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Original article

Iron supplementation for restless legs syndrome – A systematic review and meta-analysis

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ABSTRACT

Background: Iron supplementation, is recommended for the treatment of restless legs syndrome (RLS). We gathered evidence for the efficacy and safety of iron supplementation for RLS.

Methods: A systematic review and meta-analysis of randomized controlled trials that compared iron supplementation versus no iron for patients with RLS was performed. Multiple databases were searched. The primary outcome was the effect of iron on the International Restless Legs Syndrome score (IRLSS) at 4 weeks after treatment. For dichotomous data, risk ratios (RR) with 95% confidence intervals (CIs) were estimated and pooled. For continuous data, weighted mean differences (WMD) were calculated.

Results: Ten trials fulfilled the inclusion criteria. Iron therapy was associated with a significant decrease of the IRLSS of −3.55 [95% CI (−5.41) – (−1.68)] points and an increase in the percentage of patients with improvement of the IRLSS score, RR of 2.16 [95% CI 1.56–2.98]. IV FCM was associated with improvement in both the IRLSS (WMD of −2.79 (95% CI (−4.62) – (−0.96), 4 trials, $I^2 = 0\%$) and on the RLS-QOL by WMD of 8.67 (95% CI 1.68–15). Iron was associated with an increased rate of adverse events RR 2.04 (95% CI 1.46–2.85), which were not severe and not associated with increased rate of treatment discontinuation.

Conclusion: Iron supplementation is associated with improvement of the IRLSS score. Our meta-analysis supports the use of iron, oral or IV, as effective therapy for patients with RLS.

Further studies should assess subgroups of patients most likely to benefit from iron supplementation.

1. Background

Restless legs syndrome (RLS), also known as Willis-Ekbom disease, is a common neurological disorder, which significantly impacts quality of life, sleep, and health [1]. Iron metabolism and deficiency were first suggested in the early 1960s to play an active role in the pathophysiology and treatment of RLS [2]. Iron therapy attempts to correct the underlying relative brain iron deficiency and thus correct a putative major cause of RLS. Therefore, current guidelines by the International Restless Legs Syndrome Study Group (IRLSSG) regarding iron treatment for RLS [3] recommend administration of oral iron for treating RLS in patients with serum ferritin < 75 mg/l, and IV iron for treating moderate to severe RLS for patients with serum ferritin < 300 mg/l [3]. Another evidence-based review, considered oral iron sulfate therapy for RLS as possibly ineffective for patients with adequate iron storages; however, there is insufficient data to conclude on overall efficacy and thus oral iron sulfate considered as “possibly useful” [4]. In this review FCM was considered to “likely efficacious”. The authors concluded that further large trials are needed to determine the role of oral versus IV treatment and the optimal IV formulation and schedule. Due to the relatively low number of patients in each trial, a systematic review and meta-analysis has the potential to provide additional data by pooling the results from all the available trials. A previous systematic review by the Cochrane Collaboration, concluded that there is insufficient evidence to determine whether iron therapy is beneficial for the treatment of RLS, as the main objective (improvement on the International Restless Legs Syndrome score (IRLSS), showed no benefit with iron therapy [5]. Since then, several randomized controlled trials (RCTs) of iron therapy for the treatment RLS were published. We therefore performed a systematic review and meta-analysis evaluating iron therapy for RLS, in order to further shed light on the efficacy and safety of iron on the treatment of RLS.

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2. Methods

A systematic review and meta-analysis, according to the PRISMA statement [6], of RCTs that assessed all available iron formulations versus no iron or placebo, for the treatment of RLS. Included trials were those that used any iron formulation, either oral or IV iron, that recruited only adult patients, who were diagnosed with RLS according to acceptable diagnostic criteria [7]. Trials that compared iron to another treatment of RLS (such as dopaminergic agonists) were excluded, since the estimate effect of iron therapy could not be determined. Trials that were excluded were those that compared oral with IV iron. Trials were included irrespective of publication status or language.

2.1. Data sources

A search was performed in the following databases - MEDLINE (1/1966 to 6/2018), CENTRAL (The Cochrane Library), LILACS, KOREAMED, and NLM gateway. In addition, conference proceedings of the American Association of Neurology, European Association of Neurology and the American Academy of Sleep Medicine from 2014 onwards were searched. Clinical trials databases for ongoing and unpublished trials were reviewed. The references of all identified studies were inspected for additional trials. The term “restless legs” was searched as both a medical subject heading (MeSH) term and as a text word and crossed with the term “iron” (MeSH term and a text word) and specific iron formulations. The result was limited to randomized controlled trials using a highly sensitive filter [8].

2.2. Data extraction and quality assessment

Two reviewers independently extracted data from included trials. In case of disagreement between the two reviewers, a third reviewer extracted the data and results were attained by consensus. Trials were assessed for method quality and the following domains were examined: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data reporting, selective outcome reporting. Each domain was graded as low risk for bias, unclear risk -lack of information or uncertainty over the potential for bias, or high risk for bias according to the criteria specified in the Cochrane Handbook [8].

2.3. Definition of outcomes

The primary outcome was to evaluate the efficacy of iron supplementation on RLS symptoms as measured by the change from baseline in the IRLSS score or by the percentage of patients with improvement of the IRLSS score at 4 weeks or the closest follow up. In case the 4 weeks point of follow up was not available, we used the closet time point or the available time point for the main outcome. Secondary outcomes included quality of life (QOL) scales (RLS-QOL, global rating scale (GRS), clinical global impression (CGI), RLS score (as defined by Davis et al. [9]); sleep quality scales (medical outcome study quality of sleep scale, Pittsburgh sleep quality index (PSQI), sleep efficiency as defined by Early et al. [10], quality of sleep as defined by Davis et al. [9]). For further analysis, subgroup comparisons were conducted of patients that were treated by IV or oral iron and specific IV iron formulations (FCM, iron sucrose), anemia, iron deficiency (ferritin < 75 µg/l) or end stage renal disease.

2.4. Data synthesis and analysis

Dichotomous data were analysed by calculating the risk ratio (RR) for each trial with the uncertainty in each result being expressed using 95% confidence intervals (CI). Mean and standard deviation (SD) values were obtained for continuous variables. When mean or SD values were not available, they were calculated by using data obtained from figures or by recalculating them from other effect estimates and dispersion measures [8]. For continuous variables, weighted mean difference (WMD) were calculated for variables that were reported on the same scale. WMD represents the weighted combination of absolute differences between the mean values in the two groups in a clinical trial. For continuous data reported in different scales (for example different QOL or sleep quality scales) the standardized mean difference (SMD) was used. Heterogeneity (degree of difference between the results of different trials) in the results of the trials was assessed by calculating Chi-square and I^2 tests of heterogeneity. A fixed effect model was used throughout the review, except in the event of significant heterogeneity between the trials ($P < 0.10$, $I^2 > 50\%$), for which we used a random effects model (REM). Sensitivity analysis according to methodological quality of trials was conducted for the primary outcome. Analysis were done using RevMan 5.3 software. A funnel plot was used to assess small-studies effects (supplemental material).

3. Results

The literature search identified 735 publications; 10 trials performed between 2004 and 2018 fulfilled the inclusion criteria (studies flow chart, Fig. 1). These included eight trials of IV iron [9–16] and two trials of oral iron supplementation [17,18]. Pooled together, 233 patients were treated with iron and were compared to 222 control patients. Characteristics of included studies are presented in Table 1. Among the iron formulations, iron sucrose was used in three trials; FCM was used in four trials, and iron dextran in one trial. Among the oral iron formulations, oral iron sulphate was used in both trials. The total administered IV iron dosage was 1000 mg except for 2 trials [11,13] which administered 500 mg. Patients were followed up between 12 and 52 weeks, and follow up losses were between 0 and 18%. Females comprised 328/455 (72%). Those included were highly symptomatic at baseline, as mean baseline IRLSS scores were 23–30 (regarded as severe symptoms([19]. One study [15] used a different RLS score for baseline measurements and follow up, while another did not report the baseline IRLSS score [17]. Three trials included patients with iron deficiency at baseline (defined as ferritin < 75 µg/l) [14,16,18]. Among other studies, mean baseline ferritin levels ranged between 53.5 and 175 µg/l. Eight trials included patients with primary RLS, while two trials included patients with RLS secondary to end stage renal disease (ESRD) [9,15] (Table 1).

3.1. Risk of bias assessment

Risk of bias is presented in Table 2. Allocation generation was adequate in 7/10 studies. In 7/10 studies, allocation concealment was not adequately reported or was not stated. All but one [9] study reported double blinding of the results. Informed consent, ethic committee approval and conflict of interest disclosure were reported in all studies. Further data are presented in Table 2.

3.2. Primary outcome – change in IRLSS score

Results for the primary outcome are presented in and 2b. At 4 weeks, the IRLSS score was significantly decreased with iron therapy in comparison to no therapy (mean of -3.55 [95% CI (-5.41) – (-1.68), 9 trials, $I^2 = 57\%$, REM]) Fig. 2a. In the subgroup of IV iron therapy, the IRLSS score decreased by WMD of -3.13 (95% CI (-5.08) - (-1.17), 7 trials, $I^2 = 62\%$, REM) with IV iron than with no treatment. This was mainly derived from studies that used FCM (WMD of -2.79 (95% CI (-4.62) – (-0.96), 4 trials, $I^2 = 0\%$)), Fig. 2b. A statistically significant advantage of iron on IRLSS score was observed with oral iron sulfate of WMD decrease of -8.36 (95% CI (-13.83) – (-2.88), 2 trials, $I^2 = 0\%$.

When assessing dichotomous data, iron supplementation was associated with an increase in the percentage of patients with improvement

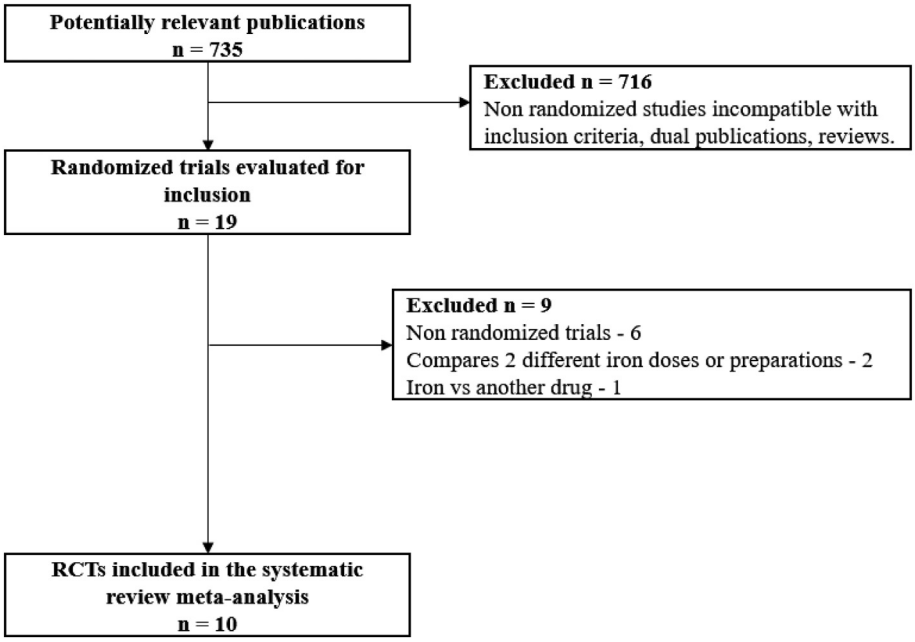

Fig. 1. PRISMA study flow chart.

in their IRLSS score, RR of 2.16 (95% CI 1.56–2.98, 6 trials, I^2 = 20%). Again, this was mainly derived from studies that used FCM, RR 2.52 (95% CI 1.61–3.95, 3 trials, I^2 = 0%), Fig. 2c.

3.2.1. Subgroup analysis

For the subgroup of patients with iron deficiency at baseline, the point estimate for improvement in the IRLSS was in favor of iron, although it did not reach statistical significance t WMD of −3.66 (95% CI (−7.42) – 0.09, 3 trials, I^2 = 58%, REM]. However, the single trial of oral iron that included iron deficient patients [18], did show an improvement in the IRLSS (WMD of −9.16 (95% CI (−15.19) – 3.13).

For the subgroup of patients with ESRD, iron therapy was not associated with a statistically significant decrease of the IRLSS (WMD -4.43 (95% CI (−8.9) – 0.04), 2 trials, I^2 = 87%, REM). We were unable to pool results for the subgroup of patients with anemia due to lack of reported data.

In a sensitivity analyses, restricted only to trials with low risk of bias, studies that recruited > 50 patients, and the weight of each study, the results were unchanged, in respect to the benefit of iron.

3.3. Secondary outcomes – IRLSS score at the longest follow up, QOL indices, adverse events

The IRLSS score at the longest follow up (which ranged from 12 to 52 weeks) showed that iron was associated with a WMD decrease of −5.47 (95% CI (−6.69) – (−4.25), 9 trials, I^2 = 27%).The effect of iron on IRLSS score at the longest follow-up was consistent with improvement with iron therapy for all trials other than Early et al. [10].

Reporting of QOL indices and sleep quality indices with iron therapy was inconsistent between the trials. IV FCM was associated with significant improvement on the RLS-QOL, by WMD of 8.67 (95% CI 1.68–15.65, 3 trials, I^2 = 44%) compared to no therapy. No change in quality of sleep was observed by pooling the different sleep quality indices (SMD of −0.31 (95% CI (−2.03) - 1.42, 5 trials, I^2 = 0%)). PLMS index was unaffected by iron therapy, WMD 2.17 (95% CI (−6.82) – 11.5, 2 trials, I^2 = 0%).

The rate of adverse events (as defined by MedDRA version 20.1) was increased with iron therapy, RR 2.04 (95% CI 1.46–2.85, 9 trials, I^2 = 24%) Fig 3a. However, there was no increase in severe adverse events, RR 1.97 (95% CI 0.46–8.42, 2 trials, I^2 = 0%) Fig 3b or adverse events requiring drug discontinuation, RR 1.00 (95% CI 0.31–3.21, 3 trials, I^2 = 38%). The reported increase of adverse events were mostly gastrointestinal related, mild, and seen both with oral and IV iron, RR 3.81 (95% CI 1.62–8.96, 6 trials, I^2 = 13%).

4. Discussion

We performed a systematic review and meta-analysis evaluating the efficacy and safety of all available iron supplementations for treatment of RLS. The results demonstrate that iron is associated with improvement in the IRLSS score at 4 weeks and at the longest follow up available. Adverse events were more common with oral iron, but they were mainly mild, gastrointestinal related events, which were not serious and did not require drug discontinuation.

Importantly, we demonstrated an improvement in the IRLSS with all formulations of iron. The improvement in IRLSS was consistent in both analyses of continuous data and dichotomous data (the percentage of patients with improvement), and with all iron formulations. A subgroup analysis according to the different IV iron formulations, demonstrated that FCM was the only formulation which was associated with a statistically significant improvement in the IRLSS. However, the point estimate was in favor of all IV formulations, suggesting a class effect for all IV formulations. Regarding QOL, IV FCM was associated with significant improvement on the RLS-QOL in three trials. However, The QOL and sleep quality indices that were pooled, were inconsistent across the studies, thus confounding the summary results, precluding more conclusions.

We show in the current analysis that treatment with iron is safe, and specifically treatment with IV iron formulations. This was already demonstrated in our previous large meta-analysis of 103 trials that assessed the safety of IV iron in different clinical settings [20]. Lack of an increase in adverse events requiring drug discontinuation also supports this.

Our review adds more data to the previous review by the Cochrane collaboration [5]. Four additional RCTs published since then were included, three of which assessed IV iron. Therefore, we were able to demonstrate a statistically significant beneficial effect of IV iron on IRLSS, which was not available in the previous large meta-analysis. In contrast to the previous review, two RCTs that assessed iron for RLS were excluded from our review. The trial by Vishwakarma et al. [21],

Table 1
Characteristics of included studies.

Study	Intervention	Included patients	Haematological inclusion criteria	Other medications for RLS	N Patients randomized	Time of efficacy measurements	Follow up duration	Age	% Female	Baseline IRLS score	Mean baseline ferritin	Mean baseline Hb
Allen 2011 [11]	IV FCM 500 mg, 2 times over 2 weeks	IRLS score ≥ 15	ferritin < 300 ng/dL, or TSAT < 45%	Not allowed	24	4 weeks	12 weeks	49.5 ± 11.4	70%	25.0 ± 5.8	28.1 ± 22.9	Not reported
	Placebo				22			54.8 ± 13.6	52%	24.2 ± 5.5	24.8 ± 20.2	
Cho 2016 [12]	IV FCM 1000 mg, once	IRLS score ≥ 15	ferritin < 300 ng/dL, Hb > 12 μg/dL, or TSAT < 45%	Not allowed	32	4 weeks	30 weeks	49.7 ± 13.7	81%	27.4 ± 4.03	53.5 ± 41.8	13.3 ± 1.42
	Placebo				32			52.3 ± 10.7	75%	28.0 ± 5.16	69.3 ± 55.4	13.5 ± 1.11
Cho 2018 [13]	IV FCM 500 mg, once	IRLS score ≥ 15	ferritin < 300 ng/dL, Hb > 12 μg/dL, or TSAT < 45%	Not allowed	32	6 weeks	30 weeks	47.3 ± 13.3	81%	28.1 ± 5.7	50.7 ± 40.8	13.5 ± 1.2
	Placebo				32			51.5 ± 12.0	81%	27.3 ± 5.3	70.2 ± 59.5	13.3 ± 0.9
Davis 2000 [17]	Oral iron sulphate, 325 mg twice daily for 16 weeks	Symptomatic RLS	Hb < 12	Allowed	14	12 weeks	26 weeks	58.6 (33–80)	64%	NS	134.8 (9–680)	14.3 (12.7–16.9)
	Placebo				14			59.9 (33–76)	71%	NS	100.6 (8–335)	13.7 (11.6–15.6)
Deng 2017 [9]	IV iron sucrose 100 mg, 10 time over 10 weeks	ESRD patients, IRLS diagnostic criteria	ferritin < 200 ng/dL or TSAT < 10%	Allowed	16	2 weeks	12 weeks	63.63 ± 4.83	62%	26.06 ± 6.84	154.75 ± 38.34	10.55 ± 0.90
	Placebo				16			64.19 ± 7.93		26.31 ± 7.14	157.13 ± 35.33	10.85 ± 1.06
Early 2009 [10]	IV iron sucrose 500 mg, 2 times over 1 week	telephone diagnostic interview with an	Hb < 12	Not allowed	11	2 weeks	41 weeks	66.4 ± 11.4	71%	30.8 ± 9.2	78.3 ± 41.7	15.0 ± 1.2
	Placebo	RLS expert			7			61.4 ± 10.0	45%	29.7 ± 2.9	70.3 ± 21.5	14.0 ± 0.84
Grote 2009 [14]	IV iron sucrose 200 mg, 5 times over 5 weeks	4 cardinal RLS diagnostic criteria, IRLS	ferritin < 30	Not allowed	29	3 weeks	52 weeks	47 ± 10	86%	24	20.1 ± 12	12.9 ± 1.8
	Placebo	score ≥ 10			31			46 ± 8	90%	26	20.4 ± 11	13.1 ± 1.2
Sloand 2004 [15]	IV iron dextran 1000 mg, once	ESRD, IRLS diagnostic	NS	Allowed	11	2 weeks	3 weeks	58 (48–65)	64	7 (5–9)*	87 (47–371)	11.1 (10.3–11.7)
	Placebo	criteria			14			53 (41–68)	28%	9 (8–10)*	175 (60–336)	11.3 (10.7–11.6)
Trenkwalder 2017 [16]	IV FCM 1000 mg, once	IRLS score ≥ 15	Ferritin < 75 or ferritin 75–300 and TSAT < 20%,	NS	59	4 weeks	12 weeks	53.0 ± 15.7	81%	25.9 ± 5.65	41.93 ± 34.55	NS
	Placebo		Hb < 11.5/12.5 (male/female),		51			55.5 ± 15.9	82%	26.0 ± 5.78	48.85 ± 45.95	NS
Wang 2009 [18]	Oral iron sulphate, 325 mg twice daily for 12 weeks	NIH diagnostic criteria for RLS, IRLS score ≥ 11	ferritin 15–75, Hb < 11.4/14 (male/female), TSAT > 15%	NS	11	12 weeks	12 weeks	60 (36–82)	54%	24.8 ± 5.72	40.6 ± 15.3	14.5 ± 1.30
	Placebo				7			58 (range 33–72)	71%	23.0 ± 5.03	36.7 ± 20.8	13.7 ± 1.50

Abbreviations: FCM = ferric carboxymaltose, Hb = haemoglobin, IRLS = International Restless Legs Syndrome, NS = not specified, RLS = restless legs syndrome, TSAT = transferrin saturation.

Table 2
Risk of bias assessment.

Study	Random sequence generation	Allocation concealment	Blinding	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Allen 2011 [11]	Low	Low	Low	Low	Low	Low
Cho 2016 [12]	Low	Unclear	Low	Low	Low	Low
Cho 2018 [13]	Low	Unclear	Low	Low	Low	Low
Davis 2000 [17]	Low	Low	Low	Low	Low	Low
Deng 2017 [9]	High	High	Unclear	Unclear	Low	Low
Early 2009 [10]	Low	Unclear	Low	Low	Low	Low
Grote 2009 [14]	Low	Unclear	Low	Low	Low	Low
Sloand 2004 [15]	Unclear	Unclear	Low	Low	Low	Low
Trenkwalder 2017 [16]	Unclear	Unclear	Low	Low	Low	Low
Wang 2009 [18]	Low	Low	Low	Low	Low	High

which compared oral iron to ropinirole and bupropion, was excluded since we could not assess the effect of the iron itself on the RLS due to another intervention. The study by Birgegard et al. [22] was excluded as well since it compared oral and IV iron, and no control group was present.

Our results favoring iron are in agreement with the current management guidelines for treatment of RLS. In the current guidelines by the International Restless Legs Syndrome Study Group (IRLSSG), Allen et al. [3], recommended considering treatment of moderate to severe RLS with IV iron FCM if the ferritin levels are under 300 μg/l, while considering oral iron for patients with mild RLS and ferritin < 75 μg/l. Our results cannot suggest certain ferritin cut-offs for the decision between oral or IV iron, because for the subgroup of iron deficient patients, iron was not associated with significant improvement. In another evidence based review, in the section regarding mineral therapy for RLS, Winkelmann et al. [4] recommend FCM as a “possibly useful” option for the treatment of adults with RLS, while considering iron sucrose as investigational and iron dextran as an unacceptable risk. Regarding oral iron, it was considered as a non-efficacious intervention for patients without iron deficiency. Considering the results of our review, we show that all iron formulations compared to control are beneficial in improving the IRLSS.

Our systematic review has some limitations. There was a high level of heterogeneity among the included studies with regards to the included population, the IRLSS baseline score, presence of ESRD, and other allowed open label treatment for RLS. However, on subgroup analysis based on the iron preparation, we removed that high heterogeneity ($I^2 = 0\%$) and could draw direct conclusions, by fixed effect model meta-analysis, on the efficacy of FCM on the examined RLS population. Second, most studies reported results on QOL and sleep quality indices that were not comparable on the same scale, and thus we resorted to use SMD as a mean to pool results on similar scales. Although this is not ideal, we were still able to demonstrate significant improvement on the pooled QOL and sleep indices, showing consistent effect of iron on both parameters. Third, we could not draw conclusions regarding the optimal dosage of IV iron and the schedule of treatment since the trials used doses that ranged between 500 mg and 1000 mg. This also applies to the dosage of oral iron, as no data for oral iron formulations other than iron sulphate were available. Finally, due to confounding effect of open label therapy for RLS, the true magnitude of iron RLS was not always appreciated from the trials thus confounding the results from some of the included trials.

In conclusion, iron is efficient and safe for the treatment of RLS. The current evidence from our meta-analysis supports the use iron, both oral or IV, as effective therapy for patients with RLS.

Further research should determine the dosage and regimens of the iron preparation, and should be adequately powered to detect treatment response and safety profile.

Author roles

Tomer Avni

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique

Shelley Reich

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3) Manuscript: A. Writing of the first draft, B. Review and Critique

Nirit Lev

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: B. Execution, C. Review and Critique;
3) Manuscript: B. Review and Critique

Anat Gafter-Gvili

1) Research project: A. Conception, B. Organization, C. Execution;
2) Statistical Analysis: B. Execution, C. Review and Critique;
3) Manuscript: B. Review and Critique

Financial disclosures of all authors for the past year:

Tomer Avni - Stock Ownership in medically-related fields, Intellectual Property Rights, Consultancies, Expert Testimony, Advisory Boards, Employment, Partnerships, Contracts, Honoraria, Royalties, Grants, Other – None

Shelley Reich - Stock Ownership in medically-related fields, Intellectual Property Rights, Consultancies, Expert Testimony, Advisory Boards, Employment, Partnerships, Contracts, Honoraria, Royalties, Grants, Other – None

Nirit Lev - Stock Ownership in medically-related fields, Intellectual Property Rights, Consultancies, Expert Testimony, Advisory Boards, Employment, Partnerships, Contracts, Honoraria, Royalties, Grants, Other – None

Anat Gafter-Gvili - Stock Ownership in medically-related fields, Intellectual Property Rights, Consultancies, Expert Testimony, Advisory Boards, Employment, Partnerships, Contracts, Honoraria, Royalties, Grants, Other – None

Financial disclosure/Conflict of interests

None to declare.

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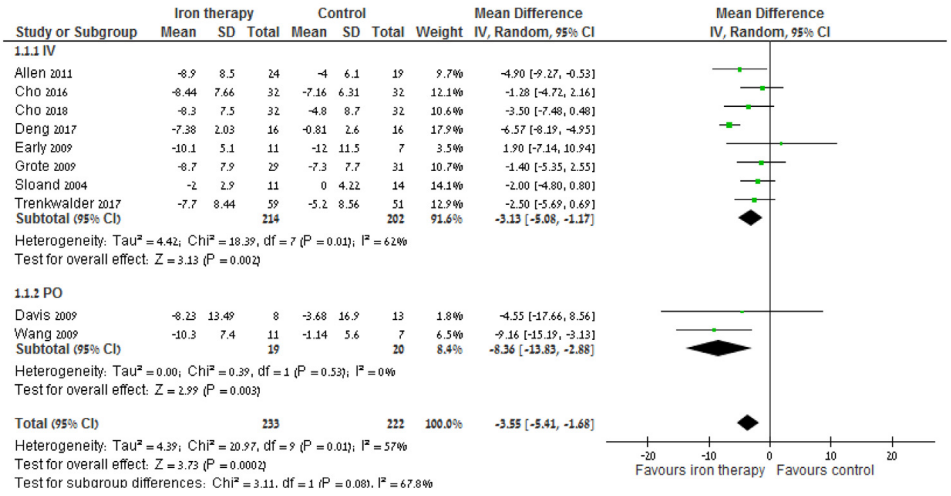

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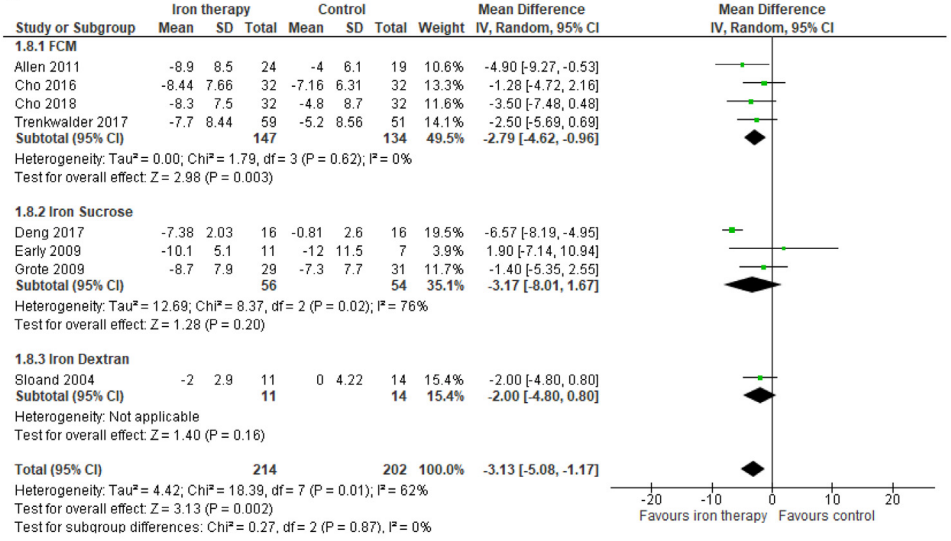

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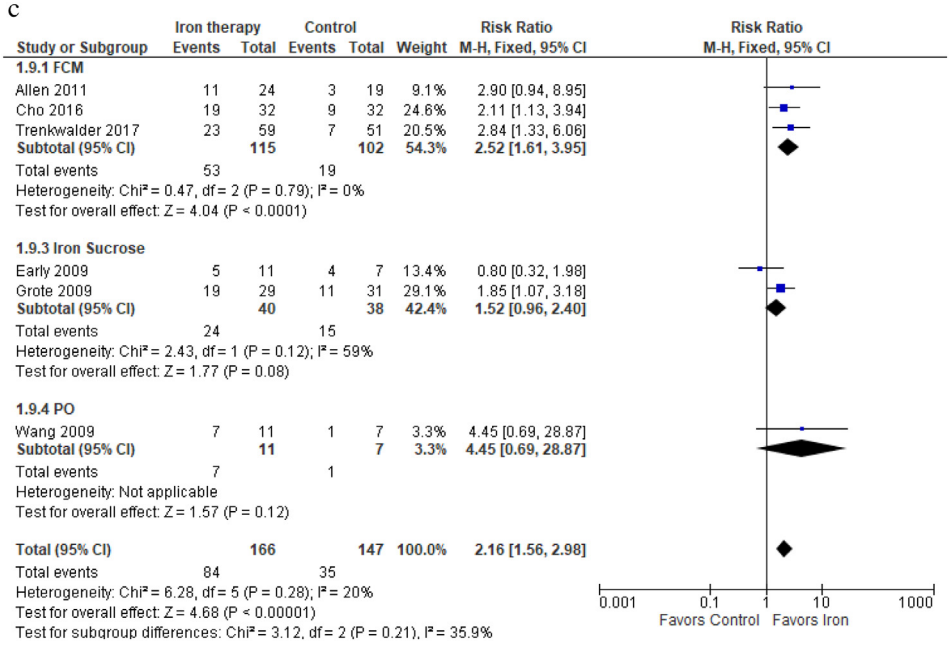

Fig. 2. a, b, c: Forrest plot: primary outcome: change in IRLS score, continuous - all iron continuous; change in IRLS score, continuous – IV iron subgroup; percentage of patients with improvement in IRLS score, dichotomous – all iron.

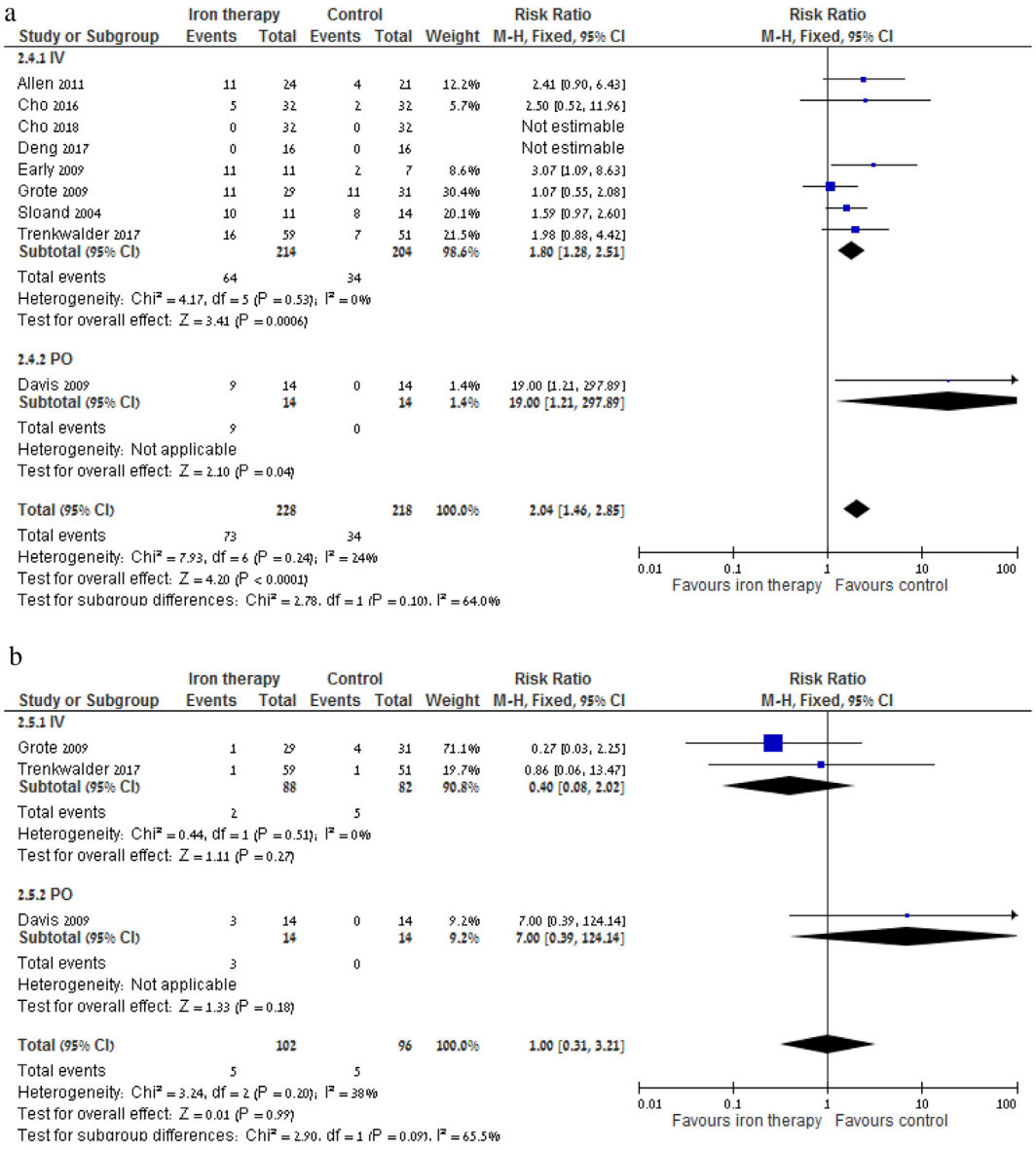

Fig. 3. a, b: any Adverse Events; severe or requiring discontinuation AEs.

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