Medical Science

pISSN 2321–7359; eISSN 2321–7367

Intravenous versus oral iron supplementation in adult patients with iron-deficiency anemia and non-dialysis dependent chronic kidney disease: A meta-analysis of randomized clinical trials

To Cite:
Alanazi MA, Alsaiari ASM, Bukhari SFM, Alanazi RMH, Altmimi SMB, Alenezi RNA, Rfadh SAM, Albalawi AAM, Almehmadi ASM, Albalawi SDM, Alatawi WLS. Intravenous versus oral iron supplementation in adult patients with iron-deficiency anemia and non-dialysis dependent chronic kidney disease: A meta-analysis of randomized clinical trials. *Medical Science* 2023; 27: e26ms2706.
doi: https://doi.org/10.54905/disssi/v27i131/e26ms2706

Authors' Affiliation:
[1]Assistant Professor and Consultant, Family Medicine, University of Tabuk, Tabuk, Saudi Arabia
[2]Medical Intern, Faculty of Medicine, University of Tabuk, Tabuk, Saudi Arabia
[3]Medical student, Faculty of Medicine, University of Tabuk, Tabuk, Saudi Arabia

*Corresponding author
Assistant Professor and Consultant, Family Medicine, University of Tabuk, Tabuk,
Saudi Arabia
Email: mansuor.alanazi88@gmail.com

Peer-Review History
Received: 18 December 2022
Reviewed & Revised: 21/December/2022 to 31/December/2022
Accepted: 04 January 2023
Published: 09 January 2023

Peer-review Method
External peer-review was done through double-blind method.

URL: https://www.discoveryjournals.org/medicalscience

Mansuor Ahmed Alanazi[1*], **Afnan Saleh M Alsaiari**[2], **Sarah Fahad M Bukhari**[2], **Renad Mohammed H Alanazi**[2], **Sarah Muqbil B Altmimi**[2], **Rahaf Naif A Alenezi**[2], **Shahad Ali M Rfadh**[2], **Abdulaziz Ahmed M Albalawi**[3], **Alaa Sulaiman M Almehmadi**[3], **Shoroug Daher M Albalawi**[3], **Wejdan Lafi S Alatawi**[3]

ABSTRACT

Objective: To compare the efficacy and safety of intravenous and oral iron supplementation in adult patients with iron deficiency anemia (IDA) and chronic kidney disease (CKD) who are not on dialysis (NDD-CKD). *Methods:* A literature search was performed for English-published studies from inception till November 1, 2022. The search included MEDLINE/PubMed, Cochrane Library, Academic Search Complete (EBSCOhost) and Web of Science using the terms ("Chronic renal insufficiency") AND ("Iron-deficiency anemia") and ("Iron Compounds"). *Results:* Twelve studies were included. Intravenous iron showed significantly higher final levels of haemoglobin (MD: 0.39, 95% CI: 0.29 to 0.49, p<0.001), ferritin (MD: 196.81, 95% CI: 113.57 to 280.05, p<0.001) and transferrin (MD: 4.02, 95% CI: 1.87 to 6.17, p<0.001). The rate of overall adverse effects was higher in the oral group (RR: 0.77, 95% CI: 0.59 to 1.00, p=0.05). However, intravenous iron was significantly associated with a higher risk of allergic reaction/hypotension (RR: 3.87, 95% CI: 2.00 to 7.51, p<0.001) and infection (RR: 1.72, 95% CI: 1.11 to 2.66, p=0.01). *Conclusions:* The evidence suggests that intravenous iron supplementation may be superior to oral iron in improving the haemoglobin, ferritin and transferrin levels in NDD-CKD patients. However, intravenous iron increases the risk of serious adverse effects. Because of the limitations of the studies included in this review, it is recommended to carry out large, randomized trials to assess

efficacy and safety of intravenous iron administration. This is an essential step before recommending routine use of these preparations in patients with NDD-CKD.

Keywords: Chronic kidney disease, iron deficiency anemia, iron compounds, intravenous administration, oral administration

1. INTRODUCTION

Anemia is more prevalent among chronic kidney diseases (CKDs) cases compared to the general population. The prevalence of anemia increases progressively with the deterioration of renal function, with more than half of CKD stage 5 patients suffering from anemia (Stauffer and Fan, 2014; St-Peter et al., 2018). The main underlying cause of anemia in CKD patients is the decreased levels of erythropoietin which is produced by the diseased kidneys. In addition, iron deficiency can contribute to the problem, increasing the severity of anemia and preventing an adequate response to erythropoietin stimulating agents (ESAs). Anemia has been linked to several complications, such as raised risk of cardiovascular events (Li and Collins, 2004; Vlagopoulos et al., 2005) and mortality (Levin et al., 2006), prolonged hospital stay (Li and Collins, 2004) and reduced quality of life (Pergola et al., 2019).

Current guidelines recommend that the haemoglobin (Hb) levels should be above 10 g/dL and not exceeding 11.5 g/dL in adult CKD patients (2012). High Hb levels in CKD patients have been linked to elevated risk of hypertension, stroke, hospitalizations, and mortality (Jing et al., 2012). Iron supplementation can be administered orally or parenterally. The most frequently prescribed oral iron preparations are ferrous sulphate, ferrous gluconate and ferrous fumarate. Parenteral iron can be administered by intramuscular or intravenous injections. Several forms of intravenous (IV) iron are currently available, e.g., iron sucrose, iron isomaltoside-1000 and ferumoxytol (Lopez et al., 2016).

Patients on oral iron supplementation frequently suffer from gastrointestinal-related adverse effects such as nausea and/or vomiting, diarrhea and constipation (Lopez et al., 2016), which may negatively impact patients' adherence to treatment. Meanwhile, IV iron administration has been associated with more serious and potentially life-threatening adverse effects, including pulmonary embolism, anaphylactic reaction, hypotension and infection; though these adverse effects are relatively rare (Fishbane et al., 2014; Lopez et al., 2016; Roger et al., 2017; Agrawal et al., 2022). Consequently, IV iron should be administered under supervision, resulting in increased costs, hospital visits and inconvenience to patients.

Although recent evidence supports the efficacy of IV iron supplementation in CKD patients on dialysis, controversies exist regarding its efficacy and safety in CKD patients who are not on dialysis (NDD-CKD) (Shepshelovich et al., 2016; Lone et al., 2019). This meta-analysis was carried out to compare safety and efficacy of iron supplementation in adult patients with iron-deficiency anemia and NDD-CKD.

2. MATERIALS AND METHODS

Methodology

This meta-analysis followed the principles of the Cochrane Handbook for Systematic Reviews of Interventions, version 6. The reporting was conducted along with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009).

The research questions

Is supplementation with intravenous iron superior to oral iron in adult patients with IDA and NDD-CKD as regards the Hb level and iron indices (ferritin and transferrin)?

Research aims and objectives

This meta-analysis aimed to compare supplementation with intravenous iron versus oral iron in adult patients with IDA and NDD-CKD. The following objectives were addressed: To compare the increase in Hb level after therapy; to compare the improvement in iron indices in the blood after therapy (ferritin and transferrin); and to compare the safety of both treatments

Eligibility criteria for studies

Types of studies

Only randomized clinical trials were included. The search was limited to studies published in English.

Participants

Eligible studies included adult patients with IDA and NDD-CKD.

Interventions

Eligible studies directly compared supplementation with intravenous and oral iron.

Exclusion criteria

The following publications were excluded: conference abstracts/posters, case reports, observational (case-series, case-control and cohort or cross-sectional) studies, review articles, editorials, commentaries and clinical guidelines. Moreover, studies were excluded if conducted on animals, pediatric patients or dialysis-dependent patients. Also, single-arm trials assessing either oral or intravenous iron compounds were excluded.

Search strategy

Electronic searches

A search was conducted for eligible articles on the electronic databases of MEDLINE/PubMed, Cochrane Library, Academic Search Complete (EBSCO host) and Web of Science (WOS). The search was limited to studies published in the English language from inception to the 1st of November 2022. The search terms used for MEDLINE/PubMed and Cochrane Library were (("Renal Insufficiency, Chronic"(Mesh)) AND "Anemia, Iron-Deficiency/therapy"(Mesh) AND "Iron Compounds/administration and dosage"(Mesh) AND "Clinical Trial" (Publication Type). For EBSCO host, we used the terms ("chronic kidney disease or chronic renal failure or CKD or ESRD or renal insufficiency or kidney failure") AND ("iron deficiency anemia") AND ("iron supplementation") AND ("clinical trial"). For searching the WOS, we used (((ALL = (chronic kidney disease)) AND ALL= (iron deficiency anemia)) AND ALL= (iron supplementation)), with the filters: English, article papers.

Other resources

The reference lists of relevant studies retrieved from electronic search were screened to identify other potentially eligible studies.

Selection of studies

Literature search and screening of the studies' titles & abstracts of the studies in the search result were performed. Then the full text of the identified potentially relevant studies was obtained and assessed for the fulfillment of the eligibility criteria. Then the search results, the screening of studies' titles & abstracts and the assessment of the full-text articles of selected studies were checked.

Data extraction

A standardized data extraction sheet was used for extracting relevant data from the selected studies. The extracted data included: (a) the study characteristics (the country and centers, study design, time period for conducting the study, the sample size, the duration of treatment and the eligibility criteria); (b) patients' characteristics (age, sex and the stage of CKD); (c) the type of drugs used, doses and routes of administration; (d) the final or change from baseline measurements of blood Hb, ferritin and serum transferrin; and (e) safety (the adverse events). We revised the extracted data for consistency and clarity. During data extraction, no blinding was done for the journal titles, authors' names or the institutions where the study was conducted.

Measured outcomes

Primary outcome

It is the improvement of Hb level after therapy. This was assessed by comparing either the level of Hb after the end of therapy or the change from baseline between patients administering oral iron and those administering intravenous iron.

Secondary outcomes

Secondary outcomes included the improvement of ferritin and transferrin levels after therapy besides the adverse events of each treatment.

Assessment of the studies' risk of bias

The risk of bias (ROB) was assessed for included studies using the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) (Sterne et al., 2019).

Data synthesis

Review Manager (Rev Man Version 5.4. The Cochrane Collaboration, 2020) was used for conducting the meta-analysis and creating forest plots. The categorical dichotomous outcomes (i.e., adverse effects) were summarized as risk ratio (RR; the incidence in the IV iron group (IVIG)/incidence in the oral iron group (OIG)) with 95% confidence intervals (CI). An RR > 1 indicated a higher risk in the IVIG, while an RR< 1 indicated a higher risk in the OIG. An RR of 1 indicated the same incidence in both groups. Continuous numerical variables (i.e., levels of Hb, ferritin and transferrin or changes from baseline) were summarized as the mean difference (MD: The IVIG minus the OIG). A positive value of MD indicated a higher level in the IVIG relative to the OIG, while a negative MD value indicated a decrease in the IVIG relative to the oral group.

The extracted data were tested for heterogeneity using the Cochrane chi-square heterogeneity test and I^2 index. Significant heterogeneity across the studies was determined at a Cochrane chi-square test with a p-value < 0.1 and an I^2 index > 50%. If testing for heterogeneity yielded non-significant results, pooling of the extracted data was performed using the fixed-effect model (Higgins et al., 2003). If significant heterogeneity was detected, the random-effects model was used. For interpreting the comparisons between outcomes, a p-value < 0.05 was considered significant.

Grading of the quality of evidence

Grading of the evidence for each studied outcome was performed using the GRADE criteria. The GRADE criteria are based on the evaluation of the ROB, directness, inconsistency (considerable heterogeneity), the precision of effect estimates and the risk of publication bias (Guyatt et al., 2008; Guyatt et al., 2011). The risk of publication bias was determined by assessing funnel plots.

3. RESULTS

Results of literature search and study selection

The results of the literature search and the selection flowchart are demonstrated in Figure 1 (Page et al., 2021). Searching the electronic databases yielded 289 records, out of which 21 duplicates were removed. The remaining 268 records underwent screening of their titles and abstracts, with the removal of 45 non-RCT records, 150 unrelated records and 57 single-arm studies. Out of the remaining 16 records, full-text articles were found for 15 and the assessment resulted in excluding five articles in which patients were on dialysis or after renal transplantation and one article for including other IV iron preparations in the control group. Two records were found to belong to the same study, so the number of included studies at this stage was eight (nine records) (Charytan et al., 2005; Wyck et al., 2005; Spinowitz et al., 2008; Qunibi et al., 2011; Nagaraju et al., 2013; Macdougall et al., 2014; Agarwal et al., 2015; Pisani et al., 2015; Roger et al., 2017). Screening of the reference lists resulted in identifying 25 potentially relevant records, but the full text was available for 12 records only. Eight of these 12 studies were excluded including patients on dialysis or after renal transplantation, while the remaining four were included (Stoves et al., 2001; Agarwal et al., 2006; Kalra et al., 2016; Agrawal et al., 2022). The final number of included studies in this systematic review was twelve (Stoves et al., 2001; Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Nagaraju et al., 2013; Macdougall et al., 2014; Agarwal et al., 2015; Pisani et al., 2015; Kalra et al., 2016; Roger et al., 2017; Agrawal et al., 2022).

Basic characteristics and risk of bias assessment

Basic characteristics of the included studies

Tables 1 and 2 summarize the characteristics of the included 12 studies. Seven studies were multi-centre and the number of sites ranged from 16 to 193 (Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Macdougall et al., 2014; Kalra et al., 2016; Roger et al., 2017). The follow-up duration ranged from as short as 30 days up to two years, with one-to-two months duration in seven studies (Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Kalra et al., 2016; Agrawal et al., 2022). Oral iron was ferrous sulphate in all studies except three studies which used ferrous fumarate (Spinowitz et al., 2008), Heme Iron Polypeptide (Nagaraju et al., 2013) and pyrophosphate liposomal iron with ascorbic acid (Pisani et al., 2015). The IV iron preparations included iron sucrose (Stoves et al., 2001; Charytan et al., 2005; Wyck et al., 2005; Nagaraju et al., 2013; Agarwal et al., 2015; Agrawal et al., 2022), Sodium ferric gluconate complex (Agarwal et al., 2006), Ferumoxytol (Spinowitz et al., 2008), Ferric carboxymaltose (Qunibi et al., 2011; Macdougall et al., 2014), Iron gluconate (Pisani et al., 2015) and Iron Isomaltoside (Kalra et al., 2016). The used doses and duration of treatment for the same preparation varied among the studies. The distribution of gender also varied, with four studies having a higher proportion of male participants than females (Stoves et al., 2001; Nagaraju et al., 2013; Agarwal et al., 2015; Agrawal et al., 2022).

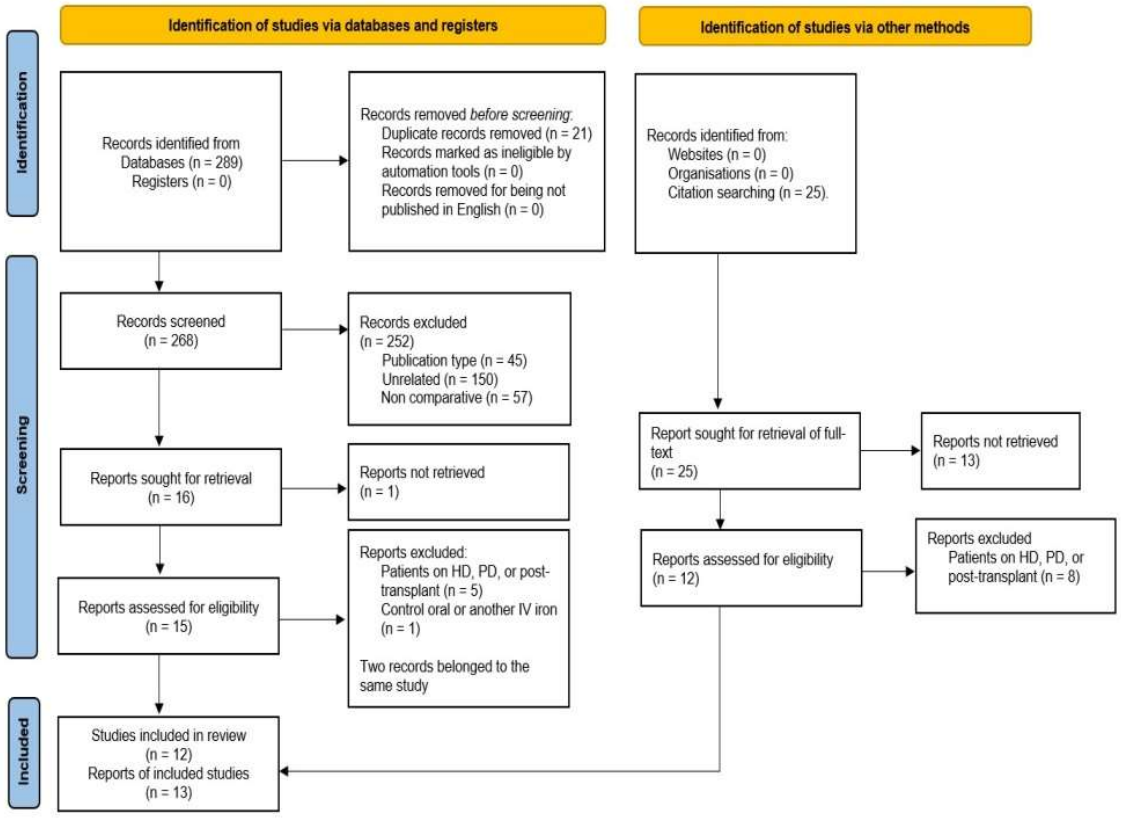

Figure 1 The PRISMA flow diagram for the results of the literature search and study selection (Page et al., 2021)

Table 1 The settings and characteristics of the included studies (n = 12)

First author	Year of publication	Country	Time period	Single/multi-centre	RCT type	Follow-up duration
Stoves	2001	UK	NR	Single	parallel RCT	6 months
Charytan	2005	USA	NR	Multicentre (16 sites)	parallel RCT	43 days
Wyck	2005	USA	NR	Multicentre (35 sites)	parallel RCT	56 days
Agarwal	2006	USA	NR	Multicentre (26 sites)	parallel RCT	70 days
Spinowitz	2008	USA	May 2004 to Aug 2006	Multicentre (Number not reported)	parallel RCT	35 days
Qunibi	2011	USA, Australia, Hong Kong	May 2005 to Feb 2007	Multicentre (47 centres)	parallel RCT	56 days
Nagaraju	2013	Canada	May 2007 to Feb 2011	Single	parallel RCT	6 months
Agarwal	2015	USA	Aug 2008 to Oct 2014	Single	Phase IV open-label RCT	2 years
Pisani	2015	Italy	Oct 2011 to Sept 2013	Single	parallel RCT	3 months
Kalra	2016	India, Germany, UK, Austria, Russia, Poland, Denmark, Romania, USA, Sweden, Ireland	Jun 2010 to Apr 2014	Multicentre (67 sites)	phase III open-label RCT	8 weeks
FIND-CKD	2014, 2017	Australia, Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Italy, the	Dec 2009 to Jan 2012	Multicentre (193 sites)	parallel 3-arm RCT	56 weeks

		Netherlands, Norway, Poland, Portugal, Romania, Spain, Sweden, Switzerland, Turkey, UK, & USA				
Agrawal	2022	India	Oct 2018 to Oct 2020	Single	parallel RCT	30 days

Table 2 The sample size, assessment of renal outcome, and follow-up of patients in the included studies (n = 9)

First author	Year of publication	Arms	Number	Age (years)	Sex M/F
Stoves	2001	Oral: FS: 200 mg 3 times/day for 6 months IV: IS: 300 mg monthly according to ferritin levels	Oral: 23 IV: 22	Oral: 59.9 ± 13.4 IV: 57.3 ±14	Oral: 15/8 IV: 10/12
Charytan	2005	Oral: FS: 325 mg 3 times/day for 29 days IV: IS: 200 mg weekly for 5 weeks	Oral: 48 IV: 48	Oral: 60 ± 14.4 IV: 62 ± 14.4	Oral: 14/34 IV: 19/29
Wyck	2005	Oral: FS: 325 mg, 3 times/day for 56 days IV: IS: 1000 mg, divided doses over 14 days	Oral: 93 IV: 95	Oral: Mean: 63.9 IV: 62.3	Oral: 26/56 IV: 26/53
Agarwal	2006	Oral: FS: 325 mg, 3 times/day for 6 weeks IV: SFGC: 250 mg weekly for 4 weeks	Oral: 84 IV: 80	Oral: 62.3 ± 15.2 IV: 65.5 ± 12.9	Oral: 15/24 IV: 20/16
Spinowitz	2008	Oral: FF: 100 mg elemental iron twice/day for 21 days IV: Ferumoxytol: 510 mg, 2 doses	Oral: 76 IV: 228	Oral: 63.7 ± 11.6 IV: 65.1 ± 14.3	Oral: 24/52 IV: 93/135
Qunibi	2011	Oral: FS: 325 mg 3 times/day for 56 days IV: FC: 1000 mg with up to 2 additional doses of 500 mg	Oral: 103 IV: 152	Oral: 66.8 ± 13.5 IV: 65.4 ± 12.6	Oral: 30/73 IV: 53/94
Nagaraju	2013	Oral: HIP 11 mg 3 times/day IV: IS 200 mg monthly for 12 months	Oral: 18 IV: 22	Oral: Median (IQR):76 (66 to 83) IV: 66 (58 to 76)	Oral: 13/5 IV: 12/10
Agarwal	2015	Oral: FS: 325 mg 3 times/day for 8 weeks IV: IS: 200 mg/week for 5 weeks	Oral: 69 IV: 67	Oral: 67.8 ± 11.5 IV: 63.2 ± 10.7	Oral: 54/15 IV: 50/17
Pisani	2015	Oral: Sideral® Forte, Pharmanutra Spa (30 mg pyrophosphate liposomal iron + 70 mg ascorbic acid) one capsule daily for 3 months IV: Iron gluconate 125mg, weekly for 3 months	Oral: 69 IV: 37	Oral: 53.1 ± 15 IV: 47.6 ± 16	Oral: 27%/73% IV: 30%/70%
Kalra	2016	Oral: IS 200 mg daily for 8 weeks IV: II 1000 to achieve a cumulative dose of 500 mg	Oral: 118 IV: 233	Oral: 57.9 ± 16.3 IV: 57.6 ± 15.5	Oral: 64/54 IV: 92/141
FIND-CKD	2014, 2017	Oral: FS: 100 mg iron twice daily to Week 52 IV: FC 200 mg single dose, then repeated every 4 weeks during weeks 4 to 48 if ferritin < 100 ug/L	Oral: 317 IV: 154	Oral: 69.3 ± 13.4 IV: 68.2 ± 13.3	Oral: 116/192 IV: 54/98
Agrawal	2022	Oral: FS: 325 mg 3 times/day for 30 days IV: IS: 200 mg/week for 4 weeks	Oral: 75 IV: 75	Oral: 49.4 ±14.8 IV: 47.6 ± 13.9	Oral 50/25 IV: 44/31

FS: Ferrous Sulphate; IS: Iron Sucrose; SFGC: Sodium Ferric GluconateCcomplex; FC: Ferric Carboxymaltose; FF: Ferrous Fumarate; HIP: Fheme Iron Polypeptide; IS: Iiron Sulphate; II: Iron Isomaltoside

Risk of bias assessment

Risk of bias assessment was performed using the RoB 2 tool for randomised clinical trials (Figures 2, 3) which comprised five main domains: Selection, performance, detection, attrition and reporting biases.

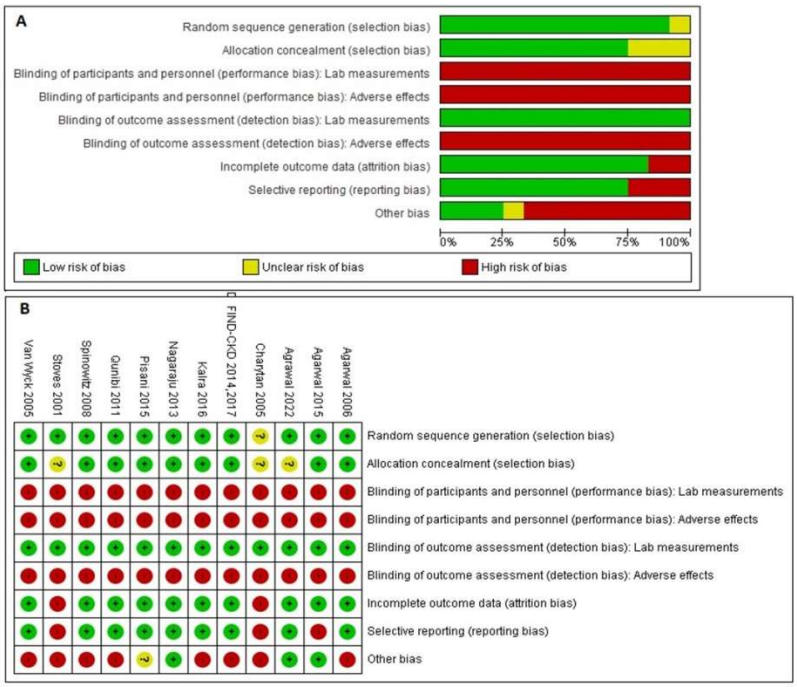

Figure 2 Risk of bias summary as assessed for each item (A) and each study (B)

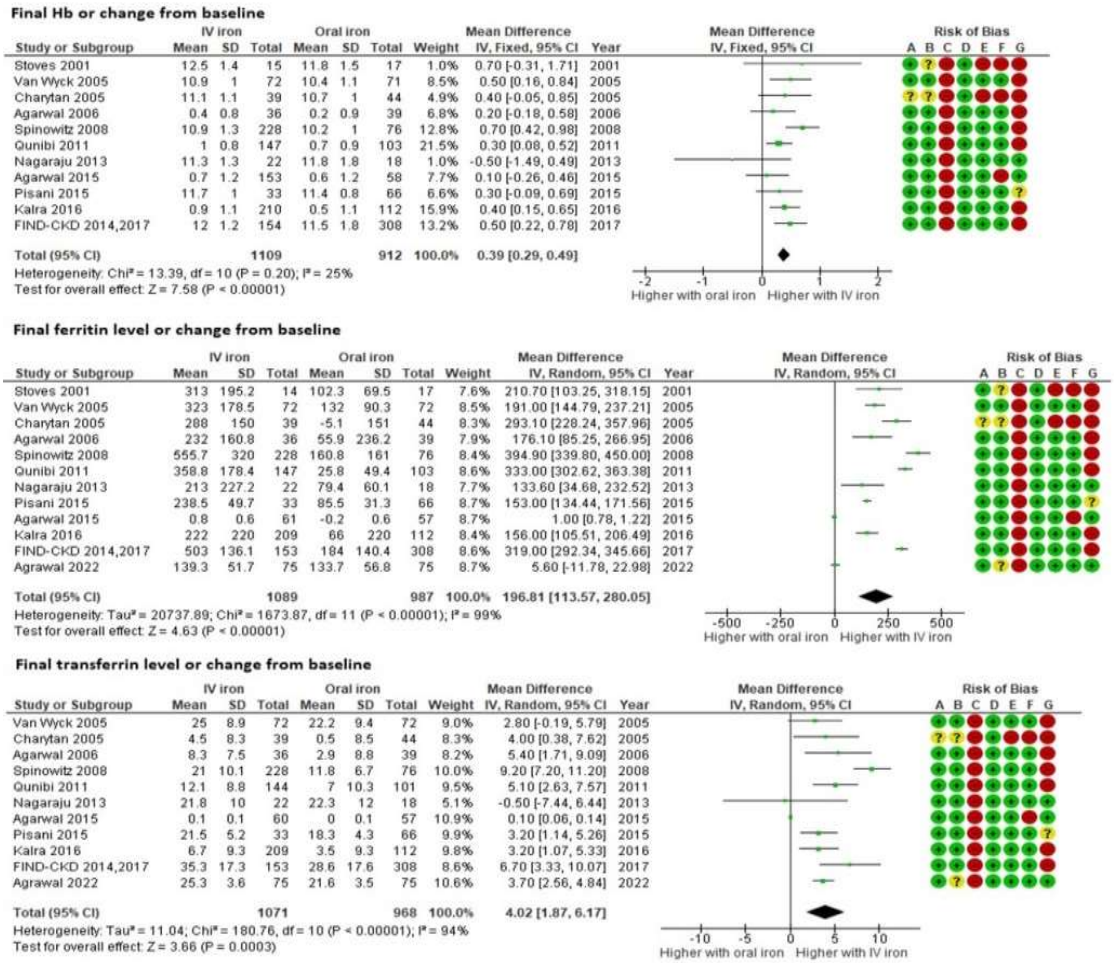

Figure 3 Meta-analysis of final levels of hemoglobin, ferritin and transferrin or change from baseline. A) Random sequence generation; B) Allocation concealment; C) Blinding of participants & personnel; D) Blinding of outcome assessment; E) Incomplete outcome data; F) Selective reporting; G) Other

As regards the selection bias, the risk was low in most studies as the randomization and allocation methods were clear and appropriate. The ROB was uncertain in the study by Charytan et al., (2005) as the method of randomization and allocation was unreported. Also, the risk was uncertain in the studies by Stoves et al., (2001) and Agrawal et al., (2022) for not reporting the methods of allocation concealment.

Regarding performance bias, the twelve studies had a high ROB due to the non-blinding of the patients or clinicians. However, the risk of detection bias was low as the primary outcomes were all laboratory parameters that are unlikely to be affected by unblinding.

Assessment of the attrition bias showed that all studies had a low risk except for two studies with a high risk. The study by Charytan et al., (2005) reported that a markedly higher percentage of patients were excluded due to missing data in the IVIG (19% vs. 8% missing in the OIG). Also, Stoves et al., (2001) reported that 29% of the patients did not complete the study, which is a large percentage that could bias the results. As for the reporting bias, all studies had a low risk except for three studies. Stoves et al., (2001), Charytan et al., (2005) and Agarwal et al., (2015) did not report the standard deviations for their assessed outcomes.

Eight studies had a high ROB regarding their funding (provided by pharmaceutical companies) (Stoves et al., 2001; Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Macdougall et al., 2014; Kalra et al., 2016; Roger et al., 2017) and one study had an uncertain risk as the funding details were not provided (Pisani et al., 2015).

Results of meta-analysis

Final Hb level or change from baseline after therapy

All studies compared the oral and IVIGs regarding the final Hb level after iron supplementation or the change from baseline Hb measurements. Seven studies reported a significantly higher level or change from baseline in the IVIG compared to the oral group (Charytan et al., 2005; Wyck et al., 2005; Spinowitz et al., 2008; Qunibi et al., 2011; Macdougall et al., 2014; Kalra et al., 2016; Agrawal et al., 2022). The improvement in Hb in the IVIG was not significant in four studies (Stoves et al., 2001; Agarwal et al., 2006; Agarwal et al., 2015; Pisani et al., 2015). Nagaraju et al., (2013) reported a slight non-significant decrease in Hb level in the IVIG. Pooling of the Hb level or change from baseline was performed by including all studies except that of Agrawal et al., (2022) as they reported the mean and standard deviation for mild, moderate and severe grades of anemia but they did not report the overall Hb level within each treatment group. Pooled analysis showed a significantly higher Hb level in the IVIG (MD = 0.39 (95% CI: 0.29 to 0.49), $p<0.001$). No significant heterogeneity was detected ($I2 = 25\%$ and $p = 0.2$) (Figure 3).

Final ferritin level or change from baseline after therapy

All studies compared the final ferritin level after therapy or the change from baseline measurements between the oral and IVIGs. Eleven studies reported a significantly higher level or change from baseline in the IVIG compared to the oral group (Stoves et al., 2001; Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Nagaraju et al., 2013; Macdougall et al., 2014; Agarwal et al., 2015; Pisani et al., 2015; Kalra et al., 2016; Roger et al., 2017). The improvement in ferritin in the IVIG was not significant in the study by Agrawal et al., (2022). Pooling of the findings of the twelve studies showed a significantly higher ferritin level in the IVIG (MD = 196.81 (95% CI: 113.57 to 280.05), $p<0.001$). There was a significant heterogeneity among the studies ($I2 = 99\%$ and $p < 0.001$; Figure 3).

Final transferrin level or change from baseline after therapy

Eleven studies compared the final transferrin level after therapy or the change from baseline measurements between the oral and IVIGs. Eight studies reported a significantly higher level or change from baseline in the IVIG compared to the oral group (Charytan et al., 2005; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Pisani et al., 2015; Kalra et al., 2016; Agrawal et al., 2022). The improvement in transferrin in the IVIG was not significant in two studies (Macdougall et al., 2014; Agarwal et al., 2015), while a non-significant decrease in the IV group was noted in the study by Nagaraju et al., (2013). Pooling of the findings of the twelve studies showed a significantly higher transferrin level in the IVIG (MD = 4.02 (95% CI: 1.87 to 6.17), $p<0.001$). There was a significant heterogeneity among the studies ($I2 = 94\%$ and $p < 0.001$) (Figure 3).

Safety

Overall adverse effects

Eight studies assessed the overall rate of adverse. Seven studies reported a lower rate of overall adverse effects in the IVIG (Spinowitz et al., 2008; Qunibi et al., 2011; Nagaraju et al., 2013; Macdougall et al., 2014; Agarwal et al., 2015; Pisani et al., 2015; Kalra et al., 2016), while Agarwal et al., (2006) found a higher rate in the IV group. Less adverse effects were associated with IV iron

compared to oral iron therapy, though the p-value was borderline (RR = 0.77 (95% CI: 0.59 to 1.00), p=0.05). Marked heterogeneity was detected (I2 = 79% and p < 0.001) (Figure 4).

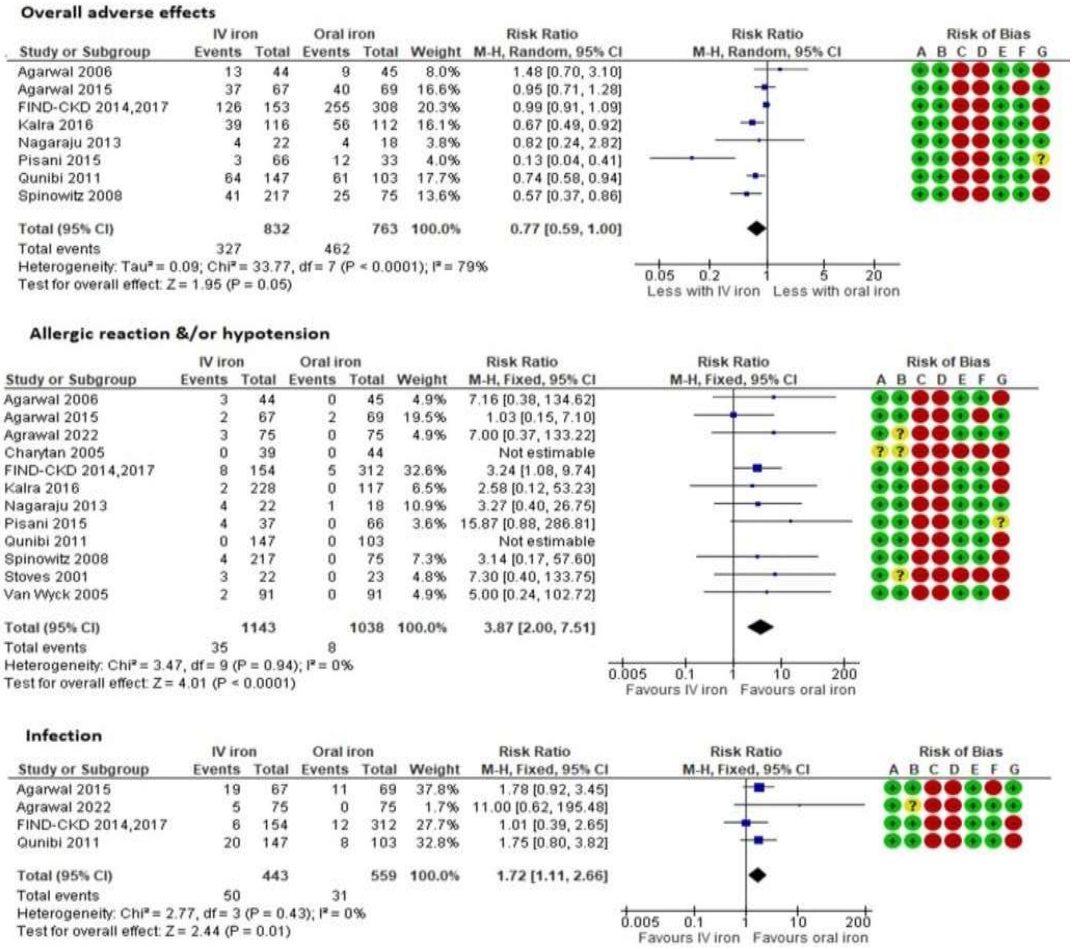

Figure 4 Meta-analysis of the overall rate of adverse effects, allergic reaction/hypotension, and infection. A) Random sequence generation; B) allocation concealment; C) blinding of participants & personnel; D) blinding of outcome assessment; E) incomplete outcome data; F) selective reporting; G) other bias

Allergic reaction &/or hypotension

All twelve studies reported the occurrence of allergic reaction/hypotension with iron therapy. Eleven studies reported a higher rate in the IVIG compared to the oral group (Stoves et al., 2001; Wyck et al., 2005; Agarwal et al., 2006; Spinowitz et al., 2008; Qunibi et al., 2011; Nagaraju et al., 2013; Macdougall et al., 2014; Agarwal et al., 2015; Pisani et al., 2015; Kalra et al., 2016; Roger et al., 2017; Agrawal et al., 2022), while one study reported the non-occurrence of allergic reactions/hypotension in any of the groups (Charytan et al., 2005). Pooled analysis showed a significantly higher risk of allergic reaction/hypotension with IV iron treatment compared to oral iron therapy (RR = 3.87 (95% CI: 2.00 to 7.51), p < 0.001). No heterogeneity was detected (I2 = 0% and p=0.94) (Figure 4).

Infection

Four studies reported the occurrence of infection with iron therapy, with a higher rate in the IVIG (Qunibi et al., 2011; Macdougall et al., 2014; Agarwal et al., 2015; Roger et al., 2017; Agrawal et al., 2022). Pooled analysis showed a significantly higher infection risk with IV iron therapy compared to oral iron (RR = 1.72 (95% CI: 1.11 to 2.66), p=0.01). No heterogeneity was detected (I2 = 0% and p=0.43) (Figure 4).

Nausea &/or vomiting

Eight studies reported the occurrence of nausea and/or vomiting. Five studies found a lower rate of this adverse effect with IV iron (Charytan et al., 2005; Wyck et al., 2005; Spinowitz et al., 2008; Nagaraju et al., 2013; Agrawal et al., 2022). However, the other three studies reported a higher rate of nausea and vomiting with IV iron therapy (Agarwal et al., 2006; Macdougall et al., 2014; Pisani et

al., 2015; Roger et al., 2017). Pooled analysis showed that the risk of nausea and vomiting in the IV iron was non-significantly lower compared to oral iron therapy (RR = 0.77 (95% CI: 0.50 to 1.19), p=0.24). Heterogeneity was not significant (I2 = 26% and p=0.22) (Figure 5).

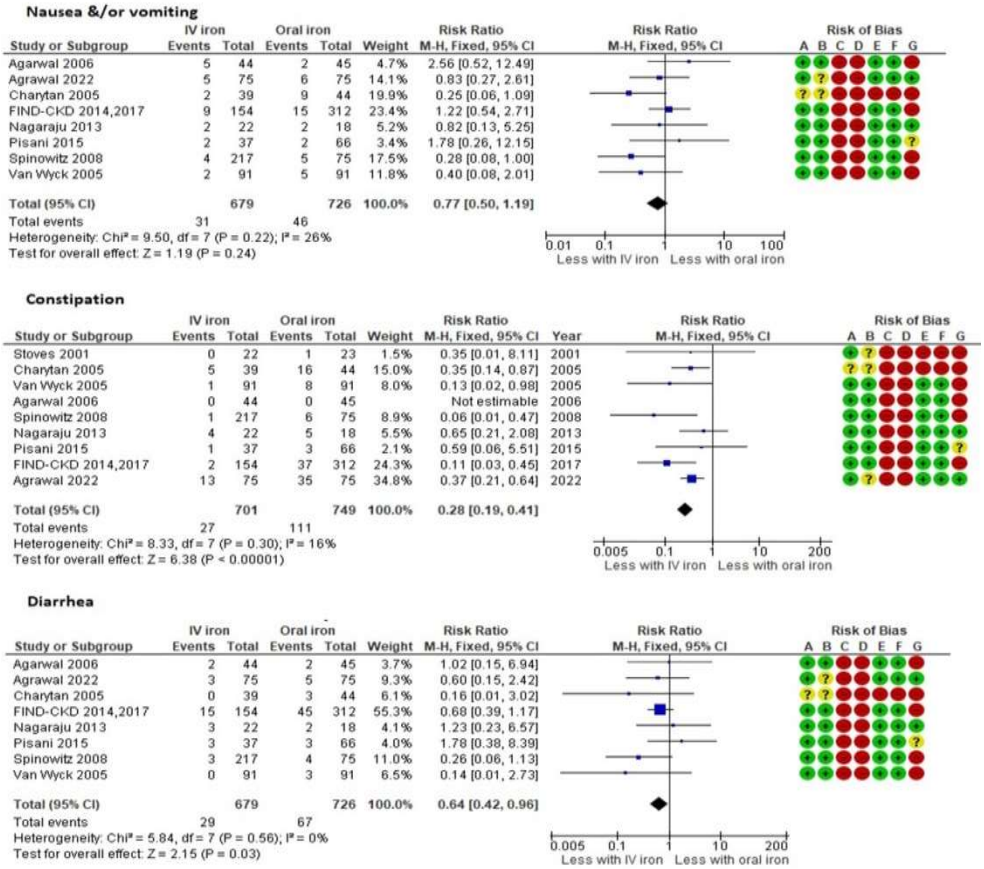

Figure 5 Meta-analysis of the overall rate of gastrointestinal adverse effects. A) Random sequence generation; B) allocation concealment; C) blinding of participants & personnel; D) blinding of outcome assessment; E) incomplete outcome data; F) selective reporting; G) other bias

Constipation

Nine studies reported constipation as a potential adverse effect of iron therapy. Eight studies found a lower rate of constipation with IV iron (Stoves et al., 2001; Charytan et al., 2005; Wyck et al., 2005; Spinowitz et al., 2008; Nagaraju et al., 2013; Macdougall et al., 2014; Pisani et al., 2015; Roger et al., 2017; Agrawal et al., 2022), while one study found that none of the patients suffered from constipation (Agarwal et al., 2006). Pooled analysis showed a significantly lower rate of constipation in the IVIG compared to that of the OIG (RR = 0.28 (95% CI: 0.19 to 0.41), p < 0.001). Heterogeneity was not significant (I2 = 16% and p=0.30) (Figure 5).

Diarrhea

Eight studies reported the occurrence of diarrhea with iron therapy. Five studies found a lower rate of diarrhea with IV iron (Charytan et al., 2005; Wyck et al., 2005; Spinowitz et al., 2008; Macdougall et al., 2014; Roger et al., 2017; Agrawal et al., 2022), while three studies found a higher rate of diarrhea in the IV group (Agarwal et al., 2006; Nagaraju et al., 2013; Pisani et al., 2015). Pooled analysis showed a significantly lower rate of diarrhea in the IVIG compared to that of the OIG (RR = 0.64 (95% CI: 0.42 to 0.96), p=0.03). Heterogeneity was not significant (I2 = 0% and p=0.56) (Figure 5).

Subgroup analysis

Subgroup analysis was done to explore the underlying causes of heterogeneity among the studies. Sub grouping of the studies was based on the total doses of IV iron and oral iron, as well as the use of erythropoietin-stimulating agents (ESA) (Tables 3, 4, 5).

Table 3 Subgroup analysis based on the total dose of intravenous iron

Outcome	Subgroups	Studies	Participants	Effect Estimate MD/RR (95% CI), P	Model	subgroup differences
Hb	IV total dose ≤ 1000	5	611	MD: 131.06 (58.70, 203.41), P<0.001	RE	Chi² = 1.35 (P = 0.25), I² = 25.9%
	IV total dose > 1000	4	838	MD: 0.51 (0.20, 0.83), P=0.002		
Ferritin	IV total dose ≤ 1000	6	669	MD: 131.06 (58.70, 203.41), P<0.001	RE	Chi² = 6.12 (P = 0.01), I² = 83.7%
	IV total dose > 1000	4	836	MD: 275.87 (186.85, 364.89), P<0.001		
Tsat	IV total dose ≤ 1000	6	668	MD: 2.98 (0.80, 5.17), P=0.007	RE	Chi² = 1.96 (P = 0.16), I² = 49.0%
	IV total dose > 1000	3	805	MD: 6.32 (2.19, 10.44), P=0.003		
Overall adverse effects	IV total dose ≤ 1000	3	324	RR: 0.65 (0.23, 1.80), P=0.40	RE	Chi² = 0.11 (P = 0.74), I² = 0%
	IV total dose > 1000	3	793	RR: 0.79 (0.47, 1.31), P=0.36		
Allergy/ Hypotension	IV total dose ≤ 1000	6	743	RR: 4.52 (1.57, 13.02), P=0.005	FE	Chi² = 0.11 (P = 0.74), I² = 0%
	IV total dose > 1000	4	843	RR: 3.59 (1.48, 8.71), P=0.005		
Infection	IV total dose ≤ 1000	2	286	RR: 2.19 (1.15, 4.14), P=0.02	FE	Chi² = 1.71 (P = 0.19), I² = 41.4%
	IV total dose > 1000	1	466	RR: 1.01 (0.39, 2.65), P=0.98		
Constipation	IV total dose ≤ 1000	5	607	RR: 0.35 (0.23, 0.56), P<0.001	RE	Chi² = 0.60 (P = 0.44), I² = 0%
	IV total dose > 1000	4	843	RR: 0.21 (0.06, 0.76), P=0.02		
Diarrhea	IV total dose ≤ 1000	5	607	RR: 0.62 (0.29, 1.34), P=0.23	FE	Chi² = 0.00 (P = 0.94), I² = 0%
	IV total dose > 1000	3	798	RR: 0.64 (0.39, 1.04), P=0.07		
N & v	IV total dose ≤ 1000	5	607	RR: 0.78 (0.34, 1.76), P=0.55	RE	Chi² = 0.03 (P = 0.87), I² = 0%
	IV total dose > 1000	3	798	RR: 0.70 (0.27, 1.85), P=0.47		

CI: Confidence Interval; FE: Fixed Effect Model; MD: Mean Difference; RE: Random-Effects Model; RR: Risk Ratio

Table 4 Subgroup analysis based on the total dose of oral iron

Outcome	Subgroups	Studies	Participants	Effect Estimate MD/RR (95% CI), P	Model	subgroup differences
Hb	Oral total dose ≤ 1000	5	848	MD: 0.42 (0.19, 0.65), P<0.001	RE	Chi² = 0.32 (P = 0.57), I² = 0%
	Oral total dose > 1000	6	1173	MD: 0.34 (0.21, 0.47), P<0.001		
Ferritin	Oral total dose ≤ 1000	6	997	MD: 188.31 (83.02, 293.59), P<0.001	RE	Chi² = 0.03 (P = 0.87), I² = 0%
	Oral total	6	1079	MD: 205.13 (33.58,		

	dose > 1000			376.69), P=0.02		
Tsat	Oral total dose ≤ 1000	6	997	MD: 4.32 (2.11, 6.52), P<0.001	RE	Chi² = 0.06 (P = 0.80), I² = 0%
	Oral total dose > 1000	5	1042	MD: 3.83 (0.65, 7.00), P=0.02		
Overall adverse effects	Oral total dose ≤ 1000	4	659	RR: 0.52 (0.32, 0.86), P=0.01	RE	Chi² = 4.49 (P = 0.03), I² = 77.7%
	Oral total dose > 1000	4	936	RR: 0.93 (0.77, 1.12), P=0.45		
Allergy/hypotension	Oral total dose ≤ 1000	6	1013	RR: 5.02 (1.59, 15.83), P=0.006	FE	Chi² = 0.34 (P = 0.56), I² = 0%
	Oral total dose > 1000	6	1168	RR: 3.31 (1.47, 7.43), P=0.004		
Infection	Oral total dose ≤ 1000	1	150	RR: 11.00 (0.62, 195.48), P=0.10	RE	Chi² = 1.72 (P = 0.19), I² = 41.9%
	Oral total dose > 1000	3	852	RR: 1.57 (1.00, 2.45), P=0.05		
Constipation	Oral total dose ≤ 1000	5	668	RR: 0.36 (0.24, 0.54), P<0.001	RE	Chi² = 3.05 (P = 0.08), I² = 67.3%
	Oral total dose > 1000	4	782	RR: 0.12 (0.04, 0.37), P<0.001		
Diarrhea	Oral total dose ≤ 1000	5	668	RR: 0.62 (0.32, 1.24), P=0.18	FE	Chi² = 0.00 (P = 0.95), I² = 0%
	Oral total dose > 1000	3	737	RR: 0.64 (0.38, 1.07), P=0.09		
N & v	Oral total dose ≤ 1000	5	668	RR: 0.55 (0.28, 1.07), P=0.08	RE	Chi² = 1.79 (P = 0.18), I² = 44.0%
	Oral total dose > 1000	3	737	RR: 1.13 (0.50, 2.57), P=0.77		

CI: Confidence Interval; FE: Fixed Effect Model; MD: Mean Difference; RE: Random-Effects Model; RR: Risk Ratio

Table 5 Subgroup analysis based on the administration of erythropoietin stimulating agent (ESA)

Outcome	Subgroups	Studies	Participants	Effect Estimate MD/RR (95% CI), P	Model	subgroup differences
Hb	ESA	9	1237	MD: 0.37 (0.25, 0.49), P<0.001	FE	Chi² = 0.50 (P = 0.48), I² = 0%
	No ESA	2	784	MD: 0.45 (0.26, 0.63), P<0.001		
ferritin	ESA	9	1144	MD: 209.58 (101.10, 318.07), P<0.001	RE	Chi² = 0.15 (P = 0.69), I² = 0%
	No ESA	3	932	MD: 160.07 (-62.34, 382.49), P=0.16		
TSAT	ESA	8	1107	MD: 3.83 (0.86, 6.80), P=0.01	RE	Chi² = 0.01 (P = 0.92), I² = 0%
	No ESA	3	932	MD: 4.00 (2.56, 5.44), P<0.001		

CI: Confidence Interval; FE: Fixed Effect Model; MD: Mean Difference; RE: Random-Effects Model; RR: Risk Ratio

The results showed the same direction (increased or decreased MD and RR) with IV iron therapy as the analysis without subgroups. However, the significance of some results was altered; though the relatively low number of studies in some subgroups renders these changes questionable. We found no significant differences between the subgroups, except for a significantly higher increase in ferritin level with IV iron total doses above 1000 mg compared to doses equal to or less than 1000 mg (MD: 275.87 vs. 131.06, p=0.01) (Table 3). We found a significant difference as regard the total dose of oral iron in the rate of overall complications, though its explanation is unclear as the rate was higher with a lower dose of oral iron. There was marked heterogeneity between the

two subgroups of oral iron dose (I^2 = 77.7%), suggesting that other underlying factors may have contributed to this result rather than the oral iron dose (Table 4).

The quality of evidence

The evidence quality was determined for each outcome according to the GRADE criteria (Table 6).

The evidence quality was moderate for the higher Hb level after therapy in the IV group. However, the evidence was of low quality for the increased ferritin and transferrin levels with IV iron therapy. The evidence quality for the adverse effects was very low due to the high risk of detection bias (due to the non-blinding of participants, personnel and outcome assessors) as well as the low number of events.

Table 6 Summary of findings and quality of evidence (GRADE criteria)

Outcomes	Anticipated absolute effects/ relative effects (95% CI)	No participants (studies)	Quality of evidence (GRADE)	Comments
Hb	The mean Hb level was 0.39 g/dl higher with IV iron compared to oral iron (0.29 to 0.49 higher)	2021 (11)	Moderate ⊕⊕⊕⊖1	1/11 had uncertain ROB of RSG & 2/11 had uncertain ROB of allocation concealment
Ferritin	The mean ferritin level was 196.81 ug/L higher with IV iron compared to oral iron (113.57 to 280.05 higher)	2076 (12)	Low ⊕⊕⊖⊖1,2	1/12 had uncertain ROB of RSG & 3/12 had uncertain ROB of allocation concealment. Considerable heterogeneity
Tsat	The mean TSAT level was 4.02% higher with IV iron compared to oral iron (1.87% to 6.17 higher)	2039 (11)	Low ⊕⊕⊖⊖1,2	1/11 had uncertain ROB of RSG & 2/11 had uncertain ROB of allocation concealment. Considerable heterogeneity
Overall	Rr 0.77 (0.59, 1.00)	1595 (8)	Very low ⊕⊖⊖⊖1,2,3	8/8 had a high ROB of blinding. Considerable heterogeneity. CI limits crossing the effect size
Allergy	Rr 3.87 (2.00, 7.51)	2181 (12)	Very low ⊕⊖⊖⊖1,3	12/12 had a high ROB of blinding. A low number of events
Infection	Rr 1.72 (1.11, 2.66)	1002 (4)	Very low ⊕⊖⊖⊖1,3	4/4 had a high ROB of blinding. A low number of events
Constipation	Rr 0.28 (0.19, 0.41)	1450 (9)	Very low ⊕⊖⊖⊖1,3	9/9 had a high ROB of blinding. A low number of events
Diarrhoea	Rr 0.64 (0.42, 0.96)	1405 (8)	Very low ⊕⊖⊖⊖1,3	8/8 had a high ROB of blinding. A low number of events
N & v	Rr 0.77 (0.50, 1.19)	1405 (8)	Very low ⊕⊖⊖⊖1,3	8/8 had a high ROB of blinding. A low number of events

1 Downgraded one level for risk of bias
2 Downgraded one level for inconsistency
3 Downgraded one level for imprecision

4. DISCUSSION

Summary of the main findings

Pooling of the findings of the included studies showed that IV iron therapy may increase the achieved Hb level or exert a higher change from baseline compared to oral iron supplementation in patients with NDD-CKD (11 studies, 2021 participants, MD = 0.39 (95% CI: 0.29 to 0.49), p<0.001, Moderate certainty). Likewise, IV iron therapy may increase ferritin level (12 studies, 2076 participants, MD = 196.81 (95% CI: 113.57 to 280.05), p<0.001, low certainty) and transferrin level (11 studies, 2039 participants, MD = 4.02 (95% CI: 1.87 to 6.17), p<0.001, low certainty) compared to oral iron.

Subgroup analysis was performed to explore the potential causes of heterogeneity. However, a significant result was found only regarding the level of ferritin where a total dose of IV elemental iron above 1,000 mg resulted in more increase relative to total doses of IV elemental iron of 1,000 or less, with considerable heterogeneity between the two subgroups of IV iron total dose. This suggests the presence of other confounding factors that need exploration, possibly including the stage of CKD and the baseline levels of Hb and iron indices. Unfortunately, the studies reported these variables for the whole sample or groups at most, without relating them to the final changes in Hb and iron indices.

Regarding the IV iron safety, the overall rate of adverse events seemed to be lower compared with oral iron (8 studies, 1595 participants, RR = 0.77 (95% CI: 0.59, 1.00)). Likewise, IV iron therapy seemed to have a lower risk of gastrointestinal adverse effects including nausea/vomiting (8 studies, 1405 participants, RR = 0.77 (95% CI: 0.50, 1.19)), constipation (9 studies, 1450 participants, RR = 0.28 (95% CI: 0.19, 0.41)) and diarrhea (8 studies, 1405 participants, RR = 0.64 (95% CI: 0.42, 0.96)). However, the evidence quality for these outcomes was very low, so it is uncertain if IV iron therapy decreases the overall risk of adverse effects or gastrointestinal-related adverse effects compared to oral iron supplementation. In addition, IV iron seemed to increase the risk of allergic reactions/hypotension (12 studies, 2181 participants, RR = 3.87 (95% CI: 2.00, 7.51)) and infection (4 studies, 1002 participants, RR = 1.72 (95% CI: 1.11, 2.66)) compared to oral iron therapy. However, the evidence certainty for these two outcomes was also very low.

Subgroup analysis was performed to explore the heterogeneity of the outcome of adverse effects across the studies. However, there was no significant association between the total doses of IV elemental iron or ESA use with the risk of adverse effects. The only significant result was found regarding the total dose of elemental oral iron on the overall rate of adverse effects, which was not clearly understood and showed also considerable heterogeneity. The difference was possibly due to the other not yet explored confounding factors.

Overall completeness, applicability and quality of the evidence

During the process of literature search and selection of studies, we found that a considerable number of studies were available only as abstracts (proceedings of conferences) or even as citations without abstracts in published studies and reviews. This may deprive our systematic review of valuable studies that may have resulted in changing the results of the analysis. On the other hand, it was infeasible to include these abstracts due to the difficulty in assessing the domains of ROB from abstracts besides the non-clarity of the reported findings.

The increase in Hb level in patients on IV iron was relatively small compared to those on oral iron supplementation in this meta-analysis (MD = 0.39 g/dL (95% CI: 0.29 to 0.49). The evidence quality was downgraded to moderate certainty for the outcome of the Hb level due to the uncertain ROB of randomization and allocation concealment in some studies. As for the outcomes of ferritin and transferrin, the evidence certainty was downgraded to low due to above mentioned ROB plus inconsistency across the studies as observed from the considerable heterogeneity, with I2 above 90%. In addition, the beneficial impact of this small increase in Hb level in patients with NDD-CKD needs to be investigated to weigh the achieved benefits in quality of life with the risks of exposure to IV iron therapy and iron overload. None of the studies that compared the quality of life between IV and oral iron supplementation in NDD-CKD patients found a significant difference (Agarwal et al., 2006; Macdougall et al., 2014; Agarwal et al., 2015; Kalra et al., 2016). A systematic review that assessed the effect of different achieved Hb values with ESA on physical health-related quality of life and functionality in CKD patients found that increasing Hb above the currently recommended targets may be associated with small, clinically significant improvement in fatigue only, while no significant improvement was observed in the physical role or physical function (Guedes et al., 2020). They found that this improvement was more recorded in younger, non-diabetic patients (Guedes et al., 2020).

The evidence was downgraded for all outcomes of safety because of the high detection bias as there was no blinding of the patients, personnel or outcome assessors. The laboratory outcomes (Hb, ferritin and transferrin) were not downgraded for unblinding as these outcomes were objectively measured and are not expected to be affected by unblinding. The situation is different when assessing the adverse events of treatment as patients or outcome assessors may exaggerate or overlook the adverse

events when they know the type of intervention. Also, the outcome of the overall adverse effects showed considerable heterogeneity across the studies and the CI limits crossed the effect size, so the evidence was further downgraded to very low quality. All the outcomes of adverse effects were linked to a small number of events (below 300), resulting in a further downgrading of the evidence. Another important limitation of the included studies is the relatively short period of follow-up in most studies, while assessment of the outcomes after a prolonged period of treatment is mandatory, particularly to assess the safety and iron overload in these patients.

Agreements and disagreements with other studies or reviews

The comparison between oral and IV iron treatment for CKD patients has been studied in several RCTs and a number of systematic reviews attempted to summarize the evidence. Rozen-Zvi et al., (2008) published a systematic review based on 13 studies (6 studies for NDD-CKD patients) which became updated in 2016 to include 24 RCTs (13 studies on NDD-CKD) (Shepshelovich et al., 2016). Both the original and updated reviews showed a significant increase in Hb, ferritin and transferrin levels with IV iron, though the effect was moderate in NDD-CKD patients. Their findings on IV iron safety were stated for all patients, not specifically on the NDD-CKD group, but were similar to our findings. Another systematic review was published in 2012 by Albaramki et al., (2012) and included 28 studies (9 studies on NDD-CKD patients), which was updated in 2019 (Lone et al., 2019) to include 39 RCTs (14 on NDD-CKD patients). The 2012 review and its update in 2019 reported also similar findings to our review. The present review differed from the previous two reviews and their updates on focusing on NDD-CKD patients only, as less evidence seemed to advocate using IV iron with this subset of patients contrary to patients on dialysis. In addition, we excluded studies that were available only as abstracts and we included an RCT that was published in 2022 (Agrawal et al., 2022).

5. CONCLUSIONS

Conclusions, implications for practice, policy and future research

The results of this meta-analysis suggest that IV iron therapy may be superior to oral iron in improving the Hb (moderate quality of evidence), ferritin and transferrin (low quality) levels in NDD-CKD patients. While the risk of gastrointestinal adverse effects may be lower with IV iron, there may be an increased allergic reactions and infection risks (very low quality). The currently available evidence does not support the routine prescription of IV iron preparations for patients with NDD-CKD. Limitations of the included studies necessitate the conduction of large-size randomized clinical trials to investigate safety as well as efficacy of the IV iron preparations before recommending their routine use in NDD-CKD patients. Future clinical trials should plan for longer follow-up periods and assess more patient-centred outcomes such as the health-related quality of life, cost-benefit analysis, inconveniences caused by either route of administration and medication adherence.

Acknowledgement

We thank the participants who were all contributed samples to the study.

Author Contributions

All authors contributed to the study conception and design. Literature search and data collection were performed by Afnan Saleh M Alsaiari, Shoroug Daher M Albalawi, Sarah Muqbil B Altmimi and Wejdan Lafi S Alatawi. Data extraction and ROB assessment were performed by Mansuor Ahmed Alanazi, Sarah Fahad M. Bukhari, Renad Mohammed H Alanazi and Rahaf Naif A Alenezi. The first draft of the manuscript was written by Afnan Saleh M Alsaiari, Shahad Ali M Rfadh, Abdulaziz Ahmed M Albalawi and Alaa Sulaiman M Almehmadi. The final draft of the manuscript was written by Mansuor Ahmed Alanazi and Afnan Saleh M Alsaiari.

Ethical approval

Not applicable.

Informed consent

Not applicable.

Funding

This study has not received any external funding.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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