Study Protocol Systematic Review

Medicine®

OPEN

Iron therapy in iron-deficiency patients with heart failure with preserved ejection fraction

A protocol for meta-analysis

Hidekatsu Fukuta, MD, PhD[a,*], Hiromi Hagiwara, PhD[b], Takeshi Kamiya, MD, PhD[b]

Abstract

Background: Nearly half of patients with heart failure (HF) have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high. However, there is no established therapy to improve survival in these patients. HFpEF patients are often elderly and their primary chronic symptom is severe exercise intolerance. Thus, improvement of exercise capacity presents another important clinical outcome in HFpEF patients. Iron deficiency is common in HF patients, and the presence of iron deficiency, regardless of concomitant anemia, is associated with worse symptoms, impaired exercise capacity, and higher mortality and hospitalization in these patients. Several meta-analyses of randomized controlled trials reported that iron administration improved HF symptoms, exercise capacity, and clinical outcomes in iron-deficiency patients with HF with reduced EF. However, there is insufficient evidence as to the effect of iron administration in iron-deficiency HFpEF patients.

Methods and Results: This meta-analysis will include randomized controlled trials on the effects of iron administration on HF symptoms, exercise capacity, and health-related quality of life in iron-deficiency HFpEF patients. Information of studies will be collected from PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov. The primary outcome will be exercise capacity (6-minute walking distance). The secondary outcomes will be HF symptoms, health-related quality of life, and mortality and hospitalization rates.

Conclusion: This meta-analysis will evaluate the effect of iron therapy in iron-deficiency HFpEF patients, providing evidence as to the iron administration in these patients.

Systematic review registration: PROSPERO CRD42020205297.

Abbreviations: EF = ejection fraction, GRADE = Grading of Recommendations Assessment, Development and Evaluation, HF = heart failure, HFpEF = heart failure with preserved ejection fraction, HFrEF = heart failure with reduced ejection fraction, PRISMA-P = Preferred Reporting Items for Systematic Review and Meta-analysis Protocols, RCTs = randomized controlled trials.

Keywords: anemia, heart failure, iron, meta-analysis

1. Introduction

Nearly half of patients with heart failure (HF) in the community have preserved ejection fraction (EF) and the mortality and morbidity of patients with HF with preserved EF (HFpEF) are high.[1–4] However, there is no established therapy to improve survival in these patients.[5–9] Patients with HFpEF are often elderly and their primary chronic symptom is severe exercise intolerance.[10,11] Thus, improvement of exercise capacity presents another important clinical outcome in HFpEF patients.

Iron deficiency is common in patients with HF with reduced EF (HFrEF), and the presence of iron deficiency, regardless of concomitant anemia, is associated with worse symptoms, impaired exercise capacity, and higher mortality and hospitalization in these patients.[12–15] Multiple randomized controlled trials (RCTs) have examined the effect of iron therapy in iron-deficiency HFrEF patients.[16–18] Several meta-analyses reported that iron administration improved HF symptoms, exercise capacity, and clinical outcomes in iron-deficiency HFrEF patients.[19,20]

It is accumulating evidence that iron deficiency is also common in HFpEF patients and that the presence of iron deficiency is associated with worse symptoms and impaired functional capacity in these patients.[21] However, there is insufficient evidence as to the effect of iron administration in iron-deficiency HFpEF patients.

Accordingly, the purpose of this meta-analysis is to evaluate the efficacy as well as safety of iron administration in iron-deficiency HFpEF patients compared with standard therapy or control group.

This study is supported by the faculty research expenses in Nagoya City University Graduate School of Medical Sciences (21k1183188).

The authors have no conflicts of interest to disclose.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

[a] Core Laboratory, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [b] Department of Medical Innovation, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

[*] Correspondence: Hidekatsu Fukuta, Core Laboratory, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi Mizuho-cho Mizuho-ku, Nagoya 467-8601, Japan (e-mail: fukuta-h@med.nagoya-cu.ac.jp).

How to cite this article: Fukuta H, Hagiwara H, Kamiya T. Iron therapy in iron-deficiency patients with heart failure with preserved ejection fraction: a protocol for meta-analysis. Medicine 2021;100:32(e26919).

Received: 16 July 2021 / Accepted: 27 July 2021

http://dx.doi.org/10.1097/MD.0000000000026919

2. Methods

This study has been registered as PROSPERO CRD42020205297 (https://www.crd.york.ac.uk/prospero/). This protocol for meta-analysis will be performed according to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) statement.[22]

2.1. Search strategy

The electronic databases for literature search will include PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov. For search of the eligible studies, the following keywords and Medical Subject Heading will be used: *diastolic heart failure*, *heart failure with normal (preserved) ejection fraction, iron, anemia*. Only articles published in the English language will be included.

2.2. Study design

Only RCTs will be included. Observational cohort and case-control studies will be excluded.

2.3. Selection criteria

Inclusion criteria for this meta-analysis included: included patients with HFpEF; RCTs; administration of iron; compared with usual therapy or placebo control group; and assessed HF symptoms, exercise capacity, quality of life, morbidity, or mortality.

2.4. Outcomes

The primary outcome will be exercise capacity (6-minute walking distance). The secondary outcomes will be HF symptoms, health-related quality of life, and mortality and hospitalization rates.

2.5. Data extraction

Information on the study and patient characteristics, methodological quality, intervention strategies, and clinical outcomes will be systematically extracted separately by 2 reviewers. Disagreements will be resolved by consensus.

2.6. Quality assessment

The Cochrane Risk of Bias tool will be used to assess quality of RCTs included.[23] The quality of evidence for the outcomes will be evaluated by the use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[24] The quality of evidence will be evaluated across the domains of risk of bias, consistency, directness, precision, and publication bias.

2.7. Statistical analysis

For continuous outcomes, the effect size for the intervention will be calculated by the difference between the means of the intervention and control groups at the end of the intervention. For morbidity and mortality, relative risk with 95% confidence interval will be calculated. For each outcome, heterogeneity will be assessed using the Cochran's Q and I^2 statistic; for the Cochran's Q and I^2 statistic, a P value of $<.1$ and $I^2 > 50\%$ will be considered significant, respectively. When there is significant heterogeneity, the data will be pooled using a random-effects model; otherwise, a fixed-effects model will be used. Publication bias will be assessed graphically using a funnel plot and mathematically using Egger test. For these analyses, Comprehensive Meta Analysis Software version 2 (Biostat, Englewood, NJ) and STATA 16 software (Stata Corp LP, TX) will be used.

2.8. Sensitivity analysis

Meta-regression will be used to determine whether the effect of iron administration will be confounded by baseline clinical characteristics. Subgroup analysis stratified by route of iron administration (oral or intravenous) will be performed.

2.9. Ethical issues

This meta-analysis is a literature study. Ethical approval is not required because this meta-analysis will not involve any subject directly.

3. Discussion

Although recent meta-analyses on the effect of iron administration in HFrEF patients have reported the potential benefits,[19,20] there is insufficient evidence as to the effect of iron therapy in HFpEF patients. To the best of our knowledge, this is the first meta-analysis protocol about iron therapy in iron-deficiency patients with HFpEF. The results will evaluate whether iron administration is beneficial for iron-deficiency patients with HFpEF, providing evidence regarding the iron administration in these patients.

Author contributions

All authors critically revised the manuscript.
Conceptualization: Hidekatsu Fukuta.
Data curation: Hiromi Hagiwara, Takeshi Kamiya.
Drafted manuscript: Hidekatsu Fukuta.
Funding acquisition: Hidekatsu Fukuta.
Literature retrieval: Hiromi Hagiwara, Takeshi Kamiya.
Methodology: Hidekatsu Fukuta, Hiromi Hagiwara, Takeshi Kamiya.
Supervision: Takeshi Kamiya.
Writing – original draft: Hidekatsu Fukuta.
Writing – review & editing: Hidekatsu Fukuta, Hiromi Hagiwara, Takeshi Kamiya.

References

[1] Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. J Am Coll Cardiol 1999;33:1948–55.
[2] Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–9.
[3] Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction. Report From the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1893–900.
[4] Pfeffer MA, Shah AM, Borlaug BA. Heart failure with preserved ejection fraction in perspective. Circ Res 2019;124:1598–617.

[5] Yusuf S, Pfeffer MA, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 2003;362:777–81.
[6] Massie BM, Carson PE, McMurray JJ, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med 2008; 359:2456–67.
[7] Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J 2006;27:2338–45.
[8] Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–92.
[9] Yamamoto K, Origasa H, Hori M. Effects of carvedilol on heart failure with preserved ejection fraction: the Japanese Diastolic Heart Failure Study (J-DHF). Eur J Heart Fail 2013;15:110–8.
[10] Kitzman DW, Little WC, Brubaker PH, et al. Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 2002;288:2144–50.
[11] Reddy YNV, Rikhi A, Obokata M, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. Eur J Heart Fail 2020;22:1009–18.
[12] Klip IT, Comin-Colet J, Voors AA, et al. Iron deficiency in chronic heart failure: an international pooled analysis. Am Heart J 2013;165:575–82.
[13] Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. J Card Fail 2011;17:899–906.
[14] Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 2010;31:1872–80.
[15] Enjuanes C, Klip IT, Bruguera J, et al. Iron deficiency and health-related quality of life in chronic heart failure: results from a multicenter European study. Int J Cardiol 2014;174:268–75.
[16] Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. J Am Coll Cardiol 2008;51:103–12.
[17] Anker SD, Comin CJ, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436–48.
[18] Beck-da-Silva L, Piardi D, Soder S, et al. IRON-HF study: a randomized trial to assess the effects of iron in heart failure patients with anemia. Int J Cardiol 2013;168:3439–42.
[19] Ponikowski P, Van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiencydagger. Eur Heart J 2015;36:657–68.
[20] Jankowska EA, Tkaczyszyn M, Suchocki T, et al. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. Eur J Heart Fail 2016;18:786–95.
[21] Beale AL, Warren JL, Roberts N, Meyer P, Townsend NP, Kaye D. Iron deficiency in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Open Heart 2019;6:e001012.
[22] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.
[23] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[24] Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011;64:380–2.