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Ferric Carboxymaltose reduces NT-proBNP and enhances functional status in chronic kidney disease and heart failure with preserved ejection fraction

La carboximaltosa férrica reduce el NT-proBNP y mejora el estado funcional en la enfermedad renal crónica y la insuficiencia cardíaca con fracción de eyección preservada

Özant Helvacı[1], Saliha Yıldırım[1], Emre Yasar[1], Asil Demirezen[1], Omer Faruk Akcay[1], Kadriye Altok[1], Yasemin Erten[1], Galip Guz[1], Ulver Derici[1], Burak Sezenoz[2], Ozden Seckin[2], Elif Isil Ay[3]

RESUMEN

Introducción: La insuficiencia cardíaca con fracción de eyección preservada (ICFEP) representa aproximadamente la mitad de los casos de insuficiencia cardíaca y suele coexistir con la enfermedad renal crónica (ERC), especialmente en estadios avanzados. La deficiencia de hierro es altamente prevalente en ambas condiciones y contribuye a la disminución de la capacidad funcional y a resultados adversos. **Objetivos**: Evaluar el efecto de una dosis única de carboximaltosa férrica (FCM) intravenosa sobre los niveles de NT-proBNP y la clase funcional NYHA en pacientes con ERC no dialítica, ICFEP y anemia por deficiencia de hierro, así como valorar la seguridad renal a corto plazo de esta intervención. **Material y métodos**: En este estudio de cohorte prospectivo, 45 adultos con ERC estadio 2–5 no dialítica, fracción de eyección del ventrículo izquierdo ≥50% y NT-proBNP ≥1000 pg/mL recibieron una infusión única de FCM (500–1000 mg). Se midieron parámetros clínicos, ecocardiográficos, hematológicos, renales y de hierro al inicio y al mes de seguimiento. **Resultados**: Los niveles de NT-proBNP disminuyeron significativamente de 3924±5841 a 2187±3652 pg/mL (p<0,001), lo que representa una reducción del 44,3%. La clase NYHA mejoró en el 42% de los pacientes (p=0,034). No se observó un cambio significativo en el eGFR (33±17 a 34±16 mL/min/1,73 m², p=0,864). Los parámetros de hierro y los niveles de hemoglobina mejoraron significativamente sin eventos adversos relacionados con la infusión. **Conclusiones**: La terapia intravenosa con hierro en dosis única en pacientes con ICFEP y ERC se asoció con una reducción significativa de NT-proBNP y mejora funcional, sin evidencias de daño renal a corto plazo. Estos hallazgos respaldan el uso de hierro intravenoso como una intervención segura y potencialmente beneficiosa en esta población de alto riesgo y poco representada.

Palabras Clave: Carboximaltosa férrica; enfermedad renal crónica; insuficiencia cardíaca con fracción de eyección preservada; anemia por deficiencia de hierro; NT-proBNP; terapia intravenosa con hierro

Correspondencia:
Özant Helvac
ORCID:
0000-0002-1382-2439
drozant@hotmail.com

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1) Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Turkey
2) Gazi University Faculty of Medicine, Department of Cardiology, Ankara, Turkey
3) Gazi University Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey

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ABSTRACT

Introduction: Heart failure with preserved ejection fraction (HFpEF) accounts for approximately half of all heart failure cases and frequently coexists with chronic kidney disease (CKD), particularly in advanced stages. Iron deficiency is highly prevalent in both conditions and contributes to impaired functional capacity and adverse outcomes. **Objectives**: To evaluate the effect of a single intravenous ferric carboxymaltose (FCM) dose on NT-proBNP levels and NYHA class in non-dialysis CKD patients with HFpEF and iron deficiency anemia, and to assess the short-term renal safety of this intervention. **Materials and Methods:** In this prospective cohort study, 45 adults with stage 2–5 non-dialysis CKD, LVEF ≥50%, and NT-proBNP ≥1000 pg/mL received a single FCM infusion (500–1000 mg). We measured clinical, echocardiographic, hematologic, renal, and iron parameters at baseline and one month post-treatment. **Results**: NT-proBNP levels declined significantly from 3924±5841 to 2187±3652 pg/mL ($p<0.001$), representing a 44.3% reduction. NYHA class improved in 42% of patients ($p=0.034$). No significant change was observed in eGFR (33±17 to 34±16 mL/min/1.73 m², $p=0.864$). Iron parameters and hemoglobin levels improved significantly without infusion-related adverse events. **Conclusions**: Single-dose IV iron therapy in HFpEF patients with CKD was associated with significant NT-proBNP reduction and functional improvement, without evidence of short-term renal harm. These findings support IV iron as a safe and potentially beneficial intervention in this underrepresented high-risk population.

Keywords: Ferric carboxymaltose; chronic kidney disease; heart failure with preserved ejection fraction; iron deficiency anemia; NT-proBNP; intravenous iron therapy.

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of all heart failure (HF) cases, with its prevalence increasing with age [1]. Recent therapeutic advances have introduced sodium-glucose cotransporter-2 (SGLT-2) inhibitors and mineralocorticoid receptor antagonists (MRAs) as evidence-based treatments for HFpEF. SGLT-2 inhibitors demonstrate 18-21% reductions in primary composite endpoints, while the recent FINEARTS-HF trial showed finerenone reduces cardiovascular events by 16% [2-4]. However, these therapies provide modest benefits, and no treatment has definitively reduced cardiovascular mortality dramatically in HFpEF, highlighting substantial unmet clinical needs.

Chronic kidney disease (CKD) represents a significant comorbidity in the HFpEF population. Extensive registry studies demonstrate that CKD prevalence is significantly higher in HFpEF patients (56%) compared to HFrEF patients (45%), with HFpEF becoming the dominant heart failure phenotype in advanced CKD stages [5]. As kidney function declines, the shift toward HFpEF predominance becomes more pronounced, with over 50% of dialysis-dependent patients having HFpEF [6,7]. This cardiorenal syndrome represents a complex pathophysiological interaction where chronic kidney disease leads to left ventricular hypertrophy and diastolic dysfunction [8].

Iron deficiency is a common complication in both HF and CKD patients, with prevalence ranging from 37-61% in heart failure populations and having prognostic significance independent of anemia status [9]. The efficacy of intravenous (IV) iron therapy in HFrEF patients has been established by randomized controlled trials including FAIR-HF [10], CONFIRM-HF [11], and AFFIRM-AHF [12], demonstrating improvements in functional capacity, quality of life, and reduced hospitalizations. This evidence led to Class IIa recommendations for IV iron therapy in symptomatic HFrEF patients with iron deficiency [13].

However, evidence regarding IV iron therapy in HFpEF patients remains limited. The FAIR-HFpEF trial showed improvement in 6-minute walk distance with ferric carboxymaltose but no significant benefits in quality of life or NYHA class. However, it included a few patients with advanced CKD and was prematurely terminated due to slow recruitment, remaining underpowered to assess efficacy in this population [14].

Given the high prevalence of iron deficiency in both HFpEF and CKD populations, and the lack of specific evidence in patients with concurrent disease, we prospectively evaluated the effects of single-dose IV iron therapy on Pro-BNP levels

and functional capacity in non-dialysis CKD patients with HFpEF and iron deficiency anemia.

MATERIALS AND METHODS

Study Design and Population

This prospective cohort study was conducted between January 2022 and December 2023 at a tertiary nephrology center. The study was approved by the institutional ethics committee and conducted following the Declaration of Helsinki.

Inclusion criteria: Patients aged ≥18 years with stage 2-5 non-dialysis chronic kidney disease, iron deficiency anemia (hemoglobin <12 g/dL for women or <13 g/dL for men; serum ferritin <100 μg/L or ferritin 100-299 μg/L with transferrin saturation <20%), Pro-BNP levels ≥1000 pg/mL, and HFpEF diagnosis confirmed by two independent cardiologists based on left ventricular ejection fraction ≥50%, clinical symptoms and signs of heart failure, and evidence of diastolic dysfunction or elevated filling pressures.

Exclusion criteria: Patients on hemo or peritoneal dialysis. Current or recent hospitalization (within 30 days), NYHA Class I or IV heart failure, transfusion requirement within 3 months, primary hematological diseases, active malignancy, recent changes in RAAS blockers, SGLT2 inhibitors, or diuretic doses (within 4 weeks), pregnancy, known hypersensitivity to iron preparations, active bleeding, and severe liver disease.

Intervention Protocol

All patients received intravenous ferric carboxymaltose as a single dose: 1000 mg for patients weighing ≥70 kg with hemoglobin <10 g/dL, 500 mg for patients weighing ≥70 kg with hemoglobin >10 g/dL, or 500 mg for patients weighing <70 kg regardless of hemoglobin level. FCM was administered as an infusion in 250 mL normal saline over 15 minutes, with monitoring for adverse reactions during and 30 minutes post-infusion.

Outcomes and Data Collection

Primary outcomes: Changes in Pro-BNP levels and NYHA functional class from baseline to 1-month follow-up.

Secondary outcomes: Changes in estimated glomerular filtration rate (eGFR using CKD-EPI 2021 equation), hemoglobin levels, and iron parameters (ferritin, transferrin saturation).

Blood samples were collected at baseline and 1-month follow-up for complete blood count, iron studies (serum iron, ferritin, transferrin saturation, total iron-binding capacity), renal function tests, and Pro-BNP levels using electrochemiluminescence immunoassay. Baseline echocardiography was performed according to American Society of Echocardiography guidelines to assess left ventricular ejection fraction, dimensions, wall thickness, and diastolic function parameters.

Sample Size Calculation

A priori power analysis for a paired-sample design (Cohen's $d = 0.5$, $\alpha = 0.05$, power = 0.80) indicated a minimum required sample size of 33 patients. To account for potential dropouts or missing data, the target enrollment was increased by 25%, yielding a final sample size goal of at least 40 patients. We enrolled 45 patients.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation for normally distributed data and median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test. For pre- and post-treatment comparisons, a paired t-test was used for normally distributed variables, a Wilcoxon signed-rank test for non-normally distributed variables, and McNemar's test for categorical variables. A p-value <0.05 was considered statistically significant.

RESULTS

Forty-five patients completed the study protocol. The mean age was 67±11 years; 29 patients (64.4%) were female. All patients had iron deficiency anemia and baseline Pro-BNP levels ≥1000 pg/mL. All patients completed the 1-month follow-up assessment.

Baseline Characteristics

Diabetes mellitus was present in 29 patients (65.1%) and coronary artery disease in 27 patients

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(61.2%). Most patients had stage 3 CKD (55.5%), with 16 patients (35.5%) having stage 3b disease. Thirty-one patients (68.8%) received 1000 mg FCM; 14 patients (31.1%) received 500 mg FCM based on weight and hemoglobin levels. All patients had heart failure with preserved ejection fraction confirmed by echocardiography (**Table 1 and Table 2**).

Table 1: Baseline Characteristics of Study Population (n=45)

Characteristic	**Value (%)**
Age (years)	67 ± 11
Female gender, n (%)	29 (64.4)
Body mass index (kg/m²)	28.4 ± 4.2
Comorbidities, n (%)	
Diabetes mellitus	29 (65.1)
Hypertension	43 (96.0)
Coronary artery disease	27 (61.2)
Cerebrovascular disease	5 (11.3)
CKD Stage, n (%)	
Stage 2 (eGFR 60-89)	5 (11.1)
Stage 3a (eGFR 45-59)	9 (20)
Stage 3b (eGFR 30-44)	16 (35.5)
Stage 4 (eGFR 15-29)	12 (26.6)
Stage 5 (eGFR <15)	3 (6.6)
Medications, n (%)	
ACE inhibitor/ARB	40 (88.8)
Beta-blocker	34 (75.5)
Thiazide-Diuretic	32 (71.1)
Loop-Diuretic	42 (93.3)
SGLT-2 inhibitor	26 (57.7)
MRA	11 (24.4)
Iron therapy dose, n (%)	
FCM 500 mg	14 (31.1)
FCM 1000 mg	31 (68.88)

Table 2: Baseline Echocardiographic Parameters

Parameter	**Mean ± SD**
Left ventricular ejection fraction (%)	58 ± 6
Left ventricular end-diastolic dimension (mm)	48 ± 5
Interventricular septal thickness (mm)	12 ± 2
Posterior wall thickness (mm)	11 ± 2
E/A ratio	0.8 ± 0.3
E/e' ratio	14 ± 4
Left atrial volume index (mL/m²)	38 ± 8

Primary Outcomes

Mean Pro-BNP levels decreased from 3924±5841 pg/mL to 2187±3652 pg/mL, representing a 44.3% reduction (p<0.001). NYHA class improved significantly: Class II patients increased from 18 (40.0%) to 28 (62.2%), while Class III patients decreased from 27 (60.0%) to 17 (37.8%) (p=0.034). Overall, 42% of patients improved by one NYHA class, including transitions to Class I (**Table 3** and **Table 4**).

Table 3: NYHA Functional Class Distribution Before and After Treatment

NYHA Class	**Baseline, n (%)**	**1-month follow-up, n (%)**	**p value**
Class II	18 (40)	28 (62.2)*	0.034
Class III	27 (60)	17 (37.8)	

***** *Class I and II combined*

Table 4: Pre and Post-treatment Laboratory Values

Parameter	**Pre-treatment**	**Post-treatment**	**p value**
Creatinine (mg/dL)	1.89±0.8	1.79±0.9	0.133
eGFR (CKD-EPI 2021)	33±17	34±16	0.864
Hemoglobin (g/dL)	10.1±1.2	11.2±1.3	<0.001
Pro-BNP (pg/mL)	3924±5841	2187±3652	<0.001

Secondary Outcomes

Mean eGFR showed no significant change from 33±17 to 34±16 mL/min/1.73m² (p=0.864), while serum creatinine remained unchanged (1.89±0.8 vs 1.79±0.9 mg/dL, p=0.133). Mean hemoglobin increased from 10.1±1.2 to 11.2±1.3 g/dL (p<0.001) (**Table 4**).

Iron parameters improved significantly: transferrin saturation increased from 15.8±4.5% to 29.3±6.8% (p<0.001), ferritin from 68±73 to 218±176 ng/mL (p<0.001), and serum iron from 49±16 to 92±26 µg/dL (p<0.001) (**Table 5**).

No immediate adverse reactions or allergic responses were observed during or within 30 minutes after infusion completion.

DISCUSSION

This prospective cohort study demonstrates a significant 44.3% reduction in NT-proBNP following IV ferric carboxymaltose therapy in HFpEF patients with advanced chronic kidney disease, addressing a critical evidence gap in this systematically excluded population. The observed NT-proBNP decline exceeds the 30% threshold associated with improved clinical outcomes [15]. This study represents one of the first to examine both cardiac and renal outcomes following IV iron therapy in the HFpEF-CKD overlap population, where patients have been systematically excluded from major clinical trials.

The substantial NT-proBNP reduction observed in our study has a strong mechanistic basis. Iron deficiency impairs mitochondrial respiratory complex function, reducing ATP production and increasing myocardial wall stress [16]. Iron repletion restores mitochondrial energetics, improves contractile efficiency, and can potentially reduce NT-proBNP secretion [17].

Our NT-proBNP findings align with early randomized data on IV iron therapy in patients with concurrent heart failure and renal dysfunction. In a 2007 trial, Toblli et al. reported an approximate 75% reduction in NT-proBNP at 6 months with IV iron versus placebo in anemic HFrEF patients with stage 3 CKD (mean eGFR ~47 mL/min/1.73 m², Cockcroft–Gault) [18]. Although their population differed in HF phenotype and anemia severity, the consistent NT-proBNP reduction supports a mechanistic link between iron repletion and decreased myocardial stress in cardiorenal conditions. However, most HFrEF trials do not report specific NT-proBNP reduction percentages as primary endpoints and do not include patients with advanced CKD [19].

The landmark FAIR-HF trial showed symptomatic improvements and quality of life benefits with ferric carboxymaltose in HFrEF patients, while CONFIRM-HF demonstrated sustained functional capacity improvements [10,11]. Both trials also showed significant improvements in NYHA functional class, with 50.5% and 45.9% of FCM-treated patients achieving ≥1 NYHA class improvement, respectively. Similarly, our study demonstrated significant improvement in NYHA class distribution (p=0.034), consistent with enhanced functional capacity.

Extensive registry studies demonstrate that CKD prevalence is significantly higher in HFpEF patients compared to HFrEF patients, with HFpEF becoming the dominant heart failure phenotype in advanced CKD stages [20]. Iron deficiency prevalence ranges from 37-61% in heart failure populations and has prognostic significance independent of anemia status [9]. Current ESC 2023 guidelines have strengthened iron therapy recommendations to Class I, Level A for symptom improvement in HFrEF and HFmrEF patients, with Class IIa recommendations for hospitalization reduction [21]. However, HFpEF-specific guidance remains limited due to insufficient evidence, making studies like ours particularly valuable. Notably, the FAIR-HFpEF trial demonstrated improved exercise capacity with ferric carboxymaltose (+49 m at 24 weeks vs. placebo). However, it included a few patients with CKD (lowest eGFR: 32 mL/min/1.73 m²) and was prematurely terminated due to slow recruitment [14].

Although our study observed no statistically significant change in eGFR at one month (p=0.864), this finding should be interpreted within the context of the short follow-up period and the complex pathophysiology of cardiorenal interactions. The stable renal function, particularly in the absence of corresponding serum creatinine decline, falls within the expected biological variability of eGFR in CKD patients and suggests no immediate deleterious effect on kidney function. Notably, large CKD trials such as FIND-CKD and REVOKE found no deleterious effect of IV iron on renal function, and our findings align with these safety observations [22,23]. These findings suggest no signal for renal harm in this patient population, though causality cannot be inferred from our data.

A significant strength of our study is the rigorous phenotypic characterization of HFpEF, which was confirmed by two independent cardiologists based on both echocardiographic and clinical criteria, thereby minimizing misclassification bias. In addition, our focus on a high-risk CKD population, systematically excluded from most iron trials, provides unique and clinically relevant evidence supporting individualized iron therapy. The combined use

of NT-proBNP as an objective biomarker and NYHA class as a functional measure further reinforces the robustness of our findings. It facilitates their interpretation by nephrologists, cardiologists, and physicians managing cardiorenal syndromes.

However, this study has several limitations that warrant consideration. The absence of a control group and the observational design preclude causal inference. As a single-center study conducted in a nephrology-referred cohort, selection bias is likely and limits generalizability. Although concurrent therapies were stable prior to inclusion, residual confounding from unmeasured clinical factors cannot be excluded. The modest sample size limited the power for subgroup analyses, and the short follow-up period does not permit evaluation of long-term cardiorenal outcomes. Collectively, these constraints led to an overestimation of the treatment effect.

Future randomized trials are needed to assess the efficacy of IV iron in HFpEF patients with CKD, using complex and composite cardiorenal outcomes as primary endpoints. These studies should evaluate long-term renal and cardiovascular effects. Clarifying patient selection and optimal monitoring strategies will also be essential.

CONCLUSION

This prospective study demonstrates that single-dose intravenous ferric carboxymaltose therapy produces reduced cardiac biomarkers and improved functional capacity in non-dialysis CKD patients with HFpEF and iron deficiency anemia. The treatment was well-tolerated without short-term adverse effects on renal function. These findings suggest that FCM might become a promising therapeutic option for this underrepresented patient population. Larger randomized controlled trials are necessary to establish definitive evidence for routine clinical use and to evaluate long-term cardiovascular and renal outcomes.

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