl) in ferric citrate group	Baseline	25	7.41	1.25	-8.79	<0.001*
	After two months	25	8.98	1.37		
Haemoglobin (g/dl) in calcium carbonate group	Baseline	25	8.16	1.03	5.494	<0.001*
	After two months	25	7.66	0.98		
MCHC (g/dl) In ferric citrate group	Baseline	25	29.78	1.16	-4.765	<0.001*
	After two months	25	30.98	1.19		
MCHC (g/dl) in calcium carbonate group	Baseline	25	30.14	1.03	1.951	0.063
	After two months	25	29.70	1.10		
Serum ferritin (ng/ml) in ferric citrate group	Baseline	25	118.60	114.17	-4.561	<0.001*
	After two months	25	209.36	126.72		
Serum ferritin (ng/ml) in calcium carbonate group	Baseline	25	401.76	338.57	1.111	0.278
	After two months	25	347.60	294.72		

*P value ≤ 0.05 was significant

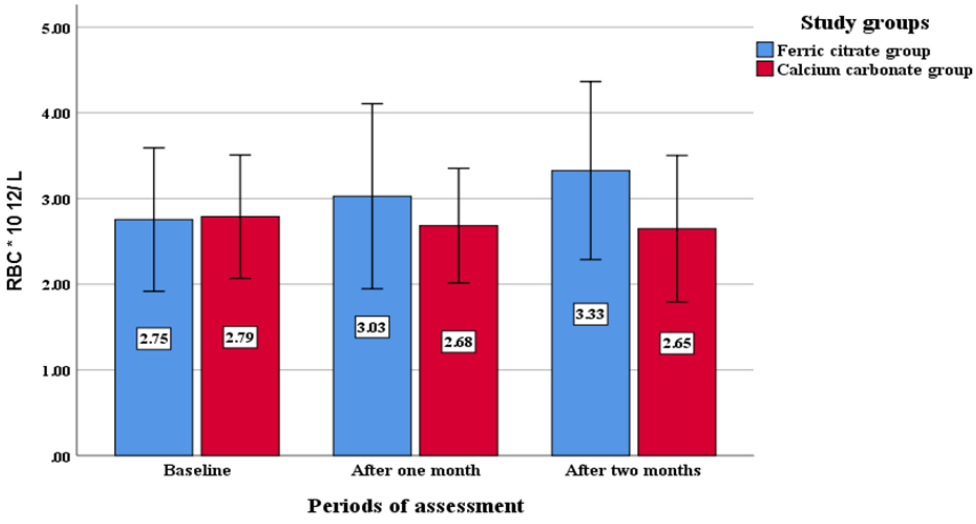

Fig. 4: Effect of treatment on RBCs

($p<0.05$) than patients in active control group, (mean cumulative dose 964 mg versus 1268mg) as seen in Table 9 and Figure 8.

Cumulative erythropoietin (units per two months) was less in ferric citrate group relative to calcium carbonate group throughout period of treatment (mean cumulative units used in two months 52000 versus 5712) as shown in Table 9 and Figure 9.

Adherence of patients to treatment: All participants in the current study responded to the Morsky questionnaire. The mean total Morsky score in the ferric citrate group was lower ($p<0.05$) than the active control group (mean score of 0.84 versus 1.44). The significant difference between the two groups was measured by the T-test (table 10, figure 10). Over all, high adherence was shown in participants who used ferric citrate.

Table 6: Comparison the effect of treatment between two groups

Study markers	*Study groups*	*N*	*Mean*	*SD*	*t-test*	*P-value*
Haemoglobin (g/dl) baseline	Ferric citrate group	25	7.41	1.25	-2.286	0.027*
	Calcium carbonate group	25	8.16	1.03		
Haemoglobin (g/dl) after one month	Ferric citrate group	25	8.08	1.40	0.865	0.392
	Calcium carbonate group	25	7.79	0.93		
Haemoglobin (g/dl) after two months	Ferric citrate group	25	8.98	1.37	3.913	<0.001*
	Calcium carbonate group	25	7.66	0.98		

*P value ≤ 0.05 was significant

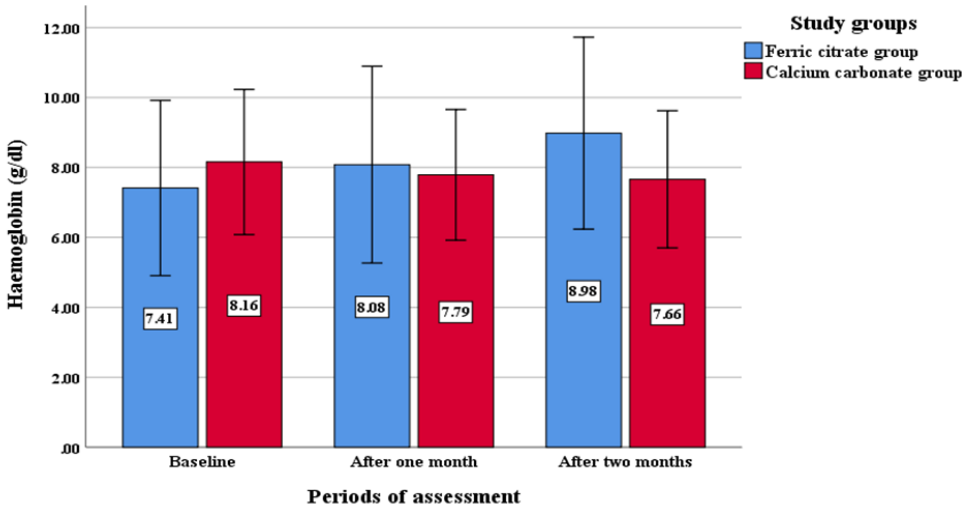

Fig. 5: Effect of treatment on haemoglobin

Table 7: Comparison the effect of treatment between two group

Study markers	*Study groups*	*N*	*Mean*	*SD*	*t-test*	*P-value*
MCHC (g/dl) baseline	Ferric citrate group	25	29.78	1.16	-1.158	0.253
	Calcium carbonate group	25	30.14	1.03		
MCHC (g/dl) after one month	Ferric citrate group	25	30.23	0.89	0.367	0.715
	Calcium carbonate group	25	30.14	0.95		
MCHC (g/dl) after two months	Ferric citrate group	25	30.98	1.19	3.937	<0.001*
	Calcium carbonate group	25	29.70	1.10		

*P value ≤ 0.05 was significant

Effect of Treatment on Gastrointestinal Tract (GIT) Side Effects

There was no significant difference in the means across all Gastrointestinal Symptom Rating Scores (GSRS) between the two treatment groups, (mean score of 9.68 of ferric citrate versus 9.88 of calcium carbonate). The comparison between the two means of both groups was done by T-test (see table 11 and figure 11).

Patients using ferric citrate have presented a high score in the GSRS dimensions with minor constipation (64%), minor abdominal pain (48%), minor indigestion (40%), moderate diarrhoea (40%), and moderate reflux (36%). While in calcium carbonate, the dimensions were minor constipation (76%), minor (reflux, diarrhea, and indigestion) (52%), and minor abdominal pain (44%). See Table 12, Figure 12.

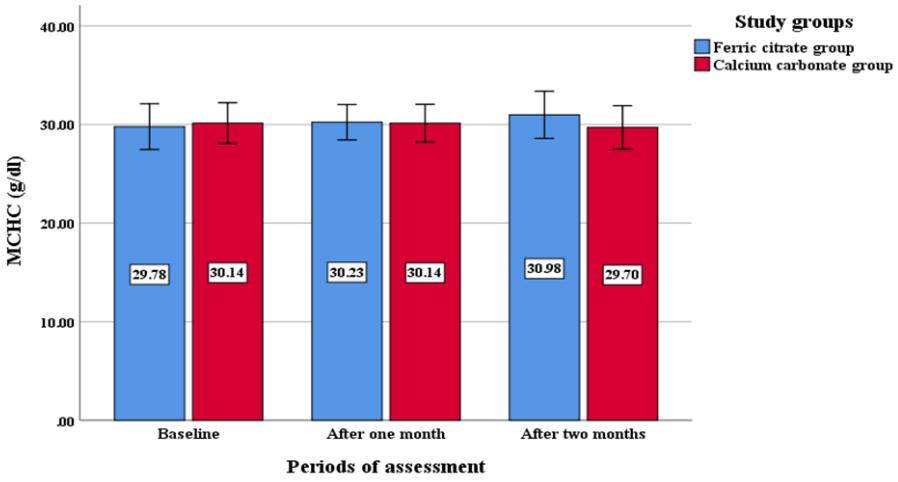

Fig. 6: Effect of treatment on MCH-C

Table 8 Comparison the effect of treatment between two groups

Study markers	*Study groups*	*N*	*Mean*	*SD*	*t-test*	*P-value*
Serum ferritin (ng/ml) baseline	Ferric citrate group	25	118.60	114.17	-3.962	<0.001*
	Calcium carbonate group	25	401.76	338.57		
Serum ferritin (ng/ml) after one month	Ferric citrate group	25	156.16	107.75	-3.314	0.002*
	Calcium carbonate group	25	364.88	295.87		
Serum ferritin (ng/ml) after two months	Ferric citrate group	25	209.36	126.72	-2.155	0.039*
	Calcium carbonate group	25	347.60	294.72		

*P value ≤ 0.05 was significant

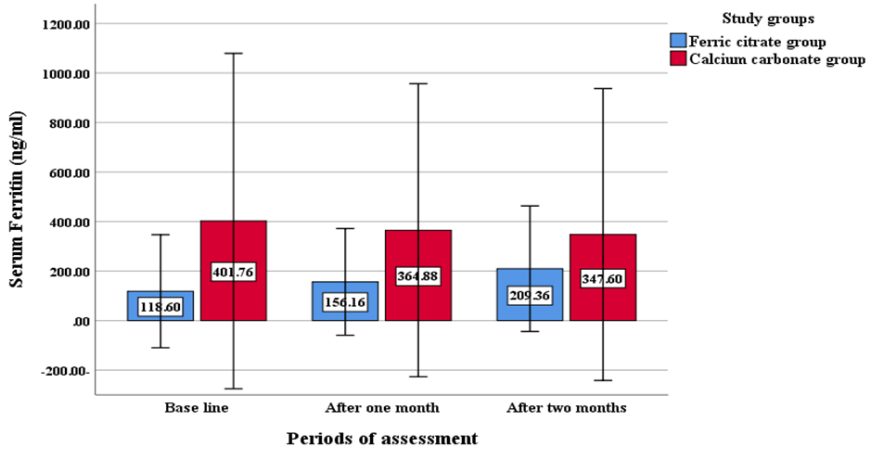

Figure 7: Effect of treatment on ferritin level

Other Reported Side Effects

All patients in the ferric citrate group have reported the appearance of black stool. This side effect was identified by asking the patients what color their stool was. In the calcium carbonate group, two patients reported an increased leg edema. This side effect was reported during the study by patients' complaints.

On the other hand, the itching improved in most patients who were using ferric citrate more than those using calcium carbonate.

Table 9: Effect of treatment on use of iron and erythropoietin between two groups

Study markers	Study groups	N	Mean	SD	t-test	P-value
Iron (mg)	Ferric citrate group	25	964.00	149.66	-8.703	<0.001*
	Calcium carbonate group	25	1268.00	90.00		
Erythropoietin (IU)	Ferric citrate group	25	52000.00	4898.97	-3.720	0.001*
	Calcium carbonate group	25	57120.00	4833.21		

*P value ≤ 0.05 was significant

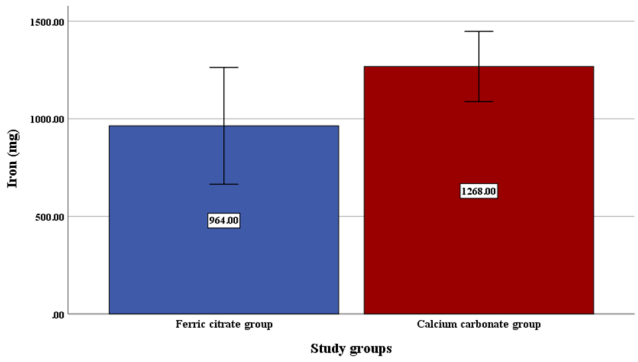

Fig. 8: Effect of treatment on use of iron between two groups

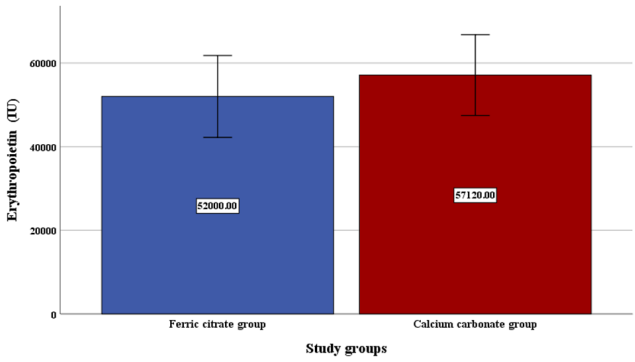

Fig. 9: Effect of treatment on use of erythropoietin between two groups

Table 10 Adherence of patient to treatment

Study markers	Study groups	N	Mean	SD	t-test	P-value
Morisky medication adherence scale	Ferric citrate group	25	0.84	0.85	-2.228	0.031*
	Calcium carbonate group	25	1.44	1.04		

*P value ≤ 0.05 was significant

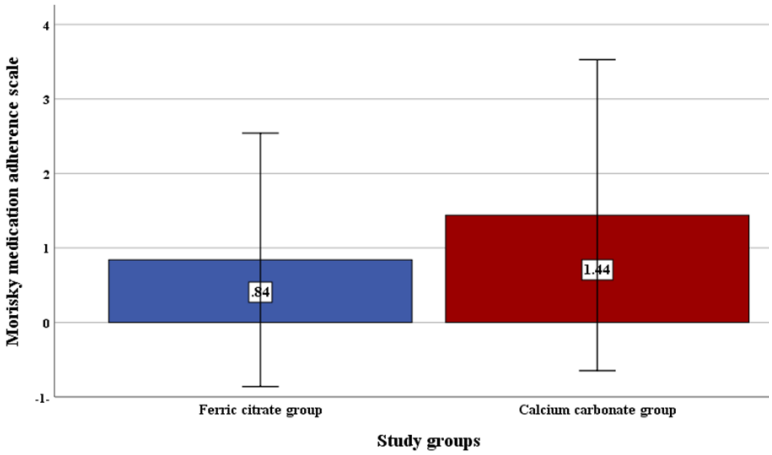

Fig. 10: Adherence of patients to treatment

Table 11: Comparison of GIT side effects between two groups

Study markers	*Study groups*	*N*	*Mean*	*SD*	*t-test*	*P-value*
Abdominal pain	Ferric citrate group	25	0.81	0.66	-0.661	0.512
	Calcium carbonate group	25	0.95	0.75		
Reflux	Ferric citrate group	25	0.88	0.82	-1.185	0.242
	Calcium carbonate group	25	1.16	0.85		
Diarrhoea	Ferric citrate group	25	1.04	0.80	1.328	0.191
	Calcium carbonate group	25	0.78	0.56		
Indigestion	Ferric citrate group	25	1.04	0.95	0.962	0.341
	Calcium carbonate group	25	0.82	0.62		
Constipation	Ferric citrate group	25	0.66	0.53	-0.725	0.472
	Calcium carbonate group	25	0.76	0.43		
Total	Ferric citrate group	25	9.68	6.07	-0.124	0.902
	Calcium carbonate group	25	9.88	5.30		

*P value ≤ 0.05 was significant

Table 12: Distribution of GIT side effects

GSRS	*Ferric citrate group*	*Calcium carbonate group*
Abdominal pain		
No discomfort at all (0)	9 (36.0)	10 (40.0)
Minor discomfort (1)	12 (48.0)	11 (44.0)
Moderate discomfort (2)	4 (16.0)	4 (16.0)
Severe discomfort (3)	0 (0.0)	0 (0.0)
Very severe discomfort (4)	0 (0.0)	0 (0.0)
Total	25 (100.0)	25 (100.0)
Reflux		
No discomfort at all (0)	9 (36.0)	2 (8.0)
Minor discomfort (1)	7 (28.0)	13 (52.0)
Moderate discomfort (2)	9 (36.0)	6 (24.0)
Severe discomfort (3)	0 (0.0)	4 (16.0)
Very severe discomfort (4)	0 (0.0)	0 (0.0)
Total	25 (100.0)	25 (100.0)
Diarrhoea		
No discomfort at all (0)	6 (24.0)	6 (24.0)
Minor discomfort (1)	9 (36.0)	13 (52.0)
Moderate discomfort (2)	10 (40.0)	6 (24.0)
Severe discomfort (3)	0 (0.0)	0 (0.0)
Very severe discomfort (4)	0 (0.0)	0 (0.0)
Total	25 (100.0)	25 (100.0)
Indigestion		
No discomfort at all (0)	6 (24.0)	6 (24.0)
Minor discomfort (1)	10 (40.0)	13 (52.0)

GSRS	*Ferric citrate group*	*Calcium carbonate group*
Minor discomfort (1)	6 (24.0)	6 (24.0)
Moderate discomfort (2)	10 (40.0)	13 (52.0)
Severe discomfort (3)	5 (20.0)	6 (24.0)
Very severe discomfort (4)	4 (16.0)	0 (0.0)
Total	0 (0.0)	0 (0.0)
	25 (100.0)	25 (100.0)
Constipation		
No discomfort at all (0)	7 (28.0)	2 (8.0)
Minor discomfort (1)	16 (64.0)	19 (76.0)
Moderate discomfort (2)	2 (8.0)	4 (16.0)
Severe discomfort (3)	0 (0.0)	0 (0.0)
Very severe discomfort (4)	0 (0.0)	0 (0.0)
Total	25 (100.0)	25 (100.0)

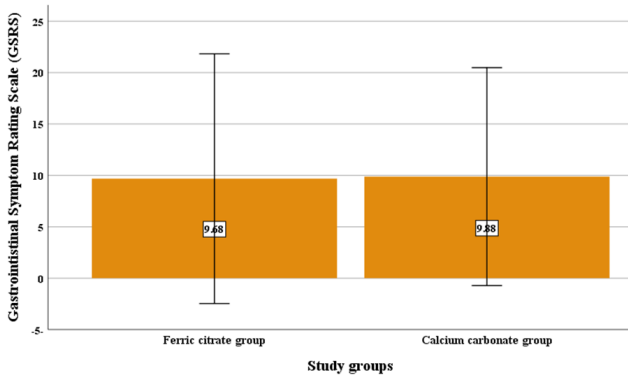

Fig. 11: Comparison of GIT side effects between two groups

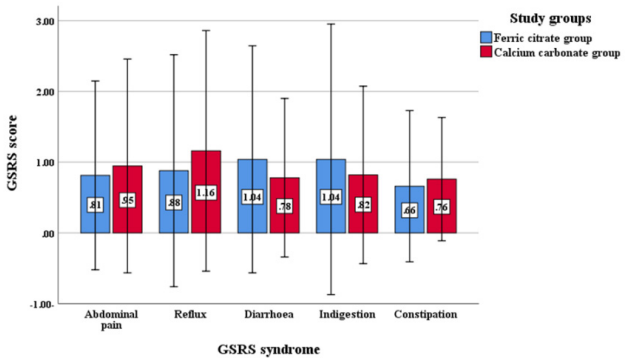

Fig. 12. Distribution of GIT side effects among patients

Discussion

The most common phosphate binders available in Iraqi hospitals are sevelamer and calcium-containing binders. The sevelamer is expensive, and the use of calcium-containing binder is associated with hypercalcemia, which limits their use in chronic kidney Iraqi patients on hemodialysis.

The emergence of ferric citrate, a new iron-containing phosphate binder, was linked to controlling phosphorus levels and reducing the need for iron supplements. Furthermore, it is considered relatively low-cost and safe, which thus decreases the burden of medicines used by CKD-patients on dialysis.(11)441 subjects were randomized (292 to FC and 149 to sevelamer carbonate and/or calcium acetate [active control (AC

Effect of Treatment on Anemia and use of IV Iron and Erythropoieti

The two-month active controlled period was a randomized clinical trial, and it showed that ferric citrate administration over two months had led to an elevated count of RBCs, hemoglobin concentration, MCH-C, and a reduction in the use of IV iron and erythropoietin, as well as an increased iron store, which was evidenced by the elevation of ferritin level in the participating patients.

Historically, oral iron supplement in different salts failed to match erythropoietic demand in iron deficiency anemic patients on dialysis, mostly because of gastrointestinal tract side effects that restricted the dose to about 200 mg of elemental iron per day. This inadequate amount of iron used has driven the extensive intravenous iron use in that population,[12,13] and use of oral and intravenous iron in patients with CKD who do not require dialysis might obviate or delay the need for treatment with eythropoiesis-stimulating agents (ESAs According to the Dialysis Outcome And Practice Pattern Study Practice Monitor, approximately 70% of dialyzing patients received intravenous iron in 2011.[14] The incoming of a new phosphate binder, Ferric citrate, could transfer higher elemental iron (about 1320 mg) per day

compared to traditional oral iron preparation, which would lead to reducing the use of intravenous iron**.**

The increment of RBCs count in the current study was related to the improvement of erythropoiesis and the large quantity of elemental iron delivered from ferric citrate. The released elemental iron was absorbed and utilized in the synthesis of hemoglobin and then RBCs, while enhancement in erythropoiesis was coordinated with controlling the levels of urea, PTH, and phosphate in this study. A number of studies have found that low erythropoiesis in bone marrow is associated with uremic toxin accumulation, iron deficiency, and an increase in PTH levels.[15,16] This finding was in alignment with the Maruyama study, which was performed on 60 Japanese participants and demonstrated the efficacy of ferric citrate to enhance erythropoiesis. While Julia Lewis's study was carried out in different centers in the United States on 441 hemodialysis patients, It reported an increase in the red blood cell count upon administration of ferric citrate.(18)randomized trial, 441 subjects on dialysis were randomized to ferric citrate or active control in a 52-week active control period followed by a 4-week placebo control period, in which subjects on ferric citrate who completed the active control period were rerandomized to ferric citrate or placebo. The primary analysis compared the mean change in phosphorus between ferric citrate and placebo during the placebo control period. A sequential gatekeeping strategy controlled study-wise type 1 error for serum ferritin, transferrin saturation, and intravenous iron and erythropoietin-stimulating agent usage as prespecified secondary outcomes in the active control period. Ferric citrate controlled phosphorus compared with placebo,with a mean treatment difference of -2.2 ± 0.2 mg/dl (mean±SEMIn the meantime, the elevation of hemoglobin concentration by 1.57g/dl was higher than that reported in a trial studied in Japan by Keitaro Yokoyama that showed the mean change in hemoglobin concentration was 0.9g/dl at the end of three months. (19)multicenter, randomized, open-label, parallel-group study, we compared the efficacy and safety of JTT-751 and sevelamer hydrochloride in patients undergoing hemodialysis. A total of 230 patients with a serum phosphate 1.97 and <3.23 mmol/L were randomized to JTT-751 (dose adjusted between 1.5 and 6.0 g/day

Regarding MCH-C, at base line, most participants had a low level of MCH-C. However, the level of MCH-C was elevated at the end of two months. Typically, in CKD, the anemic patients have normocytic normochromic anemia, while in the existing study at base line, normocytic hypochromic anemia was shown in the participants. This might be referred to the presence of anemia for a long period without treatment (iron deficiency anemia) or excessive loss of blood, but after taking ferric citrate, the iron was delivered to hemoglobin and, subsequently, the MCH-C was increased. (20)This finding was in agreement with a meta-analysis by Y. Choi that involved 16 studies and proved that ferric citrate could improve anemia in dialysis patients.[7]

In trying to explain the ferritin level in the current study, the high level of ferritin at base line in both groups despite the presence of anemia was confirmed. This could be explained as most participants might experience inflammation. In particular, the patient's blood was exposed to a foreign filter during the dialysis process, and uremia and infection in vascular access are thought to be triggers for inflammation in such patients,[21,22] nitiated within the protein cage, grow inside the cage cavity (5 or 8 nm in diameterThe use of intravenous iron was permitted if the ferritin level was less than 1000 ng/ml and the hemoglobin level was less than 12 g/dl according to exclusion criteria. In this study, the elevation in iron stores and less intravenous iron used were associated with the use of ferric citrate. This result was secondary to iron absorption through the gastrointestinal tract that was dissociated from ferric citrate and utilized to elevate iron stores. Of note, the elevation of ferritin was improbably related to inflammation because the MCH-C and hemoglobin concentrations were also increased.

The current data was consistent with a meta-analysis by Mei-Yi Wu and colleagues on nine randomized clinical trials that involved 1755 patients. The study has revealed that elevation of ferritin was associated with the use of ferric citrate rather than the placebo group.(23)we evaluated its safety and efficacy in phosphate reduction and iron supplementation in chronic kidney disease stage 3-5 requiring dialysis patients. We systematically searched for clinical trials published in PubMed, Medline, and Cochrane databases. Only randomized controlled trials on the effects of ferric citrate in chronic kidney disease stage 3-5 requiring dialysis patients were selected. The primary outcomes were changes in serum phosphate, calcium, and anemia-related parameters. The secondary outcomes were the adverse effects of ferric citrate. Nine studies providing data on 1755 patients were included in the meta-analysis. Ferric citrate significantly reduced serum phosphate compared with placebo (mean difference, -1.39; 95% confidence interval, -2.12 to -0.66

The reduction in erythropoietin use with increased hemoglobin concentration was achieved in the group who received ferric citrate. This may be attributed to the improvement of iron stores and decreased erythropoietin resistance. Iron deficiency was associated with 10%–20% of erythropoietin resistance in hemodialysis patients. This data was consistent with Kausik Umanth and colleagues, a study that was carried out in different centers in the United States and Israel on 441 participants, where 292 patients had received ferric citrate for 52 weeks. Umanth concluded that ferric citrate reduced the need for erythropoietin as a result of the decreasing phosphate level. Furthermore, another study by Tanemoto found that, a low dose of ferric citrate (750mg) decreased the need for erythropoietin.(24,25)441 subjects were randomized (292 to FC and 149 to sevelamer carbonate and/or calcium acetate [active control (AC

Adherence and GastrointestinalTract Side Effects

The rapidly relieved pruritus was observed one week of using ferric citrate which was associated with the rapidly decreased

phosphate level. This finding has shown the high adherence to ferric citrate in compared to active controlled group in the study population.[26] Additionally, the GIT side effects in this study were less in ferric citrate group but insignificant relatively to calcium carbonate group. This may be also attributed to more adherence for ferric citrate.

This finding was similar to a previously mentioned study by Jalal and colleagues. Patients who received ferric citrate (and the remaining received a sevelamer carbonate or calcium acetate or lanthanum carbonate) had a similar adherence rate to active group (sevelamer carbonate or lanthanum carbonate).[27]

Concerning adverse effects, moderate and minor diarrhea were registered in the ferric citrate group, as well as gastro-oesophageal reflux while, moderate and minor constipation were the most prominent adverse effects of calcium carbonate, as well as gastro-oesophageal reflux. Additionally, all patients using ferric citrate have reported having black stool as an adverse effect. The good tolerability of the high elemental iron dose of ferric citrate (1320 mg) has been attributed to the taking of ferric citrate with food rather than in a fasting state. (28) Several studies have shown diarrhea with dark stool as the most common side effects of ferric citrate while calcium containing phosphate binder was associated with constipation that were in alignment with the current data.[29-31]

Conclusion

Ferric citrate in the current study had been proved to elevate RBCs indices and iron store as well as reduce use of IV iron and erythropoietin. In addition, it was seen well tolerated with high adherence in a sample of Iraqi patient throughout two months. Ferric citrate may be useful alternative for restoring iron level in hemodialysis patients

Limitations in the Current Study

First, a small number of patients met the inclusion and exclusion criteria as the total number of patients in the center was 115, thus strongly limiting the sample size in the study. Secondly, this study was designed as open-label because ferric citrate use was associated with black discoloration of stool therefore, labeled medicines were administered to all patients. This may affect the tolerability variables measurement, especially adverse effects. Finally, the tolerability variables were limited to the time of study, so the well tolerability was limited to this time

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