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Clinical efficacy and safety of intravenous ferric carboxymaltose treatment of pediatric restless legs syndrome and periodic limb movement disorder

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Abstract

Background: Iron supplementation is the most commonly considered treatment option for children with restless legs syndrome (RLS) or periodic limb movement disorder (PLMD); however, there is a scarcity of evidence on the effectiveness of intravenous preparations. In this study, we evaluated the effectiveness and tolerability of intravenous ferric carboxymaltose (IV FCM) on clinical symptoms and iron indices in children with RLS or PLMD.

Methods: This was a single-center retrospective data analysis. Children with a diagnosis of RLS or PLMD, who underwent a single infusion of IV FCM, were included. Clinical Global Impression (CGI) Scale scores, serum ferritin, and serum iron profile at baseline and after eight weeks post infusion were obtained. Adverse effects were assessed.

Results: Thirty-nine children received IV FCM, 29 with RLS and 10 with PLMD. Pre-infusion CGI-Severity revealed moderate illness, with post-infusion CGI-Improvement between "very much improved" and "much improved". Ferritin increased from 14.6 µg/L±7.01 to 112.4 µg/L±65.86 ($p<0.00001$), together with improvements in iron, total iron binding capacity, and transferrin levels from baseline to post-treatment. When compared to children with RLS, those with PLMD had a similar improvement in clinical symptoms and laboratory parameters. Seven subjects (14.3%) experienced one or two adverse events; all were mild.

Conclusions: Children with RLS and PLMD responded to IV iron supplementation with improvement in both clinical severity and laboratory parameters. Treatment was well tolerated. Although larger, randomized-controlled trials are needed, IV FCM appears to be a promising alternative to oral iron supplementation for the treatment of pediatric RLS or PLMD.

Key words: restless legs syndrome; periodic limb movement disorder; ferritin; ferric carboxymaltose; iron supplementation; children

1. Introduction

Restless legs syndrome (RLS) is a common pediatric sleep disorder that affects 2–4% of children [1]. The diagnostic criteria for pediatric RLS [2] include the urge to move the legs, with or without accompanying leg sensations, commonly occurring in the evening, during periods of rest, and relieved by movement or activity. In children, RLS negatively affects sleep onset, sleep continuity, mood, daytime symptoms, and overall health [3]. It is important to consider taking the description of the symptoms in the child's own words [2] and differentiating RLS from mimics [4], including sprains, growing pains, and leg cramps, among others [5].

Unlike RLS, which is a clinical diagnosis, periodic limb movement disorder (PLMD) requires evidence of an elevated periodic limb movements during sleep (PLMS) index of ≥5/hour during polysomnography (PSG) [6, 7]. The diagnosis of PLMD requires the presence of either sleep disruption or daytime impairment, which cannot be attributable to other medical or sleep disorders [6]. Typically, PLMS are characterized by extension of the big toe, flexion of the ankle, and sometimes flexion of the knee and hip. During PSG, PLMS are characterized by activation of the tibialis anterior muscle unilaterally or bilaterally, sometimes associated with an arousal or an awakening [8]. Although, PLMD is considered rare, PLMS are seen in about 60-70% of children with RLS [9]. A common pathophysiology of decreased iron stores in the brain has been postulated in RLS and PLMD, based on neuroimaging studies demonstrating decreased brain iron stores in adults with RLS [10-12].

There is evidence in the medical literature that points towards clinical improvement after iron supplementation in children with RLS or PLMD [13-18]. In addition, children with restless sleep disorder have shown a positive response to both oral and IV iron supplementation [19]. Also, iron may have a beneficial effect for sleep in other conditions [20-23]. However, oral iron supplementation is not always successful or possible. Children with malabsorption syndromes, significant side effects to oral iron, or non-compliance may be good candidates for IV iron.

The aims of this new study were: 1) to assess the clinical and laboratory response to IV iron supplementation in children with RLS and PLMD and 2) to compare the response between these groups.

2. Methods

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

2.1. Participants and IV iron dose

Children diagnosed with RLS or PLMD by a sleep clinician at Seattle Children's Hospital, who were referred for IV iron infusion for treatment of RLS or PLMD from June 2019 until December 2020, were identified via a clinical database for this retrospective chart review. The diagnosis of RLS or PLMD was confirmed by two different sleep clinicians (the referring clinician and author LDR). Children either failed oral iron or had significant side effects and did not tolerate oral iron. Failure to respond to oral iron was defined as an increase in ferritin level of less than 4 μg/dL after a minimum of 3 months of oral supplementation and persistence of RLS or PLMD symptoms. At Seattle Children's Hospital, there is a dedicated IV iron clinic, in which a single sleep physician evaluates children before and after infusion. A detailed symptom interview is performed and risks, benefits, and alternatives are discussed. Inclusion criteria: RLS or PLMD as per the International Classification of Sleep Disorders diagnostic criteria [6]; recent video-polysomnography (vPSG) to rule out another sleep movement disorder; and completion of a single IV infusion of ferrous carboxymaltose (FCM) at an ambulatory infusion center with baseline and post-infusion bloodwork. Exclusion criteria: children unable to verbalize, severe intellectual disability or cerebral palsy. IV FCM dosage was 15 mg/kg up to a maximum dose of 750 mg. Patients were observed for 30 minutes post infusion.

2.2. Outcome metrics

Per clinical practice, a structured protocol for this clinic was employed and included standardized subjective and objective measures. For all children, the Clinical Global Impression - Severity (CGI-S) scale was used at baseline evaluation, before the iron infusion. CGI-S is 7-point scale with which the clinician rates the severity of the patient's disease at the time of observation. The rating is done with reference to the same clinician's past experience with patients affected by the same condition and ranges from 1 ("Normal, not at all ill"), to 7 ("Among the most extremely ill patients"). At the 8-week follow-up visit, improvement was assessed by clinical interview and the primary outcome measure was the Clinical Global Impression-Improvement (CGI-I) scale score. CGI-I is a 7-point scale allowing the clinician to assess the degree of improvement or worsening of the patient's illness, after iron infusion, relative to baseline, ranging from 1 ("Very much improved") to 7 ("Very much worse") [24].

Secondary outcome metrics were the changes in serum iron indices: serum ferritin, serum iron, total iron binding capacity (TIBC), and transferrin. These were obtained in all children at baseline and at 8-week follow up. In addition, serum phosphorous, to check for IV iron-induced hypophosphatemia, was part of the post-infusion evaluation. Adverse events were recorded.

2.3. Statistical analysis

The Student's t-test for independent or dependent datasets was used, for between-groups or within-group comparisons of continuous variables, respectively, followed by the Bonferroni correction for multiple comparisons. When not otherwise specified, the p-values reported in the manuscript remained significant after the Bonferroni correction. The Fisher's exact test was used for the comparison of frequencies.

3. Results

3.1. Demographics

For this study, 39 children with RLS or PLMD met inclusion criteria; 29 of them were affected by RLS while 10 were diagnosed with PLMD. These two subgroups were not different for age (table 1) but their sex composition was significantly different (Fisher exact $p = 0.0031$); in the PLMD group, all participants (10) were boys while in the RLS group there were 14 boys and 15 girls. Sixteen out of 39 children (41%) did not tolerate oral iron due to constipation after a previous attempt of treatment with oral ferrous sulfate, one reported emesis and, another, teeth staining. Twenty-three of 39 did not have improvement of ferritin levels of at least 4 μg/dL after a minimum of three months on oral iron. None of the children had a known malabsorption syndrome.

3.2. Outcome metrics

3.2.1. Clinical symptom severity

CGI-S and CGI-I were scored by a single physician (LDR) based on clinical symptoms. For RLS patients, the frequency and severity of RLS, impact of RLS symptoms on sleep, and impact of RLS symptoms on daytime activities, were assessed; these were based on pediatric RLS symptoms that have been described in the medical literature [1, 25]. For PLMD patients, the frequency and severity of sleep disturbance and related daytime symptoms were assessed.

At baseline, the mean CGI-S was 3.8 (a score of 4 corresponds to "moderately ill"). After treatment, the mean CGI-Improvement score was 1.3 (a score of 1 corresponds to "very much

improved", while a score of 2 corresponds to "much improved"). In particular, CGI-I score was 1 ("very much improved") in 30 children, 2 ("much improved") in 8 children, and 4 ("no change") in only 1 child (figure 1). Subjective comments by children and their parents included: child sleeping through the night, headaches resolved, daytime sleepiness resolved, no nocturnal awakenings, and increased energy during the day.

3.2.2. Iron indices

Table 2 shows the comparison between the laboratory results, obtained at baseline and after treatment with IV FCM, in the whole group of children with RLS or PLMD. Baseline ferritin levels were 14.6 μg/L (S.D. 7.1). All laboratory parameters were significantly different after IV FCM, with an increase in ferritin (to an average of 112.4 μg/L and S.D. 65.86), iron, and transferrin, while TIBC was decreased (table 2 and figure 2). After treatment, mean phosphorous was 4.8 mg/dL (normal 4.5-6.5 mg/dL) and none of the children had hypophosphatemia.

3.2.3. RLS vs. PLMD

RLS children differed from those with PLMD only for their slightly higher CGI-severity score at baseline (table 3). None of the remaining laboratory and clinical scale results were different between these two groups both at baseline or after treatment with IV FCM. In particular, the changes observed from baseline to follow-up in CGI-I and serum iron indices were not significantly different between RLS and PLMD children (table 3).

3.3. Adverse events

Mild extravasation during the infusion occurred in one child without skin staining, two experienced gastrointestinal discomfort, three reported feeling lightheaded, and another reported not feeling well, not better specified. Fever, headache, and blood pressure increase were reported in one child each. Overall, because a different combination of two of the above adverse events occurred in three children, 7 out of the original 39 participants (17.9%) reported one or two adverse events.

4. Discussion

Our study showed significant improvement in clinical symptom severity from "moderately ill' to "very much improved" using CGI and in serum iron parameters after a single dose of IV FCM in children with RLS and PLMD. We demonstrated a robust response in ferritin levels from a group

average of 14.6 µg/L (S.D. 7.01) to 112.4 µg/L (S.D. 65.86). Although the medical literature on treatment of pediatric RLS and PLMD is sparse, there are published data demonstrating improvement in symptoms of RLS and PLMD after iron supplementation [13-17]. Approximately 78% of children with RLS and 63% in children with PLMD have improved symptoms after oral iron supplementation [13, 16], correlating with the improvement in the laboratory levels of ferritin and iron profile [15]. Furudate et al. [26] showed that 50% of children with RLS responded to oral iron supplementation with remission of symptoms. These results match our previous work on oral iron supplementation for children with sleep-related movement disorders, in which we demonstrated that ferritin levels improved in about 50% of children taking oral iron supplementation [27]. The limited improvement in ferritin level with oral iron was correlated with poor adherence secondary to side effects and difficulty swallowing pills. Iron can cause significant constipation and teeth staining [28]. The benefits of IV iron supplementation include bypassing gastrointestinal absorption and, therefore, the majority of the side effects associated with it.

In addition to these adverse effects, there are other limitations associated with oral iron supplementation. For instance, serum values indicative of peripheral iron stores are relatively easy to assess; however, they do not adequately indicate brain iron stores. In RLS and possibly PLMD, the symptomology is probably driven by brain iron deficiency, but animal studies have shown poor correlation between serum iron measures and brain iron stores [29]. Iron homeostasis seems to be primarily regulated by iron levels in the blood or liver, resulting in a feedback of hepcidin, which decreases gastrointestinal iron uptake [30]. This results in an overall decreased amount of iron available to be recycled to other organs including the brain; it is estimated that only 0.5% to 1.5% of iron taken orally is transported to other organs including the brain [31]. The exact mechanism of brain iron homeostasis is still not clear; however, the upregulation of hepcidin in the process of iron homeostasis suppresses further iron absorption from the GI tract [31]. IV iron infusion bypasses hepcidin and theoretically allows a higher proportion of iron to be delivered to the brain [32].

Intravenous iron supplementation for RLS in adults has been studied using various preparations, including FCM, low molecular weight iron dextran, iron gluconate, iron sucrose, ferumoxytol, and iron isomaltoside [31]. The highest level of evidence is for FCM. There is a single study of IV iron in 16 children with RLS, using iron sucrose, which demonstrated improvement in symptoms in 62.5% of children [14]. In this study, children had a mean baseline serum ferritin of 16.4±6.6 µg/L, with levels increasing post-infusion to values of 45.7±22.4 µg/L. IV FCM has been used successfully in children with iron deficiency anemia [33, 34], and children with restless sleep disorder [19]. There are no previous studies directly comparing response to intravenous iron in children with RLS vs. PLMD.

Known adverse effects with IV FCM include skin discoloration in the event of extravasation, changes in blood pressure, and hypophosphatemia [35]. Overall, IV FCM was well tolerated in our study and none of the children developed hypophosphatemia.

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. 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 feasibility of IV iron in this pediatric patient population.

Because there are no validated, disorder-specific assessment tools available for pediatric RLS or PLMD, we chose CGI as the way to quantify clinical response. CGI is a well-established rating tool for research in adults and children [20]. It was developed over 30 years ago for research sponsored by the United States National Institutes for Mental Health and correlates well with standard, known treatment efficacy scales [20].

We conclude that in this open-label clinical case series, children with RLS and PLMD responded well to IV FCM supplementation with improvement in clinical sleep and daytime symptoms and objective improvement in iron laboratory parameters. Further areas of research should include randomized, controlled trials to assess the effectiveness of iron supplementation in pediatric RLS and PLMD, analysis of the benefit of iron over time, assessment of whether response varies by age or level of development, and determination of specific benefits on daytime functioning.

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CRediT authorship contribution statement

Lourdes M. DelRosso: Supervision, Conceptualization, Data curation, Project administration, Writing - original draft. Raffaele Ferri: Visualization, Conceptualization, Methodology, Data curation, Resources, Writing - original draft. Maida L. Chen: Writing - review & editing. Vidhi Kapoor: data curation. Richard P. Allen: conceptualization, methodology. Maria Paola Mogavero: Writing - review & editing. Daniel L. Picchietti methodology, visualization, conceptualization, manuscript writing and editing.

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Conflict of interest

The authors have no competing interests to declare.

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Fig 1. Individual values of the baseline Clinical Global Impressions-Severity (CGI-S) scale and the treatment CGI-Improvement (CGI-I) scale in 39 patients given intravenous ferric carboxymaltose.

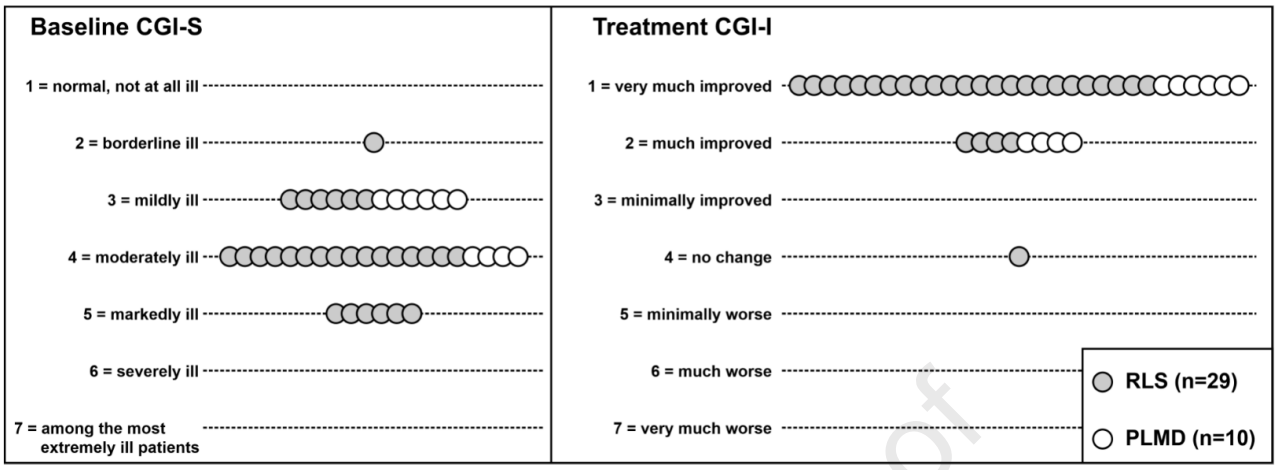

Fig 2. Comparison between the main laboratory results obtained at baseline and after treatment with IV FCM in the whole group (top panel), in children with RLS (middle panel) or PLMD (bottom panel). Data are shown as mean value (columns) and standard error (whiskers).

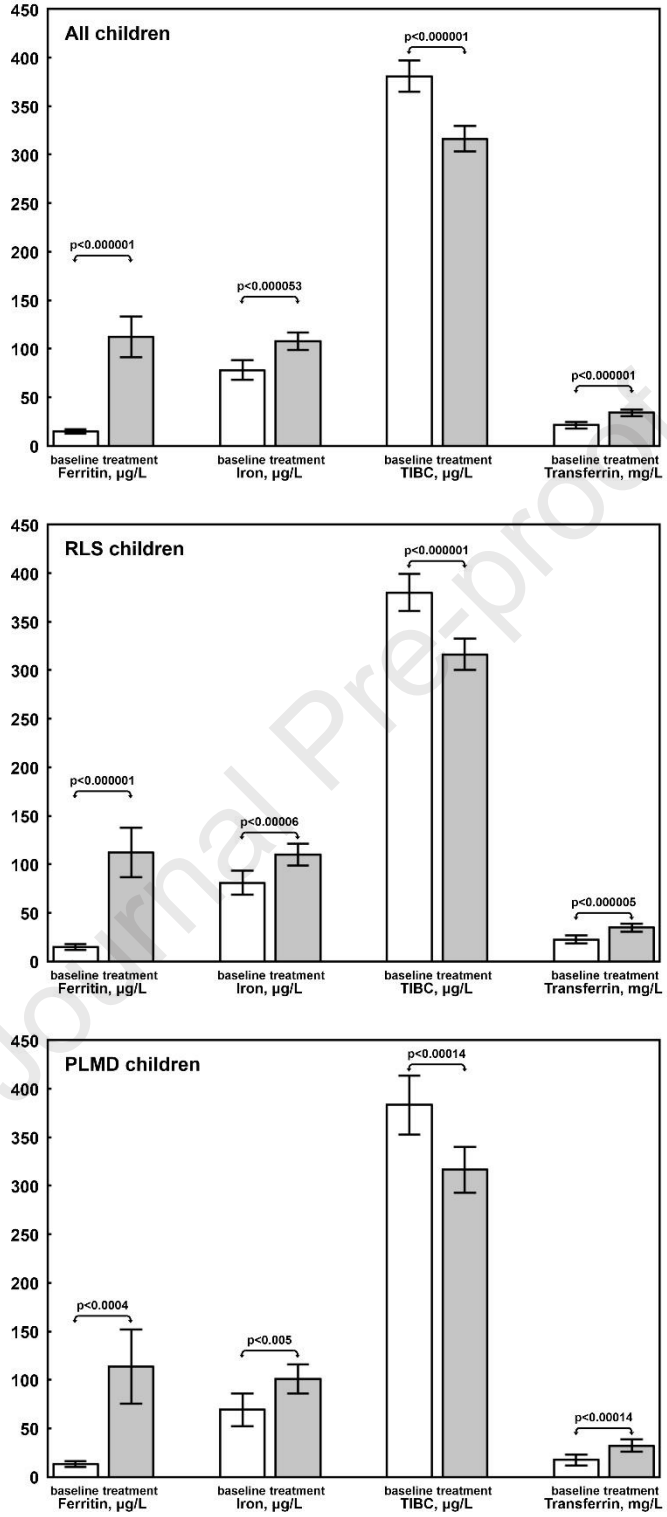

Table 1. Demographics of the whole group of participants and of the RLS and PLMD subgroups.

	All children age, years				RLS age, years				PLMD age, years				RLS vs. PLMD
	n	**mean**	**S.D.**	**range**	**n**	**mean**	**S.D.**	**range**	**n**	**mean**	**S.D.**	**range**	**Student's t test**
total	39	9.6	4.48	2.3-17	29	10.1	4.00	2.3-17	10	8.3	5.66	2.3-17	1.102
boys	24	8.5	4.21	2.3-17	14	8.6	3.03	2.3-14	10	8.3	5.66	2.3-17	0.152
girls	15	11.5	4.36	5-17	15	11.5	4.36	5-17					

S.D. = standard deviation; NS = not significant.

Table 2. Comparison between the laboratory results obtained at baseline and after treatment with IV FCM in the whole group of children with RLS or PLMD.

	Baseline (n=39)		Treatment (n=39)		Student's t-test	
	mean	**S.D.**	**mean**	**S.D.**	**t-value**	**p<**
Ferritin, µg/L	14.6	7.01	112.4	65.86	–9.768	0.000001
Iron, µg/dL	74.1	28.57	109.1	27.40	–6.165	0.000001
TIBC, µg/dL	383. 7	48.41	314.7	41.54	12.543	0.000001
Transferrin, mg/dL	20.2	9.20	34.4	10.44	–7.886	0.000001
Phosphorous, mg/dL			4.8	0.64		

FCM = ferric carboxymaltose; S.D. = standard deviation.

Table 3. Comparison between children with RLS or PLMD for the laboratory and clinical scale results obtained at baseline and after treatment with IV FCM.

	RLS (n=29)		PLMD (n=10)		Student's t-test	
	mean	**S.D.**	**mean**	**S.D.**	**t-value**	**p<**
Baseline						
Ferritin, µg/L	15.1	7.57	13.4	5.15	0.645	NS
Iron, µg/dL	81.1	32.74	69.4	25.20	0.977	NS
TIBC, µg/dL	379.8	49.51	383.3	45.54	–0.188	NS
Transferrin, mg/dL	22.8	10.09	17.7	8.91	1.400	NS
CGI-Severity	3.9	0.75	3.4	0.52	2.061	0.046*
Follow-up						
Ferritin, µg/L	112.1	68.68	113.5	60.34	–0.059	NS
Iron, µg/dL	110.3	28.96	101.1	22.47	0.865	NS
TIBC, µg/dL	316.2	42.26	316.6	35.14	–0.020	NS
Transferrin, mg/dL	35.0	10.57	32.6	9.13	0.629	NS
Phosphorous, mg/dL	4.7	0.66	4.9	0.61	–0.648	NS
Change at follow-up vs. baseline						
Ferritin, µg/L	97.0	65.02	100.1	58.03	–0.133	NS
Iron, µg/dL	27.1	58.04	28.5	54.41	–0.065	NS
TIBC, µg/dL	–59.2	135.22	–60.1	162.78	0.018	NS
Transferrin, mg/dL	11.4	17.97	11.6	17.12	–0.029	NS
CGI-Improvement	1.2	0.64	1.4	0.52	–0.711	NS

FCM = ferric carboxymaltose; S.D. = standard deviation; NS = not significant; *Not significant after Bonferroni correction; CGI = Clinical Global Impression.

Highlights

1. Iron supplementation is the first line treatment for children with restless legs syndrome or periodic leg movement disorder
2. Intravenous iron supplementation is an alternative to oral iron supplementation
3. Children receiving intravenous ferric carboxymaltose for restless legs syndrome or periodic leg movement disorder improved clinically
4. Ferritin level improved significantly after a single dose of ferric carboxymaltose

CRediT author statement

Lourdes DelRosso: Conceptualization, Methodology, Data curation, original draft preparation, reviewing

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Daniel L. Picchietti conceptualization, methodology, Original draft preparation, supervision, reviewing, editing