SLEEPJ, 2021, 1–6

doi: 10.1093/sleep/zsaa155
Advance Access Publication Date: 25 August 2020
Original Article

ORIGINAL ARTICLE

Comparison between oral ferrous sulfate and intravenous ferric carboxymaltose in children with restless sleep disorder

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Abstract

Study Objectives: Recent work has identified clinical and polysomnographic features of a newly defined pediatric sleep disorder, restless sleep disorder (RSD). One of these features is low serum ferritin. In this retrospective, pilot study, we assess the response to iron supplementation. Children were given oral ferrous sulfate (FS) or intravenous ferric carboxymaltose (IV FCM).

Methods: Children 5–18 years old with a diagnosis of RSD were evaluated clinically. Serum ferritin, iron profile, and video-polysomnography were obtained at baseline. Oral or IV iron supplementation was offered as part of routine care. Oral FS was one 325 mg tablet daily or 3 mg/kg/day liquid for 3 months. IV FCM was 15 mg/kg, up to 750 mg as a single infusion. Adverse effects were assessed. Ferritin and iron profile were checked after 2–3 months. Eight weeks after FCM, the phosphorus level was checked. Clinical Global Impression (CGI) scale was obtained pre- and posttreatment.

Results: A total of 15 children received oral FS and 15 IV FCM. Baseline RSD severity, age, gender, or pretreatment lab values did not differ significantly between groups. CGI-improvement median score was "minimally improved" after oral FS and "much improved" after IV FCM (effect size 1.008, $p < 0.023$). All iron parameters were found to be significantly higher after intravenous iron treatment than oral iron, especially ferritin (effect size 3.743, $p < 0.00003$). Adverse effects: constipation, three with FS; noncompliance, one with FS; syncope, one with FCM infusion; and hypophosphatemia, zero post-FCM.

Conclusions: In this retrospective, clinical case series, RSD responded to iron supplementation with improvement in both clinical and laboratory parameters. The response was greater with IV FCM than oral FS.

Statement of Significance

There is a scarcity of publications in the medical literature about treatment options for children with sleep-related movement disorders. This study is the first to identify a clinical response to iron supplementation in children with a restless sleep disorder (RSD). Improvements in both clinical and iron status outcome measures were more prominent with IV than oral iron. Adverse effects were common with oral ferrous sulfate but uncommon with IV ferric carboxymaltose. We believe this publication is an important addition to the literature on iron supplementation for children with sleep-related movement disorders and provides a basis for future randomized, controlled studies of iron for RSD.

Key words: restless sleep; restless sleep disorder; ferritin; ferric carboxymaltose; ferrous sulfate; iron supplementation; children

Submitted: 19 April, 2020; **Revised:** 20 July, 2020

Introduction

The first international classification of sleep disorders defined restlessness during sleep as "persistent or recurrent body movements, arousals, and brief awakenings (that occur) in the course of sleep" [1]. Since then, this definition has been deleted from sleep nosology and is not reported in the current International Classification of Sleep Disorders, 3rd edition [2]. Restless sleep, however, continues to be a common parental concern in pediatric sleep medicine [3] and, until recently, there was no identification of restless sleep as a separate sleep disorder.

Recently, we have characterized both clinically and polysomnographically children with restless sleep who do not fit criteria for other sleep diagnoses but demonstrate a persistent pattern of nocturnal large body movements with frequent repositioning and daytime symptoms—a condition we have called restless sleep disorder (RSD) [4]. We proposed diagnostic criteria that include: (1) a motor sleep pattern characterized by movements involving large muscle groups persisting through the night, occur almost every night, and comprise more than five movements per hour of sleep; (2) sleep latency and sleep time within expected for age; (3) the nocturnal movements result in perception by a parent of disrupted sleep or impairment in daytime function (sleepiness, poor school performance, irritability, or hyperactivity); and (4) the condition is not better explained by behavioral or medical disorders or medication effect [5]. Also, we identified that our cohort of children with RSD had ferritin levels below 50 μg/L (mean 20.8 and standard deviation 8.87) [4], which may point toward a common underlying pathway in motor/dopamine dysregulation similar to restless legs syndrome (RLS) [6].

The next logical step in the clinical management of children with RSD was to supplement with iron and assess the response. There is evidence of improvement in sleep after iron supplementation in children [7–10]. Similarly, we have previously published our work on oral iron supplementation and ferritin levels in children with sleep-related movement disorders [11]. In the current project, our aims were: (1) to assess the clinical response to iron supplementation in children with RSD and (2) to compare the response to two available forms of iron administration: oral ferrous sulfate (FS) and intravenous ferric carboxymaltose (IV FCM).

Methods

Participants

Children 5–18 years old with a diagnosis of RSD seen by a board-certified sleep physician (L.M.D.R.) at Seattle Children's Hospital Sleep Center from January 2019 until January 2020 were included in this retrospective, pilot chart review. A comprehensive database of clinical cases is maintained by this clinician for quality improvement. She uses a semi-structured clinical protocol with specific clinical outcome measures for patient management. Inclusion criteria: all children met diagnostic criteria for RSD as stated above. Exclusion criteria: younger than 5 years of age, unable to verbalize, severe intellectual disability, epilepsy, cerebral palsy, or another condition known to cause restless sleep (e.g. eczema, obstructive sleep apnea, or RLS). All children underwent video-polysomnography (vPSG) to rule out another sleep disorder and for evaluation of movements during sleep. All children and parents were counseled on non-pharmacological interventions. Potential pharmacologic therapy was discussed (gabapentin). Iron supplementation risks and benefits, including differences between oral and intravenous iron, were discussed in detail.

Polysomnography

The vPSG data were recorded using a Sandman Elite Natus system. Parameters recorded included EEG (two frontal, two central, and two occipital channels, referred to the contralateral mastoid); electrooculogram, electromyogram (EMG) of the submentalis muscle, EMG of the right and left tibialis anterior muscles, respiratory signals, effort signals for thorax and abdomen, oximetry, capnography, a single-lead electrocardiogram, and video and audio recording. Calibrations were performed per routine standard by a technician. Epochs were scored by a certified sleep technologist and board-certified sleep physician according to standard criteria [12]. All sleep parameters were scored using standard criteria [13]. In addition, movements were recorded and counted, based on video observation; they had to be clearly visible and only movements lasting for at least 1 s were included, as described previously [14].

Iron supplementation

The families chose which treatment modality they preferred during the clinical visit as part of routine clinical care. Some chose oral iron due to concerns about the potential adverse effects of IV iron. Some chose IV iron due to prior negative experience with oral iron, concern about potential adverse effects of oral iron, or convenience of a single treatment. None chose gabapentin.

The primary outcome measure were as the Clinical Global Impression-Improvement (CGI-I) scale score [15] and change in serum ferritin. RSD symptom severity at baseline was assessed by the Clinical Global Impression-Severity (CGI-S) scale [15]. At follow-up, improvement was assessed by the CGI-I, which was completed before availability of the follow-up lab test results. Serum ferritin, serum iron, total iron binding capacity (TIBC), and transferrin were obtained in all children at baseline and follow-up. Children taking oral iron supplementation were given FS one 325 mg tablet daily or FS liquid 3 mg/kg/day if they could not swallow a tablet. Treatment lasted for 3 months. Children given IV FCM received 15mg/kg, up to 750 mg as a single dose per the pediatric clinical infusion center protocol at Seattle Children's Hospital. Great care was taken to avoid extravasation of IV iron. Children were observed for 30 min post-infusion and discharged home. A follow-up visit was scheduled 8 weeks later for RSD symptom assessment and follow-up bloodwork, which in this group included serum phosphorous to check for IV iron-induced hypophosphatemia.

This study was approved by the institutional review board at Seattle Children's Hospital. As a retrospective chart review, no informed consent was needed.

Statistical analysis

Because of the non-normal distribution of data, nonparametric statistics were used, with the Mann–Whitney test for the

comparison between the data obtained from the two groups of patients, the Yates-corrected chi-square test for the comparison of frequencies, and the Wilcoxon signed-rank test for paired datasets.

Results

Demographics

A total of 32 children were diagnosed with RSD during the study period. Two families declined treatment. A total of 15 children received oral FS and 15 received IV FCM. Table 1 shows the comparison between age, CGI-Severity score, iron status, and vPSG parameters found at baseline in the two treatment groups, before the administration of iron, either orally or intravenously. Girls were seven in the group receiving oral FS and six in that receiving IV FCM (chi-square = 0.14, $p = 0.713$). None of the comparisons was significantly different, including baseline RSD severity (CGI-S), baseline ferritin, age, gender, and total movement index (vPSG). Of note, the baseline CGI-S score of 5 indicates "markedly ill–intrusive symptoms" [15]. The median age difference of 2 years does not appear to cross a major boundary of ability to report symptoms, given the interquartile range of 8–15 vs. 9–15 years.

Laboratory values

Serum ferritin increased significantly from baseline with both oral and IV iron, from 16.0 (13–23 µg/L) to 34.0 (25–44 µg/L), Wilcoxon test Z = 2.845, p < 0.0045 with oral FS and from 16.0 (13–20 µg/L) to 124.0 (90–143 µg/L), Wilcoxon test Z = 3.296, $p < 0.001$ with IV FCM (Table 2). However, all iron measures were found to be significantly higher after IV than oral iron. The difference in serum ferritin level is depicted further in Figure 1.

Clinical symptoms

These differences were paralleled by a more pronounced clinical improvement in the IV iron group, reflected by a CGI-Improvement median score of 2 ("much improved") compared with a median score of 3 ("minimally improved") in the oral iron group (Table 2). Six patients in the oral iron group scored 1 or 2 at CGI-Improvement (three and three, respectively), while another 3 scored 3 and 6 scored 4 (nine in total); on the contrary, 13 scored 1 or 2 at CGI-Improvement in the IV iron group (seven and six, respectively), 1 scored 3 and another scored 4 (chi-square 5.17, $p < 0.023$). Improvements reported included more restful sleep and fewer nocturnal awakenings, as well as better mood, energy, and attention.

Adverse effects

Adverse effects in the oral FS group were constipation (3) and noncompliance (1). All four of these children stopped treatment before 3 months and, as expected, no changes in symptoms were reported at the follow-up visit. Of the 11 children who completed oral iron, at least some improvement in symptoms of restless sleep was reported for all.

In the IV FCM cohort, one child experienced syncope during the infusion. This child had a history of syncope during blood draws. No other adverse effects were reported. None had hypophosphatemia at 8 weeks post-infusion. For all but one child, improvement in restless sleep symptoms was reported. Families chose IV iron due to inability to take an oral iron preparation (3), expected noncompliance (the families or patients felt they could not administer or take the oral iron dose on a consistent basis) (7), or a bad experience with oral iron in the past (5).

Statistical analysis

A post hoc power analysis was run on the values obtained for CGI-I. Given the sample size of 15 per group, our study had

Table 1. Comparison between the two treatment groups at baseline

	Oral iron		Intravenous iron		Mann–Whitney	
	Median	Interquartile range	Median	Interquartile range	*U*	*P*<
Age, years	11.0	8–15	13.0	9–15	95.5	0.494
CGI-Severity	5.0	4–6	5.0	5–6	91.5	–0.850
Ferritin, µg/L	16.0	13–23	16.0	13–20	104.0	0.740
Iron, µg/dL	85.0	59–91	86.5	59–104	61.0	0.619
TIBC, µg/dL	355.5	334–381	356.5	335–414	60.0	0.578
Transferrin, mg/dL	23.5	22–25	24.5	17–31	59.5	0.558
Total sleep time, min	453.3	426–469	433.0	420–458	100.5	0.861
Sleep efficiency, %	87.6	79.8–90.6	86.8	79.8–94	102.5	0.930
Sleep latency, min	22.9	13.5–41.5	28.9	8.7–41.2	104.0	0.983
Stage N1, %	9.1	6.2–12.4	9.0	5.5–12.6	101.5	0.896
Stage N2, %	43.6	39.7–49.4	44.9	37.9–52.8	104.0	0.983
Stage N3, %	26.5	22.4–32	22.4	19.8–31	91.0	0.556
Stage R, %	18.4	11.8–21.2	18.0	13–22	100.5	0.861
Arousal index, *n*/h	9.9	7.4–12.9	8.0	7–11.6	81.5	0.315
oAHI, *n*/h	1.1	0.5–1.3	1.0	0.5–1.5	93.5	0.631
PLMI, *n*/h	0.7	0–2.4	0.0	0–1	74.5	0.190
Total movement index, *n*/h	7.0	6–7	6.0	6–7	91.5	0.104
O_2 saturation nadir, %	92.8	91–93.9	92.0	91–94	98.5	0.793

CGI, Clinical Global Impression scale; TIBC, total iron binding capacity; oAHI, obstructive apnea/hypopnea index; PLMI, periodic limb movement index. CGI-Severity of 5 = "markedly ill".

Table 2. Comparison of outcome variables between the two treatment groups after iron supplementation

	Oral iron		Intravenous iron		Mann–Whitney	
	Median	Interquartile range	Median	Interquartile range	U	P<
CGI-Improvement	3.0	2–4	2.0	1–2	57.0	0.023
Ferritin, µg/L	34.0	25–44	124.0	90–143	0.0	0.00003
Iron, µg/dL	77.0	61–89	103.0	87–121	24.5	0.0084
TIBC, µg/dL	333.0	312–359	298.0	284–302	30.0	0.02
Transferrin, mg/dL	22.5	17–25	31.0	28–36	20.5	0.004

CGI, Clinical Global Impression Scale (3 = minimally improved; 2 = much improved); TIBC, total iron binding capacity.

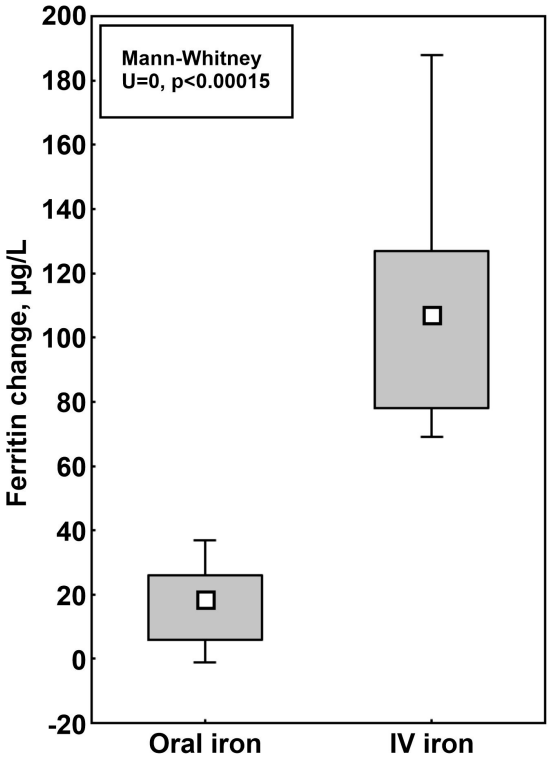

Figure 1. Comparison between the change in ferritin level observed in the two treatment groups, oral group (ferrous sulfate) and IV group (ferric carboxymaltose). The white-filled small squares show the median values, the grey-filled boxes indicate the interquartile range, and the whiskers represent the range of data.

70% power to detect the mean difference of 1.1 (SD = 1.17) observed for CGI-I, at an alpha-level of 5%. The detectable standardized effect size (Cohen's d) at >80% power and an alpha-level of 0.05 for our sample of n = 15 per group was 1.06; indeed, we observed an effect size of 1.008 for CGI-I, yielding a power of 76%, indicating a slightly underpowered analysis. On the contrary, we observed a very high effect size of 3.743 for ferritin change, corresponding to a power of ~100%.

Discussion

Our study is the first study reporting improvement of RSD in children with the use of oral and IV iron supplementation. We also compared the response of oral FS to IV FCM, finding an expected greater effect on iron status with IV iron, but also a greater clinical response. The current study also provides further evidence that children with RSD typically have ferritin levels lower than 50 µg/L [4]. Although this was not a randomized trial, baseline characteristics were very similar between the two groups, including serum ferritin, CGI-Severity, and vPSG results. Both groups had median baseline scores indicating severe RSD. Assessment of clinical and serum ferritin outcomes were at slightly different times, 3 months for oral iron and 6 weeks for IV iron, typical times for each therapy. While the time of assessment could have influenced clinical outcomes disparately, it more likely that the higher serum ferritin achieved with IV iron can account for the better clinical response.

Correcting iron deficiency in children can be challenging. As indicated by the current results, our previous work, and the extensive literature on iron deficiency in children [11, 16, 17], oral iron supplementation in children can have significant adverse effects that may hinder compliance. Constipation and gastrointestinal upset are common adverse effects of oral iron, and teeth staining can occur with liquid preparations [18]. In our group, constipation was the most common adverse effect. Oral iron requires daily adherence for at least 3 months as ferritin levels increase slowly [11]. This can be another limiting factor for children or teenagers who take the medication by themselves. In addition, accidental ingestion of a large dose of oral iron at once by a patient or sibling can be fatal. These factors can be bypassed by a single iron infusion, as demonstrated by the tolerability and low adverse effect profile in our intravenous cohort.

There are currently no published recommendations for the treatment of RSD in children. Most studies on iron supplementation for sleep disorders are in children and adults with RLS [19]. International RLS Study Group (IRLSSG) guidelines recommend iron supplementation as a first-line treatment for adult RLS. High-level evidence supports the use of IV FCM for RLS in adults [19]. A dose-dependent improvement has been proposed by Cho et al.[20], after adults with RLS responded to doses of 1,000 mg but not 500 mg. Allen et al.[21] showed that improvement in symptoms lasted up to 24 weeks in patients receiving IV FCM.

While a recent IRLSSG consensus statement found limited evidence for oral or IV iron in children with RLS, expert consensus favored the use of iron supplementation when serum ferritin is <50 µg/L [19]. Many clinicians use iron as first-line therapy for pediatric RLS and PLMD [22] and, in our clinical experience, it has been successful for the treatment of RSD. Several studies have shown symptom improvement in children with RLS and PLMD after oral iron supplementation [16, 23–25]. Studies on oral iron supplementation have shown that 78% of children with RLS and 62.8% in children with PLMS respond to oral iron [16, 23]. IV iron has also been studied in children with RLS and PLMD, who have poor tolerability to oral iron supplementation. Grim

et al.[26] used iron sucrose in 16 children with a baseline mean serum ferritin of 16.4 ± 6.6 µg/L and post-infusion levels of 45.7 ± 22.4 µg/L. The authors reported that sleep improved in 62.5% of subjects. IV FCM has been used successfully in children with iron deficiency anemia [27, 28]. However, we know of no studies directly comparing the response to iron in children with RLS vs. RSD nor any with a methodology similar to ours by which we could effectively compare response rates.

Treatment with IV compared with oral iron therapy in patients with iron deficiency has shown that IV iron is superior to oral iron in replenishing iron stores and raising hemoglobin levels [29]. Hepcidin-mediated regulation of iron absorption at the intestinal level severely limits the effect of oral iron, especially when iron stores are not low enough to cause anemia. Nonetheless, we documented significant serum ferritin and clinical responses to oral iron in RSD, albeit not as robust as with IV iron.

Potential adverse effects of IV FCM include extravasation, skin discoloration, changes in blood pressure, and more recently reported hypophosphatemia [30]. We believe the success and minimal adverse effects of IV FCM in our study can be attributed, in part, to the use of a carefully implemented protocol at a pediatric infusion center.

Nonetheless, there is a gap in the pediatric literature about the treatment of sleep-related movement disorders in children. The pathophysiologic explanation of the relationship between RLS, and potentially RSD, with low ferritin levels includes data from neuroimaging studies, which show decreased brain iron in adults with RLS [31–33]. More recently, transcranial ultrasound performed an average of 160 days after IV iron has shown increased brainstem iron stores in adults [34]. However, similar studies are lacking in children.

Limitations to our study include single-center experience, open-label design, no control group, and small, non-randomized cohorts. Our sample size was too small for a dose–response analysis, as is typical in pilot studies. This can be an important focus in future randomized clinical trials (RCTs). RCTs can minimize other limitations such as selection bias, prior treatment with oral iron, and placebo effect. Strengths include a consistent clinical treatment protocol with specific outcome measures, access to a pediatric infusion center, follow-up by a dedicated single sleep specialist, and demonstrated the feasibility of IV iron in this pediatric patient population. The baseline characteristics of the comparison groups were remarkably similar, including RSD severity and serum ferritin levels.

We conclude that in this pediatric case series RSD responded to both oral and IV iron supplementation with improvement in clinical symptoms and objective improvement in laboratory parameters. For IV iron, the effects were greater and adverse effects were fewer. Further areas of research include randomized, controlled trials to assess the effectiveness of iron supplementation in pediatric RSD, and the cost-effectiveness of oral vs. intravenous iron treatment for RSD.

Acknowledgments

The authors want to acknowledge Dr. Richard Allen, Dr. Amanda Blair, and Dr. Maida Chen for their support and advice. We also want to thank the staff from Seattle Children's Hospital infusion center.

Disclosure Statement

The authors have no financial or non-financial disclosures. This was not an industry-supported study.
Financial disclosure: none.
Non-financial disclosure: none.

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