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Infectious complications and mortality associated with the use of IV iron therapy: a systematic review and meta-analysis

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Abstract

Background Parental iron is used to optimize hemoglobin and enhance erythropoiesis in end-stage renal disease along with erythropoietin-stimulating agents. Safety of iron has been debated extensively and there is no definite evidence whether parenteral iron increases the risk of infections and mortality. We performed this meta-analysis to evaluate the incidence of infectious complications, hospitalizations and mortality with use of parenteral iron.

Methods Medical electronic databases [PubMed, EMBASE, Scopus, Web of Science, and cochrane central register for controlled clinical trials (CENTRAL)] were queried for studies that investigated the association between intravenous iron administration and infection in hemodialysis patients. 24 studies (8 Randomized control trials (RCTs) and 16 observational studies) were considered for qualitative and quantitative analysis.

Results *All-cause mortality* Data from 6 RCTs show that high-dose IV iron conferred 17% less all-cause mortality compared to controls; however, this outcome was not statistically significant (OR = 0.83, CI [0.7, 1.01], $p = 0.07$). Nine observational studies were pooled under the random effects model due to significant heterogeneity ($I^2 = 83\%$, $p < 0.001$). The overall HR showed increased risk of all-cause mortality in the high-dose group but was statistically non-significant (HR = 1.1, CI [1, 1.22], $p = 0.06$). *Infections* Four RCTs with no heterogeneity among their data ($I^2 = 0\%$, $p = 0.61$). Under the fixed effect model, there was no difference in the infection rate between high-dose iron and control group (OR = 0.97, CI [0.82, 1.16], $p = 0.77$); eight observational studies with significant heterogeneity and utilizing random effects model. Summary HR showed increased yet non-significant risk of infection in the high-dose group (HR = 1.13, CI [0.99, 1.28], $p = 0.07$) *Hospitalization* 1 RCT and six observational studies provided data for the rate of all-cause hospitalization. There was marked heterogeneity among observational studies. RCT showed no significant difference between high-dose iron and controls in the rate of hospitalization (OR = 1.03, CI [0.87, 1.23], $p = 0.71$). Summary HR for observational data showed increased rate of hospitalization in the high-dose group; however, this effect was not statistically significant (HR = 1.11, CI [0.99, 1.24], $p = 0.07$). *Cardiovascular events* One RCT compared the rate of adverse cardiovascular events between high-dose and low-dose iron. No significant difference was observed between the two groups (22.3% vs 25.6%, $p = 0.12$). Six heterogeneous observational studies ($I^2 = 65\%$, $p < 0.001$) reported on the rate of cardiovascular events. No significant difference was observed between high-dose iron and controls (HR = 1.18, CI [0.89, 1.57], $p = 0.24$).

Conclusion High-dose parenteral iron does not seem to be associated with higher risk of infection, all-cause mortality, increased hospitalization or increased cardiovascular events on analysis of RCTs. Observational studies show increased risk for all-cause mortality, infections and hospitalizations that were not statistically significant and were associated with significant heterogeneity.

Keywords Anemia · Meta-analysis · Mortality · ESRD · Infections

Introduction

Global burden of chronic kidney disease (CKD) and end-stage renal disease (ESRD) is on the rise, and anemia contributed from these diseases is associated with high

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morbidity and mortality [1, 2]. Increased hepcidin production in CKD leads to poor dietary iron uptake and mobilization of stored iron [3]. This along with erythropoietin deficiency, uremic inhibitors of erythropoiesis, low red blood cell survival and loss of blood in dialyzer circuit and arteriovenous access leads to severe anemia needing treatment with both intravenous (IV) iron and erythropoietin stimulating agents (ESA) [4]. To support optimal erythropoiesis, parenteral iron is used concurrently with ESA [5]. Since FDA mandated a black box warning (2007) for all ESA and Centre for Medicaid services introduced ESRD prospective bundled payment system (2011), the use of IV iron has increased and use of ESA has been on decline. Safety of IV iron in dialysis has been a debated topic with multiple studies and trials leading to a farrago of uncertainty. It is paradoxical that both iron deficiency and overload are associated with suboptimal neutrophil and T cell function causing impaired host defense against infections [6].

Research recommendations published by KDIGO (2016) call for further studies to be done in relation to hard endpoints such as infections, cardiovascular outcomes and mortality [7]. In light of the above, a meta-analysis done in 2016 concluded no increased risk for all-cause mortality and included patients with CKD not on dialysis and patients on dialysis [8]. Later in March 2018, another meta-analysis concluded that high-dose IV iron is not associated with higher risk of mortality, infection or hospitalization, but available randomized control trials at the time had extremely small number of participants adding to inchoate certainty [9]. Since then in January 2019, the long awaited Proactive IV Iron Therapy in Hemodialysis Patients (PIVOTAL) trial was published using the highest number of participants and included 3 times combined of all RCTs previously published [10]. This leads us to a perusal of conducting a systematic review and meta-analysis of RCTs and observational studies evaluating infectious complications and mortality with use of parenteral Iron in ESRD.

Methods

We performed this study according to the guidelines of the Cochrane handbook of systematic reviews of interventions [11] and reported it per the preferred reporting items for systematic reviews and meta-analysis (PRISMA) checklist [12].

Search results and screening

Medical electronic databases [PubMed, EMBASE, Scopus, Web of Science, and Cochrane Central Register for Controlled Clinical Trials (CENTRAL)] were queried for studies that investigated the association between intravenous iron administration and infection in hemodialysis patients. Search results were exported to Endnote X7 for management and screening. First round of screening was done by two experienced reviewers and involved title and abstract screening of all the retrieved studies. The full texts of the references that deemed eligible for this study were downloaded and further screened for final inclusion in meta-analysis. A senior author resolved any discrepancy between the two reviewers.

Eligibility criteria

Randomized controlled trials (RCTs) and observational studies (case–control and cohort studies) compared high-dose iron infusion versus controls. The comparator group included low-dose iron, no iron, and oral iron. Patients on dialysis (including hemodialysis and peritoneal dialysis) were eligible for inclusion in this study. The primary outcomes included all-cause mortality and infection. Secondary outcomes were hospitalization from any cause and cardiovascular events.

Data extraction

A standardized excel sheet was created for data extraction from the eligible studies. We extracted the baseline characteristics and outcome data (all-cause mortality, infection, hospitalization, and cardiovascular adverse events), in addition to the risk of bias assessment data from each of the finally included studies. Raw data (events and total) were extracted from RCTs while computed effect estimates (hazard ratio (HR) and confidence interval (CI) or standard error) were extracted from the observational studies. Data were extracted by two independent and blinded authors for accuracy.

Risk of bias assessment

Quality of the included RCTs was assessed using the Cochrane risk of bias assessment tool [13]. The Cochrane tool consists of six domains (random sequence generation, allocation concealment, blinding of the investigators and participants, blinding of the outcomes' assessor, incomplete outcome data, and selective outcome reporting) for assessing the risk of bias in randomized controlled trials. For observational studies, the Newcastle–Ottawa scale was used to assess the risk of bias [14].

Data analysis

We used comprehensive meta-analysis (CMA) software for meta-analysis. Most RCTs reported raw data for the studied outcomes, so data from RCTs were pooled as odds ratio (OR) and 95% CI. Survival data were reported in the observational studies, so we employed HR and 95% CI as a

summary estimate for meta-analysis of the included observational studies. Heterogeneity among studies was measured using the Chi-square test and the I^2 statistic was used to quantify its extent. Fixed effect model was used whenever there is no or minimal heterogeneity, while random effects model was employed in case of significant heterogeneity. Publication bias was investigated using funnel plot and Egger's regression test.

Results

Demographics of the included studies

Database searching retrieved 2644 unique records. Results were exported to reference manager (Endnote X7) and 328 duplicates were automatically identified and removed. Two independent reviewers performed title and abstract screening of the remaining references against our eligibility criteria. Finally, 23 studies (7 RCTs [15–21] and 16 observational studies [22–37]) were considered for qualitative and quantitative analysis (Fig. 1. PRISMA flow diagram). Summary of the included studies and baseline characteristics of their population is presented in Table 1.

Quality assessment

The included RCTs were at moderate to high risk of bias. Randomization and allocation concealment were not adequately achieved in most of the RCTs. In addition, all the studies were open label with no attempts to blind the participants and investigators. Macdougall et al. [17] performed a blinding of outcome assessment procedure. Attrition bias was present in most of the included RCTs. According to the Newcastle–Ottawa scale, 8 of the observational studies were at low risk of bias, 4 were at moderate risk, and 4 possessed high risk of bias due to questionable statistical methods.

Meta-analysis outcomes

All-cause mortality

Six RCTs provided data for all-cause mortality. The fixed effect model was used due to the absence of heterogeneity among the pooled studies ($I^2 = 0\%$, $p = 0.73$). High-dose IV iron conferred 17% less all-cause mortality compared to controls; however, this outcome was not statistically significant (OR = 0.83, CI [0.7, 1.01], $p = 0.07$); Fig. 2a.

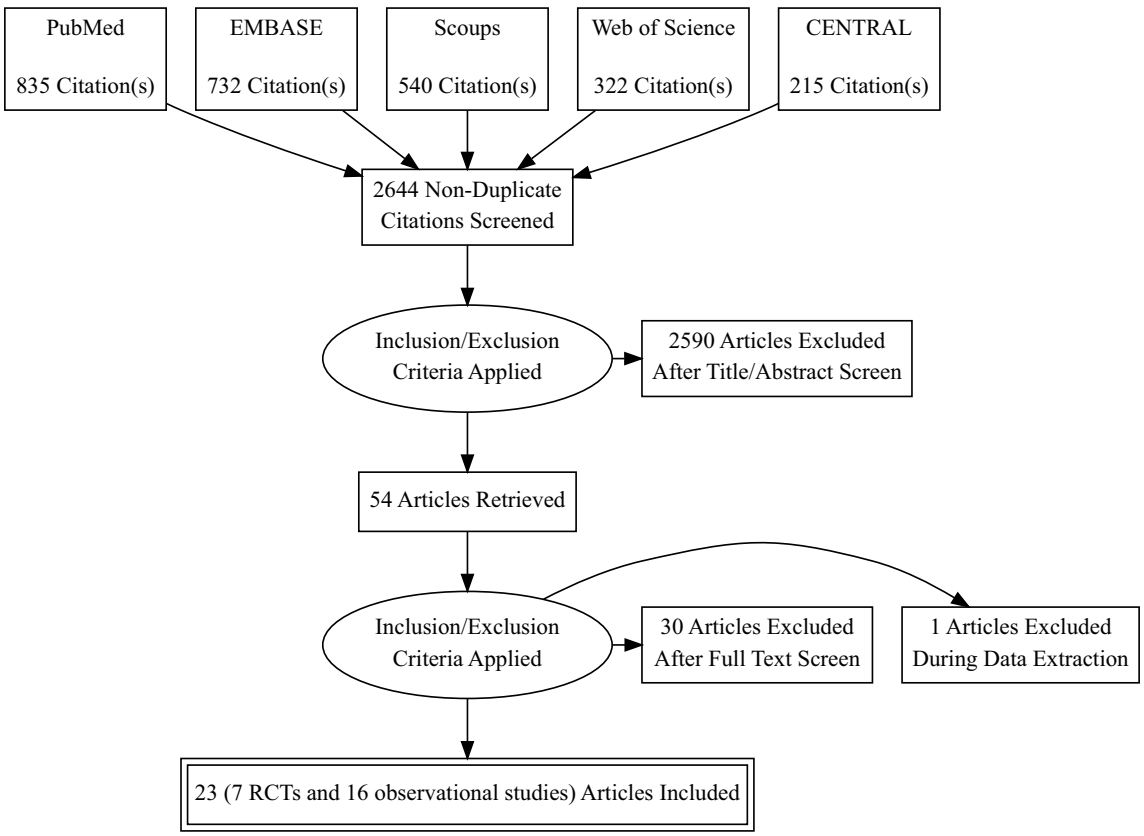


Fig. 1 PRISMA flow diagram

Table 1 Baseline characteristics of the included studies

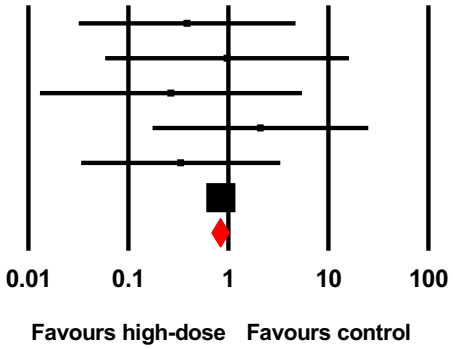
Study ID	Study design	*N*	High-dose group	Control group	Follow-up	1ry outcome(s)	2ry outcome(s)
Besarab et al. 2000 [21]	RCT	42	Iron dextran 100 mg during hemodialysis to achieve TSAT of 30% plus 25–150 mg/wk to maintain TSAT 30–50%	ID 25–150 mg/wk to maintain TSAT at 20–30%	6 months	ESA dose	Infection and mortality
Singh et al. 2006 [15]	RCT	126	IS 1000 mg iv over 28-days period as 300 mg day 1 and day 15, 400 mg day 28	No iron	8 weeks	Change from baseline to highest hemoglobin	Adverse events, blood pressure, and infection.
Fishbane et al. 1995 [19]	RCT	75	Iron dextran 100 mg twice weekly	Oral ferrous sulfate	4 months	Change in transferring saturation	Mortality
Fudin et al. 1998 [18]	RCT	48	Ferric gluconate 62.5 mg	No iron	26 months	RBC transfusion	Ferritin level, and mortality
Macdougall et al. 2018 [17]	RCT	2141	high-dose 400 mg iron sucrose/month	Low-dose 0–400 mg iron sucrose/month	42 months	Composite of nonfatal myocardial infarction, nonfatal stroke, hospitalization for heart failure, or death, assessed in a time-to-first-event analysis	Mortality, infection rate, and dose of an erythropoiesis-stimulating agent
Provenzano et al. 2009 [16]	RCT	230	Ferumoxytol 510 mg twice over a period of 5 ± 3 days	Ferrous fumarate 50 mg for 21 days	35 days	Change in hemoglobin	Proportion of patients achieving a $1-g/dl increase in HGB at day 35 and mortality
Coyne et al. 2007 [20]	RCT	134	Ferric gluconate 125 mg 8 times	No iron	6 weeks	Change in hemoglobin	Percentage of responders (HGB Increase of 2 g/dl during the Study, mortality, and infection
Kshirsagar et al. 2013 [26]	Observational	117,050	High bolus iron dose > 200 mg/month	Low maintenance iron dose 1–200 mg/month	10 months	Death from cardiac causes	hospitalization
Hoen et al. 2002 [36]	Observational	513	IV polymaltose ferric hydroxide	Ferrous sulfate, ferrous fumarate, and ferrous asorbate	12 months	Bacteremia	NA
Feldman et al. 2004 [34]	Observational	27,280	Iron sucrose, Iron glucose, and Iron dextrose > 1800 mg	Total iron dose 0–700 mg	24 months	Mortality	Comorbidities
Kalantar-Zadeh et al. 2005 [32]	Observational	58,058	High-dose iron sucrose, Iron glucose, and Iron dextrose	Low-dose iron sucrose, Iron glucose, and Iron dextrose	24 months	Mortality	CV death
Varas et al. 2017 [33]	Observational	1679	Iron sucrose > 5.8 mg/kg/month	Iron sucrose < 2.94 mg/kg/month	18 months	Mortality	Hospitalization
Freburger et al. 2014 [25]	Observational	6605	High bolus dose of 200–600 mg/month	Low maintenance dose	10 months	All-cause mortality	Infection

Table 1 (continued)

Study ID	Study design	*N*	High-dose group	Control group	Follow-up	1ry outcome(s)	2ry outcome(s)
Kapoian et al. 2008 [30]	Observational	112	High iron dose (discretion of the physician)	Low iron dose (discretion of the physician)	6 weeks	Erythropoietin dose at 6 weeks	Adverse events and infections
Pollak et al. 2009 [29]	Observational	1774	> 455 mg/month	0–202 mg/month	Until death or June 30, 2007	Survival rate	NA
Kopelman et al. 2007 [31]	Observational	39	IV ferric gluconate	No iron if ferritin > 800 ng/ml	3 months	Infection and hospitalization	NA
Brookhart et al. 2013 [27]	Observational	117,050	High-dose iron > 200 mg/month	Low-dose iron 1–200 mg/month	10 months	Infection-related death	Infection-related hospitalization
Kuragano et al. 2014 [47]	Observational	1095	High-dose IV iron	Low-dose oral/IV iron	24 months	Hospitalization	Mortality
Bailie et al. 2015 [23]	Observational	32,435	High dose: 400 mg/month	Low-dose: no iron or 1–99 mg/month	until death or transfer, modality change, loss to follow-up, or study end	All-cause mortality	Infection, hospitalization, and cardiovascular mortality
Canziani et al. 2001 [37]	Observational	111	10 doses of 100 mg iron sucrose (1 g) over 28 days	10 doses of 100 mg iron sucrose (1 g) over 70 days	150 days	Infectious episodes	NA
Tangri et al. 2015 [22]	Observational	9544	High-dose iron > 350 mg/month	No/low-dose iron 0–150 mg/month	6 months	All-cause hospitalization	Mortality, infections, and infection and cardiovascular related hospitalization
Miskulin et al. 2014 [24]	Observational	21,233	High-dose iron > 350 mg/month	No/low-dose iron 0–150 mg/month	Up to 4 years	All-cause mortality	Infection and cardiovascular mortality
Kuo et al. 2012 [28]	Observational	1239	Intravenous Ferric Chloride Hexahydrate high dose	Intravenous Ferric Chloride Hexahydrate low dose	12 months	All-cause mortality and cardiovascular events	Endothelial dysfunction

a

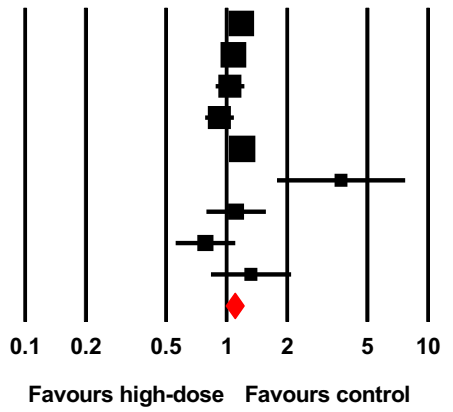
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Besarab 2000	0.386	0.032	4.625	-0.751	0.453
Coyne 2007	0.970	0.059	15.838	-0.021	0.983
Fishbane 1995	0.266	0.013	5.356	-0.864	0.387
Fudin 1998	2.091	0.177	24.734	0.585	0.558
Provenzano	0.333	0.034	3.253	-0.945	0.345
Macdougall	0.841	0.690	1.026	-1.710	0.087
	0.833	0.685	1.012	-1.836	0.066



Meta-analysis comparing mortality rate of high-dose IV iron versus control in RCTs

b

Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Bailie 2015	1.185	1.075	1.307	3.400	0.001
Brookhart 2013	1.083	0.982	1.195	1.600	0.110
Feldman 2004	1.041	0.890	1.217	0.500	0.617
Freburgur 2014	0.923	0.789	1.080	-1.000	0.317
Kalantar-Zahed 2005	1.197	1.107	1.295	4.500	0.000
Kuo 2012	3.706	1.795	7.654	3.541	0.000
Miskulin 2014	1.116	0.800	1.558	0.647	0.518
Pollak 2009	0.787	0.564	1.098	-1.412	0.158
Varas 2017	1.323	0.843	2.077	1.217	0.223
	1.103	0.996	1.221	1.885	0.059



Meta-analysis comparing mortality rate of high-dose IV iron versus control in observational studies

Fig. 2 **a** Meta-analysis comparing mortality rate of high-dose IV iron versus control in RCTs. **b** Meta-analysis comparing mortality rate of high-dose IV iron versus control in observational studies

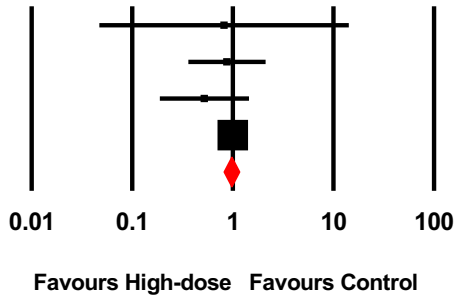
Data from 9 observational studies were pooled under the random effects model due to significant heterogeneity ($I^2 = 83\%$, $p < 0.001$). The overall HR showed increased risk of all-cause mortality in the high-dose group but was statistically non-significant (HR = 1.1, CI [1, 1.22], $p = 0.06$); Fig. 2b.

Infection

Infection rate was reported in four RCTs with no heterogeneity among their data ($I^2 = 0\%$, $p = 0.61$). Under the fixed effect model, there was no difference in the infection rate

a

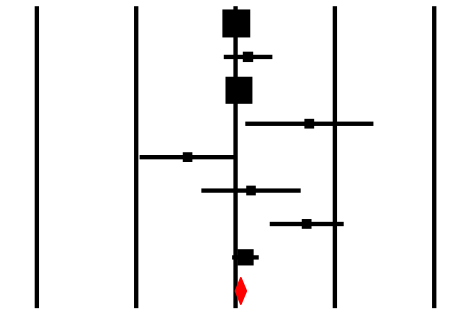
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Besarab 2000	0.818	0.048	14.017	-0.138	0.890
Coyne 2007	0.874	0.366	2.085	-0.304	0.761
Singh 2006	0.521	0.191	1.425	-1.270	0.204
Macdougall	1.000	0.833	1.200	-0.002	0.999
	0.974	0.817	1.161	-0.294	0.769



Meta-analysis comparing infection rate of high-dose IV iron versus control in RCTs

b

Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Brookhart 2013	1.020	1.004	1.036	2.500	0.012
Canziani 2001	1.336	0.772	2.314	1.036	0.300
Freburgur 2014	1.083	1.021	1.149	2.667	0.008
Hoen 2002	5.529	1.271	24.046	2.280	0.023
Kapoian 2008	0.330	0.110	0.988	-1.982	0.047
Kopelman 2007	1.433	0.460	4.467	0.621	0.535
Kuragano 2014	5.207	2.242	12.095	3.837	0.000
Tangri 2015	1.259	0.938	1.689	1.533	0.125
	1.127	0.992	1.280	1.832	0.067



Meta-analysis comparing infection rate of high-dose IV iron versus control in observational studies

Fig. 3 **a** Meta-analysis comparing infection rate of high-dose IV iron versus control in RCTs. **b** Meta-analysis comparing infection rate of high-dose IV iron versus control in observational studies

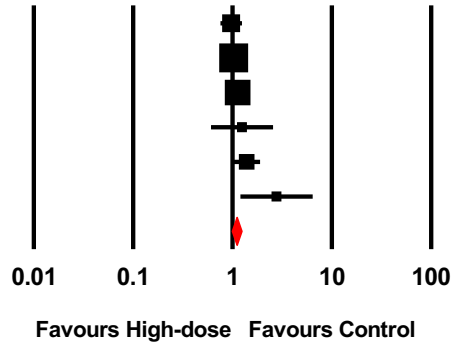
between high-dose iron and control group (OR = 0.97, CI [0.82, 1.16], $p = 0.77$); Fig. 3a. Eight observational studies reported data for infection rate in high-dose iron and control groups. Significant heterogeneity existed among these studies ($I^2 = 75\%$, $p < 0.001$); therefore, the random-effects model was employed. The summary HR showed increased yet insignificant risk of infection in the high-dose group (HR = 1.13, CI [0.99, 1.28], $p = 0.07$); Fig. 3b.

Hospitalization

One RCT and six observational studies provided data for the rate of all-cause hospitalization between high-dose vs control groups. There was marked heterogeneity among the observational studies data ($I^2 = 72\%$, $p < 0.001$). Data from the RCT showed no significant difference between high-dose iron and controls in the rate of hospitalization (OR = 1.03, CI [0.87, 1.23], $p = 0.71$). The summary HR for observational

a

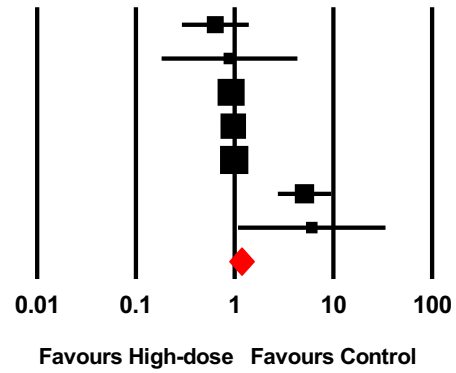
Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Tangri 2015	0.970	0.767	1.228	-0.250	0.803
Brookhart 2013	1.030	1.010	1.051	3.000	0.003
Freburgur 2014	1.127	1.022	1.244	2.400	0.016
Kopelman 2007	1.246	0.615	2.523	0.611	0.541
Varas 2017	1.391	1.037	1.866	2.200	0.028
Kuragano 2014	2.773	1.218	6.317	2.429	0.015
	1.108	0.991	1.239	1.807	0.071



Meta-analysis comparing hospitalization of high-dose IV iron versus control in observational studies

b

Study name	Point (raw)	Lower limit	Upper limit	Z-Value	p-Value
Kapoian 2008	0.638	0.297	1.369	-1.154	0.249
Kopelman 2007	0.887	0.185	4.254	-0.150	0.881
Freburgur 2014	0.923	0.774	1.101	-0.889	0.374
Tangri 2015	0.970	0.738	1.277	-0.214	0.830
Kshirsager 2013	0.990	0.952	1.030	-0.500	0.617
Kuo 2012	5.104	2.780	9.371	5.258	0.000
Kuragano 2014	6.050	1.099	33.287	2.069	0.039
	1.184	0.892	1.571	1.166	0.243



Meta-analysis comparing CV events of high-dose IV iron versus control in observational studies

Fig. 4 **a** Meta-analysis comparing hospitalization of high-dose IV iron versus control in observational studies. **b** Meta-analysis comparing CV events of high-dose IV iron versus control in observational studies

data showed increased rate of hospitalization in the high-dose group; however, this effect was not statistically significant (HR = 1.11, CI [0.99, 1.24], $p = 0.07$); Fig. 4a.

Cardiovascular adverse events

One RCT compared the rate of adverse cardiovascular events between high-dose and low-dose iron. No significant difference was observed between the two groups (22.3% vs 25.6%, $p = 0.12$). Six heterogeneous observational studies ($I^2 = 65\%$, $p < 0.001$) reported on the rate of cardiovascular events. No significant difference was observed between high-dose iron and controls (HR = 1.18, CI [0.89, 1.57], $p = 0.24$); Fig. 4b.

Publication bias

Funnel plot analysis showed no risk of publication bias for all the meta-analysis outcomes. p value of Egger's regression

test was > 0.1 for all analyses which indicates minimal to no risk of publication bias. See attached Supplemental Data figures.

Discussion

In our meta-analysis utilizing 7 RCTs and 16 observational studies, we did not find an overall increased risk of all-cause mortality, infections, hospitalizations or cardiovascular events with high-dose IV iron compared to low-dose IV iron in ESRD patients on dialysis. Strikingly high-dose IV iron conferred 17% less all-cause mortality compared to controls even though statistically not significant in RCTs. Observational studies showed a trend toward increased yet no significant risk of infection and hospitalization in the high-dose group. Both observational and RCTs used higher IV iron arm dose close to 400 mg monthly and lower iron arm close to 200 mg monthly. The maximum follow-up was 42 months in RCTs. We were fortunate enough to include pivotal trial [10] in our analysis where 40–41% access was tunneled dialysis catheters in both arms and > 2000 patients were included in the study. These catheters represent a particular point of vulnerability for infections in ESRD patients [38]. Randomization and endpoint blinding were well described in the trial report unlike previous RCTs. Except for one meta-analysis published previously [9] all other studies in dialysis patients excluded observational studies. All studies included only hemodialysis patients except one study by Singh that included 146 peritoneal dialysis patients [15], which might not be feasible to do meta-analysis separately. In addition, study provided data on infection rate only. Excluding these data from the analysis did not change the effect size for the infection rate (OR = 0.97 vs. 0.99). We kept it to avoid a decrease in the statistical power of the meta-analysis.

Hougen et al. [9] performed meta-analysis using 7 RCTs and 15 observational studies but was not able to demonstrate increase risk of infections, hospitalizations, cardiac events or mortality with high dose of IV iron. The major limitation of this well done meta-analysis was that inclusive studies had shorter follow-up and limited number of participants in RCTs, which were pointed out in the editorial. Their findings confirm our results for no increase in all-cause mortality, cardiovascular events, hospitalization or infection rate except for our findings of trend with lower mortality with higher dose IV iron in RCTs and infections, and hospitalizations showing an increased trend with higher dose IV iron in observational studies. This study also included RCT of ferric citrate [39] which is a phosphate binder where primary outcome of this study was changed in phosphorous and both arms of study used very low dose of parenteral iron 51.8 mg monthly in the ferric citrate arm versus 107.5 mg monthly in the opposite arm where binders other than ferric citrate were used. No IV iron was used on 22% of subjects in ferric citrate arm and 9% in opposite arm [40]. We chose to omit this study from our analysis due to primarily being a phosphate binder efficacy study on iron parameters and phosphorous and due to very low parenteral iron doses used in both arms.

Meta-analysis published from Israel in 2016 [8] included patients with CKD stage 3–5 and dialysis patients and excluded observational studies found that all-cause mortality remained no different between IV iron and oral iron consistent with our meta-analysis although their analysis did not compare differing doses of IV iron. Our analysis also agree with meta-analysis done by Avni et al. which showed that IV iron therapy is not associated with increased risk of infections and author compared IV iron with oral iron, no iron or intramuscular iron [41].

Previous meta-analysis shows superiority of IV iron over oral preparations in increasing hemoglobin, decreasing ESA use and avoid risks associated with blood transfusions [8, 41–43]. Anemia management protocols with use of IV iron are very diverse between countries with the United States using highest doses and Japan using the lowest doses and Europe falling in between. Analysis from dialysis outcomes and practice patterns study (DOPPS) published in 2017 shows that IV iron use < 300 mg/month might be a good strategy to keep anemia parameters at goal and there was no change in C-reactive protein with differing doses of iron [44] and DOPPS published in 2014 showed that doses > 300 mg/month are associated with increased hospitalization and mortality [23]. Although both studies had very high number of participants, they were observational studies susceptible to residual confounding. Results of these studies are in contrast to what we found in our analysis.

Newer strategies for supplementing iron in dialysis patients include ferric pyrophosphate citrate (FPC) with regard to which multiple RCTs were published. PRIME study including 103 hemodialysis patients concluded that markers of inflammation like C-reactive protein, IL-6 and malondialdehyde were not statistically different between the groups [45]. CRUISE 1 and 2 conducted in 599 hemodialysis patients reported markers of inflammation and treatment emergent adverse events was not different between the groups [46]. Indirectly these trials demonstrate that markers of inflammation are no different with the use of parenteral iron. More randomized studies related to mortality, infections and hospitalizations with larger sample size with regard to newer preparations with longer follow-up are needed.

Strengths of our study involve inclusion of RCTs with larger sample size along with longer follow-up periods including PIVOTAL trial and observational studies inclusive of large sample size and longer follow-ups. Our meta-analysis includes 3 times more subjects than previously published papers. We believe that larger sample size provides

more statistical credibility to the pooled results. There were limitations to observational studies included, which are subjected to residual confounding and selection bias and there was higher statistical heterogeneity noted likely due to non-standardization of IV iron doses along with the use of differing iron preparations. To conclude, we found no evidence of excess infections, cardiovascular events, hospitalizations, or higher mortality associated with higher doses of IV iron in RCTs even though there was an increased trend of increased hospitalizations and infections in observational studies that were not statistically significant.

Compliance with ethical standards

Conflict of interest The authors alone are responsible for the content and writing of the paper. The authors have no disclosures or conflicts of interest to report. This study did not receive any research funding.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

References

1. Jha V, Modi GK (2018) Getting to know the enemy better—the global burden of chronic kidney disease. Kidney Int 94(3):462–464
2. Pisoni RL, Bragg-Gresham JL, Young EW, Akizawa T, Asano Y, Locatelli F et al (2004) Anemia management and outcomes from 12 countries in the dialysis outcomes and practice patterns study (DOPPS). Am J Kidney Dis 44(1):94–111
3. Wish JB (2006) Assessing iron status: beyond serum ferritin and transferrin saturation. Clin J Am Soc Nephrol 1(Supplement 1):S4–S8
4. Babitt JL, Lin HY (2012) Mechanisms of anemia in CKD. J Am Soc Nephrol 23(10):1631–1634
5. Hörl WH (2002) Non-erythropoietin-based anaemia management in chronic kidney disease. Nephrol Dial Transpl 17(suppl_11):35–38
6. Moore LL, Humbert JR (1984) Neutrophil bactericidal dysfunction towards oxidant radical-sensitive microorganisms during experimental iron deficiency. Pediatr Res 18(8):789–794
7. Macdougall IC, Bircher AJ, Eckardt K-U, Obrador GT, Pollock CA, Stenvinkel P et al (2016) Iron management in chronic kidney disease: conclusions from a "kidney disease: improving global outcomes"(KDIGO) controversies conference. Kidney Int 89(1):28–39
8. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter U, Gafter-Gvili A (2016) Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. Am J Kidney Dis 68(5):677–690
9. Hougen I, Collister D, Bourrier M, Ferguson T, Hochheim L, Komenda P et al (2018) Safety of intravenous iron in dialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol 13(3):457–467
10. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA et al (2019) Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med 380(5):447–458
11. Higgins JP, Green S (eds) (2011) Cochrane handbook for systematic reviews of interventions. Wiley
12. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 151(4):264–269
13. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD et al (2011) The cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 343:d5928
14. Stang A (2010) Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 25(9):603–605
15. Singh H, Reed J, Noble S, Cangiano JL, Van Wyck DB, Group USISCT (2006) Effect of intravenous iron sucrose in peritoneal dialysis patients who receive erythropoiesis-stimulating agents for anemia: a randomized, controlled trial. Clin J Am Soc Nephrol 1(3):475–482
16. Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira BJ (2009) Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. Clin J Am Soc Nephrol 4(2):386–393
17. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, McMurray JJ, Murray H, Tomson CR, Wheeler DC, Winearls CG (2019) Intravenous iron in patients undergoing maintenance hemodialysis. N Engl J Med 380(5):447–458
18. Fudin R, Jaichenko J, Shostak A, Bennett M, Gotloib L (1998) Correction of uremic iron deficiency anemia in hemodialyzed patients: a prospective study. Nephron 79(3):299–305
19. Fishbane S, Frei GL, Maesaka J (1995) Reduction in recombinant human erythropoietin doses by the use of chronic intravenous iron supplementation. Am J Kidney Dis 26(1):41–46
20. Coyne DW, Kapoian T, Suki W, Singh AK, Moran JE, Dahl NV et al (2007) Ferric gluconate is highly efficacious in anemic hemodialysis patients with high serum ferritin and low transferrin saturation: results of the dialysis patients' response to iv Iron with elevated ferritin (DRIVE) study. J Am Soc Nephrol 18(3):975–984
21. Besarab A, Amin N, Ahsan M, Vogel SE, Zazuwa G, Frinak S et al (2000) Optimization of epoetin therapy with intravenous iron therapy in hemodialysis patients. J Am Soc Nephrol 11(3):530–538
22. Tangri N, Miskulin DC, Zhou J, Bandeen-Roche K, Michels WM, Ephraim PL et al (2014) Effect of intravenous iron use on hospitalizations in patients undergoing hemodialysis: a comparative effectiveness analysis from the DEcIDE-ESRD study. Nephrol Dial Transpl 30(4):667–675
23. Bailie GR, Larkina M, Goodkin DA, Li Y, Pisoni RL, Bieber B et al (2015) Data from the dialysis outcomes and practice patterns study validate an association between high intravenous iron doses and mortality. Kidney Int 87(1):162–168
24. Miskulin DC, Tangri N, Bandeen-Roche K, Zhou J, McDermott A, Meyer KB, Ephraim PL, Michels WM, Jaar BG, Crews DC, Scialla JJ (2014) Intravenous iron exposure and mortality in patients on hemodialysis. Clin J Am Soc Nephrol 9(11):1930–1939
25. Freburger JK, Ellis AR, Kshirsagar AV, Wang L, Brookhart MA (2014) Comparative short-term safety of bolus versus maintenance iron dosing in hemodialysis patients: a replication study. BMC Nephrol 15(1):154
26. Kshirsagar AV, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Brookhart MA (2013) Intravenous iron supplementation practices and short-term risk of cardiovascular events in hemodialysis patients. PLoS One 8(11):e78930
27. Brookhart MA, Freburger JK, Ellis AR, Wang L, Winkelmayer WC, Kshirsagar AV (2013) Infection risk with bolus versus maintenance iron supplementation in hemodialysis patients. J Am Soc Nephrol 24(7):1151–1158
28. Kuo K-L, Hung S-C, Lin Y-P, Tang C-F, Lee T-S, Lin C-P et al (2012) Intravenous ferric chloride hexahydrate supplementation induced endothelial dysfunction and increased cardiovascular risk among hemodialysis patients. PLoS One 7(12):e50295

29. Pollak VE, Lorch JA, Shukla R, Satwah S (2009) The importance of iron in long-term survival of maintenance hemodialysis patients treated with epoetin-alfa and intravenous iron: analysis of 9.5 years of prospectively collected data. BMC Nephrol 10(1):6
30. Kapoian T, O'Mara NB, Singh AK, Moran J, Rizkala AR, Geronemus R et al (2008) Ferric gluconate reduces epoetin requirements in hemodialysis patients with elevated ferritin. J Am Soc Nephrol 19(2):372–379
31. Kopelman RC, Smith L, Peoples L, Biesecker R, Rizkala AR (2007) Functional iron deficiency in hemodialysis patients with high ferritin. Hemodial Int 11(2):238–246
32. Kalantar-Zadeh K, Regidor DL, McAllister CJ, Michael B, Warnock DG (2005) Time-dependent associations between iron and mortality in hemodialysis patients. J Am Soc Nephrol 16(10):3070–3080
33. Varas J, Ramos R, Aljama P, Pérez-García R, Moreso F, Pinedo M et al (2017) Relationships between iron dose, hospitalizations and mortality in incident haemodialysis patients: a propensity-score matched approach. Nephrol Dial Transpl 33(1):160–170
34. Feldman HI, Joffe M, Robinson B, Knauss J, Cizman B, Guo W et al (2004) Administration of parenteral iron and mortality among hemodialysis patients. J Am Soc Nephrol 15(6):1623–1632
35. Feldman HI, Santanna J, Guo W, Furst H, Franklin E, Joffe M et al (2002) Iron administration and clinical outcomes in hemodialysis patients. J Am Soc Nephrol 13(3):734–744
36. Hoen B, Paul-Dauphin A, Kessler M (2002) Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. Clin Nephrol 57(6):457–461
37. Canziani MEF, Yumiya ST, Rangel EB, Manfredi SR, Neto MC, Draibe SA (2001) Risk of bacterial infection in patients under intravenous iron therapy: dose versus length of treatment. Artif Organs 25(11):866–869
38. Fülöp T, Tapolyai MB, Agarwal M, Lopez-Ruiz A, Molnar MZ, Dossabhoy NR (2017) Bedside tunneled dialysis catheter removal—a lesson learned from nephrology trainees. Artif Organs 41(9):810–817
39. Lewis JB, Sika M, Koury MJ, Chuang P, Schulman G, Smith MT et al (2015) Ferric citrate controls phosphorus and delivers iron in patients on dialysis. J Am Soc Nephrol 26(2):493–503
40. Umanath K, Jalal DI, Greco BA, Umeukeje EM, Reisin E, Manley J et al (2015) Ferric citrate reduces intravenous iron and erythropoiesis-stimulating agent use in ESRD. J Am Soc Nephrol 26(10):2578–2587
41. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A (2015) The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clin Proc 90(1):12–23
42. Rozen-Zvi B, Gafter-Gvili A, Paul M, Leibovici L, Shpilberg O, Gafter U (2008) Intravenous versus oral iron supplementation for the treatment of anemia in CKD: systematic review and meta-analysis. Am J Kidney Dis 52(5):897–906
43. Susantitaphong P, Alqahtani F, Jaber BL (2014) Efficacy and safety of intravenous iron therapy for functional iron deficiency anemia in hemodialysis patients: a meta-analysis. Am J Nephrol 39(2):130–141
44. Robinson BM, Larkina M, Bieber B, Kleophas W, Li Y, Locatelli F et al (2017) Evaluating the effectiveness of IV iron dosing for anemia management in common clinical practice: results from the dialysis outcomes and practice patterns study (DOPPS). BMC Nephrol 18(1):330
45. Gupta A, Lin V, Guss C, Pratt R, Ikizler TA, Besarab A (2015) Ferric pyrophosphate citrate administered via dialysate reduces erythropoiesis-stimulating agent use and maintains hemoglobin in hemodialysis patients. Kidney Int 88(5):1187–1194
46. Fishbane SN, Singh AK, Cournoyer SH, Jindal KK, Fanti P, Guss CD et al (2015) Ferric pyrophosphate citrate (Triferic™) administration via the dialysate maintains hemoglobin and iron balance in chronic hemodialysis patients. Nephrol Dial Transpl 30(12):2019–2026
47. Kuragano T, Matsumura O, Matsuda A, Hara T, Kiyomoto H, Murata T, Kitamura K, Fujimoto S, Hase H, Joki N, Fukatsu A (2014) Association between hemoglobin variability, serum ferritin levels, and adverse events/mortality in maintenance hemodialysis patients. Kidney Int 86(4):845–854

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