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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

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

Definition of Outcomes

The primary outcome we extracted was the occurrence of SAEs. We defined an SAE as a grade 3 through 5 reaction per each AE as defined by the Common Terminology Criteria for Adverse Events grading system.[22] We included infections and infusion, cardiovascular, neurologic, respiratory, gastrointestinal, thromboembolic, and constitutional severe reactions. The SAEs were further divided by indication for IV treatment, type of IV iron preparation, and comparator. Secondary outcomes included AEs by system involved as mentioned above, all-cause mortality, AEs requiring discontinuation, AEs regarded by authors as treatment related, and any AEs.

Data Collection

We recorded data from all trials with regard to the type of iron preparation, treatment dosage, cumulative dosages, schedule, length of treatment, and follow-up. Two reviewers (T.A., A.B.) independently extracted data from included trials. In case of disagreement, a third reviewer (A.G.G.) extracted the data, and results were attained by consensus. We contacted the investigators of included trials for missing data.

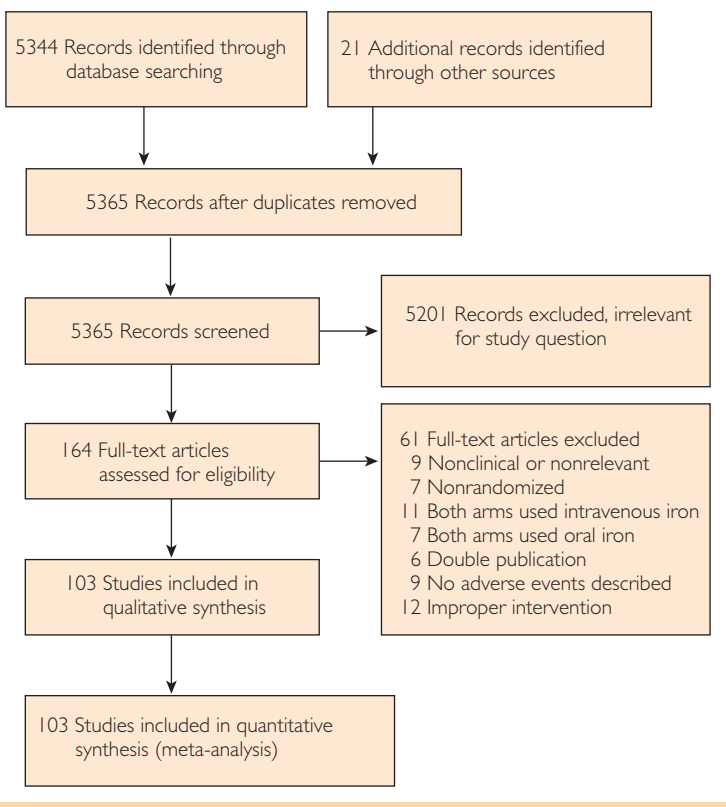

FIGURE. Study flowchart.

Data Synthesis and Statistical Analyses

To include trials with no occurrence of AEs, we used the value 0.1 instead of 0 in the event counter, thus enabling trials that did not observe AEs in both study arms to be used for calculation of the RR.[23] Furthermore, we also calculated commutative risk difference (RD) (which is synonymous to absolute risk reduction) and number needed to harm (NNH) or NNP for all outcomes. Dichotomous data were analyzed by calculating the RR for each trial, with the uncertainty in each result being expressed using 95% CIs. Heterogeneity was assessed by calculating the χ^2 and I^2 tests of heterogeneity. A fixed-effect model was used throughout the review, except in the event of significant heterogeneity among the trials ($P<.10$, $I^2>40\%$), in which we used a random-effects model (REM). We explored potential sources of heterogeneity: type of IV iron preparation, comparator (placebo, oral, no iron, IM iron, or other), indication for iron therapy, adequacy of collecting and reporting methods of the AEs, and the adequacy of allocation generation, concealment, and masking. We used Review Manager, version 5.2 for Windows (The Cochrane Collaboration) and Comprehensive Meta-Analysis, version 2.2 (BioStat) for statistical calculations.

RESULTS

The literature search identified 5326 publications; of them, 164 were potentially eligible publications on IV iron therapy. A total of 103 trials[16,24-125] published from January 1, 1966, through December 31, 2013, fulfilled the inclusion criteria (Figure). Pooled together, 10,390 patients treated with IV iron were compared with 4044 patients treated with oral iron, 1329 treated with no iron, 3335 treated with placebo, and 155 treated with IM iron. Study characteristics are presented in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org). Ferric carboxymaltose (FCM) was used in 15, IS in 57 trials, FG in 7, ID in 14, ferumoxytol in 4, iron polymaltose in 3, and iron isomaltoside in 2 (1 trial used both FCM and IS[31]). Control arms included 14 trials of no iron, 20 trials of placebo,

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56 trials of oral iron, 4 trials of IM iron, 8 trials of oral iron and placebo or no iron, and 1 trial of IM iron and no iron. Among the trials that reported the total amount of IV iron given, the median dosage was 1400 mg (range, 70-3200 mg). Patients were followed up for 1 to 52 weeks (median, 8 weeks); follow-up losses were reported in only a few trials. Other trial characteristics, including inclusion criteria, hematologic data, and treatment schedule, are detailed in Supplemental Table 1.

Risk of Bias Assessment

Allocation generation was adequate in 61 trials (59%), inadequate in 1 trial (1%), and unclear in 41 (40%). Allocation concealment was adequate in 52 trials (50%), inadequate in 3 trials (3%), and unclear in 48 (47%). Double blinding was used in 20 trials. In 29 trials (28%), intent-to-treat analysis of primary outcome was performed. Industrial sponsorship was declared in 44 trials (42.7%), nonindustrial or academic sponsorship in 10 trials (9.7%), and sponsorship was unclear in 49 trials (47.5%).

A total of 20 trials had valid AE grading (14 trials used the Common Terminology Criteria for Adverse Events grading system[22] or a similar grading system; 6 trials developed an acceptable AE grading system). In 83 trials (80%), the grading system for AEs was not reported or invalid. Thirty-three trials reported AEs by intent to treat, 11 trials reported only treatment-related AEs, and 23 reported both any and treatment-related AEs. In 36 trials, the reporting of the relevance of AEs to the treatment was unclear. Severity threshold for the reporting of AEs was not used, but 6 trials reported AEs only if there was more than a 1% to 5% occurrence rate. Adverse events that required discontinuation of treatment were reported in 80 trials; rules for discontinuation were reported in 2 trials. Other methodologic details are presented in Supplemental Table 2 (available online at http://www.mayoclinicproceedings.org).

Primary Outcome: Occurrence of SAEs

Serious adverse events were reported by 97 trials (95%). Overall, there was no increase in the risk of SAEs with IV iron compared with control (RR, 1.04; 95% CI, 0.93-1.17; I^2=9%; Supplemental Figure 1; available online at http://www.mayoclinicproceedings.org). Further classification (Table 1) revealed a statistically nonsignificant lower risk of SAEs when IV iron was compared with placebo in double-blind trials (RR, 0.83; 95% CI, 0.64-1.03; I^2=41%). Sensitivity analysis restricted to studies that reported SAEs with adequate allocation concealment (n=49) and studies with adequate AE definitions (n=19) did not alter the results (RR, 1.02; 95% CI, 0.93-1.18; I^2=9%; and RR, 0.94; 95% CI, 0.74-1.20; I^2=48% [REM]; respectively).

Indication for Therapy

A subgroup analysis performed on the basis of the indication for therapy revealed that the use of IV iron in patients with chronic heart failure

TABLE 1. Primary Outcomes[a]

SAE	RR (95% CI)	NNH or NNP (95% CI)
All studies	1.04 (0.93-1.17)	NA
By indication		
Chronic heart failure	0.45 (0.29-0.70)[b]	NNP, 10 (6-25)[b]
Obstetrics and gynecology	2.0 (1.15-3.62)[b]	NNH, 119 (61-1725)[b]
By comparator		
Placebo	0.83 (0.64-1.08)	NA
No iron	1.06 (0.90-1.25)	NA
Oral iron	1.13 (0.95-1.35)	NA
Intramuscular iron	1.36 (0.22-8.49)	NA
By compound		
IS	1.33 (0.96-1.83)	NA
FCM	0.82 (0.64-1.06)	NA
FML	1.04 (0.71-1.53)	NA
ISM or IPM	1.09 (0.43-2.80)	NA
ID	1.05 (0.77-1.45)	NA
FG	1.12 (0.96-1.30)	NA
By system involved		
Infections	0.96 (0.63-1.46)	NA
Gastrointestinal	1.03 (0.64-1.66)	NA
Cardiovascular	0.94 (0.60-1.46)	NA
Thromboembolic	0.99 (0.52-1.86)	NA
Respiratory	0.91 (0.27-3.86)	NA
Neurologic	1.05 (0.47-2.36)	NA
By infusion reaction		
All	2.47 (1.43-4.28)[b]	NNH, 292 (164-1316)[b]
IS	1.75 (0.69-4.43)	NA
FCM	1.47 (0.40-5.39)	NA
FML	2.26 (0.19-26.22)	NA
ISM or IPM	1.00 (0.99-1.01)	NA
ID	3.10 (0.86-11.22)	NA
FG	5.32 (1.49-18.99)[b]	NNH, 118 (68-423)[b]
Placebo comparator	2.96 (1.16-7.51)[b]	NNH, 255 (136-1910)[b]

[a]FCM = ferric carboxymaltose; FG = ferric gluconate; FML = ferumoxytol; ID = iron dextran; IPM = iron polymaltose; IS = iron sucrose; ISM = iron isomaltoside; NA = not applicable; NNH = number needed to harm; NNP = number needed to prevent; RR = relative risk; SAE = severe adverse event.

[b]Indicates statistically significant results.

TABLE 2. Secondary Outcomes[a]

AE	RR (95% CI)	NNH or NNP (95% CI)
Mortality	1.06 (0.81-1.39)	NA
Any	1.04 (0.99-1.08)	NA
Treatment related	1.08 (0.96-1.21)	NA
Requiring discontinuation		
Total	0.92 (0.76-1.12)	NA
FCM	0.69 (0.46-1.00)[b]	NNP, 127 (60-1377)[b]
Infections	1.17 (0.83-1.65)	NA
Gastrointestinal		
Total	0.55 (0.51-0.61)[b]	NNP, 10 (8-14)[b]
ID	0.28 (0.14-0.53)[b]	NNP, 15 (6-32)[b]
FCM	0.57 (0.48-0.68)[b]	NNP, 15 (8-173)[b]
IS	0.38 (0.32-0.45)[b]	NNP, 7 (5-12)[b]
Placebo	1.39 (1.13-1.71)[b]	NNH, 54 (34-128)[b]
No iron	0.84 (0.72-0.92)[b]	NNP, 24 (12-738)[b]
Oral iron	0.33 (0.29-0.38)[b]	NNP, 6 (5-7)[b]
Infusion reaction		
Total	2.74 (2.13-3.53)[b]	NNH, 64 (44-115)[b]
IS	3.59 (2.30-5.61)[b]	NNH, 44 (25-183)[b]
FCM	3.36 (2.08-5.44)[b]	NNH, 46 (29-110)[b]
FG	5.85 (1.53-22.30)[b]	NNH, 141 (79-627)[b]
Placebo	2.42 (1.50-3.91)[b]	NNH, 92 (52-422)[b]
Oral iron	3.49 (2.22-5.49)[b]	NNH, 50 (32-113)[b]
No iron	2.19 (1.05-4.56)[b]	NNH, 92 (52-422)[b]
Cardiovascular		
Total	0.99 (0.83-1.17)	NA
FCM	0.57 (0.42-0.79)[b]	NNP, 28 (17-71)[b]
FG	1.33 (1.05-1.69)[b]	NNH, 39 (21-235)[b]
Respiratory	1.14 (0.72-1.81)	NA
Neurologic		
Total	1.35 (1.13-1.61)[b]	NNH, 78 (44-336)[b]
IS	1.63 (1.10-2.42)[b]	NNH, 71 (30-237)[b]
Oral iron	2.14 (1.54-2.98)[b]	NNH, 50 (33-100)[b]
Intramuscular iron	0.09 (0.03-0.26)[b]	NNP, 14 (4-42)[b]
Thromboembolic	0.92 (0.62-1.38)	NA
Hypotension		
Total	1.39 (1.09-1.77)[b]	NNH, 97 (58-305)[b]
IS	3.01 (1.12-8.11)[b]	NNH, 68 (37-364)[b]
No iron	3.83 (1.33-11.02)[b]	NNH, 50 (25-100)[b]
Skin	1.60 (1.05-2.45)[b]	NNH, 99 (59-304)[b]
Muscle or skeletal		
Total	1.58 (1.15-2.17)[b]	NNH, 36 (28-53)[b]
FCM	3.42 (2.02-5.79)[b]	NNH, 32 (23-49)[b]
Hypertension	2.25 (1.00-5.08)[b]	NNH, 36 (28-51)[b]
Constitutional	1.35 (0.97-1.87)	NA
Electrolytes	2.45 (1.84-3.26)[b]	NNH, 19 (11-67)[b]
Abnormal laboratory results	1.57 (0.91-2.71)	NA
Iron overload	1.40 (0.95-2.07)	NA

[a]AE = adverse event; FCM = ferric carboxymaltose; FG = ferric gluconate; ID = iron dextran; IS = iron sucrose; NA = not applicable; NNH = number needed to harm; NNP = number needed to prevent; RR = relative risk.

[b]Indicate statistically significant results.

was associated with a decreased rate of SAEs compared with controls (RR, 0.45; 95% CI, 0.29-0.70; I^2=0%; NNP, 10; 95% CI, 6-25). In trials in gynecology and obstetrics, the use of IV iron was associated with an increased rate of SAEs (RR, 2.00; 95% CI, 1.15-3.62; I^2=0%; NNH, 119; 95% CI, 61-1725). Subdividing the trials by indication for therapy (pregnancy, peripartum, and other) or compound revealed a trend toward increased rate of SAEs with IV iron that was statistically nonsignificant in all subgroups. In trials of chronic kidney disease, inflammatory bowel disease, and cancer-induced anemia, perioperative trials, and other trials of mixed causes, there was no increased risk of SAEs with IV iron therapy.

SAEs by System Involved

There was no increased risk of serious infections with IV iron (RR, 0.96; 95% CI, 0.63-1.46; I^2=8.2%). Serious infusion reactions were increased with IV iron (RR, 2.47; 95% CI, 1.43-4.28; I^2=0%; NNH, 292; 95% CI, 164-1316) and particularly with FG (RR, 5.32; 95% CI, 1.49-18.99; I^2=0%; NNH, 118; 95% CI, 68-423). The other iron preparations were not associated with a statistically significant increased risk of severe infusion reactions (IS: RR, 1.75; 95% CI, 0.69-4.43; FCM: RR, 1.47; 95% CI, 0.40-5.39; ferumoxytol: RR, 2.26; 95% CI, 0.19-26.22; ID: RR, 3.1; 95% CI, 0.86-11.22). A subgroup analysis restricted to trials that used placebo as the comparator revealed an increased risk of a severe infusion reaction (RR, 2.96; 95% CI, 1.16-7.51; I^2=0%; NNH, 255; 95% CI, 136-1910). The risk of cardiovascular, neurologic, thromboembolic, or gastrointestinal SAEs was not increased with IV iron. Sensitivity analysis was performed on the basis of quality measures did not alter the reported results. Subgroup analysis was performed on the basis of indication for treatment, type of comparator, and type of IV iron formula did not alter the results. No deaths related to SAEs were reported.

Secondary Outcomes: Mortality, AEs Requiring Discontinuation, and Any AEs

Results are presented in Table 2. All-cause mortality was reported in 57 trials, and of these trials, no deaths occurred during the

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follow-up period in 29 trails. Overall, there was no increased risk of mortality with IV iron (RR, 1.06; 95% CI, 0.81-1.39; I^2=0%). There was no increased risk of AEs that required discontinuation of treatment with IV iron (RR, 0.92; 95% CI, 0.76-1.12; I^2=11%). There was a trend toward decreased risk of AEs requiring discontinuation with FCM (RR, 0.69; 95% CI, 0.46-1.00; I^2=8%). The occurrence of any AEs was reported by 38 trials. There was no increased risk of any AEs with IV iron (RR, 1.04; 95% CI, 0.99-1.08; I^2=74% [REM]). Among the trials that defined AEs as treatment related (n=43), there was no increased risk of treatment-related AEs (RR, 1.08; 95% CI, 0.96-1.21; I^2=78% [REM]). Subgroup analysis was performed on the basis of indication for treatment and comparator did not change these results.

Secondary Outcomes: Infections and Cardiovascular, Gastrointestinal, and Infusion Reactions

The occurrence of infections was not increased with IV iron regardless of compound, comparator, and indication (RR, 1.17; 95% CI, 0.83-1.65; I^2=0%; Supplemental Figure 2; available online at http://www.mayoclinicproceedings.org). There was no increased risk of cardiovascular AEs; however, FCM was associated with a decreased risk of cardiovascular AEs (RR, 0.57; 95% CI, 0.42-0.79; I^2=0%; NNP, 28; 95% CI, 17-71), and FG was associated with an increased risk of cardiovascular AEs (RR, 1.33; 95% CI, 1.05-1.69; I^2=0%; NNH, 39; 95% CI, 21-235). The use of IV iron was associated with a decreased risk of gastrointestinal AEs (RR, 0.55; 95% CI, 0.51-0.61; I^2=84% [REM]; NNP, 10; 95% CI, 8-14), particularly with IS, ID, and FCM and when the comparator was oral iron or no iron (Table 2). Infusion reactions were increased with IV iron (RR, 2.74; 95% CI, 2.13-3.53; I^2=26%; NNH, 64; 95% CI, 44-115) and further increased when compared with oral iron (RR, 3.49; 95% CI, 2.22-5.49; I^2=0%; NNH, 50; 95% CI, 32-113), placebo (RR, 2.42; 95% CI, 1.50-3.91; I^2=0%; NNH, 92; 95% CI, 52-422), and no iron (RR, 2.19; 95% CI, 1.05-4.56; I^2=0%, NNH, 86; 95% CI, 41-133). Infusion reactions were further increased when IS, FG, and FCM were used (Table 2).

Secondary Outcomes: Other AEs

There was an increase in neurologic AEs (RR, 1.35; 95% CI, 1.13-1.61; I^2=35%; NNH, 78; 95% CI, 44-336), which was more pronounced when IS was used (RR, 1.63; 95% CI, 1.10-2.42; I^2=0%; NNH, 71; 95% CI, 30-237). Hypotension was increased with IV iron (RR, 1.39; 95% CI, 1.09-1.77; I^2=39%; NNH, 97; 95% CI, 58-305). This effect was more pronounced when IS was used (RR, 3.01; 95% CI, 1.12-8.11; I^2= 0%; NNH, 68; 95% CI, 37-364) and when compared with no iron (RR, 3.83; 95% CI, 1.33-11.02; I^2=38%; NNH, 50; 95% CI, 25-100). The use of IV iron was associated with an increased risk of electrolyte disorder (most trials reported on the occurrence of hypophosphatemia) (RR, 2.45; 95% CI, 1.84-3.26; I^2=49% [REM]; NNH, 19; 95% CI, 11-67). Adverse events related to skin (excluding urticaria) were increased with IV iron (RR, 1.60; 95% CI, 1.05-2.45; I^2=35%; NNH, 99; 95% CI, 59-304). Finally, muscle and skeletal AEs were increased with IV iron and particularly FCM (RR, 3.42; 95% CI, 2.02-5.79; I^2=40%; NNH, 32; 95% CI, 23-49). There was a trend toward hypertension responses with IV iron (RR, 2.25; 95% CI, 1.00-5.08; I^2=0%). No statistically significant increase in the occurrence of abnormal laboratory results, constitutional symptoms, or thromboembolic and respiratory AEs was found with any IV iron preparation, comparator, or indication of use. Sensitivity analysis restricted to studies with adequate allocation concealment and studies with adequate AEs definitions did not alter any result.

DISCUSSION

Our systematic review assesses safety of IV iron by compiling data from all randomized clinical trials evaluating IV iron treatment. We found that IV iron is not associated with an increase in SAEs (RR, 1.04; 95% CI, 0.93-1.14; I^2=9%). Moreover, certain IV formulations were associated with a decreased risk of SAEs. Gastrointestinal AEs were decreased, and the risk of discontinuation of therapy was lower with IV iron. There was no increase in the risk of infections.

Although the efficacy of IV iron was found in many settings,[5-7,10] there are still concerns regarding safety. The most important finding of our systematic review is the lack of increase in all SAEs with iron. In addition, there was no

increase in AEs that required discontinuation and no increase in mortality. Moreover, there was no increased risk of cardiovascular, respiratory, neurologic, thromboembolic, constitutional, or gastrointestinal SAEs with IV iron.

Another interesting finding is the decrease in cardiovascular AEs and risk of discontinuation of therapy with FCM. However, 86% of all patients in trials of chronic heart failure were treated with FCM, thus outweighing other formulations and potentially creating reporting bias. This is a promising new formulation of a non—dextran-containing iron complex that allows administration of a large dose of iron (up to 1000 mg) in a single infusion. Our review included 16 trials with FCM. A previous systematic review of the efficacy and safety of FCM for various indications[126] suggested that FCM is largely effective in achieving a superior hemoglobin response than oral iron treatment. The safety profile of FCM in that review was similar to our results, including infusion reactions (regarded as general and administration site reaction).

Another significant finding is the lack of increase in any infections (RR, 1.17; 95% CI, 0.83-1.65) and serious infections (RR, 0.96; 95% CI, 0.63-1.46). Experimental data have suggested that IV iron might promote infection by supplying iron to pathogenic bacteria.[17] In our review, this did not translate into an increase in infection. A prospective study of 988 patients undergoing hemodialysis in 19 European centers followed up for 6 months with 51 episodes of bacteremia found on multivariate analysis that there was no association between IV iron and risk of infection.[127,128] The lack of increase in infection may possibly be related to the fact that low free iron concentrations are associated with the newer IV iron preparations. In contrast to our findings, a recent systematic review and meta-analysis by Litton et al[12] found a statistically significant increase in the rate of infection (RR, 1.33; 95% CI, 1.1-1.64) with IV iron. This review included a total of 75 trials, and data regarding infections were derived from only 24 trials, whereas our study compiled the data from 103 trials and the infection data from 32 trials. Moreover, in the study by Litton et al, trials that did not report any events in the intervention and comparison groups were excluded, whereas we were able to use the data from these studies for calculation of the RR. Thus, the comprehensiveness of our meta-analysis may explain the difference. Of note, although the study by Litton et al found an increase in infections, it did not find a dose response association with iron and infection risk, and there was no difference in mortality and other SAEs in the IV iron groups (as shown in our meta-analysis).

The fact that no increase in infections in the IV iron arm is revealed in our meta-analysis is important, although the other therapeutic option for treatment of anemia, red blood cell transfusion, needs to be taken into account. A large meta-analysis,[129] including 21 randomized clinical trials with 8735 patients that compared a restrictive and a permissive red blood cell transfusion strategy, found that a restrictive transfusion strategy was associated with a reduced risk of health care—associated infection compared with a liberal transfusion strategy. Therefore, implementing restrictive strategies may have the potential to lower the incidence of health care—associated infection. Intravenous iron administration may possibly help facilitate this.

Of note, an increase in any and serious infusion reactions was demonstrated (RR, 2.47; 95% CI, 1.43-4.28). However, the NNH was 200 for serious infusion reactions, and no death or anaphylaxis was reported by any trial. The feared anaphylactic reaction is extremely rare and occurs mainly with the high-molecular-weight ID. When assessing each of the formulations separately, there was no statistically significant increase for any of the formulations except FG, and overall, 35 severe infusion reactions were reported for 9223 patients (1:263; range, 101-481), none of which resulted in death. Thus, it seems that the newer formulations are safer to administer and no test dose is required.

There might be still a reluctance to incorporate IV iron as a standard in the treatment of iron deficiency and other settings of iron restricted erythropoiesis. For many of the examined conditions, 1 or 2 infusions ease care, and the incorporation of IV iron into chemotherapy and dialysis regimens may increase adherence. Therefore, it may be the safety issue rather than convenience that is responsible for the failure of patients to use IV iron. Another explanation may lie in the

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fear of minor infusion reactions and the addition of antihistamines as premedication before IV iron infusion.[130] This practice may result in an apparently severe anaphylactic reaction with IV iron therapy and should probably be abandoned because these reactions usually resolve without therapy and rarely recur with rechallenge.[131]

The strength of our systematic review stems primarily from the large volume of trials and patients (103 trials that included 10,390 patients). Several limitations merit consideration. The included trials were heterogeneous regarding the type of patients, different iron preparations, schedule, and total dose of IV iron administered. Of note, tests for heterogeneity were low (<40% and most often 0% for SAEs), Although most trials were of good methodologic design and reporting, 80% of the trials did not report quality measures addressed by the CONSORT guidelines for AEs.[21] Another possible concern comes from including trials that were diverse in follow-up time and methods. Trials of chronic heart failure, for instance, had relatively long follow-up and concentrated on cardiovascular AEs in contrast to trials of obstetric or perioperative iron administration, which had short follow-up and concentrated on administration and general AEs.

We found that IV iron formulations are safe. They should be considered as an alternative to red blood cell transfusions. Red blood cell transfusions are associated with events that cause major morbidity in 1 in 21,413 components issued according to the Serious Hazards of Transfusion 2012 data.[132] Intravenous iron, on the other hand, is associated with an estimated SAE incidence of less than 1 in 200,000 (when high-molecular-weight ID is avoided).[133]

CONCLUSION

Intravenous iron formulations are safe and may be given to iron deficient individuals without fear of infection or cardiovascular events. Newer preparations may have the highest safety threshold and may be given safely in 1 or 2 doses. Further research should focus on head-to-head comparisons of IV iron formulations for specific conditions.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org.

Abbreviations and Acronyms: **AE** = adverse event; **FCM** = ferric carboxymaltose; **FG** = ferric gluconate; **ID** = iron dextran; **IM** = intramuscular; **IS** = iron sucrose; **IV** = intravenous; **NNH** = number needed to harm; **NNP** = number needed to prevent; **RD** = risk difference; **REM** = random-effects model; **RR** = relative risk; **SAE** = severe adverse event

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