Optimum Frequency and Timing of Oral Iron Administration for Childhood Restless Leg Syndrome/Periodic Limb Movement Disorder

NCT04610827

February 2, 2021

Date of protocol: February 2, 2021

Optimum Frequency and Timing of Oral Iron Administration for Childhood Restless Leg Syndrome/Periodic Limb Movement Disorder

Principal Investigator: Julie Baughn, MD

Co-investigators: Wendy Edlund, MD; Robin Lloyd, MD; Julie Baughn, MD; Mai Uyen Alissa Le, Pharm.D, R.Ph.

Sleep Fellow Research Project for Wendy Edlund, MD; Approved by Sleep Research Committee 7/28/2020; IRB # 20-007655

RESEARCH QUESTION:

Does every other morning dosing of liquid ferrous sulfate increase ferritin more than daily or twice daily dosing in children with iron deficiency (ferritin less than 24) and sleep disturbance?

BACKGROUND:

Oral iron is frequently used to treat low ferritin in childhood sleep disorders, including restless legs syndrome (RLS), periodic limb movement disorder (PLMD), and restless sleep. Children under 6 years of age lack the language skills to describe their RLS symptoms, so polysomnography is often done to assess for the objective finding of periodic limb movements, as 80% of children with RLS have PLMs. In RLS, increased serum ferritin correlates with increased CSF ferritin and RLS symptom improvement (1). Two prospective and four retrospective studies have shown that oral iron supplementation in children with RLS leads to an increase in serum ferritin and a corresponding decrease in RLS symptoms (2-7). The International Restless Legs Syndrome Study Group guidelines recommend 3 mg/kg/day of oral iron as first line treatment of RLS, with a goal of increasing ferritin to greater than 50 µg/L (1). The optimal timing of dosing is unclear and thus there is practice variation. Pediatricians and pediatric sleep specialists are seeking guidance on how to best dose oral iron.

Emerging evidence about the diurnal variation of hepcidin and its sustained increase for 36-48 hours after iron intake suggest taking iron every other morning may be more effective than daily or twice daily. Hepcidin is a regulatory hormone that prevents iron deficit or overload by tightly controlling iron absorption via the GI tract as well as its bioavailability within the circulation (8). Hepcidin is lowest in the morning (9), and is regulated by an innate diurnal rhythm (10). Hepcidin levels are decreased by both circulating and stored body iron; levels remains increased for 36 (9) to 48 (15) hours following oral iron intake, limiting absorption of subsequent doses. Studies in adult women with iron deficiency have shown significantly greater fractional iron absorption in patients taking iron every other day compared to daily (21.8% vs 16.3%) (16). Hepcidin levels are higher in children under 12 years of age (11), possibly

further decreasing absorption in this population. Hepcidin levels are also increased by infection or inflammatory disorders (14).

Several additional factors impact oral iron uptake. When not taken on an empty stomach, phosphates, phytates and tannates in food bind iron and impair its absorption (18). Oral iron should also be taken separately from dairy intake (12), and with juice (13) for optimal absorption. Antacids, H_2 blockers, and proton pump inhibitors may also reduce pharmacologic iron absorption (14). Anemic patients with malabsorption, *Helicobacter pylori* infection, atrophic gastritis, or previous gastric or duodenal surgery do not respond or only partially respond to oral iron treatment (14).

Children often have poor compliance with oral iron due to the bad taste or GI upset, thus less frequent dosage schedules may be better tolerated. In an adult anemia population, nausea, vomiting, constipation, or diarrhea led to noncompliance with therapy in 30% to 70% of cases (17). In a retrospective chart review of 77 children with RLS treated with oral iron, adherence to therapy occurred in 55% and was the only predictor of an increase in ferritin of ≥10 µg/L (19).

SPECIFIC AIMS:

1) To determine the relative increase in ferritin between children taking 3 mg/kg/day of oral liquid ferrous sulfate daily in the morning, twice daily, or every other morning.
2) To determine the relative side effects for these dosage schedules.
3) To determine adherence to these dosage schedules.

STUDY DESIGN:

Study design: Prospective, randomized clinical trial

Subjects: Consecutive patients age 2 years to 10 years seen in in the sleep medicine clinic with ferritin ≤ 24 µg/L until the minimum number obtained. It is estimated that 2-5 such patients are seen per day in the Mayo sleep clinic.

Inclusion criteria:

- Ferritin equal to or lower than 24 µg/L drawn within the past 30 days.
    - Note: If ferritin ~10 µg/L, ~20% of oral iron absorbed; If ferritin between 50-75 µg/L, ~2% is absorbed, oral iron not recommended over 75 µg/L (1).
- Age 2 years through 10 years
- RLS, PLMD, or sleep disturbance

Exclusion criteria:

- Currently taking oral iron other than a multivitamin.

- Untreated Obstructive Sleep Apnea.
- Presence of GI disorder, including GERD, Celiac disease.
- Prior GI surgery, such as gastrectomy, duodenal bypass, presence of G tube.
- Use of H2 blocker, antacid, or proton pump inhibitor.
- Presence of inflammatory disorders, such as JIA or IBD.
- Elevated CRP at time of initial ferritin or report of illness in past 4 weeks.

Intervention: ferrous sulfate suspension. (Note: Generic and name brand are interchangeable per Peds Pharmacist)

Methodology:

- Patient selection
    - All patients 2 to 10 years of age presenting to the sleep medicine clinic with a ferritin $\leq$24 drawn in the past month who meet the inclusion/exclusion criteria are eligible for enrollment.
    - Mai Uyen Le, Pharm.D. or Wendy Edlund, MD will review the pediatric sleep schedules a few days prior to the Sleep Medicine appointment and identify possible subjects for inclusion. They will contact the families by phone to alert them that they may be eligible for the study.
    - The pediatric sleep medicine providers will be informed which of their patients may qualify.
- Patient enrollment
    - Telephone consent – if the subject is below age 8 years and qualifies for study enrollment, one of the investigators will reach out to the parent via telephone, explain the study further, and inquire whether the parent / guardian would like to have their child enrolled in the study. If the parent is agreeable to having the child enroll in the study, the phone consent script will be shared with the parent, any additional questions of the parent answered, and consent obtained over the phone. Subject assent will not be considered due to the possibility that the subject may not fully comprehend details of participation.
    - Provider will ask if patient would like to hear more about the study and page Wendy Edlund, MD or Mai Uyen Le, Pharm.D., who will meet with the family.
    - Wendy Edlund, MD or Mai Uyen Le, Pharm.D. will ensure the patient meets the inclusion and exclusion criteria.
    - Informed consent will be obtained from parent, and assent from the child, when applicable. This will be done remotely via video or telephone, as needed.
    - Enrolled patients will be randomized (via computer randomization) to three arms, each with the guideline-recommended 3 mg/kg/day dosing:
        - 3 mg/kg oral iron in the morning
        - 1.5 mg/kg oral iron BID
        - 6 mg/kg oral iron every other day in the morning

    - In order to facilitate adherence, and control for other variables that impact oral iron absorption, patients will be given study materials which provide:
        - Instructions specific to their arm of the study (e.g., how often to take the ferrous sulfate, dosage).
        - A chart to track medication adherence and side effects.
        - Instructions to maximize the uptake of oral iron (e.g., to take the iron on an empty stomach, with citric juice, and avoid dairy 1 hour prior and 2 hours after the dose).
        - A list of side effects (e.g., stool color change, nausea, constipation, teeth staining) and instructions for how to mitigate (e.g., half capful of MiraLAX, wipe off teeth after taking iron).
- Tracking adherence and side effects
    - Patients will track adherence and side effects with a daily chart.
    - Patients' parents will be called to be reminded of study protocol and check on progress by Wendy Edlund, MD or Mai Uyen Le, Pharm.D. at week 2 and 5.
- Obtaining outcomes at 2 months
    - Patients will have a ferritin drawn (standard of care).
    - Patients' parents will turn in the tracking sheet.
- Data collected
    - Patient data (age, gender, weight, dose, sleep diagnosis, comorbidities, other medications)
    - Pre and post ferritin (to calculate change in ferritin)
    - Side effects
    - Adherence

Analysis:

- Primary outcome measures: change in ferritin, side effects
- Secondary outcome measure: adherence.
- Null hypothesis: Ferritin will increase equally between the three arms.
- Statistical analyses: 1 way ANOVA F-test.

One-Way Analysis of Variance F-Tests

Numeric Results

Number of Groups: 3

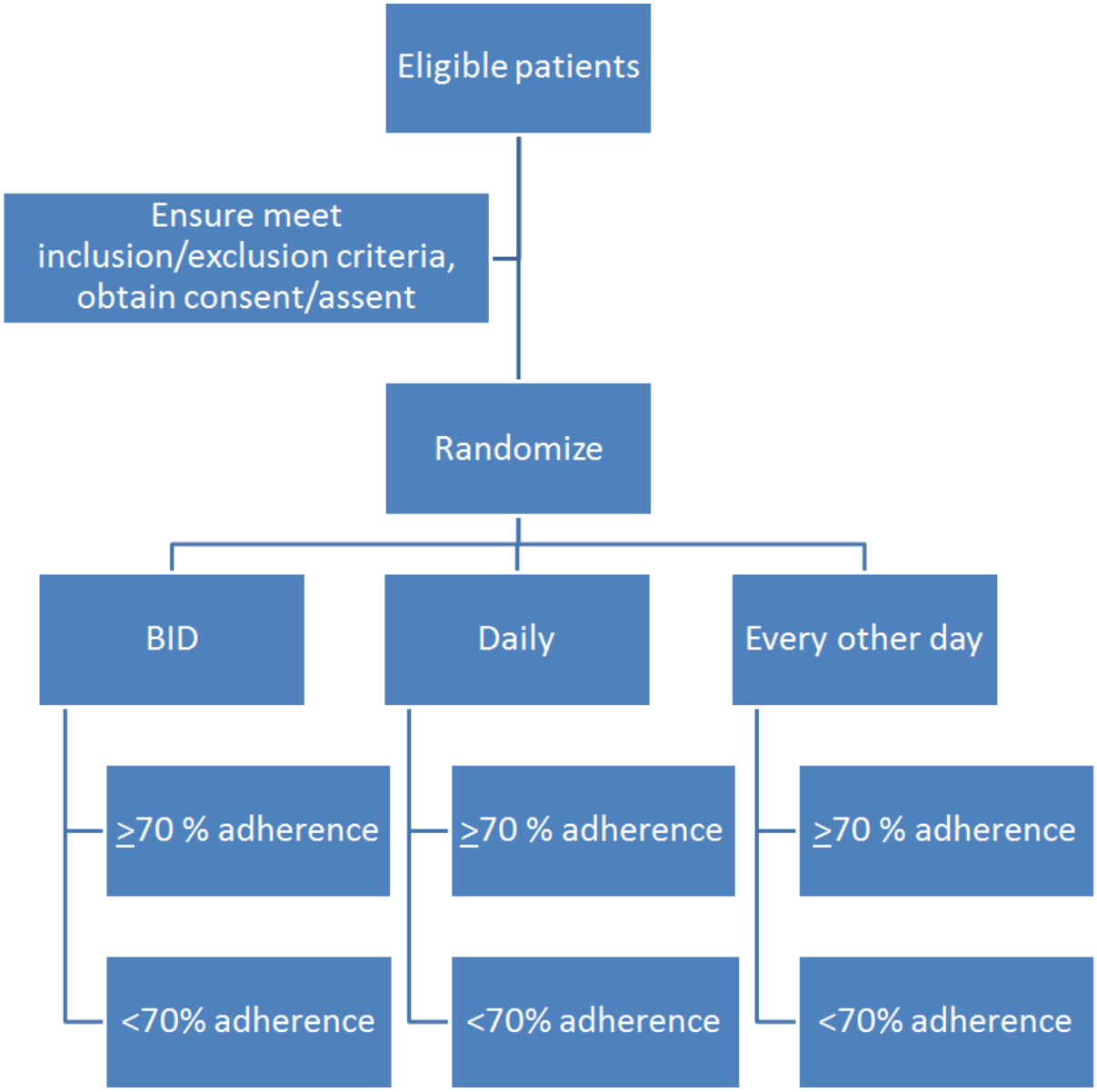
Power	Total Sample Size N	Group Alloc Set ri Set	Group Means Set μi	SD of Group Means σm	Std Dev σ	Effect Size σm/σ	Alpha
0.8143	48	ri(1)	μi(1)	0.94	2.00	0.471	0.050

Set(Set Number): Values

ri(1): 0.333, 0.333, 0.333

μi(1): 5.00, 3.00, 3.00

- The sample size required to identify a difference of ≥2 in the mean increase in ferritin between the three treatment arms is 48 total patients, 60 to allow for 20% drop out rate.
- Intention to treat analysis.
- To minimize the impact of adherence on our data, we will analyze patients with ≥70% adherence separately from those with <70% adherence within each of the three treatment arms.



REFERENCES:

1. Allen, P, et al on behalf of the International Restless Legs Syndrome Study Group (IRLSSG). Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs

syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. Sleep Medicine 41 (2018) 27-44.
2. T.J. Dye, S.V. Jain, N. Simakajornboon. Outcomes of long-term iron supplementation in pediatric restless legs syndrome/periodic limb movement disorder (RLS/PLMD). Sleep Med, 32 (2017), 213-219.
3. N. Furudate, Y. Komada, M. Kobayashi, et al. Daytime dysfunction in children with restless legs syndrome. J Neurol Sci, 336 (2014), 232-236.
4. Amos LB, Grekowicz ML, Kuhn EM, et al. Treatment of pediatric restless legs syndrome. Clin Pediatr (Phila) 2014;53:331-6.
5. Tilma J, Tilma K, Norregaard O, et al. Early childhood-onset restless legs syndrome: symptoms and effect of oral iron treatment. Acta Paediatr 2013;102, e221-6.
6. Mohri I, Kato-Nishimura K, Kagitani-Shimono K, et al. Evaluation of oral iron treatment in pediatric restless legs syndrome (RLS). Sleep Med 2012;13:429-32.
7. Simakajornboon N, Gozal D, Vlasic V, et al. Periodic limb movements in sleep and iron status in children. Sleep 2003;26:735-8.
8. Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. Cell. 2017;168(3):344-361.
9. Troutt et al. *Clinical Chemistry 2012; 58(8): 1225-32*
10. Schapp et al. *Clinical Chemistry*, Volume 59, Issue 3, 1 March 2013, Pages 527–535.
11. Donker AE, Galesloot TE, Laarakkers, CM, Klaver SM, Bakkeren DL, Swinkels DW. Standardized serum hepcidin values in Dutch children: Set point relative to body iron changes during childhood. *Pediatr Blood Cancer*. 2020;67:e28038
12. Leifer G, Keenan-Lindsay L. Leifer's Introduction to Maternity & Pediatric Nursing in Canada, Saunders Canada, 2019. p.643.
13. Abrams SA, O'Brien KO, Wen J, et al. Absorption by 1-year-old children of an iron supplement given with cow's milk or juice. Pediatr Res 1996; 39:171.
14. Camaschella, C. Iron deficiency. Blood (2019) 133 (1): 30–39.
15. Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015: 126 (17):1981-1989.
16. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol* 2017; 4 (11):e524-e533
17. Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS On* 2015;10(2):e0117383.
18. Baird-Gunning J, Bromley, J. Correcting Iron Deficiency. Aust Prescr. 2016 Dec;39(6):193-199.
19. Delrosso L, Yi T, Chan J, Wrede J, Lockhart C, Ferri, F. Determinants of ferritin response to oral iron supplementation in children with sleep movement disorders. Sleep. 2020 Mar 12;43(3):zsz234.