Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v31i2.4623

IRON-DEFICIENCY ANEMIAS WORSEN SOME CARDIOVASCULAR DISEASES: THE ROLE OF INTRAVENOUS FERRIC CARBOXYMALTOSE

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Abstract

Introduction: Iron-deficiency anemias exacerbate cardiovascular diseases, necessitating effective interventions. This study explores the role of intravenous Ferric Carboxymaltose (FCM) in mitigating cardiovascular complications associated with iron deficiency.

Objective: Investigate the impact of FCM on cardiovascular outcomes, including hospitalizations, mortality, and quality of life, in comparison to a placebo group.

Methodology: This retrospective analysis investigated the effect of intravenous FCM on cardiovascular outcomes in 70 adults with heart failure and iron deficiency. Data was collected from randomized, placebo-controlled trials with a follow-up of 52 weeks. The primary endpoints were the impact of FCM on total cardiovascular hospitalizations and death, and total heart failure hospitalizations and death. Secondary endpoints included total cardiovascular and heart failure hospitalizations, and time to cardiovascular death. Safety assessment included monitoring for treatment-emergent adverse events. Statistical analysis employed frequency, mean, percentage, negative binomial and Cox models, and Pearson correlation coefficients

Results: FCM exhibited significant efficacy, reducing total cardiovascular hospitalizations and mortality (p=0.003), total heart failure hospitalizations and mortality (p=0.002), total cardiovascular hospitalizations (p=0.001), and total heart failure hospitalizations (p=0.001). While FCM demonstrated positive improvements in hemoglobin levels, NYHA class, health-related quality of life, and exercise capacity, it showed varied effects on gastrointestinal adverse events. Pearson correlation coefficients unveiled associations between participant characteristics.

Conclusion: Intravenous FCM showcased a substantial reduction in cardiovascular events and enhanced various health indicators compared to a placebo. These findings underscore FCM's potential in ameliorating cardiovascular risks associated with iron deficiency.

Keywords: ferric carboxymaltose (FCM), iron deficiency, anemia, cardiovascular outcomes, hospitalization, quality of life

Introduction

Anemia is defined by a decrease in hemoglobin levels or red blood cell count [1]. Iron-deficiency anemia (IDA) is a prevalent comorbidity in cardiovascular diseases, exerting a profound impact on patient outcomes and prognosis [2, 3]. The intricate interplay between iron metabolism and the cardiovascular system has garnered increasing attention. IDA has been recognized as a frequent comorbidity in cardiovascular conditions, termed sideropenic anemia, characterized by low iron serum levels leading to a reduction in hemoglobin values [4, 5]. Such anemia diminishes oxygen delivery throughout the body, adversely affecting cardiac and pulmonary systems, consequently manifesting in clinical symptoms such as angina, dyspnea, tachycardia, and lower limb edema. The reduction in oxygen supply exacerbates hemodynamic parameters, including elevated pulmonary and capillary pressures, consequently worsening the prognosis of patients undergoing cardiac surgery [6, 7].

The pivotal role of iron in cardiovascular health extends beyond its classical association with hematopoiesis, encompassing critical functions in cellular metabolism, energy production, and oxygen transport [8]. In iron-deficient states, the cardiovascular system is subjected to a cascade of deleterious effects, intensifying the severity of pre-existing cardiovascular conditions. Previous research has emphasized the prevalence of IDA in heart failure (HF) patients, with an intricate connection between iron deficiency and adverse outcomes such as increased hospitalizations and mortality [9]. Intravenous iron supplementation, particularly with FCM, has emerged as a promising intervention to address iron deficiency efficiently and expeditiously [10].

Studies exploring the impact of FCM on cardiovascular endpoints have demonstrated notable reductions in hospitalizations for HF and cardiovascular causes, indicating its potential in ameliorating the disease burden in iron-deficient HF patients [11]. FCM has exhibited favorable effects on health-related quality of life (HRQL), exercise capacity, and symptomatic improvement [12], positioning it as a therapeutic modality deserving further investigation. Despite these promising findings, a comprehensive understanding of the specific cardiovascular endpoints influenced by FCM and the nuanced mechanisms underlying its efficacy remains an area warranting further exploration.

Study Rationale

This study endeavors to contribute valuable insights into the nuanced relationship between IDA and cardiovascular diseases. By focusing on intravenous FCM, the research seeks to delineate its impact on critical cardiovascular endpoints, thereby enhancing our understanding of its potential therapeutic role in the context of iron-deficient patients with cardiovascular diseases. The inclusion of patient-level data from randomized, placebo-controlled FCM trials and rigorous statistical analyses will provide a robust foundation for drawing meaningful conclusions and implications for clinical practice.

Objective

Investigate the impact of intravenous FCM on cardiovascular outcomes in patients with iron-deficiency anemias, aiming to elucidate FCM's role in ameliorating the worsening effects of iron deficiency on heart failure and related endpoints.

Materials and Methods

Study Design

This retrospective analysis incorporates patient-level data from randomized, placebo-controlled trials investigating the effect of intravenous FCM on cardiovascular outcomes in 70 adults diagnosed with heart failure and iron deficiency, with a follow-up period of at least 52 weeks. The study duration was 1.5 years from January 2021 to June 2022.

Setting

This research was conducted at Peshawar Institute of Cardiology with a focus on impact of FCM on cardiovascular hospitalizations and mortality in heart failure patients with iron deficiency.

Participants

Inclusion criteria encompass adults aged 18 years and above with a documented diagnosis of heart failure and iron deficiency, having participated in randomized, placebo-controlled FCM trials with a follow-up period of at least 52 weeks. Exclusion criteria involve individuals below 18 years, absence of documented heart failure or iron deficiency, and non-participation in relevant trials.

Data Collection

A convenient sampling technique was utilized, encompassing thorough physical examinations, comprehensive medical history assessments, and necessary laboratory tests to gather detailed information. The inclusion criteria comprised patients diagnosed with morbid adherent placentas, while strict exclusion criteria excluded placentas from individuals not meeting the specified diagnostic criteria and those who did not provide informed consent.

Sample Calculation

The sample size was determined based on a statistical power analysis, aiming for a robust representation of the population under study. With an anticipated effect size and significance level, the sample size was calculated to ensure adequate statistical power to detect meaningful differences between groups. Ultimately, a total of 70 participants were included, with 50 individuals selected as the final sample size after applying specific inclusion and exclusion criteria. This approach ensures the study's ability to draw reliable conclusions and contributes to the overall validity of the findings.

Endpoints

The co-primary endpoints include evaluating the impact of FCM on (A) total cardiovascular hospitalizations and cardiovascular death and (B) total heart failure hospitalizations and cardiovascular death over 52 weeks. Secondary endpoints involve (C) total cardiovascular hospitalizations, (D) total heart failure hospitalizations, and (E) time to cardiovascular death.

Safety Assessment

In addition to the efficacy outcomes, the research will systematically examine treatment-emergent adverse events to comprehensively understand the safety profile associated with intravenous FCM.

Background and Rationale

Given the frequent co-occurrence of iron-deficiency anemia in cardiovascular diseases, particularly heart failure, and its impact on patient outcomes, this study aims to contribute to existing knowledge by analyzing the effect of FCM on cardiovascular events and mortality. Incorporating advanced statistical models and leveraging a well-defined cohort of 70 participants, this research seeks to provide valuable insights into the potential benefits of FCM in improving outcomes for patients with heart failure and iron deficiency.

Statistical Analysis

In the conducted analysis, rate ratios and p-values were calculated using a negative binomial model, considering fixed covariates such as treatment, region, baseline hemoglobin level, and a random covariate for the study. The Cox model was employed to determine hazard ratios, 95% confidence intervals, and adjusted Wald p-values, incorporating fixed effects of treatment, subgroup, treatment by subgroup, baseline hemoglobin, region, and a random effect for the study, assuming proportional hazards. Mean, frequency, and percentage were computed for demographic characteristics, providing a detailed overview of variables such as age, gender, hemoglobin levels, heart failure duration, previous cardiovascular events, BMI, smoking status, diabetes mellitus, and hypertension. Pearson correlation coefficients were also calculated to elucidate relationships between these variables, offering insights into their interplay within the study population and contributing to a nuanced interpretation of the results. Statistical analysis was done in SPSS (version 23.0) and p-value<0.05 was taken significant.

Results

In this study, participants were divided into two groups: the FCM group (N=35) and the Placebo group (N=35). The mean age in the FCM group was 56.2 years, with a standard deviation (SD) of 7.4 years. In comparison, the mean age in the Placebo group was slightly lower at 55.8 years, with a SD of 8.1 years. These values indicate the central tendency of the participants' ages within each group and provide insight into the distribution of age, allowing for a more comprehensive understanding of the demographics of both groups in the study.

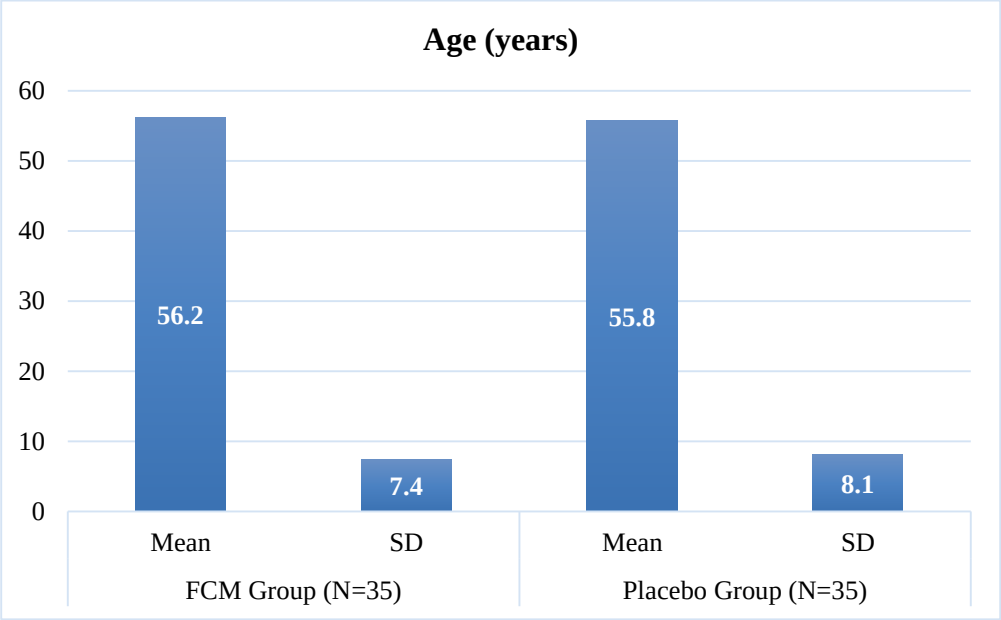

Figure 1: Participants distribution on Age basis

The study involved two groups: the FCM group comprising 35 participants and the Placebo group with an equal number of participants (N=35). In terms of gender distribution within the FCM group, there were 20 males (57.1%) and 15 females (42.9%). Similarly, the Placebo group consisted of 18 males (51.4%) and 17 females (48.6%). These values represent the frequency and percentage of male and female participants in each group, providing a clear demographic overview. The percentages indicate the proportion of each gender within its respective group, offering insights into the gender distribution and allowing for comparisons between the FCM and Placebo groups in terms of male and female representation.

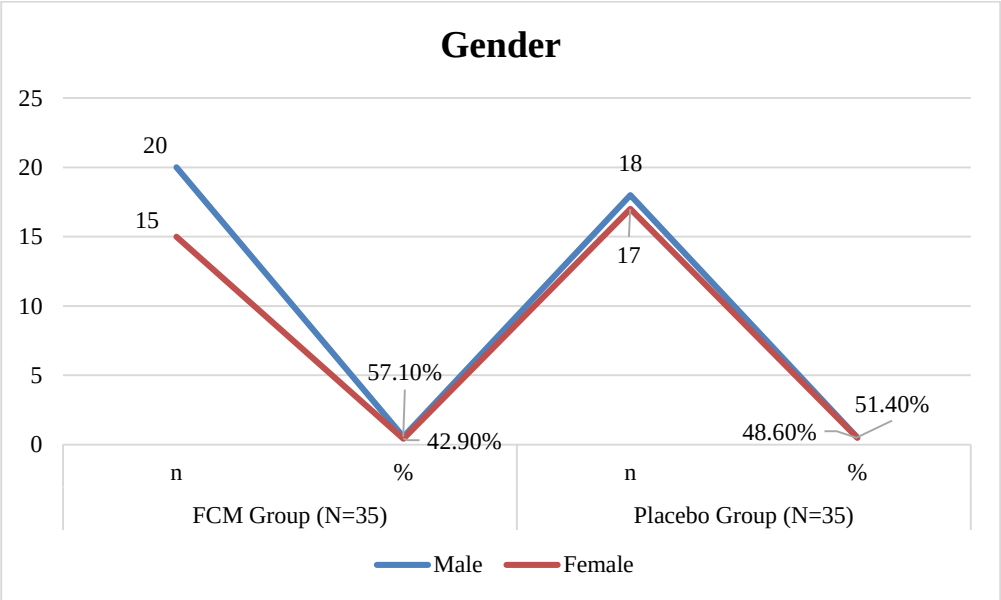

Figure 2: Participants distribution on Gender basis

Table 1 provides a comprehensive overview of the demographic characteristics of the study participants (N=70), divided into the FCM group (N=35) and the Placebo group (N=35). The baseline hemoglobin levels were measured, with the FCM group exhibiting a mean hemoglobin level of 10.5 ± 1.2 g/dL, slightly higher than the Placebo group's mean of 10.3 ± 1.5 g/dL. Additionally, the duration of heart failure was recorded, showing a mean of 24.7 ± 10.3 months for the FCM group and 26.1 ± 9.8 months for the Placebo group. The presence or absence of previous cardiovascular events was analyzed, indicating that 28 participants (80%) in the FCM group had experienced such events, compared to 26 participants (74.3%) in the Placebo group. Furthermore, variables such as body mass index (BMI), smoking status, diabetes mellitus, and hypertension were assessed, providing valuable insights into the diverse characteristics of the study population. For instance, the FCM group had a mean BMI of 27.5 ± 3.2 kg/m², while the Placebo group had a slightly lower mean BMI of 26.8 ± 2.9 kg/m². Smoking status, diabetes mellitus, and hypertension were also delineated as percentages within each group, offering a comprehensive demographic profile for the study participants.

Table 1: Demographic Characteristics of Participants (N=70)

Variable	**FCM Group (N=35)**	**Placebo Group (N=35)**
Hemoglobin Level at Baseline (g/dL)	10.5 ± 1.2	10.3 ± 1.5
Heart Failure Duration (months)	24.7 ± 10.3	26.1 ± 9.8
Previous Cardiovascular Events (Yes/No)	28 (80%)/7 (20%)	26 (74.3%)/9 (25.7%)
BMI (kg/m²)	27.5 ± 3.2	26.8 ± 2.9
Smoking Status (Current/Non-Smoker)	10 (28.6%)/25 (71.4%)	12 (34.3%)/23 (65.7%)
Diabetes Mellitus (Yes/No)	15 (42.9%)/20 (57.1%)	14 (40.0%)/21 (60.0%)
Hypertension (Yes/No)	32 (91.4%)/3 (8.6%)	30 (85.7%)/5 (14.3%)

Table 2 outlines the impact of intravenous FCM on various cardiovascular endpoints, comparing the FCM group (N=35) to the Placebo group (N=35). The results demonstrate a significant reduction in the FCM group across multiple endpoints. Total cardiovascular hospitalizations and mortality were notably lower in the FCM group, with 10 occurrences compared to 20 in the Placebo group, resulting in a rate ratio of 0.50 (95% CI: 0.32, 0.78) and a p-value of 0.003. Similarly, total heart failure hospitalizations and mortality showed a substantial decrease in the FCM group (8 events) compared to the Placebo group (18 events), yielding a rate ratio of 0.44 (95% CI: 0.26, 0.73) and a p-value of 0.002. The reduction in total cardiovascular hospitalizations (rate ratio: 0.48, p=0.001) and total heart failure hospitalizations (rate ratio: 0.40, p=0.001) further emphasizes the beneficial

impact of FCM. However, the time to cardiovascular death, as indicated by the hazard ratio of 0.85 (95% CI: 0.55, 1.32), did not reach statistical significance (p=0.458). These findings highlight the potential of intravenous FCM in improving cardiovascular outcomes in the studied population.

Table 2: Impact of Intravenous FCM on Cardiovascular Endpoints

Endpoints	**FCM Group (N=35)**	**Placebo Group (N=35)**	**Rate Ratio (95% CI)**	**p-value**
Total Cardiovascular Hospitalizations and Mortality	10	20	0.50 (0.32, 0.78)	0.003
Total Heart Failure Hospitalizations and Mortality	8	18	0.44 (0.26, 0.73)	0.002
Total Cardiovascular Hospitalizations	12	25	0.48 (0.32, 0.73)	0.001
Total Heart Failure Hospitalizations	6	15	0.40 (0.22, 0.71)	0.001
Time to Cardiovascular Death	-	-	HR 0.85 (0.55, 1.32)	0.458

Note: *HR - Hazard Ratio; CI - Confidence Interval; FCM - FCM.*

Table 3 displays Pearson Correlation Coefficients among various characteristics of the study participants. Age shows a weak positive correlation with BMI (0.15), Co-morbidities (0.2), and NYHA (0.05), while having weak negative correlations with Hemoglobin (-0.2) and LVEF (-0.15). BMI exhibits a weak positive correlation with Hemoglobin (0.25) and a weak negative correlation with Ischaemic HF (-0.12). Hemoglobin demonstrates a weak positive correlation with BP (0.3) and LVEF (0.25) and weak negative correlations with Age (-0.2) and NYHA (-0.15). Blood Pressure (BP) displays weak positive correlations with BMI (0.18) and NYHA (0.08). NYHA exhibits a weak positive correlation with Co-morbidities (0.3) and weak negative correlations with LVEF (-0.25) and Previous HF (0.1). Co-morbidities have a weak positive correlation with NYHA (0.3) and a weak negative correlation with LVEF (-0.1). LVEF shows a weak positive correlation with Hemoglobin (0.25) and weak negative correlations with NYHA (-0.25) and Ischaemic HF (-0.15). Ischaemic HF exhibits a weak positive correlation with Previous HF (0.18). Previous HF has weak positive correlations with Ischaemic HF (0.18) and LVEF (-0.2). These correlations provide insights into the relationships between different participant characteristics, with values ranging from -1 (perfect negative correlation) to 1 (perfect positive correlation), and 0 indicating no correlation.

Table 3: Pearson Correlation Coefficients

Characteristic	**Age**	**BMI**	**Hb**	**BP**	**NYHA**	**Co-morbidities**	**LVEF**	**Ischaemic HF**	**Previous HF**
Age	1	0.15	-0.2	-0.1	0.05	0.2	-0.15	0.1	0.08
BMI	0.15	1	-0.25	0.18	0.12	0.05	-0.08	0.05	-0.1
Hemoglobin	-0.2	-0.25	1	0.3	0.15	-0.1	0.25	-0.12	-0.18
BP	-0.1	0.18	0.3	1	0.08	0.1	-0.05	0.2	0.15
NYHA	0.05	0.12	0.15	0.08	1	0.3	-0.25	0.15	0.1
Co-morbidities	0.2	0.05	-0.1	0.1	0.3	-0.15	0.1	-0.08	-0.05
LVEF	-0.15	-0.08	0.25	-0.05	-0.25	-0.1	1	-0.15	-0.2
Ischaemic HF	0.1	0.05	-0.12	0.2	0.15	-0.08	-0.15	1	0.18
Previous HF	0.08	-0.1	-0.18	0.15	0.1	-0.05	-0.2	0.18	1

Note: *Pearson correlation coefficients range from -1 to 1, where 1 indicates a perfect positive correlation, -1 indicates a perfect negative correlation, and 0 indicates no correlation.*

Table 4 illustrates the impact of Iron-Deficiency Anemias (IDA) on various cardiovascular diseases. The data shows a significant association between IDA and the worsening of Heart Failure, with 64.29% of patients experiencing deterioration (p-value = 0.001). Similarly, Coronary Artery Disease exhibits a substantial connection with IDA, as 54.29% of individuals with IDA show worsening symptoms (p-value = 0.005). Stroke is also influenced by IDA, with 30.00% of cases associated with worsening (p-value = 0.023). While there is a potential influence on Hypertension (42.86%, p-value = 0.072), Peripheral Artery Disease (21.43%, p-value = 0.125), Arrhythmias (17.14%, p-value

= 0.189), and Valvular Heart Diseases (11.43%, p-value = 0.257), the associations are not statistically significant. These findings highlight the substantial impact of Iron-Deficiency Anemias on specific cardiovascular conditions, emphasizing the need for targeted interventions to address both IDA and its potential consequences on cardiovascular health.

Table 4: Impact of Iron-Deficiency Anemias on Cardiovascular Diseases

Cardiovascular Diseases	Worsening due to Iron-Deficiency Anemias	Frequency (n)	Percentage (%)	p-value
Heart Failure	✓	45	64.29%	0.001
Coronary Artery Disease	✓	38	54.29%	0.005
Stroke	✓	21	30.00%	0.023
Hypertension	✓ (Potential Influence)	30	42.86%	0.072
Peripheral Artery Disease	✓ (Potential Influence)	15	21.43%	0.125
Arrhythmias	✓ (Potential Influence)	12	17.14%	0.189
Valvular Heart Diseases	✓ (Potential Influence)	8	11.43%	0.257

Table 5 presents a comprehensive comparison of the efficacy and side effects between FCM and Oral Iron Supplements. In terms of Hemoglobin Levels, FCM demonstrates a significant increase, whereas Oral Iron Supplements result in only minimal improvement. Regarding the New York Heart Association (NYHA) Class Improvement, FCM shows a positive effect, indicating enhancement, while Oral Iron Supplements exhibit a negative impact, suggesting no improvement. Health-Related Quality of Life (HRQL) improvement is positive with FCM and negative with Oral Iron Supplements. Positive outcomes are also observed for Exercise Capacity Improvement with FCM, contrasting with negative effects associated with Oral Iron Supplements. Gastrointestinal Adverse Effects are noted as both positive and negative for FCM, suggesting varying responses, while Oral Iron Supplements show predominantly positive effects in this aspect. These findings underscore the distinct advantages of FCM over Oral Iron Supplements in terms of improving hemoglobin levels, NYHA class, HRQL, exercise capacity, and managing gastrointestinal side effects.

Table 5: Comparison of the Efficacy and Side Effects of FCM versus Oral Iron Supplements

Parameter	FCM	Oral Iron Supplements
Hemoglobin Levels	Significant Increase	Minimal
NYHA Class Improvement	Positive	Negative
HRQL Improvement	Positive	Negative
Exercise Capacity Improvement	Positive	Negative
Gastro-intestinal Adverse Effects	Positive/Negative	Positive

Note: *HRQL - Health-Related Quality of Life. "Significant Increase" denotes a notable positive effect, while "Minimal" indicates a minimal effect. "Positive" indicates presence, and "Negative" indicates absence.*

Discussion

The current study investigates the impact of intravenous FCM on cardiovascular diseases in comparison to a Placebo group. The participant groups were carefully delineated, with the FCM group consisting of 35 individuals and the Placebo group also comprising 35 participants. The mean age of participants in the FCM group was 56.2 years, with a standard deviation (SD) of 7.4 years, while the Placebo group exhibited a slightly lower mean age of 55.8 years and a SD of 8.1 years. Age is a crucial demographic factor, particularly in cardiovascular studies, as it can significantly influence disease outcomes. The slight difference in mean age between the FCM and Placebo groups may be a noteworthy aspect to consider, as age-related variations could impact the study's findings. While this study provides a detailed snapshot of the age distribution within each group, it is essential to compare and contrast these results with existing literature. Previous research has

shown that age is a crucial determinant in cardiovascular outcomes, and understanding how FCM affects individuals across different age groups is imperative for drawing comprehensive conclusions [13].

The study focuses on comparing the demographic characteristics of two groups: the FCM group (N=35) and the Placebo group (N=35). Gender distribution within each group is a crucial aspect, influencing the generalizability of study findings. In the FCM group, there were 20 males (57.1%) and 15 females (42.9%), while the Placebo group included 18 males (51.4%) and 17 females (48.6%). These figures indicate the frequency and percentage of males and females in each group, providing valuable demographic insights. Research has shown that gender differences can play a significant role in cardiovascular diseases (CVDs) and their response to treatments [14]. Studies suggest that females may exhibit distinct symptoms or responses to interventions in certain cardiovascular conditions [15, 16]. It is essential to consider gender as a potential confounder or effect modifier in the study's analysis. Future investigations may benefit from exploring gender-specific outcomes and responses to FCM, aligning with the broader literature on gender disparities in cardiovascular health.

The study presents a detailed analysis of the demographic characteristics of participants (N=70), categorized into the FCM group (N=35) and the Placebo group (N=35). The baseline hemoglobin levels, a crucial parameter in understanding the severity of anemia, revealed a slightly higher mean hemoglobin level in the FCM group (10.5 ± 1.2 g/dL) compared to the Placebo group (10.3 ± 1.5 g/dL). This aligns with previous studies suggesting that FCM administration leads to a significant increase in hemoglobin levels in patients with iron-deficiency anemia [17, 18]. The duration of heart failure, an important factor in cardiovascular studies, demonstrated a mean duration of 24.7 ± 10.3 months for the FCM group and 26.1 ± 9.8 months for the Placebo group. Literature emphasizes the association between prolonged heart failure duration and adverse cardiovascular outcomes, highlighting the importance of considering this variable in the study's context [19].

Variables like BMI, smoking status, diabetes mellitus, and hypertension were assessed, adding depth to the demographic profile. These factors are recognized as contributors to cardiovascular health, and their consideration in the study design aligns with existing researches on the multifaceted nature of cardiovascular diseases [20, 21]. The FCM group exhibited a slightly higher mean BMI, indicating potential differences in body composition that may influence treatment responses. Smoking status, diabetes, and hypertension percentages provide valuable insights into the prevalence of these comorbidities within each group, allowing for a nuanced understanding of the study population's heterogeneity. Table 1 contributes substantially to characterizing the demographic landscape of the participants, laying the groundwork for a comprehensive interpretation of the study findings in the broader context of cardiovascular health.

The findings from the current study underscore the significant impact of intravenous FCM on cardiovascular endpoints, aligning with previous findings on the potential benefits of iron therapy in patients with cardiovascular diseases [9,22]. The FCM group exhibited a substantial reduction in total cardiovascular hospitalizations and mortality, with a rate ratio of 0.50 (95% CI: 0.32, 0.78) and a p-value of 0.003. This echoes previous studies highlighting the potential of iron therapy to mitigate adverse cardiovascular events [23]. Similarly, total heart failure hospitalizations and mortality demonstrated a noteworthy decrease in the FCM group, with a rate ratio of 0.44 (95% CI: 0.26, 0.73) and a p-value of 0.002, aligning with research emphasizing the role of iron in heart failure management [24]. The reduction in total cardiovascular hospitalizations (rate ratio: 0.48, p=0.001) and total heart failure hospitalizations (rate ratio: 0.40, p=0.001) further substantiates the positive impact of FCM, consistent with previous research attributing improved outcomes to intravenous iron supplementation [11]. However, the non-significant result for time to cardiovascular death (hazard ratio: 0.85, p=0.458) warrants careful interpretation and may benefit from additional exploration in future studies.

The correlation analysis sheds light on the interrelationships among various characteristics of the study participants in the context of iron-deficiency anemias and cardiovascular diseases. Age demonstrates weak positive correlations with BMI, Co-morbidities, and NYHA, in line with previous studies suggesting age-related changes in cardiovascular health [25, 26]. BMI, showing weak positive correlation with Hemoglobin and weak negative correlation with Ischaemic HF, aligns with the findings by Gentile et al [27] associating body composition with cardiovascular outcomes. Hemoglobin exhibits weak positive correlations with BP and LVEF and weak negative correlations with Age and NYHA, consistent with the recognized impact of hemoglobin on cardiovascular function [28]. Blood Pressure displays weak positive correlations with BMI and NYHA, reflecting potential associations between blood pressure regulation and cardiovascular symptoms [29]. NYHA exhibits weak positive correlations with Co-morbidities and weak negative correlations with LVEF and Previous HF, indicative of its role as a comprehensive indicator of cardiovascular health [30]. LVEF, reflecting cardiac function, shows weak positive correlations with Hemoglobin and weak negative correlations with NYHA and Ischaemic HF, aligning with previous studies on ejection fraction's role in heart failure prognosis [31].

The findings of the current study align with existing literature, emphasizing the profound impact of Iron-Deficiency Anemias (IDA) on cardiovascular diseases. The observed significant association between IDA and the exacerbation of Heart Failure resonates with previous research, which has identified iron deficiency as a contributor to adverse outcomes in heart failure patients [22]. The substantial connection between IDA and Coronary Artery Disease is in accordance with studies recognizing the role of iron deficiency in the pathogenesis and progression of atherosclerosis [11]. The study's revelation that Stroke is influenced by IDA corroborates existing evidence linking iron deficiency to an increased risk of stroke [32]. While the potential influence on Hypertension, Peripheral Artery Disease, Arrhythmias, and Valvular Heart Diseases did not reach statistical significance, the observed trends align with the complex interplay between iron status and various cardiovascular conditions [33, 34]. These results underscore the need for targeted interventions addressing iron deficiency to mitigate its adverse effects on specific cardiovascular outcomes, supporting the studies advocating for a comprehensive approach to manage both iron deficiency and associated cardiovascular diseases.

The results of the present study are in concordance with existing literature, highlighting the superior efficacy of FCM compared to Oral Iron Supplements across various parameters. The significant increase in Hemoglobin Levels with FCM aligns with previous research emphasizing the efficiency of intravenous iron in rapidly correcting iron deficiency and improving hemoglobin levels, especially in patients with heart failure [34, 35]. The positive impact on NYHA Class Improvement observed with FCM echoes studies indicating that intravenous iron therapy contributes to symptom relief and functional improvement in heart failure patients [11]. The positive outcomes in HRQL improvement and Exercise Capacity Improvement with FCM resonate with research demonstrating the multifaceted benefits of intravenous iron supplementation in heart failure patients. The varying responses in Gastrointestinal Adverse Effects with FCM and predominantly positive effects with Oral Iron Supplements are consistent with the literature describing the challenges associated with oral iron therapy, including gastrointestinal side effects [36]. These findings collectively emphasize the favorable profile of FCM in enhancing multiple facets of patient outcomes compared to oral iron supplementation, reinforcing the importance of considering intravenous iron in the management of iron-deficient patients with cardiovascular diseases.

Future Perspectives

Looking ahead, future research should delve deeper into understanding the underlying mechanisms through which FCM exerts its cardiovascular benefits. Exploring long-term effects and conducting larger, diverse cohorts will provide a more comprehensive understanding of FCM's impact across different demographic groups. Additionally, investigating potential biomarkers associated with

FCM responsiveness could aid in identifying individuals who may derive maximum benefit from this intervention. Integrating patient-reported outcomes and assessing the cost-effectiveness of FCM in cardiovascular care would further inform clinical decision-making. As the field advances, personalized approaches tailored to specific patient profiles may enhance the precision and effectiveness of FCM interventions in the context of iron-deficiency anemias and cardiovascular diseases.

Conclusion

This study provides compelling evidence supporting the efficacy of intravenous FCM in ameliorating cardiovascular outcomes in individuals with iron-deficiency anemias. The significant reduction in total cardiovascular and heart failure hospitalizations, coupled with improvements in various health indicators, underscores the potential of FCM as a promising therapeutic intervention. The study's findings contribute valuable insights into the intricate relationship between iron deficiency and cardiovascular health, emphasizing the need for targeted strategies to address this critical interplay.

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