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The Safety of Intravenous Iron Preparations: Systematic Review and Meta-analysis

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Abstract

Objective: To amass all available evidence regarding the safety of intravenous (IV) iron preparations to provide a true balance of efficacy and safety.

Methods: Systematic review and meta-analysis of all randomized clinical trials comparing IV iron to another comparator. All electronic databases until January 1, 2014, were reviewed. Primary outcome was occurrence of severe adverse events (SAEs). Secondary outcomes included all-cause mortality and other adverse events (AEs). Subgroup analysis was performed on the basis of type of IV iron, comparator, treated condition, and system involved.

Results: A total of 103 trials published between 1965 through 2013 were included. A total of 10,390 patients were treated with IV iron compared with 4044 patients treated with oral iron, 1329 with no iron, 3335 with placebo, and 155 with intramuscular iron. There was no increased risk of SAEs with IV iron (relative risk [RR], 1.04; 95% CI, 0.93-1.17; I^2=9%). Subgroup analysis revealed a decreased rate of SAEs when IV iron was used to treat heart failure (RR, 0.45; 95% CI, 0.29-0.70; I^2=0%). Severe infusion reactions were more common with IV iron (RR, 2.47; 95% CI, 1.43-4.28; I^2=0%). There was no increased risk of infections with IV iron. Gastrointestinal AEs were reduced with IV iron.

Conclusion: Intravenous iron therapy is not associated with an increased risk of SAEs or infections. Infusion reactions are more pronounced with IV iron.

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Iron deficiency anemia is an integral part of many disorders, such as chronic renal failure, chronic heart failure, and cancer. Anemia at presentation is a negative prognostic factor in patients with both solid and hematologic tumors,[1] as well as in patients with heart failure.[2] Iron formulations are among the most prescribed drugs.[3] The efficacy of intravenous (IV) iron was found in dozens of randomized clinical trials and meta-analyses in several fields of medicine.[4] Intravenous iron is superior to oral iron or no iron in achieving a sustained hemoglobin response, reducing the need for packed red blood cell transfusions and improving quality of life in various clinical settings: chronic heart failure,[5] inflammatory bowel disease,[6] chronic kidney diseases and hemodialysis,[7-9] cancer-related anemia,[10] and pregnancy.[11] A recent meta-analysis revealed a decreased need for transfusions for all indications (relative risk [RR], 0.74; 95% CI, 0.62-0.88; which translates to a number needed to prevent [NNP] of 1 transfusion of 18).[12]

However, there is a concern regarding the safety of IV iron. The most feared adverse reaction to IV iron is anaphylaxis. This reaction is rare, much more common with high-molecular-weight iron dextran (ID) than with the more novel preparations.[13,14] According to the Gambro Healthcare US medical database, the incidence of life-threatening adverse events (AEs) to ID was 0.035%, and the overall rate of AEs was 0.5% per year.[14]

Another concern is that IV iron might cause endothelial damage and promote atherosclerosis by generating oxidative stress.[15] This concern is supported by laboratory studies that found enhanced oxidative stress induced by iron sucrose (IS) and ferric gluconate (FG) in vitro and in vivo. The clinical implications of these observations are still unknown, and in the several trials that evaluated IV iron in patients with chronic heart failure, most patients had a priori coronary heart disease.[16]

Another concern is that IV iron might promote infection by supplying iron to pathogenic

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bacteria.[17] Experimental evidence indicates that iron treatment might decrease chemotaxis, phagocytosis, and intracellular killing ability of polymorphonuclear cells and hence limit the ability to control infection. In addition, the above mentioned meta-analysis[12] found an increase in the rate of infections with IV iron.

Oral iron is less expensive, easier to administer, and possibly safer than IV preparations. The AEs of oral iron are mainly gastrointestinal (approximately one-third of treated patients). These AEs may limit adherence and the dose that may be administered.[18]

Randomized clinical trials are not the best tools for examining the risk of rare and severe adverse events (SAEs). On the other hand AEs are less dependent on the underlying disorder, which is why we have chosen to look at AEs of IV iron in all the trials of IV iron. We conducted a systematic review and meta-analysis assembling data from all randomized clinical trials that evaluated IV iron for any clinical indication.

METHODS

Data Sources

We searched MEDLINE (January 1, 1966, through December 31, 2013), CENTRAL (The Cochrane Library up to 2013, March, issue 3), LILACS, KOREAMED, and NLM gateway from inception to December 31, 2013. The conference proceedings of the American Society of Hematology, European Haematology Association, American Society of Nephrology, European Renal Association, European Dialysis and Transplant Association, and American Heart Association from 2008 onward and the clinical trials databases for ongoing and unpublished trials were also searched online for further trials. The references of all identified studies were inspected for more trials. The term *iron* was searched as a Medical Subject Heading term and as a text word for specific iron preparations. The result was limited to randomized clinical trials using a highly sensitive filter.[19] The search study is reported in the Supplemental Appendix (available online at http://www.mayoclinicproceedings.org).

Study Selection

We included randomized clinical trials that compared IV iron with no iron, placebo, oral iron, intramuscular (IM) iron, or other treatment for any indication. Trials were included regardless of publication status (published, conference proceedings, or unpublished), trial years, and language. Trials that compared IV iron preparation, different dosages, and administration schedules and trials that did not report AEs were excluded.

Quality Assessment

We assessed trials for method quality and examined the following domains: random sequence generation, allocation concealment, masking of participants and personnel, incomplete outcome data reporting, and selective outcome reporting. We graded each domain as low risk of bias, unclear risk (lack of information or uncertainty over the potential for bias), or high risk of bias according to the criteria specified in the *Cochrane Handbook for Systematic Reviews of Interventions,* version 5.1.0.[19,20] We have also assessed quality measures addressed by the CONSORT guidelines for AEs[21] and adjusted to the design of the included trials. For each item below, we scored whether the item was present or absent and recorded the data when presented.

Definitions and Rules

- The AE and severity grading score definitions (or reference to standardized definitions): We regarded the use of a standardized criteria or a similar form[22] for grading as appropriate
- Mode of data collection: active or passive, questionnaires, or interviews
- Timing and frequency of AE assessments
- Rules for discontinuation

Attribution and Selective Reporting

- Reporting of AEs by intention to treat
- Attribution of AEs to the trial drugs
- The use of a severity threshold (eg, reporting of AEs only above a certain severity grade)
- The use of an occurrence threshold (eg, reporting of AEs occurring only above a certain percentage of patients)

AE-Related Outcomes

- Treatment discontinuations or modifications due to AEs
- Deaths due to AEs