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Original article

Repeated IV doses of iron provides effective supplemental treatment of restless legs syndrome

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Abstract

Background and purpose: To evaluate in RLS patients the efficacy and safety of repeated infusions of iron in order to maintain symptomatic improvements achieved with a prior single 1000 mg infusion of iron.

Patients and methods: Subjects who had demonstrated initial improvement in RLS symptoms after a single 1000 mg infusion of iron were evaluated monthly for serum ferritin and RLS severity. If symptoms returned at any time in the 2-year period after initial iron treatment, supplemental 450 mg iron gluconate infusions could be given, provided the ferritin was <300 mcg/l. The primary outcome measures were side effect profile, duration (weeks) of sustained improvement, and rate of change of serum ferritin.

Results: Ten subjects received the initial single 1000 mg dose of iron dextran, but only five subjects were eligible to receive supplemental iron infusions. RLS symptoms returned on average 6 months after the initial 1000 mg infusion. Because of noncompliance with monthly visits one subject was dropped after receiving three supplemental iron infusions. Because of a ferritin >300 mcg/l, a second subject was dropped after having received one supplemental treatment. Three subjects completed the 2-year period of the study, having received between two and four courses of supplemental iron. After the initial 1000 mg iron infusion, the ferritin declined on average 6.6 mcg/l/week, which was substantially higher than the predicted value of <1 mcg/l per week. The rate of ferritin decline decreased toward normal with repeated IV iron treatments: the average rate of decline in ferritin for the last treatment course was 2.3 mcg/l/wk. The slower the rate of ferritin decline the more prolonged the symptom improvements.

Conclusions: Supplemental iron treatments can sustain previously achieved improvements with a single IV iron treatment, but achieving high ferritin levels was not in themselves a guarantee of sustained improvements. The most notable finding was the post-infusion changes in serum ferritin and its implication for altered iron excretion.

Keywords: Restless legs syndrome; Iron; Ferritin; Treatment; Ferrlecit; Intravenous

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder for which low brain iron concentrations may play a key role in the pathophysiology [1]. Studies using magnetic resonance imaging (MRI) to quantify brain iron and autopsy material have consistently shown reduced iron concentration in selected brain regions [2,3]. The findings of decreased cerebrospinal fluid (CSF) ferritin and increase CSF transferrin in RLS patients also supports the hypothesis of a relative decrease in brain iron status for RLS patients compared to unaffected individuals [4]. Oral iron supplement in RLS patients with iron deficiency has been reported to improve symptoms [5]. However, when body stores of iron are normal, oral preparations of iron are poorly absorbed [6]. Intravenous iron offers an alternative to oral iron in that it eliminates the barrier to absorption seen in oral preparations. Nordlander used multiple, low-dose infusions of iron and successfully improved symptoms in 95% of the RLS patients [7]. More recently, Earley et al. [8] reported somewhat similar efficacy for a single 1000 mg IV dose of iron. Both studies found that almost complete relief from RLS symptoms lasted on average 5–6 months with subsequent return of all symptoms. It is not known whether repeated IV iron treatments would serve to maintain efficacy and would also be safe.

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Two of the puzzling findings from these prior studies involve basic concepts of iron metabolism. First, why do the symptoms return in only a few months when the amount of iron given should have produced an elevated iron status lasting for at least two years? Under normal circumstances the average individual excretes 1 mg of iron each day [9]. Therefore, if a 1000 mg were given intravenously it would be predicted to take about 1000 days to excrete it. So why were the improvements in RLS symptoms lasting only on average 180 days, instead of 1000? Second, the decrease in serum ferritin indicating the loss of iron was more rapid than expected following the 1000 mg infusion [8]. Serum ferritin was checked 1–2 times a month. As expected the ferritin rose after the infusion. Unexpectedly the ferritin had a rapid linear drop with time that persisted for months after the infusion. Ferritin rises and falls in response to iron availability: decreasing iron results in decreasing concentrations of serum ferritin and vice-a-versa [6]. Therefore, the relatively rapid decrease in ferritin seen after the 1000 mg iron infusion suggests increased iron loss at rates of 2–12 normal. This second finding might in part explain the earlier than expected return of RLS symptoms.

The reason for this rapid iron loss is not clear. It might, on one hand, be a natural response to the large IV iron dose but on the other hand it might represent some aspect of the pathophysiology of RLS. Current theories on the management of body iron stores consider excretion to occur at relatively stable rates independent of iron status [9,10], but this seems not to be the case for these RLS patients. These data suggest repeated IV dosing of iron may be required to maintain treatment effectiveness. This study, therefore, evaluated supplemental iron doses repeated over two years to study safety and effects on RLS symptoms and body iron stores.

2. Methods

The 10 subjects who had enrolled in a previous study [8] and had received an initial 1000 mg of Iron Dextran intravenous were potential candidates for this study. To be eligible for this study subjects needed to demonstrate an initial response to the 1000 mg of iron. The primary indicator of the initial response was the subject's decision at two weeks post-infusion, to remain off all RLS medications owing to lack of RLS symptoms. Those subjects that chose to remain off RLS medications were followed monthly until symptoms returned or 2.5 years (130 weeks) had lapsed since the initial 1000 mg treatment. On monthly assessments subjects gave blood to measure ferritin and rated their RLS symptoms severity using a 10-point analog, global rating scale (GRS) where 0 = very severe and 10 = no symptoms. If symptoms returned within two years (104 weeks) of the initial 1000 mg infusion subjects were eligible to receive intravenous iron supplements provided their ferritin was less than 300 mcg/l and they were compliant with monthly follow-up visits and had remained off of alternative RLS medications. The supplemental treatment was 450 mg of iron gluconate (Ferrlecit) given as a course of three separate, 150 mg infusions delivered over a 5–10 day period.

The primary outcome measures were side effect profile, duration (weeks) of sustained improvement, and rate of change of serum ferritin. As part of the safety concerns, any subject with ferritin >300 mcg/l at the conclusion of the study had repeated assessments of ferritin until values fell below 300 mcg/l.

Descriptive statistics provided an overall evaluation of the response to the repeated IV iron treatments. Statistical analyses also included a linear regression evaluating the rate of fall of serum ferritin using all available data points starting at four weeks after treatment until the last value before a repeat treatment or end of study. The correlations were evaluated for the relation between duration of treatment benefit, determined as the time after injection when the patient reported no need for any added medications to treat the RLS symptoms, and the rate of fall of ferritin.

3. Results

Of the 10 subjects who initially received 1000 mg of iron, six reported complete relief from all RLS symptoms. All 6 reported a GRS = 10 following the initial 1000 mg dose. Of those six, one subject never experienced a return of RLS symptoms. All of the remaining five subjects had serum ferritin less than 300 mcg/l and so were eligible to receive supplemental treatment. Symptoms returned as early as 12 weeks (subject no. 3) and as late as 52 weeks (subject no. 7) after the initial 1000 mg infusion (Table 1). Two subjects were unable to complete the study. Subject no. 2 whose symptoms returned at 100 weeks post-infusion, having received one course of supplemental iron at week 25, was not eligible to receive further supplemental doses because of ferritin >300 mcg/l. Of note, the ferritin for subject no. 2 just prior to supplemental treatment was 331 mcg/l. The error occurred when the value on the faxed laboratory sheet was read as 231 mcg/l. Subject no. 3 who received three supplemental courses of iron was excluded at 50 weeks for failure to comply with monthly follow-up evaluations. Three subjects completed the study and received as little as two supplemental courses (subjects no. 3 and 5) or as many as four courses (subject no. 1) during the 104 week period. Although not eligible to receive further supplemental treatments after the 2-year period lapsed, these last 3 subjects were followed monthly for a further 26 weeks to collect GRS and serum ferritin data. Subject no. 1 experienced a return of RLS symptoms (GRS = 5) by week 120 while subjects no. 3 and 5 were still not reporting significant symptoms (GRS = 10) at the closure of the study (week 130).

Table 1
Patient characteristics and response to supplemental IV iron therapy

Subject	Age	Gender	Supplemental treatments		Global[a] RLS rating: initial, best, last month	Serum ferritin (mcg/l)		Rate of ferritin decline (mcg /l/wk)[b]	
			Number given	Given at week[c]		Initial	Final	Initial	Final
No. 1	51	F	4	26, 32, 56, 85	0, 10, 5	26	291	2.6	0.3
No. 2	68	M	1	25	0, 10, 4.5	188	514	11.6	1.1
No. 3	51	F	3	12, 25, 37	0, 10, 5	8	140	7.3	7.4
No. 4	54	M	2	20, 48	0, 10, 10	84	296	8.9	1.0
No. 5	58	F	2	52, 103	0, 10, 10	9	145	6.0	1.5

[a] Global rating 0–10: 0 = severe, 10 = no RLS.
[b] Estimated normal ferritin decrease = 0.8 mcg/l/week.
[c] Weeks after initial IV iron treatment.

Fig. 1 shows the rate of decline in ferritin after the initial 1000 mg dose and then over the course of this study with acute rises associated with each supplemental treatment. Subject no. 1 received a set of supplemental treatments starting at week 26 and then soon afterwards received another set of treatments starting at week 32. Data from week 26 was not sufficient enough to define a slope for that very short period. The average rate of decline in ferritin after the initial 1000 mg was 6.6 mcg/l/week (see Table 1), which is substantially higher than the predicted value of <1 mcg/l/wk. The slowest rate after the initial treatment was 2.6 mcg/l/week and the fastest was 11.6 mcg/l/wk. Subsequent supplemental courses led to decreases in the rate of ferritin decline. The average rate of decline in ferritin for the last treatment course was 2.3 mcg/l/wk with a range of 0.3–7.4 mcg/l/wk. There was a strong correlation between rate of ferritin change and the log of duration (weeks) of symptom improvement ($r = 0.71$, $P < 0.006$), with slower rates associated with more prolonged improvements.

During the course of treatment with Ferrlecit no subjects had any allergic reaction or any significant side effects that prevented the individual from getting the full treatment. No late or delayed side effects were reported. Subject no. 2 had ferritin of 514 mcg/l when he concluded the study. He had ferritin checked every 6 months and only after 2.5 years from the conclusion of the study did his ferritin drop below 300 mcg/l.

4. Discussion

The primary purpose of this study was to evaluate the feasibility of supplemental treatments with intravenous iron in those who responded to an initial 1000 mg iron infusion. The patients originally received iron dextran, which is well known to cause potentially dangerous allergic reactions; indeed one patient suffered a reaction. The value of iron dextran was the ability to give a large single dose. Because of concerns about allergic reactions, we used iron gluconate instead for the supplemental portion of this study, which is safer but requires several administrations to achieve total dosage of 450 mg. The improved safety with gluconate or sucrose formulations may outweigh the slight inconvenience. The most significant limitation of the study was its open-label design and the use of only subjective measures of response. Although periodic leg movements (PLM) were used as an objective measure of the response to the initial 1000 mg [8], these were not used in the supplemental treatment arm of the study. However, all five subjects experienced greater than 50% improvement in periodic leg movements following their initial treatment [8]. Such large decreases are not reported for placebo treatment of RLS [11], thus it seems unlikely their treatment changes represent a placebo response.

The study indicates supplemental iron can sustain previously achieved improvements but achieving high ferritin levels were not in themselves a guarantee of sustained improvements (e.g. subject no. 2). The most notable finding was the consistent change in the rate of drop in ferritin with repeated IV iron treatments, which suggests altered iron excretion. Serum ferritin concentrations under normal conditions reflect the amount of iron stored in the body [12]. Therefore, drops in ferritin indicate loss of iron from the body or possibly increased utilization. A 1 mcg/l ferritin drop reflects approximately a 10 mg loss of iron [12]. The estimated daily excretion rate of iron is between 0.8 and 1 mg/day. If all absorption of iron were stopped, then the predicted or hypothetical ferritin drop would be estimated to be about 0.8 mcg/l/wk [6,9]. The estimated rate of iron loss following the administration of 1000 mg of iron was on average seven times higher than this predicted value. Since there have been no studies examining the effects of giving high doses of iron to an otherwise normal subject, it is not clear whether the findings are applicable to only an RLS subject or would be found in anyone at the same level of ferritin.

Ferritin is an acute phase reactant [6]. One could argue that the drop in ferritin is related to a slow decline in the phase reactivity. There is clearly a sharper drop seen in the ferritin from 2 to 4 weeks after initial 1000 mg treatment, which is assumed to be a result of acute phase reactivity to the initial treatment. Because of this we used only ferritin

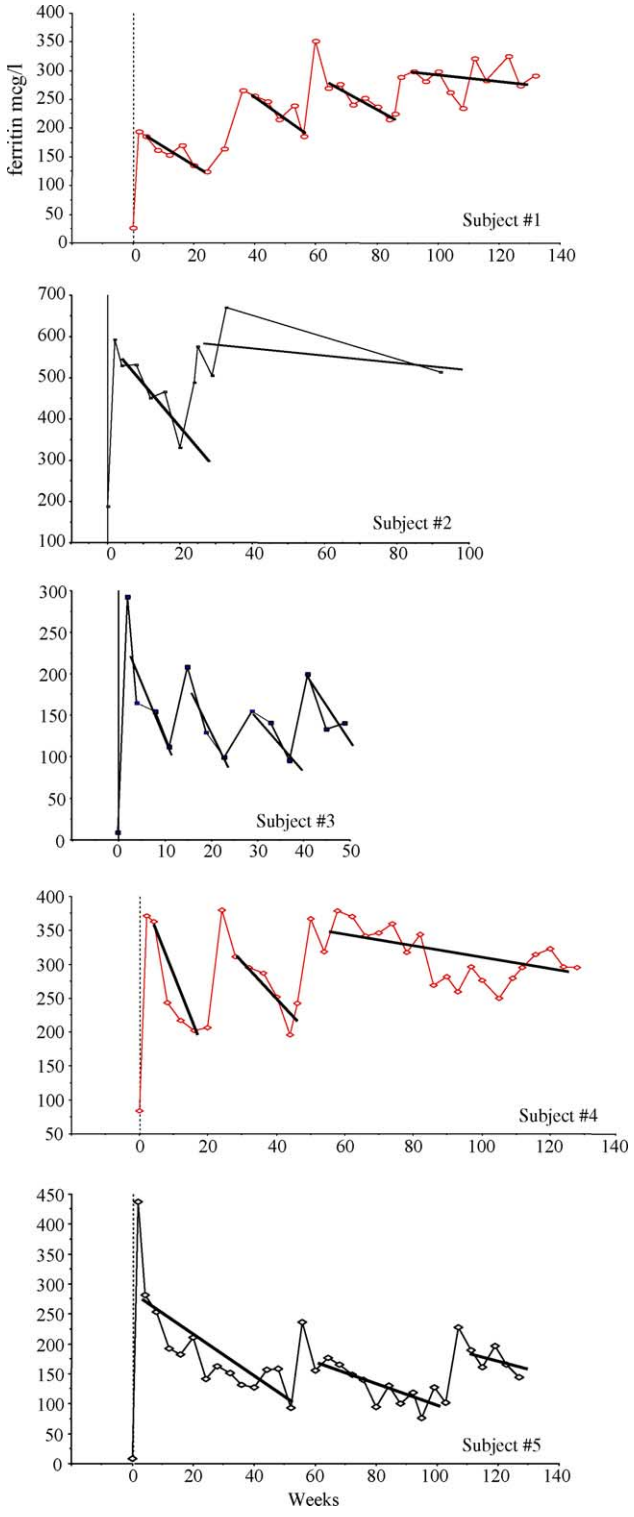

Fig. 1. Serum ferritin (mcg/l) with regression lines for the change in ferritin over the weeks after each iron infusion.

values obtained at 4 weeks or later. Acute phase reactivity, however, cannot explain the prolonged progressive decline in ferritin over subsequent weeks. It could be argued that anyone getting excessive amounts of iron will excrete more. However, the current teaching is that excretion is not a variable mechanism but is unchangeable even in the face of iron overload [9,10]. This arises in part from research on iron overload conditions like hemochromatosis, where absorption is the problem and the body excretion rate remains unchanged [10]. However, even if we were to consider iron excess as a possible mechanism, what do we mean by excess? The normal range for ferritin is 10–300 mcg/l; therefore, one definition of excess could be ferritin >300 mcg/l under non-inflammatory conditions. All of the subjects experienced continuous rapid drops in ferritin even when ferritin values were in the normal range. Subject no. 3, despite receiving 2350 mg of iron, never reached a ferritin of 300 mcg/l and continued to have drops of ferritin even when in the mid-normal range. Blood loss, which would be the obvious cause of iron loss, was never identified in any of the subjects: there was no history of bleeding and no change in stool color or blood donation, and none of the women were menstruating. The possibility that the change in ferritin reflects increased iron utilization is another possible argument. Under conditions of iron deficiency anemia or with anemia of chronic disease with erythropoietin, ferritin would acutely decrease as iron moved into new red blood cells. However, our patients were not anemic, and it is unclear how this process would continue for months.

An alternative possibility is that for any given individual there is a threshold for body iron stores above which iron is excreted faster than usual; so for some individuals 'excess' iron stores could mean ferritin >10 mcg/l and for someone else a ferritin >150 mcg/l or for others >500 mcg/l. However, this does not explain the decrease in rates of ferritin loss with repeated treatments. Hepcidin, a peptide produced by the liver, has been found to have broad regulatory effects on iron uptake, release and distribution [10]. It could be postulated that hepcidin or another yet-to-be-identified hormone is responsible for defining the normal threshold for 'excess' iron. Repeated iron loading might then operate to shift that threshold, which then leads to progressive changes in cellular storage or retention. Clearly the rates of iron loss vary across individuals, but the finding suggests that the mechanisms behind the iron loss may be adjustable or even 'normalized' depending upon exposure to increased iron. Unfortunately there is nothing in the current iron literature that explains these phenomena.

The putative iron loss following IV iron administration does help us explain the unexpected short-lived improvements seen by Nordlander [7] and Earley [8] after a high dose of iron. Whether the 'normalization' of iron excretion with repeated iron dosing is important for sustained long-term benefits awaits further evaluation, but it is encouraging to see that both the duration of treatment benefits increased and the abnormal rapid fall in ferritin decreased with repeated IV iron treatment of RLS patients. Perhaps repeated IV iron administration not only reduces symptoms but actually corrects at least one of the pathologies for some RLS patients.

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