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Systematic Review/Meta-analysis

The Efficacy and Safety of Iron Supplementation in Patients With Heart Failure and Iron Deficiency: A Systematic Review and Meta-analysis

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See editorial by O'Meara et al., pages 148-150 of this issue.

ABSTRACT

Background: Iron deficiency (ID) is a common comorbidity in patients with heart failure (HF) and has been associated with increased mortality and hospitalizations. However, the benefit and safety of iron supplementation in treating HF and ID in randomized controlled trials (RCTs) are inconclusive. We therefore performed a meta-analysis to overcome this limitation.

Methods: PubMed, the Cochrane Library, and ClinicalTrials.gov were systematically searched for eligible trials up to December 31, 2014. We also searched the references of all relevant studies and reviews for more trials. Only RCTs reporting the clinical impact of iron therapy in patients with HF with ID compared with no iron treatment were enrolled in our meta-analysis.

RÉSUMÉ

Introduction : Une carence en fer (CF) est une comorbidité fréquente chez les patients atteints d'insuffisance cardiaque (IC) et elle est associée à une augmentation de la mortalité et des hospitalisations. Toutefois, le bénéfice et la sécurité d'une supplémentation en fer dans le traitement de l'IC et de la CF dans des essais contrôlés randomisés (ECR) ne sont pas concluants. Nous avons donc réalisé une méta-analyse pour surmonter cette limitation.

Méthodes : PubMed, la Cochrane Library, et le site ClinicalTrials.gov ont été systématiquement fouillés pour des essais admissibles jusqu'au 31 décembre 2014. Nous avons également cherché les références de toutes les études et commentaires pertinents pour plus d'essais. Seuls les ECR rapportant l'impact clinique d'un apport

Iron deficiency (ID) is now viewed as a frequent and important comorbidity in patients with heart failure (HF). Studies have reported a high prevalence of ID in patients with chronic HF of up to 30%-50%.[1,2] Traditionally, the clinically related influences of ID were considered only in the context of anemia. However, ID anemia can be regarded as the end phase of a process beginning with the gradual depletion of iron stores.[3] Accordingly, even in patients with a preserved hemoglobin level, ID may already exist in chronic HF.[4] ID, with or without anemia, is associated with exercise intolerance, low quality of life, and increased mortality and hospitalization in patients with HF.[5-7]

Besides improving erythropoiesis, intravenous iron has been shown to maintain energy metabolism by augmenting aerobic metabolism and oxidative phosphorylation.[8] Cells with high-energy demand, such as cardiomyocytes and skeletal myocytes, are particularly sensitive to ID. As the impaired energy generation and utilization in the myocardium and the peripheral tissue are always involved in the pathophysiological process of HF,[9] correction of ID may be an efficient treatment for HF and ID. In the past few decades, a number of trials have explored the effect of erythropoiesis-stimulating agents (ESAs) and iron preparations in treating patients with chronic HF. Treatment with ESAs alone failed to reduce mortality or hospitalization for HF while it increased the risk of thromboembolic events.[10] ESAs are thus not recommended to treat anemic patients with HF.[11] ESAs combined with iron have been shown to improve cardiac function, New York Heart Association (NYHA) functional class, and exercise capacity.[12-14] Two observational studies, together with 1 pre-post trial, have found that monotherapy with intravenous iron improved symptoms, cardiac remodelling and exercise intolerance.[15-17] In addition, iron therapy alone has shown to have the same benefits as the combination of ESAs and iron in patients with HF.[18] Although almost all randomized controlled trials (RCTs) have observed that intravenous iron could improve the exercise capacity, functional status, and

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Results: Five clinical trials comprising a total of 907 patients were finally included. Compared with placebo or no treatment, additional iron therapy was associated with a significantly reduced rate of hospitalization for HF (odds ratio [OR], 0.28; 95% confidence interval [CI], 0.16-0.49), though all-cause mortality was not significantly different (OR, 0.81; 95% CI, 0.42-1.57). In 4 studies where these endpoints were combined, the incidence of hospitalization for HF and death was lowered in the iron supplementation group (OR, 0.47; 95% CI, 0.29-0.76). There was no increase in the risk of adverse events.
Conclusions: Iron supplementation significantly reduced the risk of (a) hospitalization for HF and (b) the combined endpoint of hospitalization for HF and death, without increasing the risk of adverse events in patients with symptomatic systolic HF and ID. However, the current data are inadequate to make a clear determination upon mortality.

Résultats : Cinq essais cliniques comprenant un total de 907 patients ont finalement été inclus. Comparativement au placebo ou aucun traitement, une thérapie supplémentée en fer a été associée à un taux significativement réduit d'hospitalisation en cas d'IC (ratio d'incidence approché [RIA], 0,28; intervalle de confiance [IC] à 95 %, de 0,16 à 0,49), bien que la mortalité toutes causes confondues n'était pas significativement différente (RIA, 0,81; IC à 95 %, 0,42 à 1,57). Dans quatre études où ces points limites ont été combinés, l'incidence des hospitalisations pour IC et de la mortalité était diminuée dans le groupe avec une supplémentation en fer (RIA, 0,47; IC à 95 %, 0,29 à 0,76). Il n'y avait pas d'augmentation du risque d'événements indésirables.
Conclusions : La supplémentation en fer réduit significativement le risque (a) d'une hospitalisation pour IC et (b) du critère combiné des hospitalisations pour IC et de la mort, sans augmenter le risque d'effets indésirables chez les patients présentant des symptômes d'IC systolique et de CF. Cependant, les données actuelles sont insuffisantes pour obtenir un avis tranché concernant la mortalité.

quality of life in iron-deficient patients with HF, whether it has benefit in terms of reducing mortality or hospitalization remains unknown. Individual RCTs also have not been large enough to detect the prognostic effects of iron supplementation. Therefore, a meta-analysis pooling the data from RCTs is needed to overcome this limitation.

Methods

Data sources and search strategy

This study was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[19] We performed systematic literature searches in the database of PubMed, the Cochrane Library, and ClinicalTrials.gov for eligible studies. The reference lists of relevant studies and reviews were also checked to find additional trials. We combined the following search terms: "iron" or "ferrous" or "ferric," and "heart failure" or "cardiac failure" or "myocardial failure" or "heart decompensation." Our search was limited to human and English articles published until December 31, 2014.

Inclusion criteria

Clinical studies that met the following requirements were included in our meta-analysis: (a) RCTs; (b) enrolled patients with established HF and ID regardless of left ventricular ejection fraction (LVEF); (c) compared iron therapy with no iron therapy (placebo or no treatment); (d) reported data about hospitalization for HF, all-cause mortality, a combined endpoint of hospitalization for HF and death, and adverse events. Trials that compared the combined treatment of ESAs and iron with no iron treatment were excluded.

Data extraction

Two reviewers (C.Q. and B.W.) independently extracted the details regarding study and patient characteristics, treatment strategy, ID definition, and duration of follow-up. The total number of clinical endpoints and effect sizes (odds ratio [OR]) were also recorded for the pooled analysis. All discrepancies between the two reviewers were resolved by discussion with a third reviewer (J.D.).

Quality assessment and study outcome

The quality of the included articles was assessed according to Cochrane collaboration's tool for assessing the risk of bias.[20] The efficacy endpoints for this analysis included hospitalization for HF, all-cause mortality, and a combined endpoint of hospitalization for HF and death, whereas adverse events (AEs) were recorded as the safety endpoint. We collected the quantitative data on only severe AEs reported in each RCT for synthesis, because their concrete definition was stated only in 1 eligible study.[21]

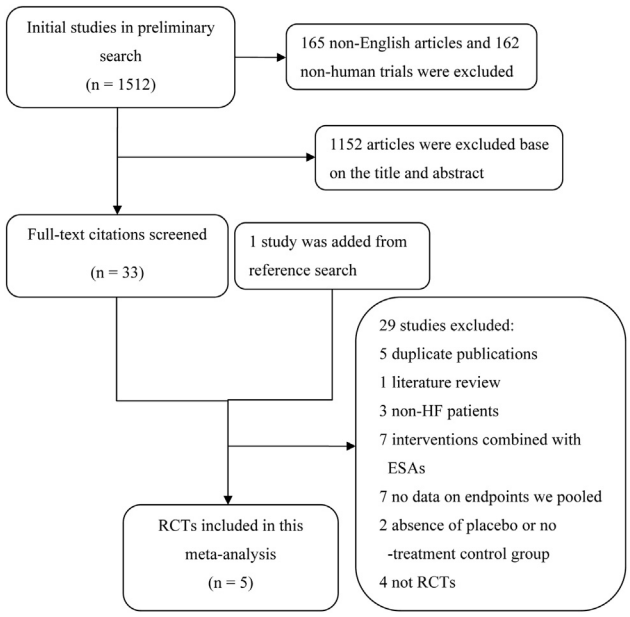

Figure 1. Flow diagram for inclusion of studies in this meta-analysis.