VOLUME-9, ISSUE-1, JANUARY-2020 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Nephrology

A COMPARATIVE STUDY OF FERRIC CITRATE IN PATIENTS OF CARDIO RENAL ANEMIA SYNDROME

Avinash Chaudhari	Professor&Head, Department of Nephrology ,D Y Patil college & hospital, Navi mumbai
Amar Kulkarni*	Senior resident, Department of Nephrology ,D Y Patil college & hospital, Navi mumbai *Corresponding Author
Mehak Trikha	Junior resident,Department of General medicine, D Y Patil college & hospital, Navi mumbai
Dinesh Gupta	Professor, Department of General medicine, D Y Patil college & hospital, Navi mumbai

ABSTRACT

INTRODUCTION: The Cardio Renal Anemia syndrome is a process involving the deterioration of heart and kidney function linked with worsening anemia. Hyperphosphatemia is crucial indicator of poor prognosis in cardio renal anemia syndrome. Ferric citrate has proven to be effective in reducing serum phosphorus and increasing iron stores and hemoglobin in individuals with non-dialysis-dependent CKD who have iron-deficiency anemia.

MATERIALS AND METHODS: After the approval of EC, this prospective study was conducted in D.Y Patil Hospital Navi Mumbai. 50 patients were enrolled in the study and randomized into two treatment groups- one group receiving oral ferric citrate and other ferrous fumarate.

RESULTS: Out of 50 patients, 18 (36%) were females and 32 (64%) were male. Most common sub type of CRAS was type 2 comprising of 25 patients (50%). The rise in mean biochemical parameters in ferric citrate group at week 52 were statistically significant as compared to baseline. Serum phosphate levels were reduced towards normal level in ferric citrate group at week 52, as compared to in ferrous fumarate group at same time point in the study($p<0.05$).

CONCLUSION: The present study has shown ferric citrate to be superior to ferric fumarate in improving the hemoglobin, iron, RBC indices and as a phosphate binder in patients with CRAS.

KEYWORDS : Cardiorenal anemia syndrome, phosphate, ferric citrate

INTRODUCTION:

Anemia as a co morbidity of chronic heart failure (HF) has been frequently observed by almost every clinician involved in the care of affected patients. Interestingly, its existence and clinical significance have been greatly neglected in these patients, unless the situation was deemed life threatening The Cardio Renal Anemia syndrome is a terminology that was coined by Silverberg et al to explain the link between chronic heart failure, chronic kidney disease and anemia.[2,3] It describes a process involving the deterioration of heart and kidney function linked with worsening anemia, which is contributed to, by the interaction between both physiological conditions. There is paucity of Indian epidemiology data on CRAS. One Indian study by Abdullah et al reported the prevalence of CRAS to be 40%[4].

Cardiorenal anemia (CRA) syndrome, defined as anemia (hemoglobin <130 g/L for men, <120 g/L for women) and stage 3 or greater chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73 m), with heart failure.[5] The cardio renal anemia syndrome, therefore, is a vicious cycle where worsening of one factor negatively impacts the others. Correction of the anemia, may prevent the deterioration of both the heart and the kidneys[3].The only effective treatment is erythropoietin stimulating agents (ESA) with replenishment of iron stores.[6] KDIGO recommends to give oral iron trial in CKD patients whenever transferrin saturation is less than 30% and serum ferritin is less than 500ng/L[7].

Ferric citrate is an FDA-approved oral phosphorus binder that has been shown to be effective in reducing serum phosphorus and fibroblast growth factor 23 (FGF23) concentrations and increasing iron stores and hemoglobin in individuals with non-dialysis-dependent CKD who have iron-deficiency anemia.[8] It is an intestinal phosphate binder that has been shown previously to replete iron stores, increase hemoglobin levels, and reduce serum phosphate levels in patients with ESRD undergoing hemodialysis.[9,10] If ferric citrate is shown to not only improve phosphorus levels, but also the overall iron status, as compared to conventional ferric fumarate.

Thus, the present study was initiated to test the efficacy of ferric citrate in Indian patients of cardio-renal syndrome.

MATERIALS AND METHODS:

This prospective, comparative study was done in department of nephrology, DY Patil hospital, Navi Mumbai. The study duration was of one year (January 2018 to December 2018). The inclusion criteria of the CRAS patients were age 18 years or greater, moderate to severe CKD (eGFR < 60ml/min/1.73 m2 by CKD-EPI), hemoglobin <130 g/L for men, <120 g/L for women, absolute iron deficiency (serum ferritin <300ng/ml and Transferrin Saturation < 30%) NYHA class 3 and 4 and LVEF-<40%. The exclusion criteria were patients with known disorder of iron homeostasis, gastrointestinal disorder, liver disease, isolated DD, valvular heart disease, recent MI (<12weeks),serum phosphorus concentrations < 3.0 mg/dL, any known cause of anemia other than iron deficiency or CKD, symptomatic gastrointestinal bleeding within 12 weeks prior to the screening visit, pregnancy or lactation ,receipt of erythropoiesis stimulating agents within 4 weeks of screening, receipt of intravenous iron therapy within 8 weeks of screening, blood transfusion within 4 weeks of screening, known allergies or severe adverse reactions to previous oral iron therapy. Heart failure was diagnosed according to Framingham criteria.. All the relevant data was fed in EXCEL format by independent investigator. The patients were randomly assigned by a centralized interactive voice-response system with allocation generated by an independent biostatistician. Ferric citrate as 1-g ferric citrate caplets containing 210 mg of ferric iron and ferrous fumarate of 300mcg was administered to the patients after random selection. Patients were seen at weeks 1 and 2 and subsequently at 2-week intervals for any side effects, followed

by 12 weekly testing of hematological parameters.

Statistical analysis: The descriptive and analytical statistics were done. All the data was analyzed using statistical software (IBM SPSS V20.1, IBM Corporation, Armonk, NY, USA). Results was expressed as mean ± standard deviation and proportions. Comparisons between categorical variables was performed with Fisher's exact and chi-square tests. The statistical significance was determined at $p<0.05$.

Ethics Committee Approval was taken .A written signed informed consent was taken prior to enrolling the subjects in the study.

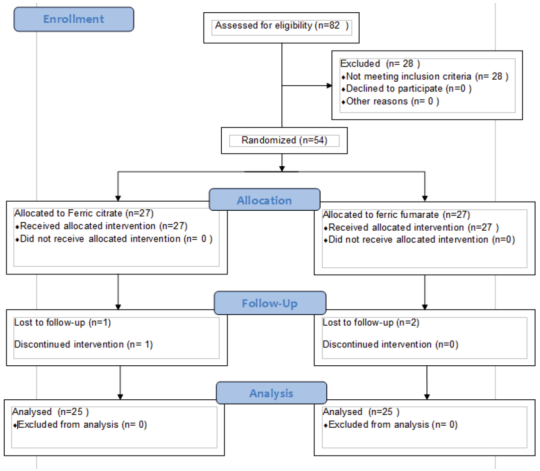

Figure 1: showing flow of methodology adopted for the present study.

RESULTS:

Demographic- The mean sex wise, age-wise and distribution of patients according to sub types of cardio renal anemia syndrome (CRAS) is shown in table1

Table 1: Demographic results

	FERRIC CITRATE	FERRIC FUMARATE
SEX		
FEMALE	10	8
MALE	15	17
AGE (years)	60±3.5	59 ±2.9
WEIGHT (kg)	72.16	72 7
CRAS sub type		
TYPE 2	13	12
TYPE3	5	3
TYPE4	9	17

BIOCHEMICAL:

On comparing the mean biochemical parameters (hemoglobin (Hb), PCV, MCV, Serum ferritin, TSAT, and phosphorus levels) in ferric citrate and ferrous fumarate groups, it was found that ferric citrate effectively improved the iron and blood cell indices. There is statistically significant improvements on all the parameters as compared to baseline and week 52 in the ferric fumarate group. ($p < 0.05$) [table 2,3

TABLE 2: MEAN BIOCHEMICAL CHANGES WITH FERRIC CITRATE

	BASELINE MEAN± SD	WEEK52 MEAN± SD	P VALUE
HAEMOGLOBIN	8.7±1	12.0±1.3	<0.001
PCV	29.4±4.1	43.6 ±6	<0.05
MCV	69.2±1.8	92.1±2.4	<0.05
S.FERRITIN	10.5±1.5	74.4±10.3	<0.05
TSAT	9.3±1	35.6±3.9	<0.05
S.PO4	7.5±1	5.1± 0.7	<0.05

TABLE 3: MEAN BIOCHEMICAL CHAGES WITH FERRIC FUMARATE

	BASELINE	WEEK52	P VALUE
HAEMOGLOBIN	8.5±1	10.3±1.2	>0.05
PCV	27.9± 4.5	41.3±6.6	>0.05
MCV	70.9±1.6	91.2±2.1	>0.05
S.FERRITIN	10±1.6	56.9±9.1	>0.05
TSAT	9.1±1	35±4.0	>0.05
S.PO4	6.2±1	6.4±1	>0.05

DISCUSSION:

In the present study, males outnumbered females. Similar rates were reported in an Indian study by Shah et al.[11] However, Chertow et al[12] and Fishbane et al reported more female sex predilection towards CRAS[6]. This can be attributed to increased occurrence of risk factors like coronary vascular events, diabetes, hypertension, etc. in males, which are comparatively less prevalence in female sex[11].

The mean age in the present study was found to be around 60 years. Similar trend was noted in clinical studies by Nitya Nand et al[1] and Shah et al[11]. This can be due to the fact that prevalence of major risk factors for CRAS and their complications increase with advancing age.

In the present study, most common subtype of CRAS was type 2 comprising of 25 patients (50%). These findings were different than that reported by Shah et al in their cardio-renal syndrome: clinical outcome study, in which type 1 was most common[11].

In the present study, the rise in Hb in ferric citrate at week 52 was highly statistically significant as compared to baseline and in ferrous fumarate group at week 52 ($p <0.001$) which is consistent with Nitya Nand et al[1] Fishbane et al in their clinical study on ferric citrate in CKD have reported similar rise in hemoglobin. They have additionally found that sustained rise in Hb was more in patients treated with ferric citrate as compared to placebo[6].

The significant rise in mean serum ferritin level in patients taking ferric citrate was found to be similar to ferritin rise reported in studies done by Panicker et al[13], Nitya nand[1], Chertow et al[12]. Ferritin is the storage form of iron. In cases of anemia, iron stores are already exhausted, and so is ferritin[18].Thus, it is clear from the findings of the present study that ferric citrate is effective in creating and maintaining positive iron balance in patients of CRAS, as indicated by rise in hemoglobin, iron indices like ferritin and transferrin saturation values, which were statistically significant in patients taking ferric citrate. There are multiple reasons of iron deficiency in patients of CKD, especially those undergoing hemodialysis chronically. Reduced iron are reflected as reduced Hb levels due to diminished erythropoiesis[17].

In the present study, serum phosphate levels were reduced towards normal level in ferric citrate group with similar results reported by Koyama et al [14]. The researchers of this clinical trial concluded that long term use of ferric citrate controls serum phosphorus concentrations and reduces the need for ESAs and intravenous iron in patients receiving hemodialysis. Hyperphosphatemia in CKD leads to persistently increased FGF 23 levels. It is found in various clinical studies that ferric citrate reduces serum phosphate as well as FGF 23 levels in CKD, thus better outcomes[15,16].

CONCLUSION:

In the present study, ferric citrate has been found to be effective in reducing hyperphosphatemia ,as well as maintaining positive iron balance in patients with CRAS.

The improvement in the hemoglobin, iron and RBC indices

has proven to be superior to ferric fumarate.

Thus, the dual action of ferric citrate in cardio renal anemia is feasible choice for managing anemia and hyperphosph atemia of cardio renal syndrome. The dual role also reduces pill load and improved adherence in CRAS patients.

Source of funding: None declared.
Conflicts of interest: None declared by the authors.

REFERENCES:

1. Nand N, Giri K, Jain D. Role of Ferric Citrate in Hyperphosphatemia and Iron Deficiency Anemia in Non Dialysis CKD Patients. J Assoc Physicians India. 2019 Apr; 67(4):53-56.
2. Silverberg D, Wexler D, Blum M. The correction of anemia in severe resistant heart failure with erythropoietin and intravenous iron prevents the progression of both the heart and renal failure and markedly reduces hospitalization. Clin nephrol. 2002; 58(1):37 – 45.
3. Silverberg D, Wexler D, Blum. The interaction between heart failure, renal failure and anemia – the cardio renal anemia syndrome. Blood Purify. 2004; 22(3):277 – 84.
4. Bilal B A, Nida N, Khalid M, Chirajit S. Cardiorenal Syndrome Type I A-A Study of its Incidence, Risk Factors, Laboratory Parameters and Outcome. J Cardiol & Cardiovasc Ther. 2019; 14(3): 555887. DOI: 10.19080/ JOCCT. 2019.14.555887.
5. Lu K, Kearney L, Hare D. Cardiorenal anemia syndrome as a prognosticator for death in heart failure. Am J Cardiol. 2013; 111(8): 1187-1191.
6. Fishbane S, Spinowitz B . Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. Am J Kidney Dis 2018; 71:423-3.
7. Iain C, Macdougall AJ, Bircher, Kai-UweEckardt, Gregorio T, Obrador Carol A, et al. Iron management in chronic kidney disease: conclusions from a "Kidney Disease: Improving Global Outcomes" (KDIGO) Controversies Conference. Kidney International 2016; 89:28-39.
8. ClinicalTrials.gov.in [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 September 21. Identifier NCT 02888171, Impact of ferric citrate vs ferrous sulfate on iron parameters and hemoglobin in individuals with CKD and iron deficiency; 2017 March 22 [cited 2017 October 18] Available from : https://clinicaltrials.gov/ct2/show/NCT02888171.
9. Lee C, Wu I, Chiang S, et al. Effect of oral ferric citrate on serum phosphorus in hemodialysis patients: multi center, randomized, double-blind, placebo-controlled study. J Nephrol. 2014; 28(1): 105-13.
10. Yokoyama K, Hirakata H, Akiba T, et al. Effect of oral JTT-751 (ferric citrate) on hyperphosphatemia in hemodialysis patients: results of a randomized, double-blind, placebo-controlled trial Am J Nephrol. 2012;36(5): 478-487.
11. Shah HR, Singh NP, Aggarwal NP, Singhania D, Kumar A. Cardiorenal Syndrome: Clinical Outcome Study. J Assoc Physicians India. 2016 Dec; 64(12):41-46.
12. Chertow GM, Block GA, Neylan JF, Pergola PE, Uhlig K, Fishbane S. Safety and efficacy of ferric citrate in patients with non dialysis-dependent chronic kidney disease. PLoS One. 2017 Nov 29;12(11):e0188712.
13. Panicker N, Hridya A, Prabhu R. Comparison of Efficacy and Safety Profile of Oral Iron Formulations in Patients with Iron Deficiency Anemia. Int. J. Pharm. Sci. Rev. Res. 2016; 41(2): 248-252
14. Hiratsuka M, Koyama K, Sengo K, Yamamoto J, Narita A, Ito C, et al. Long-term iron accumulation in dialysis patients treated with ferric citrate hydrate: a single-center, 80-week retrospective study in Japan. Renal Replacement Therapy 2017; 3:37:1
15. Ospina M, Holguín M, Escobar D, Restrepo. Importance of hyperphosphatemia in chronic kidney disease, how to avoid it and treat it by nutritional measures. Rev. Colomb. Nefrol. 2017;4(1): 24 – 41.
16. Ganz T, Bino A, Salusky I. Mechanism of Action and Clinical Attributes of Auryxia ® (Ferric Citrate). Drugs 2019; 79:957–968.
17. Al-Atrakji MQ. The effects of ferrous sulfate as an iron supplement on ejection fraction in patients with iron deficiency anemia associated with decompensated heart failure. Mustansiriya Med J 2018;17:22-8
18. Pinto-Sietsma SJ, Navis G, Janssen WM, de ZD, Gans RO, de Jong PE. A central body fat distribution is related to renal function impairment, even in lean subjects. Am J Kidney Dis. 2003;41:733-741.