Sleep Medicine 61 (2019) 110–117

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Efficacy and tolerability of intravenous iron for patients with restless legs syndrome: evidence from randomized trials and observational studies

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ARTICLE INFO

Article history:
Received 9 August 2018
Received in revised form
11 November 2018
Accepted 8 January 2019
Available online 21 February 2019

Keywords:
Restless legs syndrome
Ferric carboxymaltose
Iron sucrose
Iron dextran

ABSTRACT

Objective: Restless legs syndrome (RLS) is a common neurological disorder of unclear pathophysiology that appears to involve an iron deficiency in the brain. Some studies, but not others, suggest that intravenous injection of iron can reduce RLS severity.
Method: The databases Web of Science, PubMed, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed were searched for randomized controlled trials, cohort studies and case-control studies of intravenous iron therapy to treat RLS. Eligible studies were meta-analyzed using Stata 12.0.
Results: This analysis indicated that IV iron was more efficacious than placebo in treating RLS (OR: 4.71,95%CI 4.21−5.21,$p < 0.0001$). According to sub-group analysis, either IV ferric carboxymaltose (FCM) or iron sucrose was more efficacious than placebo in treating RLS. Adverse events did not differ significantly between patients receiving intravenous iron or placebo (OR 1.68, 95%CI 0.92−3.07, $p = 0.093$). The present study also indicated after accepting IV iron treatment the IRLS score in RLS patients decreased (OR = 6.75,95%CI 4.02−9.49, $p < 0.0001$). The subgroup analysis showed that IV iron dextran, iron sucrose, and FCM could alleviate the IRLS score.
Conclusion: The available evidence suggests that intravenous iron is effective and tolerable for patients with RLS regardless of peripheral iron status.

1. Introduction

Restless legs syndrome (RLS) is a common neurological disorder diagnosed solely on clinical criteria. RLS symptoms are triggered by rest or inactivity and worsen at night. Movements such as walking, stretching, or bending the legs provide partial or complete relief, but symptoms return as soon as movement ceases [1]. RLS appears to involve the dopaminergic pathway because it responds to dopaminergic receptor agonists and it can occur in patients with Parkinson's disease (PD), which is characterized by dysfunction of the dopaminergic pathway [2,3]. RLS prevalence is higher among PD patients than in the general population [4]. Nearly 50 years ago, Ekbom postulated that iron deficiency causes or contributes to RLS [5]. In initial studies, oral iron therapy improved or even eliminated RLS symptoms in patients with peripheral iron deficiency [5,6]. However, normal serum ferritin was detected in most RLS patients, and there was less evidence of abnormal peripheral iron stores [7]. Thus, the pathophysiology of RLS appears to be more associated with central nervous system iron status [7]. IV iron has been recommended as a treatment for RLS [8], and it is generally assumed this corrects the regional brain iron deficiency in an iron deficiency animal model [9]. Many subsequent clinical trials sought to use IV iron to treat RLS patients irrespective of serum iron, but results were inconsistent. One study reported that a total intravenous dose of 1000 mg iron sucrose (500 mg over two consecutive days)

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https://doi.org/10.1016/j.sleep.2019.01.040
1389-9457/

improved mean global RLS symptom severity, with 60% of patients showing complete remission of RLS symptoms without the further need for RLS medication for 3–36 months [10]. This study did not compare the treatment with placebo, and a subsequent placebo-controlled study of a single intravenous dose of 1000 mg iron sucrose did not show therapeutic efficacy [11]. Six other randomized controlled trials (RCTs) have evaluated the efficacy of intravenous iron therapy [12–17]; three case-controlled studies [18–20] and five cohort studies [21–25] have explored different iron formulations or dosing regimens.

Recently, IV iron has been recommended to treat RLS by the International Restless Legs Syndrome Study Group (IRLSSG). We wished to gain a coherent understanding of the efficacy and tolerability of intravenous iron therapy for RLS, based on the literature; we meta-analyzed relevant studies from six databases.

2. Methods

2.1. Search strategy

The databases PubMed, Web of Science, Embase, Chinese National Knowledge Infrastructure, Wanfang, and SinoMed were systematically searched for eligible studies published up to 28 June 2018. The search string (iron OR ferric carboxymaltose OR iron sucrose OR iron dextran) AND (restless legs syndrome OR RLS) was used to scan the texts and Medical Subject Headings of indexed articles. No language or date restrictions were applied.

2.2. Study selection criteria

To be included in the meta-analysis, studies had to (1) feature an RCT, case-control or observational design analyzing the efficacy and/or tolerability of intravenous iron treatment in adults with RLS (2) in terms of iron dextran only studies using the low molecular weight iron dextran were included (high molecular weight dextran carries an unacceptable risk of anaphylaxis) (3) a diagnosis of RLS according to the criteria of the International Restless Legs Syndrome Study Group (IRLSSG) and patient data obtained through clinical interviews (4) assessment of RLS severity using the International RLS Severity Scale (IRLS) recommended by the IRLSSG (5) reporting IRLS scores before and after parenteral treatment with placebo or iron-containing compounds of any dose and regimen. If more than one study evaluated the same cohort, only the study with the most complete data was included.

Studies were excluded if they (1) were editorials, reviews, case reports, letters without original data, commentaries or critiques (2) did not report IRLS scores before and after intravenous iron treatment, or the change in IRLS score; or (3) did not involve individuals with RLS.

2.3. Data extraction

Literature was searched, and data were extracted independently by two authors (XLY and SML). Inconsistencies were resolved by discussion with the corresponding author (BL). The following data were obtained from studies: surname of the first author, year of publication, country of study cohort, diagnostic criteria of RLS, number of patients, difference between pre- and post-treatment IRLS scores in case and control groups as well as the absolute IRLS scores before and after treatment in the treatment group.

2.4. Statistical analysis

Data were meta-analyzed using Stata 12.0 (StataCorp, USA). In the case of RCTs, we calculated the ΔIRLS score as the difference between the mean baseline score and the score on the last study visit, and we compared these values between the iron and placebo groups. In the case of cohort and case-control studies, we compared pre- and post-treatment IRLS scores in terms of the odds ratio (OR) and associated 95% confidence interval (CI). Significance in all analyses was defined as $p < 0.05$.

I^2 was calculated to evaluate heterogeneity among studies: I^2 <25% was considered as absence of heterogeneity (=homogeneity); $25\% \leq I^2 < 50\%$, low heterogeneity; $50\% \leq I^2 < 75\%$, moderate heterogeneity; and $I^2 \geq 75\%$, substantial heterogeneity. A fixed-effect model was used to meta-analyze pooled data classified as homogeneous or of low heterogeneity. A random-effect model was used to meta-analyze data classified as of moderate or substantial heterogeneity. Egger's and/or Begg's tests were used to evaluate publication bias [26].

3. Results

3.1. Literature search and included studies

After searching the six databases and removing duplicates, 586 potentially eligible articles were identified (Fig. 1). After eliminating 552 articles based on the title and abstract, the remaining 36 were read in full and 21 were excluded because they were review articles ($n = 8$), correspondence ($n = 2$) or single cases or case series ($n = 3$) or because they did not provide IRLS scores or enough data to calculate such scores ($n = 5$), or based on the same cohort ($n = 1$), or because they evaluated only oral iron therapy ($n = 2$).

The remaining 15 studies were included in the meta-analysis; these comprised eight RCTs, three case-control studies and four cohort studies involving 553 individuals with RLS (Tables 1–2).

3.2. Literature evaluation

The Cochrane Handbook for Systematic Reviews was used to assess the risk of bias in seven RCTs (Table 1); ΔIRLS scores were missing for one RCT, and we could not calculate the scores from data provided by the author [25]. All the evaluations were done independently by two authors (XLY and SML); if there was a difference of opinion about the grading of the quality of evidence the corresponding author (BL) was consulted. Though all RCTs stated that they were randomized, only three described the method of randomization (eg, by computer or random number generator). Six RCTs described appropriate concealment allocation, six reported blinding of participants and four reported blinding of outcome assessors. Only one RCT reported incomplete outcome data. All trials showed non-selective reporting. Two trials showed a certain degree of other potential threats to validity. All in all, the seven RCTs were judged to have a low risk of bias (Fig. 2).

3.3. ΔIRLS score between iron and placebo groups (RCTs)

Heterogeneity was low among the seven RCTs ($I^2 = 35.1\%$, $p = 0.16$), so a fixed-effect model was used to meta-analyze the data. This analysis indicated that intravenous iron was more effective than placebo for treating RLS (OR 4.71, 95%CI 4.21–5.21, $p < 0.0001$; Fig. 3). The funnel plot was visually symmetrical, suggesting no significant publication bias (Fig. 4). A similar conclusion was suggested by Egger's test ($p = 0.176$) and Begg's test ($p = 0.542$). Sub-group analysis based on the type of intravenous iron therapy indicated that ferric carboxymaltose and iron sucrose were more effective than placebo at reducing RLS severity (Fig. 3).

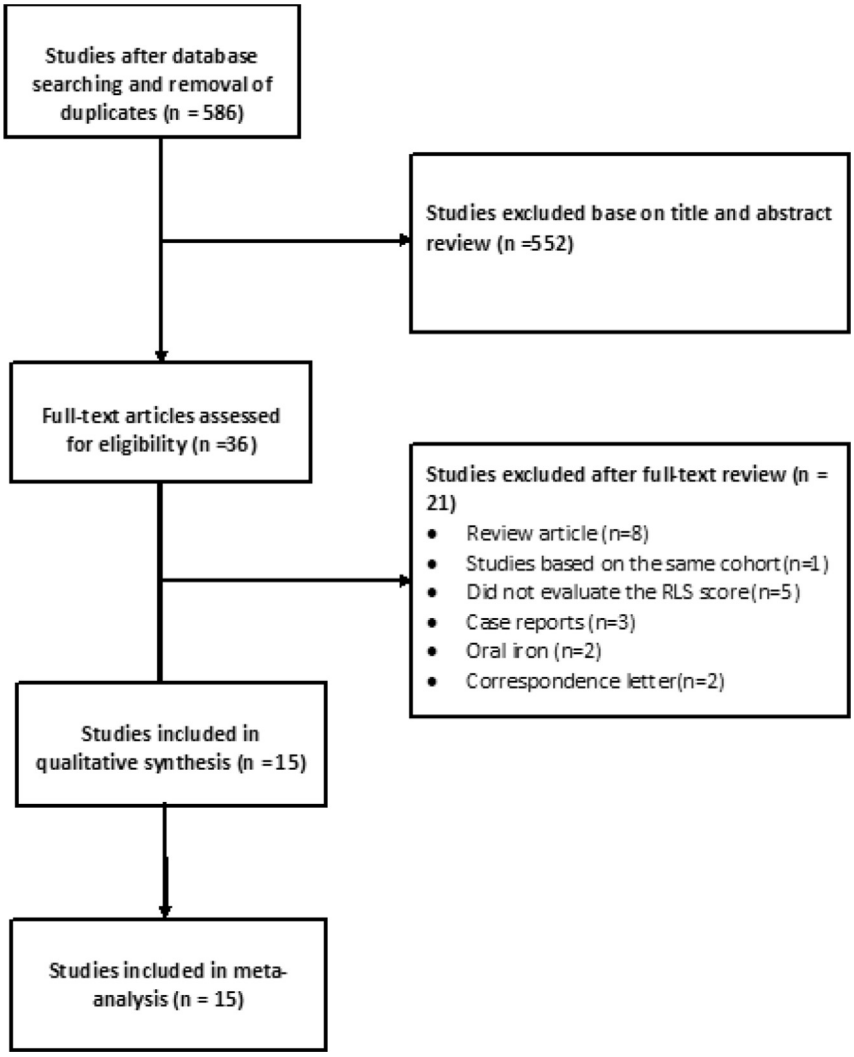

Fig. 1. Flow diagram for publication selection in the present meta-analysis.

Table 1
Characteristics of randomized controlled trials included in the meta-analysis.[a]

Study	Year	Country	Ferritin[c]	n[b]	iron type/dose	follow-up, weeks	ΔIRLSS in I	ΔIRLSS in P	AEs in I	AEs in P
Trenkwalder	2007	Germany	<300ug/L	110 (59)	FCM (1000 mg, single dose)	12	9.6 ± 1.4	5.0 ± 1.5	16.59	7.51
Grote	2009	Sweden	<45ug/L	60 (29)	Iron sucrose (200 mg × five in three weeks, total 1000 mg)	52	8.7 (9.4)	6.9 (9.7)	18.29	14.31
Earley	2009	USA	NA	18 (11)	Iron sucrose (500 mg over two consecutive days)	2	10.1 ± 5.1	12.0 ± 11.5	NA	NA
Allen	2011	USA	<300ug/L	43 (24)	FCM (500 mg on days 0 and five)	4	8.9 ± 8.5	4.0 ± 6.1	10.24	9.19
Cho	2016	South Korea	<300ug/L	64 (32)	FCM (1000 mg single dose)	6	11.9 ± 8.04	7.88 ± 5.89	NA	NA
Deng	2017	China	<200ug/L	32 (16)	Iron sucrose (100 mg, three times/week, total 1000 mg)	2	7.38 ± 2.03	0.81 ± 2.61	0.15	0.17
Cho	2018	South Korea	<300ug/L	64 (32)	FCM (500 mg single dose)	6	8.3 ± 7.5	4.8 ± 8.7	NA	NA

Abbreviations: FCM, ferric carboxymaltose; AEs, adverse events; I, iron group; P, placebo group.
ΔIRLS score, difference in mean score between baseline and last follow-up.
[a] All patients with RLS in these studies were diagnosed according to criteria of the International Restless Legs Syndrome Study Group.
[b] The first number indicates the total number of participants; the number in parentheses indicates the number of patients who underwent iron treatment.
[c] The serum ferritin value used for accepting patients.

3.4. ΔIRLS score before and after iron treatment (RCTs and non-RCTs)

Three RCTs, four cohort studies and three case-control studies reported IRLS scores before and after treatment. Heterogeneity was low across the studies ($I^2 = 49.4\%$), so a fixed-effect meta-analysis was performed. Intravenous iron treatment was associated with a significant reduction in IRLS score (OR 6.75, 95%CI 4.02–9.49, $p < 0.0001$; Fig. 5). The funnel plot was visually symmetrical (Supplemental Figure 1), and Egger's and Begg's tests were associated with $p > 0.05$, suggesting no significant risk of publication bias. Subgroup analysis based on the type of intravenous iron

Table 2
Characteristics of studies in the meta-analysis that compared RLS scores before and after intravenous iron treatment.[a]

Study	Year	Country	n	Study design	iron therapy	follow-up, weeks	IRLS score before iron therapy	IRLS score after iron therapy
James	2004	USA	11	RCT	iron dextran (1000 mg, one dose)	4	7 ± 3.39	5 ± 3.39
Wang	2007	China	12	Case-control	iron dextran (600 mg, one dose)	4	8.63 ± 2.52	5.63 ± 4.19
Grote	2009	Sweden	29	RCT	iron sucrose (200 mg *x* five in three weeks, total 1000 mg)	52	24 ± 8.25	14.6 ± 10.6
Wu	2012	China	20	Case-control	iron sucrose (100 mg/W, total 1000 mg)	10	16.29 ± 10.08	10.02 ± 8.14
Hornyak	2012	Germany	20	Cohort	FCM (500 mg, one dose)	3	30.1 ± 5.9	23.07 ± 9.5
Cho	2013	South Korea	23	Cohort	iron dextran (250 mg/W, total 1000 mg)	3	23.5 ± 6.6	16.7 ± 9.5
Schneider	2015	Switzerland	20	Cohort	FCM (500 mg)	4	23 ± 7	8 ± 5
Lieske	2015	Germany	17	Cohort	FCM (500 mg)	12	30.2 ± 4.3	23.2 ± 6.6
Xia	2016	China	23	Case-control	iron sucrose (100 mg/W, total 1200 mg)	12	21.91 ± 8.4	15.65 ± 5.92
Deng	2017	China	16	RCT	Iron sucrose (100 mg, three times/week, total 1000 mg)	2	26.06 ± 6.84	18.69 ± 5.59

ΔIRLS score, difference in mean score between baseline and last follow-up.
Abbreviations: FCM, ferric carboxymaltose; RCT, randomized controlled trial.
[a] All patients with RLS in these studies were diagnosed according to criteria of the International Restless Legs Syndrome Study Group.

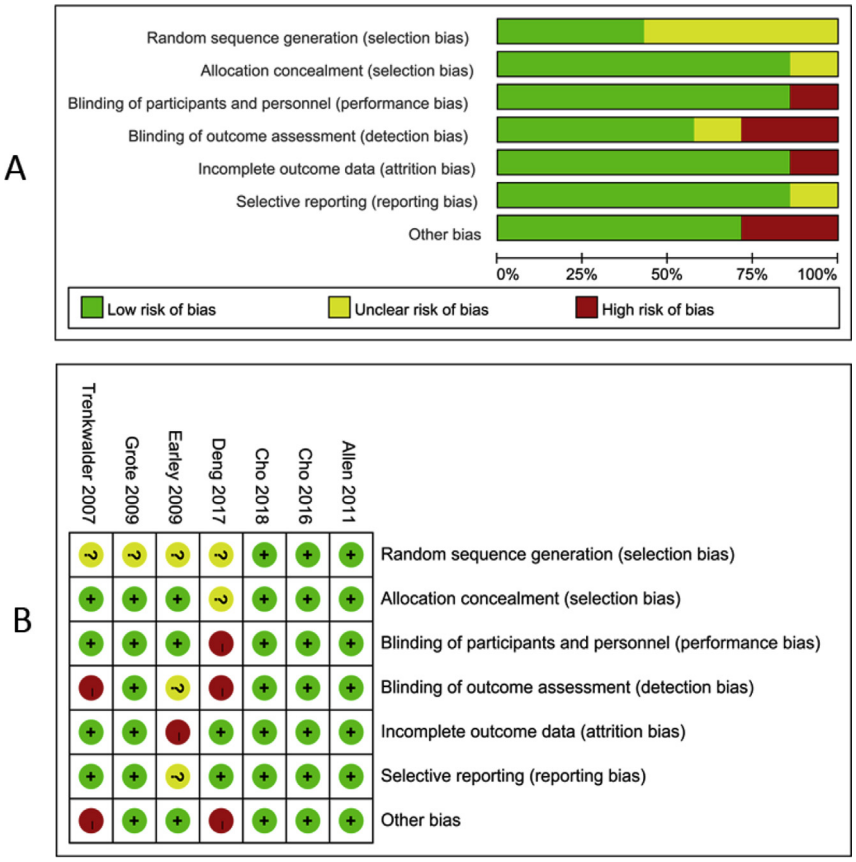

Fig. 2. A. Plot of the risk of bias. B. Summary of the risk of bias.

therapy indicated that ferric carboxymaltose, iron dextran, and iron sucrose could alleviate RLS severity (Fig. 5).

3.5. Tolerability of intravenous iron and placebo in RLS treatment

Four studies evaluated adverse effects in the intravenous iron and placebo groups. Heterogeneity was not detectable across the studies (I^2 = 0.4%; Table 2), so results were meta-analyzed using a fixed-effect model. The occurrence of adverse events did not differ significantly between the groups (OR 1.68, 95%CI 0.92–3.07, p = 0.093; Fig. 6). The funnel plot appeared symmetrical (Supplemental Figure 2), and Egger's and Begg's tests were associated with p > 0.05, suggesting no significant risk of publication bias.

4. Discussion

The present meta-analysis suggests that, based on available evidence, intravenous iron is more effective than placebo for

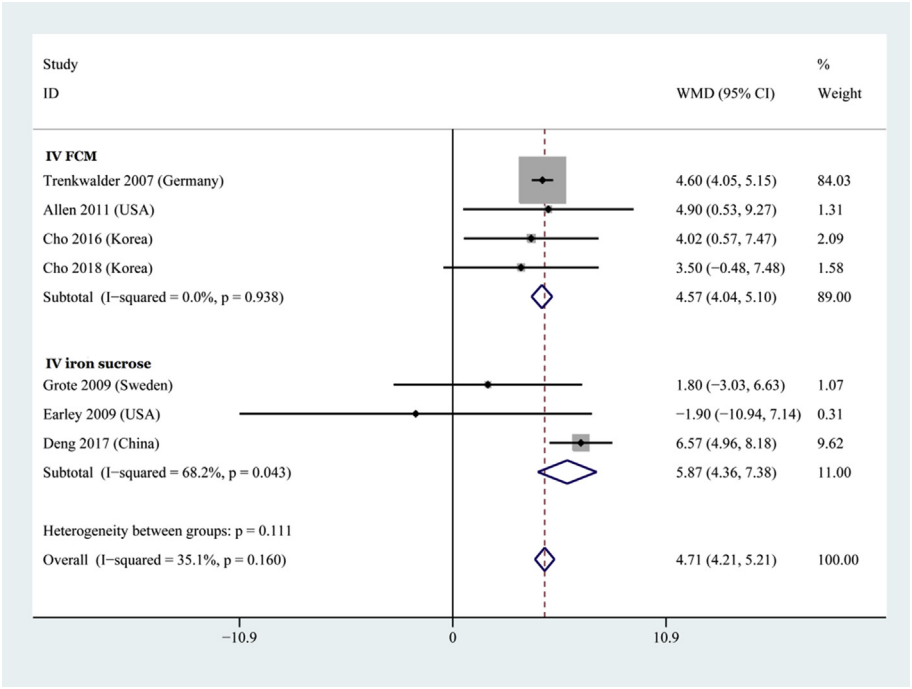

Fig. 3. Forest plot comparing the efficacy of intravenous iron or placebo to treat RLS, expressed as a weighted mean difference. The x-axis indicates the 95% confidence interval.

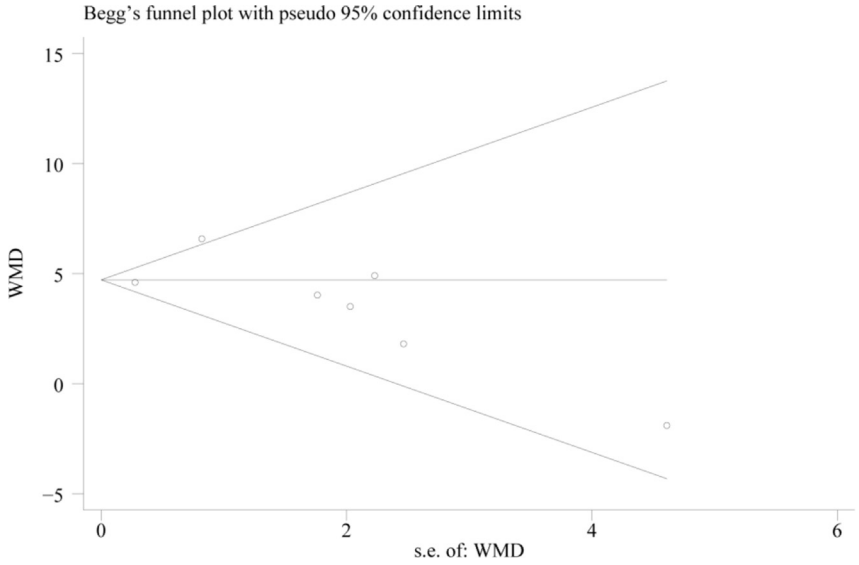

Fig. 4. Funnel plot of randomized controlled trials evaluating the efficacy of intravenous iron and placebo for treating RLS.

treating RLS and decreasing RLS severity. Intravenous iron is also well tolerated by patients.

RLS has been proposed to involve dysfunction in the substantia nigra dopaminergic pathway since RLS responds well to dopaminergic receptor agonist treatment and RLS is much more prevalent among PD patients than in the general population [4]. However, unlike PD, RLS is not associated with an obvious loss of tyrosine hydroxylase neurons in the substantia nigra nor with inclusion bodies. In contrast to PD, RLS is associated with decreased brain iron content in the substantia nigra [27] as well as in the thalamus and dentate nucleus [28]. Pathology has confirmed these results, showing lower iron content in RLS patients than in healthy controls. Cerebrospinal fluid contains dramatically lower ferritin in RLS patients than in controls [29]. The relatively low brain iron concentrations in RLS may be caused by misregulation of iron transport across the blood-brain barrier: the profile of iron management proteins in the blood-brain interface differs between RLS patients and controls [30]. Intravenous iron may be an effective way to ease this iron deficiency without overloading the brain with iron. Administration of iron isomaltoside (equivalent to 1000 mg for humans) to iron-deficient mice via the tail vein reversed the iron deficit in the substantia nigra without increasing iron levels in other brain areas that already had normal iron levels [9].

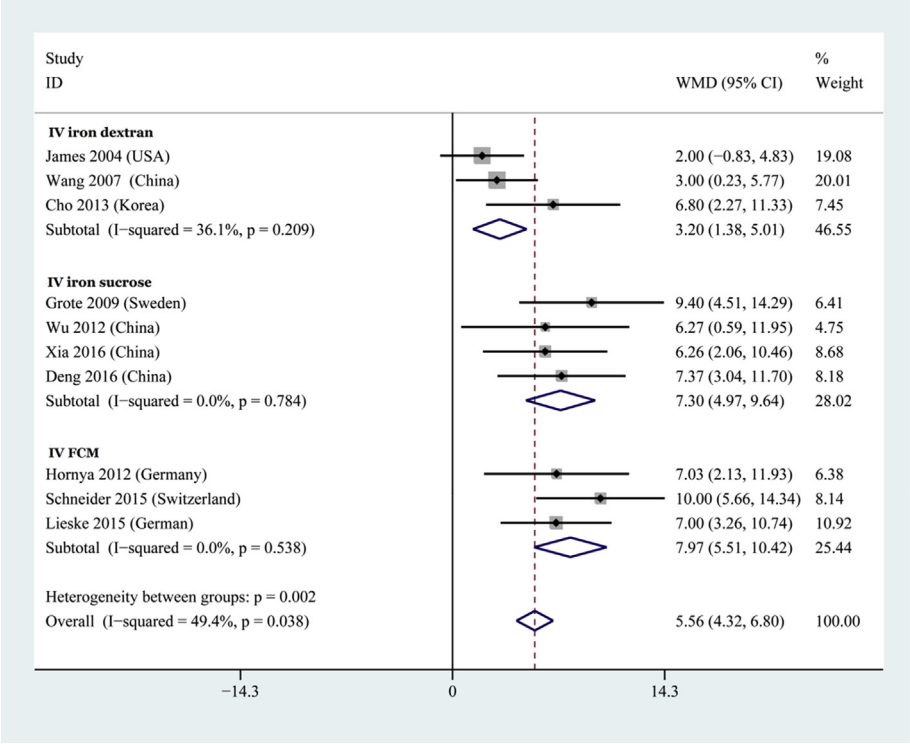

Fig. 5. Forest plot of the difference in IRLS score before and after intravenous iron therapy, expressed as weighted mean difference. The x-axis indicates the 95% confidence interval.

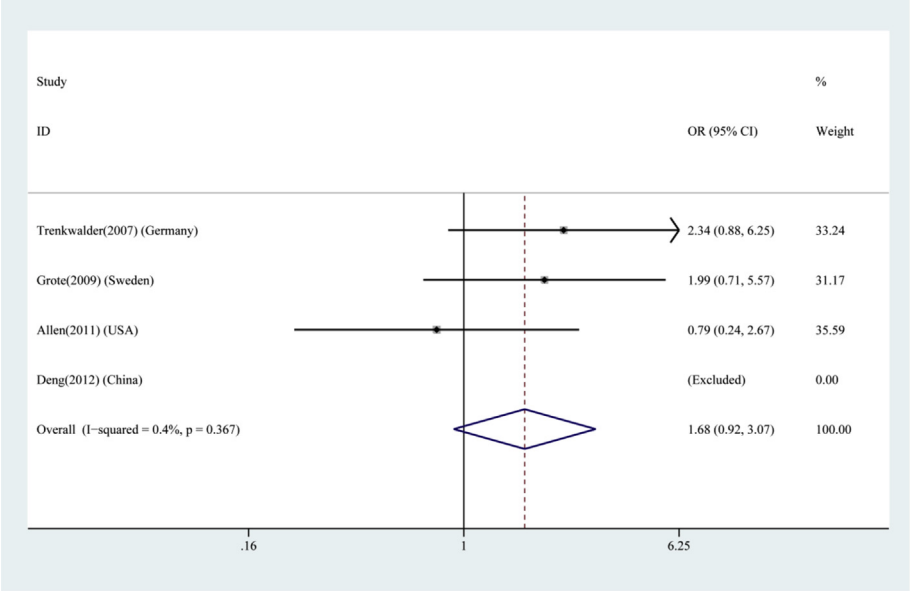

Fig. 6. Forest plot comparing the tolerability of intravenous iron and placebo, expressed as a weighted mean difference. The x-axis indicates the 95% confidence interval.

Of the seven RCTs comparing intravenous iron with placebo, four used ferric carboxymaltose and three used iron sucrose; the results were similar in both cases. Two RCTs administered ferric carboxymaltose as a single dose of 1000 mg, one as two doses totaling 1000 mg and one as a single dose of 500 mg. In the study in which ferric carboxymaltose was administered in two doses of 500 mg each at five days apart, the iron and placebo groups showed a five-point difference in total mean IRLS score at week four ($P = 0.04$). Longer-term studies are needed to assess efficacy. In the study in which ferric carboxymaltose was administered as a single dose of 1000 mg, IRLS total score had decreased more in the iron group than in the placebo group by week six. In a second RCT in which ferric carboxymaltose was administered as a single dose of 1000 mg, IRLS score did not differ significantly between the iron and placebo groups after four weeks of treatment, however, it provided a clinically meaningful difference by 12 weeks. This result may reflect early or late responder phenotypes. It is possible that the higher dose of 1000 mg, given either as a single dose or as two doses of 500 mg five days apart, may be superior to smaller doses. One

study in which ferric carboxymaltose was administered as a single 500-mg dose showed no significant difference in IRLS score between iron and placebo groups over six weeks.

Our meta-analysis suggests that iron sucrose can treat RLS effectively, although this form of iron gave disappointing results in two studies. One should note that the RCT studies on iron sucrose used a treatment regimen that involved smaller single doses (100 mg-300 mg) with multiple injections. The smaller single doses may be the reason for the inferior results. Larger studies involving a new treatment protocol should confirm the efficacy of this type of intravenous iron therapy.

Meta-analysis of differences in IRLS scores before and after intravenous iron therapy showed that it was associated with a significant decrease in IRLS score, regardless of whether the therapy was delivered as ferric carboxymaltose, iron dextran, or iron sucrose. Only one study showed similar IRLS scores before and after iron treatment. This may reflect that the baseline IRLS score was already the lowest among the 10 studies reporting IRLS score differences (Table 2). Another potential limitation is the follow-up period of only four weeks, which may not have captured a delayed response to therapy. The other studies in our meta-analysis consistently showed decreases in IRLS scores, regardless of the dose and type of iron therapy. Thus, intravenous iron may provide greater clinical benefit to patients with moderate or severe RLS.

Our study provides the most up-to-date assessment of efficacy and tolerability of intravenous iron therapy for RLS; Egger's and Begg's tests suggested no significant risk of publication bias. At the same time, our results should be interpreted with caution because of limitations in our meta-analysis. First, only 537 RLS patients were involved, and smaller studies are more likely than larger ones to report larger beneficial effects and may be subject to random error [31,32]. Second, the iron status, RLS severity, dose and type of iron therapy, and follow-up duration varied among the studies. This variation may affect our results to some extent. Our results should be verified in long-term, large RCTs. Moreover, the fact that we did not evaluate any change in the quality of life after IV iron may be a limitation of the present study.

Despite these limitations, the present meta-analysis provides evidence that intravenous iron can treat moderate or severe RLS regardless of peripheral iron (<300 ug/l). Our meta-analysis supports the IRLSSG recommendation of using a single ferric carboxymaltose dose of 1000 mg or two doses of 500 mg given 5–7 days apart [8]. Another promising choice is iron dextran at 250 mg/W for a total dose of 1000 or 600 mg as a single dose. More evidence is needed to determine whether iron sucrose (100 mg, three times/week, total 1000 mg) is effective. Furthermore, we should also notice that most of the RLS subjects involved in the present survey had normal peripheral iron with serum ferritin values > 20 ug/l. This suggests again that it was the iron deficiency in the brain but not in the periphery that was the underlying pathophysiology of RLS. The present meta-analysis highlights the need to explore further the relationship between iron and RLS.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2019.01.040.

Conflict of interest

This research was supported by Yunnan Province Medical Health Research Institute Project (2018NS0102), Yunnan Applied Basic Research Project-Union Foundation of China (201801CH00572), The First Affiliated Hospital of Kunming Medical University Doctoral Research Fund Project (2017BS005) and the National Natural Science Foundation of China (81371281, 81860247). The authors declare no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.01.040.

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