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Original Article

The Outcome of Use of Intravenous Iron Carboxymaltose on the NYHA Class and the Six-Minute Walk-Test in Patients with Heart Failure: Assessing Functional Improvement

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ABSTRACT

Background: Chronic heart failure (CHF) significantly impairs quality of life and exercise capacity, often exacerbated by concurrent iron deficiency. Intravenous ferric-carboxymaltose (FCM) has shown promise in addressing these deficiencies, improving both biomarkers of iron status and functional outcomes.

OBJECTIVE: To evaluate the effects of intravenous ferric-carboxymaltose on functional class and exercise capacity, as measured by the six-minute walk-test (6MWT), in patients with iron-deficient chronic heart failure.

METHODS: This prospective, single-arm study was conducted from April to September 2023 at the Cardiology unit of Frontier Corps Teaching Hospital, Shakas Peshawar, and Mardan Medical Complex, Mardan, Pakistan. Participants underwent baseline evaluations including demographic information, medical histories, physical examinations, and functional tests such as the 6MWT. Follow-up evaluations after three months of FCM therapy assessed changes in functional indicators. Statistical analyses included tests for significance and descriptive statistics.

RESULTS: Sixty patients participated, with a mean age of 55.87 ± 13.22 years and a mean BMI of 28.14 ± 9.71 kg/m^2. Initial assessments showed a mean LVEF of 33.54 ± 6.68%, with 75% classified as NYHA class III. Baseline 6MWT completion was 10 laps. Initial mean hemoglobin was 11.82 g%, MCV 78.48 fl, TSat 20.43%, and serum iron 50.55 mcg/dL. After treatment, hemoglobin increased to 13.65 g%, MCV to 80.23 fl, TSat to 23.05%, and serum iron to 55.40 mcg/dL. Participants completed 19 laps in the 6MWT, with 63.34% improving to NYHA class II. P-values were <0.0001 for these changes, indicating statistical significance.

CONCLUSION: Intravenous ferric-carboxymaltose significantly enhances functional capacity and iron status in patients with CHF and iron deficiency, irrespective of anemia status. Future research should explore how comorbid conditions like hypertension, diabetes, and renal failure influence treatment outcomes.

KEYWORDS: 6MWT, Chronic heart failure, Ferric-carboxymaltose, Heart failure, Iron deficiency, Intravenous iron, NYHA.

INTRODUCTION

Chronic heart failure (CHF) is a significant global health challenge, affecting approximately 64 million individuals worldwide and imposing substantial burdens on healthcare systems (1). Despite advancements in CHF management, patients frequently experience diminished physical function, limited exercise tolerance, and compromised quality of life. These challenges stem from factors such as reduced cardiac output and imbalanced myocardial oxygen supply-demand dynamics (2).

Iron deficiency (ID) and iron-deficiency anemia (IDA) commonly co-occur in cardiovascular diseases, significantly affecting prognosis and patient outcomes. ID is particularly prevalent among individuals with heart failure (HF), affecting 30–50% of those with stable chronic HF and a higher percentage in acute HF cases (4). This prevalence is thought to be due to decreased absorption of iron, depletion of iron reserves, and impaired recycling of iron, leading to symptoms such as lack of energy, dyspnea, and exercise

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intolerance. Notably, ID serves as an indicator of poor outcomes in HF patients, increasing rates of hospitalization and mortality, even in the absence of anemia (5-6).

The complex relationship between iron metabolism and cardiovascular function has garnered increasing attention. Iron deficiency impairs oxygen delivery to the heart and lungs, adversely affecting cardiac and pulmonary performance (7). This deficiency not only worsens hemodynamic parameters but also patient prognoses, especially following heart surgery, presenting with clinical manifestations such as anginal pain, difficulty breathing, tachycardia, and lower limb edema (8). Beyond its traditional role in hematopoiesis, iron is essential for cellular metabolism, ATP synthesis, and oxygen transport, all critical to cardiovascular health (9). Intravenous (IV) supplementation with ferric carboxymaltose (FCM) has emerged as an effective and rapid treatment for iron deficiency in heart failure patients (10-11). Administration of FCM has been shown to significantly improve health-related quality of life, enhance exercise tolerance, and reduce hospitalizations due to heart failure and cardiovascular causes (12). Despite these promising findings, further research is required to fully understand the impact of FCM on NYHA class and the mechanisms underlying its effectiveness.

In light of these considerations, this study aims to rigorously assess the specific effects of intravenous ferric carboxymaltose infusion on the functional status and six-minute walk-test (6MWT) in patients with chronic heart failure and iron deficiency, both with and without anemia. By objectively measuring functional improvements, this research seeks to elucidate the potential use of FCM as a personalized strategy to enhance outcomes and reduce the burdens associated with CHF.

MATERIAL AND METHODS

This study was conducted from April to September 2023, at the Cardiology departments of Frontier Corps Teaching Hospital, Shakas Peshawar, and Mardan Medical Complex, Mardan, Pakistan, following approval from the institutional ethical board. It involved a prospective single-arm investigation into the impact of intravenous ferric carboxymaltose (FCM) on functional outcomes in patients diagnosed with iron-deficient congestive heart failure (CHF). The participants comprised 60 patients—20 females and 40 males—with heart failure characterized by a left ventricular ejection fraction (LVEF) of ≤45% as determined by echocardiography. Eligibility for inclusion required patients to exhibit iron deficiency, defined either by a serum ferritin level below 100 ng/mL or ferritin concentrations between 100-299 ng/mL alongside a transferrin saturation (TSat) less than 20%, and to be classified under the New York Heart Association (NYHA) functional class II/III. Exclusion criteria included physical incapacity to walk, inflammation, severe liver or kidney dysfunction, pregnancy, uncontrolled arterial hypertension (blood pressure greater than 180/110 mmHg), hemoglobin disorders, deficiencies in vitamin B12 or folic acid, a resting heart rate exceeding 120/min, and resting SpO2 below 85%.

Upon enrollment, participants provided signed informed consent. The initial visit involved recording demographic data, medical history, physical examination findings, and laboratory values including hemoglobin level, mean corpuscular volume (MCV), and TSat, along with a 12-lead electrocardiogram, NYHA functional class assessment, and six-minute walk test (6MWT) results, documented using a pre-designed checklist. The intervention phase consisted of administering a tailored dose of intravenous ferric carboxymaltose based on hemoglobin levels: 1000 mg for those with levels above 11 mg/dL (indicative of anemia) and 500 mg for those with levels exceeding 14 mg/dL (non-anemic).

After three months of treatment, follow-up assessments were conducted to evaluate changes in functional parameters, including NYHA class and the distance covered during the 6MWT. Statistical analyses were performed using IBM-SPSS version 23.0. Descriptive statistics included percentages for categorical variables and mean ± standard deviation for continuous variables. The normality of the data was assessed using the Kolmogorov-Smirnov test. Changes within the group were analyzed using paired t-tests or Wilcoxon signed-rank tests as appropriate, with a significance threshold set at a p-value of less than 0.05.

RESULTS

The study included 60 participants, with a male predominance of 66.66% (40 males) and 33.34% females (20 females). The mean age of the cohort was 55.87 years, with a standard deviation of 13.22 years. The average body mass index (BMI) was recorded at 28.14 kg/m^2, reflecting a varied distribution of body weights within the study group. Cardiac function, assessed by left ventricular ejection fraction (LVEF), averaged at 33.54%, with a standard deviation of 6.68%, indicating a predominant presence of reduced cardiac output among the participants. The initial classification according to the New York Heart Association (NYHA) showed 25% (15 participants) in class II and 75% (45 participants) in class III, highlighting a higher incidence of moderate to severe heart failure symptoms within the group.

During the baseline six-minute walking test (6MWT), the participants managed to complete an average of 10 laps, with a standard deviation of 1.50 laps, which served as a measure of their functional capacity and endurance. The biochemical parameters revealed a mean hemoglobin (Hb) level of 11.82 g%, mean corpuscular volume (MCV) of 78.48 fl, transferrin saturation (TSat) of 20.43%, and

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a serum iron level of 50.55 mcg/dL. The prevalence of comorbid conditions was notable, with diabetes mellitus affecting 68.33% (41 participants), hypertension 56.66% (34 participants), dyslipidemia 41.66% (25 participants), and coronary artery disease 76.66% (46 participants), underscoring the cohort's high cardiovascular risk profile.

At the three-month follow-up, significant improvements were observed across several key variables. Hemoglobin levels increased from the baseline mean of 11.82 g% to 13.65 g%, suggesting a positive response to treatment and potential amelioration of iron deficiency. Likewise, mean corpuscular volume (MCV) and transferrin saturation (TSat) showed upward trends, increasing from 78.48 fl to 80.23 fl and from 20.43% to 23.05%, respectively. Serum iron levels rose from 50.55 mcg/dL to 55.40 mcg/dL, indicating an improvement in iron status.

Most notably, there was a significant enhancement in exercise tolerance and physical function, as evidenced by the six-minute walking test (6MWT), where participants increased their average laps completed from 10 to 19. Additionally, the NYHA classification showed a marked shift, with 63.34% (38 participants) improving to class II from the initial 25%, indicating an overall improvement in symptom severity and functional status. Statistical analysis confirmed the significance of these changes, with calculated p-values of 0.0001 for each variable, suggesting that the observed improvements were statistically significant.

Table-1: Initial baseline features of the study group (N=60)

Variables		Values (n)/ Percentage (%)/ Mean ± SD
Gender	Male(s)	40 (66.66%)
	Female(s)	20 (33.34%)
Mean-age, years		55.87 ±13.22
Body mass index (BMI), kg/m2		28.14 ±9.71
LV ejection fraction (LVEF)		33.54 ±6.68
NYHA Class	NYHA-II	15 (25%)
	NYHA-III	45 (75%)
6MWT (no. of 60-meter laps)		10 ± 1.50
Initial Biochemistry		
Hemoglobin (Hb), g%		11.82±1.18
Mean Corpuscular Volume (MCV), fl		78.48±2.51
Transferrin Saturation (TSat), %		20.43±1.24
Serum Iron, mcg/dL		50.55±6.50
Co-morbidities		
Diabetes mellitus (DM)		41 (68.33%)
Hypertension (HTN)		34 (56.66%)
Dyslipidemia		25 (41.66%)
Coronary artery disease (CAD)		46 (76.66%)

Table-2: Biochemical and 6MWT changes observed at 03 months follow-up

Variables		Values (n)/ Percentage (%)/ Mean ± SD	p-value
Hemoglobin (Hb), g%		13.65±1.45	0.0001
Mean Corpuscular Volume (MCV), fl		80.23±2.36	0.0001
Transferrin Saturation (TSat), %		23.05±1.02	0.0001
Serum Iron, mcg/dL		55.40±6.32	0.0001
NYHA Class	NYHA-II	38 (63.34%)	0.0001
	NYHA-III	22 (36.66%)	
6MWT (no. of 60-meter laps)		19 ± 5.0	0.0001

DISCUSSION

The ongoing investigation into iron metabolism in chronic heart failure (CHF) underscores a complex interplay between inflammatory mediators and iron homeostasis. Research has shown that proinflammatory factors such as interleukin-1, tumor necrosis factor-α, and interleukin-6, contribute to iron retention in macrophages by downregulating ferroproteins, thereby limiting iron availability, restricting erythropoiesis, and often resulting in anemia (13-14). Iron deficiency (ID) is a prevalent comorbidity in heart failure,

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affecting up to 70% of patients with acute HF and nearly half of those with chronic stable HF (7). The negative impact of ID on quality of life and functional ability in HF patients is well-documented, although responses to iron replacement therapy have varied.

Previous studies such as the IRONOUT HF trial highlighted that oral iron supplementation did not improve exercise capacity nor correct iron deficiency in HF patients (15). In contrast, intravenous administration of iron has shown effectiveness in ameliorating deficiency and enhancing functional capacity. The study herein reflects these findings, demonstrating that intravenous ferric-carboxymaltose (FCM) significantly improved both the New York Heart Association (NYHA) functional class and the six-minute walk test (6MWT) outcomes in patients with CHF and ID, irrespective of anemia status.

The results align with those from the PRACTICE-ASIA-HF trial, where intravenous FCM in patients with acute decompensated heart failure showed improvements in 6MWT outcomes. However, these gains were modest over the 12-week period, indicating that longer follow-up might be required to fully ascertain the effects of FCM treatment (16). Similarly, the CONFIRM-HF trial, which extended over a year and involved multiple doses of FCM, reinforced the benefits of FCM in improving functional capacity and quality of life in iron-depleted HF patients (17).

Despite the shorter duration and single-dose regimen of this study compared to CONFIRM-HF, the outcomes were consistent, supporting the efficacy of FCM in improving functional outcomes in CHF patients with ID. These findings underscore the potential of intravenous iron therapy as a valuable intervention for managing ID and enhancing clinical outcomes in HF patients (18,19).

Strengths of this study include its focus on a well-defined patient cohort and the use of robust, objective measures such as the 6MWT and NYHA functional class for assessing functional improvement. Limitations, however, must be acknowledged. The single-arm design and relatively short follow-up period may limit the generalizability and long-term applicability of the findings. Additionally, the study did not account for potential variations in patient compliance or the influence of concurrent treatments, which could affect the outcomes (20,21).

In conclusion, the current study contributes to the growing body of evidence supporting the use of intravenous FCM in the management of iron deficiency in patients with CHF. It provides a basis for further research, particularly in exploring the long-term effects of intravenous iron supplementation and its role in comprehensive HF management strategies.

CONCLUSION

This study demonstrates that a single cycle of intravenous ferric-carboxymaltose significantly enhances functional capacity in patients with iron deficiency and chronic heart failure, regardless of the presence of anemia. The findings highlight the potential of intravenous iron therapy in improving clinical outcomes in this patient population. However, given the complexity of chronic heart failure compounded by common comorbidities such as hypertension, type 2 diabetes, and renal failure, future research should investigate how these conditions influence the effectiveness of treatment. Understanding these interactions is essential for refining patient care strategies and optimizing therapeutic approaches in managing chronic heart failure with concurrent iron deficiency.

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