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A Randomized, Double-Blind, Placebo-Controlled Trial of Intravenous Iron Sucrose in Restless Legs Syndrome

Christopher J. Earley, MB, BCh, PhD, FRCP[1], **Alena Horská, PhD**[2], **Mona A. Mohamed, MD**[2], **Peter B. Barker, DPhil**[2], **John L Beard, PhD**[3], and **Richard P. Allen, Ph.D**[1]

1*Department of Neurology, Johns Hopkins University, Baltimore, MD*

2 *Department of Radiology, Johns Hopkins University, Baltimore, MD*

3 *Department of Nutrition, Penn State University, University Park, PA*

Abstract

Objective: The aim of this study was to ascertain whether high-dose intravenous (IV) iron sucrose could improve symptoms and change brain iron concentrations in idiopathic RLS.

Methods: The study was a randomized, parallel-group double-blind study of 1000 mg iron sucrose given IV versus placebo. Primary measures of the clinical status were global rating scale (GRS) and periodic leg movements of sleep (PLMS). Primary measures of brain iron status were CSF ferritin and MRI-determined iron in the substantia nigra.

Results: At the time of the interim analysis there were 7 placebo and 11 iron-treated subjects. At 2-weeks post-treatment, iron treatment resulted in a small but significant increase in CSF ferritin and decrease in RLS severity (GRS) but did not change PLMS or MRI iron index. None of the secondary outcomes changed with treatment. There was no single case of clear treatment benefit in any of the patients. This interim analysis revealed an effect size that was too small to allow for adequate power to find significant differences with the planed 36-subject enrollment for either the primary objective outcome of PLMS or any of the secondary outcomes. The study was stopped at this planned break-point given the lack of both adequate power and any indication for clinically significant benefit.

Conclusions: High-dose IV iron failed to demonstrate the robust changes reported in three prior open-label studies. Differences in iron formulation, dosing regiment, and peripheral iron status may explain some of the discrepancies between this and previous IV iron treatment studies.

Keywords

Restless leg syndrome; cerebrospinal fluid; MRI; substantia nigra; iron infusion; treatment; ferritin

Introduction

In 1954 Nordlander first proposed the iron deficiency hypothesis of Restless Legs Syndrome (RLS) [1]. In the last 10 years there have been several studies which have examined this

Correspondence: Christopher J Earley; Johns Hopkins Bayview Medical Center; 5501 Hopkins Bayview Circle, AAC 1B-82; Baltimore MD 21224 Telephone: 410-550-1044. Fax: 410-550-3364. Email: E-mail: cearley@jhmi.edu.

hypothesis in regards to brain iron. CSF analyses of ferritin, MRI quantification and B-mode imaging of iron in the brain, and finally autopsy studies have all implicate brain iron insufficiency as a primary player in the underlying pathology of RLS [2-7]. The CSF, MRI and B-mode imaging studies demonstrated brain iron changes despite measures of plasma iron status being in the normal clinical range. .

In patients with RLS symptoms and a peripheral iron deficiency, treatment with oral iron will improve, or in some cases eliminate the RLS symptoms [8-10]. What is less clear is whether or not increasing the peripheral iron load in patients, who have otherwise "normal" serum iron values, will improve RLS symptoms and change iron in the brain. Nordlander [1] treated 22 patients who had otherwise normal serum iron levels with intravenous iron dextran and was able to demonstrate improvements in 21 out of 22 patients. Parrow [11] presented retrospective data from his 89 patients with RLS who had been treated using various iron formulations. They found between 67 and 86 percent of the patients treated with the different iron formulations had complete resolution of symptoms. Both these studies were unblinded with no placebo controls using patients' subjective statement of improvements. A study by Earley [12], though similarly unblinded with no placebo controls, used periodic leg movements which are only marginally affected by placebo, as one of their primary measures. This study found that with 1000 mg infusion of iron dextran, 60 percent of the patients had complete resolution of symptoms and a concomitant marked reduction in PLMS. The current study was designed to validate and extend the prior IV iron studies using a randomized, double-blind, placebo-control trial design, with a complete battery of iron status assessment parameters along with the inclusion of assessment for brain iron status RLS.

Methods

Subjects

This was an IRB-approved protocol. Screening questionnaires, which were filled out by consenting applicants and reviewed by one of the authors (CJE), covered medical, sleep and RLS diagnostic issues. Those applicants considered to be eligible had blood studies performed. Following the serology assessment a potential candidate were then evaluated using the Johns Hopkins telephone diagnostic interview with an RLS expert (RPA) conducting the interview. Exclusion criteria included: possible secondary forms of RLS; hemoglobin <12 g/dl; any pain-related conditions or any other sleep-related problems, that might interfere with the interpretation of the outcome measures; sleep apnea rates > 25/hr; any organ problems (by history or blood study), which would affect RLS symptoms or the treatment with iron. Patients were required to have periodic leg movements of sleep (PLMS), greater than 15 per hour on the second-night polysomnogram, which was performed during their stay in the General Clinical Research Center (GCRC).

All subjects were required to stop consuming any herbal agents or over-the-counter vitamins which might contain iron, at least one week prior to the treatment initiation, and were required to not use any of these supplements until the conclusion of the study. Any medications that were being used to treat the RLS symptoms were discontinued at least one week prior to the GCRC visit. The patient was required to cease using all other treatments for their RLS for the duration of the study. Patients were instructed not to donate blood for at least 6 weeks prior to the study and not to donate blood as long as they remained in the study.

Patients were admitted to the GCRC for both an initial evaluation and treatment and 2 weeks later for a post-treatment evaluation. The medical history and RLS diagnosis were all reviewed and the subject examined by one of the investigators (CJE) at the time of the first admission. Subjects then had infusions (iron or placebo) on day 3 and day 4 with discharge the on day 5.

The second GCRC admission at 2 weeks after treatment followed the same evaluation procedures done on the first 3 days of the initial visit.

Treatment design

The Johns Hopkins Bayview Research Pharmacy performed the randomization using a 2 (iron) to 1 (placebo) randomization design. The Pharmacy wrapped the solution and all tubing with black opaque plastic coverings to prevent the subjects from seeing the color of the solution. Patients were blindfolded during the brief period for setting up the intravenous line thereby ensuring the treatment blind was maintained. The Nurse setting up and administrating the solution was not blinded to the treatment, but were specifically instructed not to discuss treatment condition with anyone. One of the investigators (CJE) dealt with all of the medical issues that arose with treatment and therefore would not have been always blind to the treatment options. However, this investigator was not involved in any collection, processing or analysis of data until the blind was broken. All other investigators and study coordinators were blind to treatment. All data were recorded using a randomly selected numerical identifier assigned to each subject.

Evaluations

The initial and follow-up GCRC visits were approximately 14 days apart and included 3 days of identical testing. During the first 2 days after admission the subjects had a Suggested Immobilization Test (SIT) on each of the two evenings between the hours of 9:30 PM and 10:30 PM followed by a standard polysomnogram. On Day 2, subjects had an MRI of the brain for the determination of brain iron concentrations. On the third day, patients had fasting morning blood collected for determination of iron-related proteins; filled out several questionnaires and then had a lumbar puncture for CSF collection.

On the third day of the initial GRCR visit, all subjects received a 500 ml NaCl intravenous infusion over 10 hours and a second 500 ml infusion over 12 hours on day 4. The solution contained either 500 mg iron sucrose (Venofer) or NaCl (placebo). During the period of the infusion blood pressure and heart rate were monitored continuously.

The patient was discharged home on Day 5 with specific instructions to remain off all RLS medications. The patient was contacted on a daily basis for the first week after they left the GCRC by their coordinator. For the second week, patients were contacted at least twice during that period of time. Patients returned to the GCRC approximately two weeks after the first visit for a follow-up evaluation.

On the third day of the second GCRC visit, patients filled out questionnaires about their perceived response to treatment. If the subject felt that the symptoms still required further treatment, the subject was allowed to go back on their usual RLS medications and was finished with the study. If the subject indicated that they did not require any further RLS medication then they were scheduled for further evaluating in two weeks and then would be followed every month until either the RLS symptoms required treatment or 2 years had past since the initial treatment.

Adverse events were monitored on all subjects during the period of infusion by the GCRC nursing staff, between the 2 GCRC visit by frequent phone calls from the study coordinator and then monthly by the study coordinator as long as the subject remained in the study. All adverse events were reported to the IRB. As a safety issue over concerns of iron overload, all subjects had serum ferritin measurements at 4 weeks post-treatment and then every month thereafter if their serum ferritin > 300 mcg/l until ferritin dropped below 300 mcg/l on 2 consecutive measures.

Questionnaires and Procedures

Standard, all-night polysomnogram (PSG) was obtained for 2 consecutive nights and scored by board certified sleep experts following the accepted criteria [13]. One-hour Suggested Immobilization Tests (SIT) were performed and scored using the published criteria [14]. The PSG and SIT tests included bilateral surface electrode measurements of the anterior tibialis EMG. These were scored for periodic limb movements in sleep (PLMS) and waking using the standard criteria [15], except for the SIT, the maximum duration of a movement was 10 seconds following the recommended scoring for the SIT test [16] and consistent with the new WASM criteria for scoring PLM [17]. The PSG also provided measures of the total sleep time and sleep efficiency defined as time in bed divided by total sleep time. The Global Rating Scale (GRS), a 7-point scale for patient's assessment of RLS symptoms, used in this study has also been used in previous iron treatment studies [18]. The scale goes from “no symptoms” (score = 0) to “very severe symptoms” (score = 6). A Sleep-Wake diary was completed by each subject for each day in the GCRC. The diary provides a simple hourly record of the severity and duration of any RLS symptom. This tool has been used in previous treatment studies of RLS and is described elsewhere [18]. The International RLS Study Group severity scale was used as secondary outcome measures (IRLS) [19,20]).

The lumbar puncture between L4/L5 or L5/S1 lumbar interspace was performed with the subject sitting up. CSF was collected in 1ml aliquots, immediately placed on dry ice, and stored at −80°C. CSF ferritin was measured by IRMA analysis on frozen material using commercial reagents (ICN). These antibodies were prepared to primarily identify L ferritin. CSF transferrin was measured by ELISA using assay conditions previously described [21]. Primary Ab (Santa Cruz Biologicals, Ca) was used at a 1:1000 dilution and 2^{Nd} antibody at 1:2500 dilution. Hb was measured by cyanmethemoglobin using standard clinical protocol.

MRI imaging was used to quantify iron in the brain as has been done in prior brain iron assessments of RLS patients [4,22]. All brain scans were performed on a 3.0 Tesla Philips MR scanner. This provided the data required to construct multi-slice maps of the transverse relaxation times R_2*, R_2 and R_2', which (particularly R_2') can be regarded as surrogate markers of iron in the brain, as described by Gelman et al. [23].

Aims and statistical analysis

The primary aims of this study were as follows.

1. To test the hypothesis that high dose IV iron therapy can improve RLS symptoms—The primary outcome measures used to assess symptomatic improvement were changes in the global rating scale (GRS) and in PLMS on second-night PSG between the first and second GCRC visit. Secondary outcome measures included changes between the first (pretreatment) and second (2 weeks after treatment) GCRC visit in: hours of report RLS symptoms, PLM on the SIT test; and IRLSS scale,

2. To test the hypothesis that IV iron therapy will improve the CNS iron status of RLS patients—The primary outcome measures for assessment of improvement in CSN iron status were changes in CSF ferritin or changes in MRI iron index for the substantia nigra.

The placebo and iron-treatment groups were compared for differences in baseline characteristics and in changes in outcome variables (values at 2 weeks, post-treatment – those at baseline). A two-sample t-test was used when data were distributed normally otherwise a Mann-Whitney test was used. A sample of 36 subjects (24 on IV iron and 12 placebo) was planned to provide adequate power (80%) to detect significant differences of the same order of magnitude as that seen in our previous iron-dextran studies [12]. An interim analysis was

also planned after 18 subjects had been enrolled to determine if the effect size justified continuing the study.

Results

Of the total of 119 subjects who signed consent forms and were screened, 25 were fully eligible for treatment. Three subjects dropped out because of inability to come off of their RLS medications, 1 subject was excluded because of PLMS < 15/hr and 3 subjects never entered the last stage because the study was closed following the results of the interim analyses. Eighteen subjects received either iron sucrose (11) or placebo (7) at the time of the interim analysis. The essential baseline characteristics of both groups are presented in table 1. As can be seen from Table 1, the two groups were very well matched. On average subjects were in their 60's and had moderate to severe symptoms as indicated by both RLS severity scales and by the high number of PLMS per hour that were found. As expected serum ferritin was significantly increased (p =0.0001) at 2-weeks post-treatment in those who received IV iron (see table 2).

In regards to the first hypothesis to be tested, IV iron treatment significantly reduced symptom severity as indicated by the improvement in GRS but treatment did not change PLMS (see table 2). No other secondary “subjective” (IRLSS scale and Hrs of RLS) or “objective” (PLMW/hr) measure of the clinical condition improved with treatment (see table 2). At 2-weeks post-treatment 57% (4/7) of the placebo and 46 % of the iron-treatment (5/11) group reported some improvements in symptoms sufficient enough not to go back on any RLS medications at that visit. These patients were therefore followed as treatment “responders”. The median number of weeks off RLS medications was 41 weeks for the 4 placebo and 28 weeks for the 5 iron-treatment responders. On the other hand, only 2 subjects both in the iron-treatment group had a 50% or greater reduction on PLMS at 2-weeks post treatment. It was estimated that with the planned subject enrollment of 36 subjects, the power to detect a difference between groups, using PLMS/hr as an index of clinical improvement, was only 21%.

In regards to the second hypothesis to be tested, IV iron resulted in a small but significant increase in CSF ferritin but no significant change in MRI iron index for the substantia nigra was found (see table 2). CSF transferrin, a secondary measure of CNS iron status, was also not significantly different. With the planned subject enrollment of 36 subjects, the power to detect a difference between groups, using SN MRI iron index as a measure of the CNS iron status, was only 11%. Given the probability that differences in the other primary outcome measures (PLMS and MRI iron index) were unlikely to be found with full enrollment and given the general lack of significant changes in any of the secondary outcome measures, it was felt that the current study was unlikely to demonstrate clinically relevant and convincing treatment effects even if we were to double the sample size. The interim analyses did not justify continuing the study.

The commonest reported side effects from treatment (see table 3) were edema in either hands or feet (36%) and nausea or vomiting (36%). Hypotension (18%), dizziness (18%) and abdominal pain (9%) were also reported with treatment. All of the reported side effects occurred during treatment and resolved within minutes to hours of completing the infusion. No adverse effects were reported at 2-week follow up after the iron treatment.

Discussion

This is the first randomized, double-blind, placebo-controlled trial of IV iron in the treatment of RLS. Unlike the open-labeled studies [1,11,12], this study did not find dramatic improvements in symptoms with IV iron. In fact the improvements seen in the GRS, though

significant, were small and not clinically significant. The other measures of the clinical status, particularly the objective measure of PLMS, were not found to be changed by treatment. In the open-label studies, subjects who had reported improvements in symptoms had complete resolution of all of their symptoms [1,12]. The basis for the different findings may reflect a placebo-effect in these open label-trials. Our study had a very high number of placebo-responders (57%) based on reported symptoms improvements. However, none of these subjects reported complete remission of symptoms with zero hours of RLS in a given day. In contrast in our prior open-label study 6 of the patients reported no RLS symptoms, i.e. zero hours of RLS every day during the two-week follow-up period. Similarly the PLMS, which have been shown to be minimally affected by placebo conditions in other RLS-treatment trials [24], were decreased in all subjects reporting an improvement with 1000 mg iron dextran but not in those without symptomatic improvement [12]. Thus neither the large clinical response nor the decrease in objective PLMS reported in the prior open-label IV iron treatments were observed for placebo responses in this trial. Therefore the unblinded, non-placebo-controlled conditions fail to account completely for the positive treatment results seen in the prior IV-iron treatment trials.

The differences in treatment effect seen between this study and all previous studies may also be related to iron formulation or dosing regiment. Iron dextran was used in all the prior studies while iron sucrose was used in this study. Iron dextran has a much longer serum half life than iron sucrose: 18-20 versus 6-8 hours. Iron dextran appears to be cleared by macrophage uptake of dextran while iron sucrose is taken up by transferrin-based systems (i.e., bone marrow and liver). Iron re-distribution to organs, including the brain, may differ based on initial organ deposition of the iron. That is, immediate iron clearance to macrophages with subsequent controlled release in response to normal physiological signals is likely to provide a different temporal profile for iron availability to the brain than a iron formulation that very quickly disappears from the plasma into slowly exchanging tissue pools of iron [25]. In the studies by Nordlander [1] and Parrow [11] low dose, multiple infusions of iron dextran were used over several weeks to months as their treatment paradigm. We gave two, 500 mg infusions over a 36-hour period. Therefore, the difference between our results and other prior results may also relate to how the iron was administered. However, our prior IV iron-dextran study used a single 1000 mg infusion and produced in some subjects the same dramatic treatment benefit reported in the earlier studies.

Serum protein iron saturation measured during the iron sucrose administration demonstrated marked over-saturation of the transferrin by up to 500 to 600 percent (data not shown). That means a significant portion of the iron was likely bound to other proteins that are not usually meant for transporting iron (e.g., albumin) or generic low MW iron chelators such as citrate or oxalate. Once bound to these other proteins, its organ distribution is unknown and thus it availability for redistribution to brain also unknown and may be compromised. At a minimum, the findings suggest that a large (500 mg) single doses of iron sucrose is probably not a feasible form of iron delivery.

Several case series have indicated that RLS patients with anemia or low serum ferritin may benefit from iron treatment [8-10]. This study excluded subjects who were anemic and included subjects with a broad range of ferritin values. Therefore this study does not exclude the possibility that those with low (< 10 mcg/l) or low normal (< 50 mcg/l) ferritin or those with iron-dependent anemia would not benefit from this form of IV iron. Future studies of IV iron treatment in RLS need to consider the possibility that those with low ferritin or anemia are the ones most like to benefit from iron treatment and that small but multiple infusions of iron may be more effective than one large treatment. Iron dextran may also provide more effective treatment and the newer formulation may have significantly less problems with anaphylaxis [26].

We did see a small, statistically significant change in the GRS which was consistent with the similar small and statistically significant increase in CSF ferritin, but no other indices were changed and the degree of change seen in the GRS was no where near the effect size seen in the prior studies. Given the very small effect seen with the CSF ferritin, it is not surprising that no effect was found for the MRI. As has been shown elsewhere, the MRI determination of brain iron is substantially less sensitive then that of CSF ferritin [2,4]}. The mean changes with treatment seen in this study for MRI iron index of the substantia nigra and for the CSF ferritin were similar order but the variance for MRI data was nearly 10 times that for CSF ferritin. The number of patients in this trial even if three times our current sample would not have provided adequate power to to detect significant differences for the observed effect sizes. Clinically the degree of reported improvement never matched that observed in the previous trials with other formulations of iron. Therefore we conclude that the amount of benefit observed was not clinically significant and would not justify further clinical evaluation of RLS treatment using this large, single dose of iron sucrose.

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Table 1

The major baseline characteristics between placebo and iron-treatment groups presented as mean ± standard deviation when normally distributed and median (quartiles) otherwise. The p values are provided comparing iron-treatment and placebo groups using the t-test for those normally distributed and Mann-Whitney test otherwise.

Essential baseline characteristics	Placebo	Iron-treatment	p value
N (% females)	7 (71%)	11 (55%)	NS
Age	61.4 10.0	66.4 ± 11.4	NS
Serum ferritin	70.3 ± 21.5	78.3 ± 41.7	NS
Hemoglobin	14.0 ± 0.84	15.0 ± 1.2	NS
early-onset RLS	57%	55%	NS
Total Sleep Time	271.0 ±123,7	300.7 ±71.1	NS
Sleep Efficiency	74.2 ±17.1	76.2 ±13.8	NS
PLMS/hr	123 ± 87	107 ± 93	NS
PLMW/hr	188 ± 108	189 ± 98	NS
SN R2′ MRI	22 ± 7.4	20 ± 9.2	NS
CSF ferritin	2.9 ± 1.3	2.4 ± 1.2	NS
CSF transferrin	39.2 ± 14.0	43.4 ± 19.6	NS
JHRLSS scale	2.1 ± 0.9	1.8 ± 0.8	NS
IRLSS scale	29.7 ± 2.9	30.8 ± 9.2	NS
GRS	3.4 ± 0.8	3.5 ± 1.1	NS
Hrs of RLS	4.1 ± 3.4	5.8 ± 2.2	NS

Abbreviations: PLMS/hr (the rate per hour of periodic leg movements during sleep); PLMW/hr (rate of periodic movement during the SIT study); SN R2′ MRI (iron index for the substantia nigra as determined by MRI); JHRLSS scale (Johns Hopkins RLS severity scale); GRS (global rating scale); International RLS severity scale (IRLSS scale); Hrs of RLS (average daily hours of RLS symptoms). NS indicates p>0.10.

Table 2

The changes in the primary and secondary outcome measures and PSG sleep measures found at 2-weeks (pre – post values). These are presented as mean ± standard deviation when normally distributed and median (quartiles) otherwise. The p values are provided comparing iron-treatment and placebo groups using the t-test for those normally distributed and Mann-Whitney test otherwise.

Outcome Measures	Placebo	Iron-treatment	p value
SN R2′ MRI**	−1.1 ± 12.9	0.7 ± 10.9	NS
CSF transferrin	4.7 ± 8.9	−0.9 ± 15.1	NS
CSF ferritin**	0.0 ± 0.4	0.97 ± 1.1	0.04
Serum ferritin	−6.63 ± 16	304.3 ± 119.4	0.0001
Total Sleep Time	30.3 (5.1,42.6)	−1.5 (-143.4, 25.8)	NS
Sleep Efficiency	−41.4 ±98.2	−35.5 ± 92.0	NS
PLMS/hr**	−11.7 ± 32.9	−24.8 ± 89.4	NS
PLMW/hr	−65.4 ± 118.5	−46.4 ± 84.6	NS
GRS**	0.01 ± 0.75	−1.02 ± 0.94	0.02
IRLS	−12.0 ± 11.5	−10.1 ± 5.1	NS
Hrs of RLS	−1.3 ± 3.9	−2.9 ± 2.5	NS

Abbreviations: PLMS/hr (the rate per hour of periodic leg movements during sleep); PLMW/hr (rate of periodic movement during the SIT study); SN R2′ MRI (iron index for the substantia nigra as determined by MRI); GRS (global rating scale); International RLS severity scale (IRLSS scale); Hrs of RLS (average daily hours of RLS symptoms).

** These are the designated primary outcome measures for this study.

Table 3

Incidence of reported side effects associated with treatment in those that received iron sucrose or placebo

Side Effects	Iron Sucrose	Placebo	Total
Edema hands/feet	4	0	4
Dizziness	2	1	3
Nausea/vomiting	4	0	4
Muscle aches	0	1	1
Hypotension	2	0	2
Abdominal pain	1	0	1