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REVIEW ARTICLE

Iron replacement therapy in inflammatory bowel disease patients with iron deficiency anemia: A systematic review and meta-analysis☆

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Abstract

Background and aims: Iron deficiency anemia (IDA) is a common problem in patients with Inflammatory Bowel Disease (IBD) and has a significant negative impact on quality of life. The aim was to compare the clinical efficacy of intravenous (IV) versus oral (PO) iron replacement in adult IBD with iron deficiency anemia (IDA).
Methods: A systematic search for randomized controlled trials comparing the efficacy of IV versus PO iron therapy in the treatment of IDA in adult IBD patients. The primary outcome was the mean change in the hemoglobin at the end of study and secondary outcomes include mean change in ferritin, clinical disease activity index, quality of life score and the adverse reaction rate.
Results: The search strategy identified 757 articles while only three industry-funded articles met the inclusion criteria for systematic review and meta-analysis. The total sample size was 333 patients with 203 patients receiving IV therapy. IV route was associated with a 6.8 g/L higher mean hemoglobin increment and 110 μg/L higher mean ferritin increment. The IBD activity index and Quality of Life scores were comparable between the two treatment groups. More adverse events were reported in the oral treatment group with the odds for discontinuation being 6.2 (CI 2.2, 17.1).

☆ This work has not been presented at any conference.

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Conclusions: Intravenous iron treatment is better tolerated and more effective than oral iron treatment in improving ferritin. The higher hemoglobin gain with the IV route was small and of uncertain clinical significance. The combined sample size of the included studies was small and further clinical trials are required.

Contents

1. Introduction

The prevalence of anemia during the course of inflammatory bowel disease (IBD) diagnosis has been reported to be as high as 75% with iron deficiency being the most common.[1,2] Recent Scandinavian data indicated the prevalence of iron deficiency anemia (IDA) at 20% and 30% had isolated iron deficiency (without anemia). After treatment is stopped, IDA normally recurs after 10 months and iron deficiency recurs about 19 months after treatment.[3,4] IDA can be associated with reduced quality of life with complaints including fatigue, concentration difficulties and slower cognitive response.[5,6] IDA has traditionally been treated with oral iron supplements, however, concerns regarding its variable absorption in patients with IBD[7]and the possibility that oral (PO) iron could exacerbate IBD has led to an increase in the use of intravenous (IV) iron. Animal models have suggested that PO iron therapy might exacerbate IBD through oxidative radicals mediated mucosal injury[8-10]or by alterations in the luminal microbiota.[8,11] Moreover, animal models have demonstrated that oxidative radicals may promote or upregulate carcinogenic pathways as evidenced by a significantly higher dysplasia rate in the colonic mucosa of mice given PO iron replacement.[12-14] It is unclear whether these animal data have any clinical consequences for the management of human IBD patients with IDA. Thus far, one human study demonstrated PO iron replacement therapy in patients with Crohn's disease (CD) reduces plasma antioxidants levels (such as cysteine and glutathione) and increases CD activity.[15] Another disadvantage of PO iron supplementation is the potential for side effects such as nausea, abdominal cramping or pain and altered bowel habits. Intolerance to oral iron therapy leading to discontinuation has been reported to be as high as 20%.[16,17]

The advantage of using IV iron is that it bypasses the need for gastrointestinal absorption, which is known to be variable in IBD patients. Moreover, adherence with daily medication is less of an issue with IV iron as total iron replacement can be achieved with 1–2 doses of low molecular weight Dextran or iron carboxymaltose infusions or more frequent infusions[3,4] if iron sucrose is used. The total dose of iron given is determined by the degree of anemia and the patient's body weight. However, there had been concerns with the safety profile of IV iron infusion, especially with the high molecular weight Dextran formulation which has been reported to have an increased risk of anaphylaxis. More recent formulations such as iron sucrose, low molecular weight iron dextran and iron carboxymaltose appear to have a better safety profile[2,18–20] Despite the improved safety profile, IV iron infusions add additional costs to the health care system which limit its widespread use.

Despite the fact that a few reviews have been published on this topic[2,21–23] including two qualitative systematic reviews,[4,24] confusion still exists as to what is the best way to treat IDA in patients with IBD. The general awareness of

the management options for IDA in patients with IBD is suboptimal among some gastroenterologists.[22] Some authors propose that the route of iron replacement therapy should depend on the degree of anemia. For example, it has been suggested that IV replacement should be considered in patients with hemoglobin (HB) less than 100 g/L and those with HB>100 g/L receive PO iron replacement.[23]

Several reviews have been written about this topic.[1,2,4] A problem with the existing reviews is that studies which used concurrent Erythropoiesis-Stimulating Agents (ESA) in the treatment of IDA in IBD are included..[24,25] ESA is used in patients whose anemia is refractory to intravenous iron therapy and it is not a first line treatment.[24] Moreover recent studies in hemodialysis patients using ESA in the treatment of anemia of chronic disease have raised concerns regarding the association between the rapidity of HB improvement and adverse cardiac outcomes[26] Therefore caution is needed with the addition of erythropoietin to the iron supplementation treatment of IBD patients with IDA and its use has been reserved for patients not responding to adequate amounts of intravenous iron replacement.

As more recent clinical trials have been published, the objective of this systematic review and meta-analysis is to compare the efficacy of IV versus PO iron replacement in the treatment of IDA in patients with IBD. The primary outcome measure was the mean change in HB and the secondary outcome measures included the mean change in ferritin, clinical disease activity indices, quality of life scores and adverse reaction rate.

2. Materials and methods

2.1. Search methods

A systematic search of the following databases was performed in January 2010. MEDLINE (1950 to February 2010, Ovid interface), EMBASE (1980 to 2010 Week 04, Ovid interface), Web of Science (2000–January 2010), Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (1991–January 2010), ClinicalTrials.gov (2000–January 2010) and Database Abstracts of Reviews of Effectiveness (1991–January 2010) was performed. MeSH subject headings and text-words used include inflammatory bowel disease, Crohn's disease, Crohn's colitis, ulcerative colitis, anemia, iron deficiency, ferric or ferrous compounds and administration and dosage, adverse effects, deficiency, therapeutic use. Abstracts from the American Gastroenterology meeting — Digestive Disease Week (2004–2011) and the European Gastroenterology meeting — United European Gastroenterology Week (2004–2010) were hand searched for additional publication. This search strategy was updated in January 2011 followed by review of 2011 DDW abstracts performed in June 2011.

2.2. Selection criteria

Randomized controlled clinical trials comparing the efficacy of IV versus PO iron replacement therapy in adult IBD patients with IDA were included. Anemia was defined as HB<120 g/L for females and HB<130 g/L for males.[27] Iron deficiency was defined as a serum ferritin<30 μg/L or saturation<20% if C Reactive Protein (CRP) was raised.[28-30] Studies with concurrent use of erythropoietin and those published in non-English or that employed a cross over study design were excluded. Cross-over study design was excluded because the assumptions made in crossover study design are that symptoms would return to baseline during the washout period and the disease state is constant overtime.[31] The measured HB and ferritin improvement at the end of the second period of intervention is likely influenced by the treatment given during the first period. Therefore the crossover design is not appropriate in IDA patients undergoing treatment for IDA.

One author (TL) searched the database and screened the retrieved citations by examining the abstracts. Abstracts that met the broad inclusion criteria were selected for further review. By following a pre-determined inclusion and exclusion form, two reviewers (TL and MRK) independently graded the abstracts as relevant (meeting all of the pre-determined inclusion criteria), possibly relevant (meeting some, but not all of the inclusion criteria), unclear or rejected (failure to meet any of the inclusion criteria). Finally, both reviewers independently reviewed the full text of all studies which, based on the data in the abstract, were considered as relevant or possibly relevant. The final decision regarding eligibility was reached by consensus and any disagreement was resolved through discussion.

2.3. Outcome measures

The primary outcome measure was the mean difference in HB at the end of study compared to baseline. Secondary outcomes included the mean difference in ferritin, the quality of life (QoL) score using Short Form-36 questionnaire, inflammatory bowel disease activity indices such as Colitis Activity Index (CAI) for ulcerative colitis and Crohn's Disease Activity Index (CDAI) for CD and the adverse event rate. Study authors were contacted to help with data clarification where needed.

2.4. Data extraction

Both reviewers independently extracted the data using a predetermined data extraction form. In studies where the outcome measures were reported as medians, they were accepted as means for the purpose of analysis. The inter-quartile Range (IQR) was converted to an estimated standard deviation (SD) using the formula 'IQR/1.35' and the range was converted to an estimated standard deviation using the formula 'range/4'[32] The study by Kulnigg et al. expressed their results as median and range; we successfully contacted the author and obtained the results expressed as mean and standard deviation. The mean end of study HB and ferritin in the study by Lindgren et al. was presented graphically; therefore these values were directly taken from the graph. After attempts to contact the authors of the study were unsuccessful to provide standard deviations pertaining to the end of study HB and ferritin, it was decided to use the standard deviation from Kulnigg's study instead, as the two studies had similar methodology and study population.[33] TL and MRK assessed the methodological quality of the studies independently based on the Cochrane

Collaboration's tool for assessing risk of bias form.[34] A final decision regarding the overall risk of bias was reached through discussion.

2.5. Statistical analysis

Data was analyzed using Review Manager (RevMan) Version 5.1. [Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2011]. The methodology and outcome measures of the included studies were similar and this allowed for pooling of results. All data were analyzed on an intention-to-treat basis. A random effect model was used as it provides a more conservative estimate of effect size. Heterogeneity of the studies was assessed by I2. Publication bias was not assessed because of the small number of included studies.

3. Results

The literature search identified 757 potential articles, 25 of which were duplications. After initial review of the titles and abstracts of 732 articles, 722 articles were excluded. Two reviewers independently examined the full text of the 10 remaining articles resulting in exclusion of a further seven of the retrieved articles (Fig. 1). Table 1 summarizes the characteristics of the included studies and Table 2 summarizes the reasons for excluding the 7 retrieved articles. The three included studies have a total sample size of 333 patients, 203 of whom received IV iron replacement and 130 received PO iron replacement. An updated literature search was performed in January 2011 and it did not yield any new relevant clinical trial for inclusion in this review.

For the three studies, treatment allocation was done by an external clinical trial company (Kulnigg study), by computer generated random number table[35] and by an Internet based method.[36] The allocation was not concealed in the study by Schroder et al. as a computer generated random number table was used to assign treatment group. There was no blinding of participants or study staff members in any study; however, study personnel were blinded to treatment allocation in the Lindgren study.

There was incomplete outcome data reporting by Lindgren. The end of treatment HB and ferritin was presented graphically and no standard deviation was reported. The other two studies presented all relevant outcome data, including the reasons for screen failures. An external clinical trial company on behalf of the sponsor in the Schroder and Kulnigg study performed the data analysis. It is unclear from the manuscript if the authors had full access to the collected data. It is also unclear why

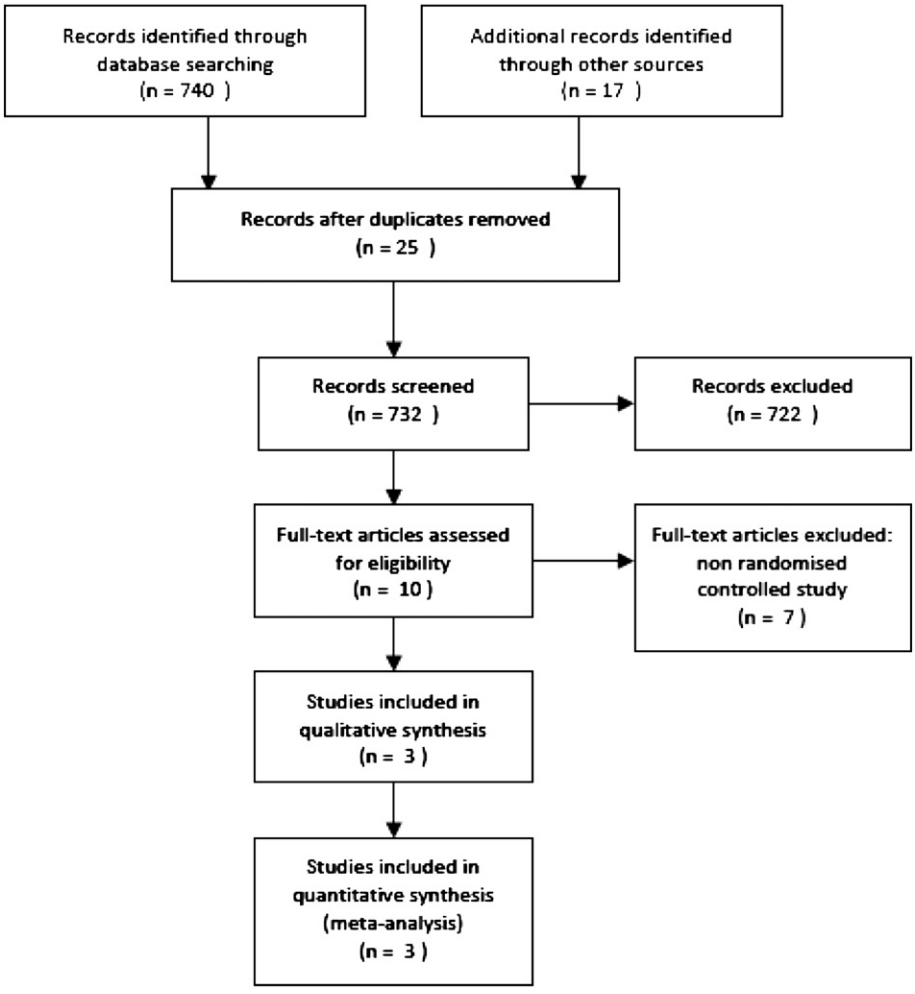

Figure 1 Flow chart of literature search outcomes.

Table 1 Characteristics of the included studies.

	Route	N	Baseline HB (g/L)	Baseline ferritin (μg/L)	EOT HB (g/L)	EOT Ferritin (μg/L)	mean total Fe given (g)	Rx time (week)
Schroder (2005) (median, IQR)	PO	24	96(93–101)	8(5–39)	117 (111–129)	24 (11–49)	Fe sulfate 4.2 (4.2–8.4)	6
F: Hb ≤ 105 g/L M: Hb ≤ 115 g/L TSAT ≤ 20% or Ferritin ≤ 20 μg/L	IV	22	98(88–104)	12(5–37)	123 (109–126)	240 (186–427)	Fe sucrose 1.4 (1.4–1.5)	6
Kulnigg (2008) (median, range)	PO	60	91(53–111)	6.5(1–383)	121 (65–174)	28.5(2–255)	Fe sulfate 16.8	12
	IV	136	87(50–115)	5 (1–399)	123 (60–159)	43.5(2–586)	Fe carboxymaltose 1.0	12
Hb < 100 g/L TSAT < 20% or Ferritin < 100 μg/L								
Lindgren (2009) (mean ± SD)	PO	46	103.8 **±11.4**	12.4 **±14.5**	114 (**using SD from Kulnigg**)	70 (**using SD from Kulnigg**)	Fe sulfate 38.4 ±20	20
Hb < 115 g/L Ferritin < 300 μg/L Low TSAT	IV	45	104.9 **±9.0**	14.0 **±17.6**	129 (**using SD from Kulnigg**)	140 (**using SD from Kulnigg**)	Fe sucrose 1.7 ±0.3	20

TSAT: Transferrin saturation.

Kulnigg performed an interim analysis that resulted in the early termination of the study. Based on the results from the interim analysis the authors felt that sufficient statistical power was achieved with a lower recruitment number. Therefore 52 fewer subjects were recruited. However, it is known that by performing an interim analysis power may be overestimated. This could potentially bias the results in favor of the intravenous cohort. Finally, all three studies received financial sponsorship from the makers of IV iron and this could influence the study outcomes and the decision regarding its publication. The risk of bias from the study design and reporting point of view is low for study by Schroder et al. Risk of bias was high in the study by Kulnigg et al. because the reason for conducting the interim analysis which led to early termination of the study was unclear. The Risk of bias was also high in study by Lindgren et al. because of incomplete data reporting. Moreover, having pharmaceutical support and the possibility of limited access to the study data were the basis for the overall assessment of a high risk of bias.

3.1. Primary endpoint

3.1.1. Mean change in hemoglobin

The range of the mean baseline HB was 89.7–103.8 g/L for PO and 85.4–104.9 g/L for IV route and the range of the mean end of study HB was 114–122.6 g/L for PO and 121.5–129 g/L for IV route (Table 1). Fig. 2 shows the forest plot comparing the mean difference in the amount of HB improvement between IV and PO iron replacement from

Table 2 Characteristics of excluded studies.

Authors	Year	Journal	Reason for exclusion
De Silva A. et al.[42]	2003	Inflamm Bowel Dis	Retrospective review, oral iron therapy
Rosado B. et al.[43]	2003	Gastroenterology DDW Supplement	Retrospective review of IV iron replacement therapy
Bodemar G. et al.[44]	2004	Scand J Gastroenterol	Retrospective review of iron sucrose infusions
De Silva A. et al.[17]	2005	Aliment Pharmacol Ther	Prospective study with oral iron therapy in IBD and non-IBD patients
Erichsen K. et al.[45]	2005	Scand J Gastroenterol	Prospective crossover design; sub-therapeutic dose of iron used how defined Patients were treated with either iron fumarate 120 mg/day for 2 weeks or 600 mg IV iron sucrose. The treatment duration was too short to enable measurable improvement in Iron study or Hb.
Katsanos K. et al.[46]	2007	J Crohn's and Colitis	Prospective iron infusion study
Gisbert J.P. et al.[23]	2009	Inflamm Bowel Dis	Prospective non-randomized study

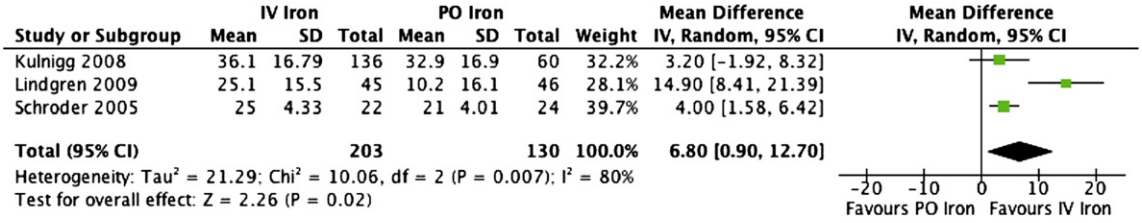

Figure 2 The mean hemoglobin improvement between IV and PO routes of iron replacement therapy. CI: confidence interval.

baseline to end of study. The IV route was associated with a greater improvement in the HB level than the PO route, weighted mean difference in HB of 6.8 g/L (CI 0.9, 12.7). This was statistically significant, p=0.02. There was significant heterogeneity in the data with I2=80%. Heterogeneity may be explained by the difference in the magnitude of HB improvement (not the direction of treatment effect as all studies showed improvement in favor of the IV route), the duration of iron therapy and by follow up, which ranged from 6 weeks to 20 weeks.

3.2. Secondary endpoints

3.2.1. Mean change in the end of treatment ferritin

The baseline ferritin ranged from 5–383 μg/L for PO and 5–399 μg/L for the IV route (Table 1). Fig. 3 demonstrates that IV iron replacement was superior in improving serum ferritin level over PO iron replacement therapy: the mean difference was 109.7 μg/L (CI 5.37, 214), p=0.04. There was significant heterogeneity in the data with I2=99%. The high I2 value observed reflects the difference in the magnitude but not the direction of ferritin improvement and this is likely explained by differences in the duration of iron therapy, which ranged from 6 weeks to 20 weeks.

3.3. Adverse events/discontinuation

Table 3 describes the number and the nature of adverse event that led to the discontinuation of iron replacement therapy. Five out of 203 patients who received IV iron discontinued because of infusion related reactions,[2] small bowel hemorrhage,[1] thrombophlebitis[1] and thrombocytopenia.[1] In comparison, 21 out of 130 patients in the PO iron replacement cohort discontinued iron replacement because of gastrointestinal related side effects such as nausea, abdominal pain and diarrhea. The odds ratio for discontinuing PO iron treatment due to side effects compared to IV iron replacement was 6.2 (CI 2.21, 17.1) (Fig. 4). One patient with a history of cardiac disease died of cardiac arrest 1 day after receiving iron carboxymaltose. The study authors reported that 'the event was considered unrelated to study medication but related to the underlying cardiac disease.'[37]

3.4. Quality of life score

The studies by Schroder et al. and Kulnigg et al. reported an increase in SF-36 score at the end of iron replacement therapy irrespective of the route of replacement: 7–17 points increment with IV iron and 8–17 points increment with PO iron therapy. Both routes had a comparable improvement in SF 36 scores, the pooled mean difference between PO and IV was 1.4 (CI −0.7, 3.5), which was not statistically significant (Fig. 5). Lindgren et al. did not report on the effect of iron therapy on quality of life.

3.5. Effects of treatment on disease activity

Schroder et al. did not demonstrate that there was a difference in change of disease activity when the two treatments were compared. The median Crohn's Disease Activity Index (CDAI) and the median Colitis Activity Index (CAI) were lower at the end of the study compared to baseline in both

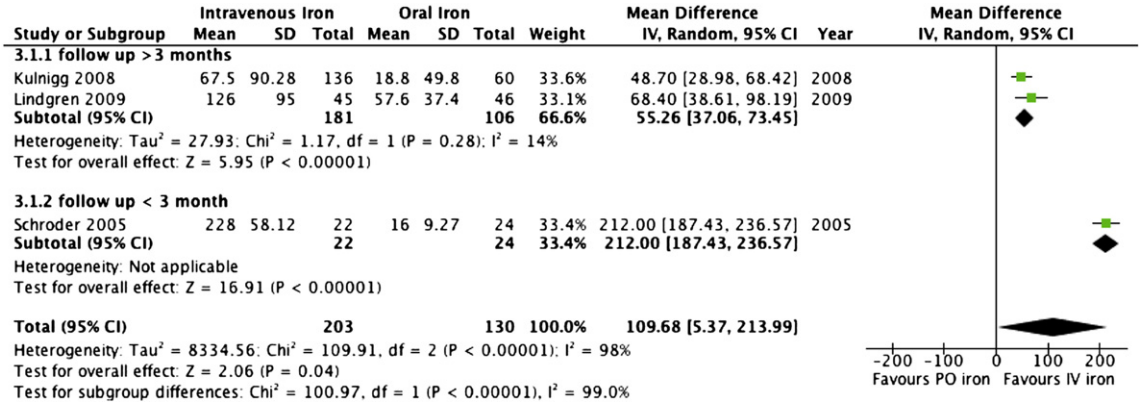

Figure 3 The mean difference in ferritin improvement between IV and PO routes of iron replacement therapy. CI: confidence interval.

Table 3 Number of patients discontinued iron replacement therapy due to adverse event as reported by the study authors.

	Studies	Oral	Intravenous
Number of patients discontinued	Schroder	5/24: Gastrointestinal side effects	2/22: rash, nausea, edema; thrombophlebitis
	Kulnigg	5/60: flare of ulcerative colitis; diarrhea; asthma; vomiting; Stomach pain	2/136: (+1 death) erythematous rash; small bowel hemorrhage
	Lindgren	11/46: Gastrointestinal symptoms	1/45: (thrombocytopenia)

IV and PO iron replacement cohorts suggesting an improvement in the clinical disease status. The changes in the median serum C-reactive protein levels at the end of study compared to baseline were not statistically significant in PO and IV group. Kulnigg et al. reported worsening of IBD in two of the enrolled patients, one given PO and one IV iron. Lindgren et al. did not comment on the effect of iron therapy on IBD activity.

Both Schroder et al. and Kulnigg et al. listed the use of concurrent medications including 5 amino-salicylates, immunomodulator such as azathioprine and corticosteroids. During the 6 weeks of iron replacement therapy in the study by Schroder et al., 25% of study participants had ongoing active IBD as indicated by a persistently elevated disease activity index. Successful prednisone tapering occurred in 75% of the study participants suggesting that clinically these patients were improving. The study by Lindgren et al. did not report on concurrent medication usage.

4. Discussion

The comprehensive literature search for randomized controlled trials comparing IV and PO iron therapy in iron deficient anemic IBD patients only identified three studies, which combined, included a total of 333 patients. There was a small (6.8 g/L) but statistically significant difference in favor of IV iron therapy in improving HB levels. Whether this small difference is also clinically important is a matter of debate as there is no agreement in the literature and none of the studies a priori defined what amount of improvement would be considered clinically important. For the outcomes of serum ferritin levels and rate of adverse events IV iron therapy clearly favored over PO therapy. There were no differences in quality of life or IBD activity but the number of patients available for these outcome measures is small.

This review has several methodological limitations. Most importantly the total sample size was small. In addition there were problems with data reporting, especially in the study by Lindgren et al.,[36] which did not report the standard deviations for the end of study HB and ferritin levels. For that reason these values were derived from the study by Kulnigg et al., as they used the study design with similar inclusion criteria for patients.

Another limitation is that the duration of post iron replacement therapy follow up, varying from 8 to 20 weeks, was relatively short. This makes it difficult to interpret if the higher ferritin level is of clinical significance in terms of a more durable HB improvement. Further clinical trials with a longer duration of post infusion follow up are needed to investigate this aspect. Some may also argue that the PO dose of iron replacement therapy was low which would bias the results in favor of IV therapy. In that regard the severity of side effects of oral therapy is important as the withdrawal

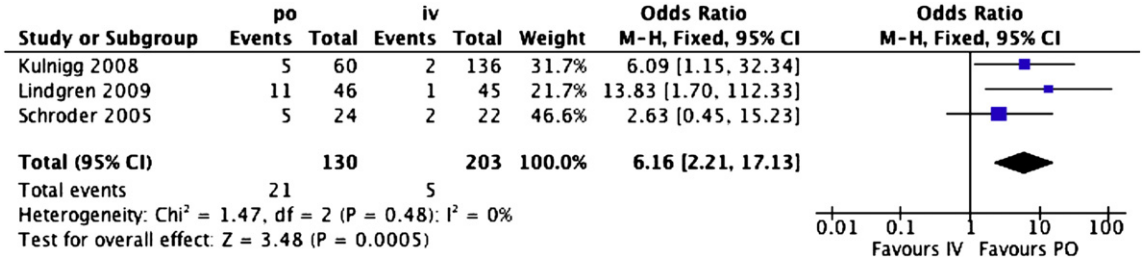

Figure 4 Odds ratio for discontinuation of iron replacement therapy due to adverse events. CI, confidence interval; M–H, Mantel–Haenszel test.

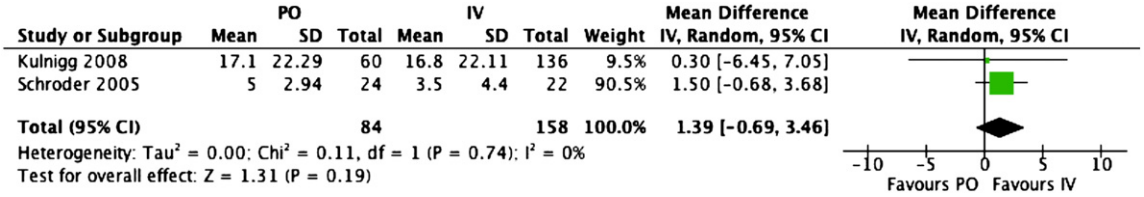

Figure 5 The mean change in SF-36 score between IV and PO routes of iron replacement therapy. CI: confidence interval.

rate was higher in patients receiving PO iron therapy. Higher doses of PO iron may therefore affect patient compliance further.

All three studies were analyzed on an intention to treat basis. Using Cochrane Collaboration's risk of bias tool, the overall risk of bias of the included studies was determined to be high on multiple levels, including incomplete data reporting of the primary end point by Lindgren et al., an interim analysis which led to early termination of study by Kulnigg et al. and industry sponsorship in all three included studies.

The cost of using IV iron replacement therapy is also important. Direct costing components include the intravenous iron itself. In Canada the cost of one vial of iron sucrose containing 100 mg iron is $37.50, which is more expensive than oral iron pills ($30/100 tablets of 300 mg iron sulfate). The need for a medically supervised environment to give the iron infusion ($238/infusion) and nursing time (4 h infusion time +1 h preparation/observation time, @$52/h) also need to be considered as well as the indirect costs related to travel costs and possible time lost from work. The estimated total cost for 900 mg iron sucrose infusion (three infusion of 300 mg iron sucrose) is CAD $1831.50 ($337.50 for iron sucrose + $714 for infusion facility fee + $780 for nursing). In contrast, 100 tablets of 300 mg iron sulfate costs CAD $30. A cost effectiveness study comparing two different intravenous iron formulations (iron carboxymaltose versus iron sucrose) has been done in anemic IBD patients[38]but none comparing PO versus IV iron therapy for the treatment of IDA in adult IBD patients. Compared to iron sucrose, treatment with iron carboxymaltose would save CAD $475 (US $460) per patient because total iron replacement can be achieved with fewer iron carboxymaltose infusions.

Hepcidin has been shown to be an important regulator of iron homeostasis.[39] Chronic inflammation is associated with an elevated serum hepcidin concentration, which resulted in sequestration of iron stores in the reticuloendothelial system and impaired intestinal iron absorption. In contrast, iron deficiency anemia is associated with a low serum hepcidin concentration, which enhances intestinal iron absorption and the release of iron from the reticuloendothelial system.[40,41] With this in mind, oral iron therapy may not be as effective as intravenous iron therapy in the setting of a chronic active inflammatory state in the small bowel and colon.

Moreover, we were surprised with the small number of published randomized controlled studies in this important area. Despite the fact that so few studies met our inclusion criteria, we decided to continue the review as we believe it is important to highlight how limited the evidence from the available literature is.

In conclusion, it is not surprising that IV iron replacement therapy was superior in improving ferritin levels in IBD patients with iron deficiency anemia, however the difference in the mean HB increment was small and the clinical significance is uncertain. IV iron was associated with fewer adverse events. Further studies are needed to examine this important area to help establish the optimal management of iron deficiency in these patients and to determine whether IV iron therapy is cost effective.

Conflict of interest

Authors hava no conflict of interest to declare. The study received no financial support

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