Protocol H-46363

Administrative information

Title

ALTERNATE DAY VERSUS DAILY ORAL IRON THERAPY IN ADOLESCENTS WITH IRON DEFICIENCY ANEMIA AND HEAVY MENSTRUAL BLEEDING: A RANDOMIZED CLINICAL TRIAL

Trial registration

Pending registration at clinicaltrials.gov

Protocol version

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Protocol contributors

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OA and CAK conceived of the study. CAK, OA, JP and LS initiated the study design. HZ provided statistical expertise in the clinical trial design and will be conducting the primary statistical analysis. All authors contributed to refinement of the study protocol and approved the final protocol.

I. Introduction

IA. Background and rationale

Anemia is a significant public health problem with high prevalence in both non-pregnant females (29%) and children (43%) [Stevens 2013]. Iron deficiency is the most significant contributing risk factor to anemia globally, affecting at least half of all cases [Stoltzfus 2004]. In the pediatric population, adolescent females are one of the populations at greatest risk for developing iron deficiency due to inadequate dietary iron intake and menstrual blood loss during a time of rapid growth [Wang 2013]. Until recently, there was little data in the literature characterizing iron deficiency and its course in adolescent females [Cooke 2017]. In adolescents with heavy menstrual bleeding (HMB), iron deficiency anemia (IDA) is a common co-morbid condition, as high as 60% in severe (defined as requiring inpatient stay or blood transfusion) HMB [Cooke 2017, Wang 2013, ACOG 2019]. Iron deficiency without anemia is also common in young women with non-severe anemia (not requiring blood transfusion), noted in 50% of this population in one study [Johnson 2016].

Iron deficiency and HMB have been separately associated with decreased quality of life and fatigue in adolescents. HMB in adolescents has been independently associated with fatigue compared to healthy controls [Wang 2013]. Treatment of iron deficiency in non-anemic women has been shown to improve fatigue, especially in women with very low ferritin (<15 ng/mL) [Krayenbuehl 2011]. Iron supplementation has also been shown to increase quality of life and cognitive function [Murray-Kolb 2011]. A large observational study of school children showed a correlation between iron deficiency and

decreased math scores [Halterman 2001]. A randomized trial of oral iron therapy versus placebo in iron deficient adolescent girls demonstrated that those receiving iron supplementation had improved scores on specific cognitive function tests [Bruner 1996].

First line therapy for IDA is considered oral iron supplementation [CDC 1998, ACOG 2019]. This recommendation may seem straightforward; however, iron absorption from supplements is generally poor, and significant gastrointestinal side effects can decrease compliance, resulting in worse clinical outcomes [Smith 2014, Tolkien 2015]. Recently, pharmacologic studies have shown promise that alternate day dosing increases the fractional iron absorption per dose. After an individual dose of an iron supplement, an increase in hepcidin (an iron regulatory hormone) is observed and results in decreased subsequent iron absorption for up to 24 hours. Thus recent studies have shown promise that iron absorption is increased when given at 48 hour intervals compared to 24 hour intervals [Stoffel 2017, Stoffel 2019, Moretti 2015]. This data also suggests that less frequent iron supplementation dosing (i.e. with an alternate day regimen) may decrease unwanted side effects while increasing the absorption per dose, resulting in improved treatment compliance. A longer-term, pragmatic trial of iron supplementation comparing daily versus alternate day dosing has not yet been performed.

IB. Objective

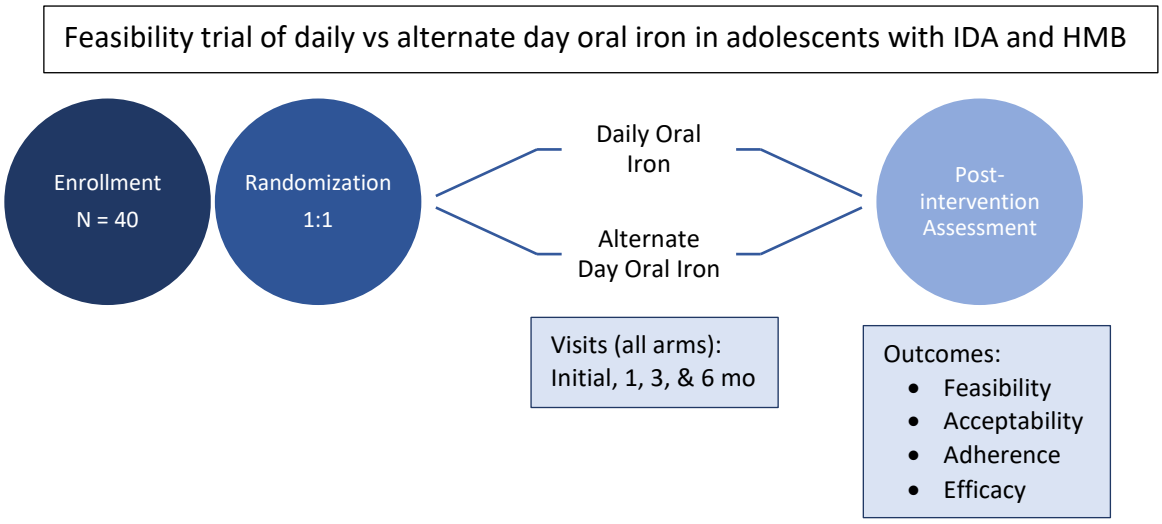
i. *Objective*: To assess the feasibility of performing a randomized trial comparing standard care daily dosing of oral iron to alternate day dosing of oral iron in adolescent girls with iron deficiency anemia (IDA) and heavy menstrual bleeding (HMB).

ii. *Research Hypotheses*:

- **a.** Enrollment will be feasible (>50% of patients who meet eligibility criteria will agree to enroll in the trial).
- **b.** The interventions will be acceptable (>75% study retention rate in both arms at 12 week follow up and >80% adherence rate in both arms).

IC. Trial design

This study is a randomized, open-label, two arm feasibility trial. The subjects will be randomized 1:1 to (a) daily dosing of oral iron or (b) alternate day dosing of oral iron. The pilot trial of 40 subjects will test the (1) feasibility of randomization of daily versus alternate day oral ion, (2) acceptability of alternate day oral iron versus standard daily oral iron dosing, (3) oral iron adherence rates in both arms, and (4) clinical efficacy of both arms as measured by change in hemoglobin concentration at 1-, 3- and 6-month clinic visits.



II. Methods

IIA. Study setting

The study will be conducted at Texas Children's Hospital in Houston, Texas, United States of America. The study will be conducted in pediatric gynecology inpatient service and outpatient clinic settings.

IIB. Eligibility criteria

Patients (or their parent/legal guardian) must provide written, informed consent before any study procedures occur. Patients under age 18 must also provide verbal assent which will be recorded by the parent in the presence of study personnel.

IIC. Inclusion Criteria

Patients eligible for the trial must meet all of the following criteria at enrollment:

Criteria	**Rationale**
Age 9 years or greater and less than age 22 years	Age group most affected by HMB and severe anemia
Heavy menstrual bleeding, defined as a Pictorial Blood Assessment Chart (PBAC) Score >100 (see "PBAC" attachment)	Used in many studies as a standard definition of HMB, and has been studied for use in adolescents.
Iron deficiency anemia, defined as: • Hemoglobin <12 g/dL AND • Ferritin <15 ng/mL	Hemoglobin <12 is the definition of anemia in teenage girls and women. Severely low ferritin is defined as <15 in many studies and patients in this category are most in need of iron therapy.

IID. Exclusion Criteria

Patients will be excluded from enrollment in the study if they have any of the following:

Criteria	**Rationale**
Non-uterine cause of vaginal bleeding	Outside the scope
Pregnancy	Protected population, different physiology
Chronic kidney disease	Multifactorial etiology for IDA, difficult to treat with oral iron alone
Gastrointestinal (GI) disease, defined as: • Serology confirmed celiac disease • Active GI blood loss (gross blood, hemoccult positive stool)	Increased risk of additional causes of anemia
Active malignancy	May cause increased risk of bleeding
Inability to follow-up at TCH	
Receipt of intravenous iron within 30 days prior to enrollment	Expect IDA resolution to occur
Known inability to tolerate oral iron or allergy to oral iron	

IIE. Interventions

i. Oral iron therapy

a. At enrollment, patients will be randomized 1:1 between daily versus alternate day dosing of ferrous sulfate 325 mg tablet (65 mg elemental iron). Randomization will occur as described in section IIIFi.
    i. Arm A: ferrous sulfate 65 mg elemental iron once every morning
    ii. Arm B: ferrous sulfate 65 mg elemental iron once every other morning
b. Subjects in both arms will receive an informational handout on how to properly take iron for maximal absorption every 24 or every 48 hours depending on the arm. (Please see attachments "Patient Iron Info Alternate Day" and "Patient Iron Info Daily").
c. All subjects will receive a 28 day pill box at enrollment. Subjects in Arm A will receive 100 iron tablets and subjects in Arm B will receive 50 tablets for first 12 weeks of therapy.
d. At the end of 12 weeks of oral iron therapy, those subjects with resolution of IDA will be instructed to discontinue iron therapy. Those subjects who have partial or incomplete resolution of IDA will receive next 100 tabs (Arm A) or 50 tabs (Arm B) for continuation of study treatment for an additional 12 weeks.

ii. Laboratory follow up
a. All subjects will have the following labs obtained as part of the study:
    i. CBC without differential obtained at 4, 12 and 24 weeks (standard of care)
    ii. Iron panel at 12 and 24 weeks (standard of care)
    iii. Iron panel at 4 weeks (study purposes, will be obtained with standard of care blood draw and require 0.5-1mL of additional blood drawn)

iii. Clinical assessment
a. All subjects will complete the following procedures at enrollment, 4, 12 and 24 weeks:
    i. Menstrual bleeding: Pictorial blood assessment chart (PBAC) will be filled out and score calculated at enrollment and each subsequent visit (see attachment "PBAC") [Sanchez 2012, El-Nashar 2015]
    ii. Gastrointestinal side effects: Participants will be asked a standardized set of questions regarding common side effects of iron therapy (see attachment "GI side effects") [Pereira 2014]
    iii. Fatigue assessment: NIH PROMIS Pediatric Fatigue – Short Form 10a will be used to assess fatigue at enrollment and each subsequent visit (see attachment "PROMIS Pediatric Fatigue 10a")
b. All subjects will complete the following procedures at 4, 12 and 24 weeks:
    i. Adherence: patients will be asked to bring any remaining pills to the visit and these will be counted as a direct measure of adherence.

iv. Concomitant care
a. Subjects will be instructed that they should not take a multivitamin containing iron during the study. Otherwise, there will be no limitation on concomitant hormonal therapy, antifibrinolytic therapy, or other treatment of HMB.
b. There will be a prohibition of IV iron administration. Any receipt of IV iron prior to 12 week follow up would lead to withdrawal from the study.
c. Patients who develop severe anemia requiring pRBC transfusion >7 days after enrollment and prior to 12 week follow up will be removed from the study.
d. Other hematologic treatments (i.e. Amicar, Lysteda) will not be directed by or have an effect on the study protocol but will be recorded as part of the study.
e. Hormonal therapies (i.e. IV estrogen, combined contraceptive pills, levonorgestrel intrauterine device, etc.) will not be limited but will be recorded as part of the study.

f. Additional imaging and laboratory studies (pelvic ultrasound, bleeding disorder work up) will not be directed by the study protocol but will be recorded as part of the study.

TIMELINE

Study procedures	**Baseline**	**Week 4 (+/- 3 days)**	**Week 12 (+/- 1 week)**	**Week 24 (+/- 1 week)**
Screening	X			
Consent/Enrollment	X			
Randomization	X			
Clinical visit	X	X	X	X
*Laboratory studies	X	X	X	X
Medication dispense	X		X	
Adverse effects review		X	X	X
Questionnaires (PBAC, fatigue)	X	X	X	X
Adherence assessment		X	X	X

*Laboratory studies at each visit include: CBC without differential and iron panel

III. Outcomes

IIIA. Primary outcome measures

The primary outcome will be the percentage of eligible patients enrolled.

IIIB. Secondary outcome measures

i. The following outcomes will be assessed for the pilot study:
   a. Agreement with randomization (willingness to receive treatment arm assigned)
   b. Retention (visit follow-up adherence)
   c. Adherence (rate of adherence to medication at 12 weeks in both arms based on returned medication volume)

ii. The following laboratory and clinical data will be collected to inform future clinical trial design (i.e. estimates of variability).
   a. CBC, iron studies at 4, 12 and 24 week follow up
   b. Additional laboratory data collected on the patient at enrollment
   c. PBAC score
   d. Fatigue score
   e. Gastrointestinal side effects
   f. Demographic information at enrollment
   g. Gynecologic medical and/or surgical treatment
   h. Hematologic treatment
   i. Adverse events

IIIC. Sample size

We plan to enroll 40 patients in this feasibility study. This sample size was calculated based on hypothesized feasibility of enrollment and data on patient population of the pediatric gynecology service. On average from July to December 2019, 2-4 patients were admitted to the gynecology inpatient service and 5-10 patients who present to the gynecology outpatient service per month who would meet criteria for enrollment in the study. At minimum, this would mean 84 patients would present over 12 months (7 per month) who would meet eligibility criteria. With an anticipated study

enrollment rate of 50% of eligible patients, it will be reasonable to enroll 40 patients over a 12 month period.

IIIE. Recruitment

i. The PI will inform all gynecology providers of the study and eligibility criteria prior to study implementation. Two of the PIs are included in a total of ten gynecology providers who practice at the Texas Children's Hospital Main campus (including 4 attendings, 2 nurse practitioners and 4 fellow physicians). Information about the clinical trial will be provided via direct communication by the PI and co-investigators with these practitioners at Texas Children's Hospital.

ii. Potential subjects will be identified through review of new patient referrals to Texas Children's Pediatric and Adolescent Gynecology Division, inpatient admissions and/or consultations for HMB. The PI has access to these patient's clinical data as part of routine clinical care and shared patient lists. The outpatient gynecology clinic schedule will be pre-screened daily by the data manager who will notify the PI of potential patients. The PI will assess eligibility and notify the gynecology provider about those subjects who are potentially eligible. The PI or a Co-I will describe the study to eligible patients and their parent/guardian (if less than 18). The voluntary nature of the study will be emphasized.
    a. If interested in enrollment and meets eligibility criteria, then informed consent will be obtained and the subject enrolled. Patients or parents must provide written, informed consent before any study procedures occur.
    b. If interested but laboratory evaluation not yet obtained and eligibility unable to be determined at the time of the visit, the PI or a Co-I will obtain a phone number and permission to contact the patient/patient's parent for follow up if eligible. If the patient then meets eligibility criteria and has given permission to be contacted, the data manager will call the patient or her parent to schedule a research only visit within 1 week. At this visit, informed consent will be obtained. Patients or parents must provide written, informed consent before any study procedures occur.

iii. Screening and enrollment log
    a. A secure screening and enrollment log will be kept. Each screened patient will be categorized as either: ineligible, eligible but not approached, eligible and enrolled, eligible and declined. If the latter (eligible and declined), the reason for declining will also be obtained and noted in the study log.

IIIF. Allocation

i. *Sequence generation and concealment:* Participants will be randomly assigned to either the control (daily) or intervention (alternate day) group with a 1:1 allocation per a computer-generated randomization schedule stratified by initial (or post-transfusion if transfusion is given) hemoglobin (less than or equal to 8 g/dL vs greater than 8 g/dL).

ii. *Implementation*: The study personnel enrolling the participant will enter the participant's study ID number and enrollment hemoglobin (initial or post-transfusion) into REDCap software programmed for allocation and the software will then assign the subject to an intervention group. The study personnel will then provide information regarding the intervention to the participant, who will not be blinded to the intervention.

iii. *Blinding*: Due to the nature of the intervention, blinding of participants or staff is not feasible. Every attempt will be made, in the study literature and in training of personnel, to avoid bias of participants related to expected outcomes especially as related to adverse effects. An employee outside the research team will have information regarding the allocated group assignment in a

separate data sheet so the researchers and statistician can analyze data without having access to information regarding the allocation.

IIIG. Data

i. *Collection:* Data on the primary outcome will be collected by study personnel as the number of patients enrolled out of the number of patients approached for enrollment. Secondary outcomes will either be obtained through data entry from the medical record for demographic information, lab results and gynecologic or hematologic treatment received by the patient during the study period. Participants will be assessed for adherence, PBAC score, fatigue score and GI side effects at each subsequent visit.

ii. *Retention:* All reasonable efforts will be made by study investigators and staff to promote participant retention in the study. Data collection will continue on participants who are known to have discontinued the study intervention regardless of reason for discontinuation, which will not be a reason for withdrawal from the study. Participants may withdraw from the study at any time and no additional data collection would be performed on patients who choose to withdraw.

iii. *Management:* All data will be entered electronically and housed in Texas Children's Hospital REDCap. REDCap is a self-managed, secure, web-based data support system. The data is backed up offsite nightly and hosted in a secure environment maintained by Information Resources. This password protected study database will include a subject's personal identifiers and all Protected Health Information (PHI) such as medical history. All personnel who will be accessing the data will be trained in REDCap and have individual user ID and passwords. Subjects will have a study ID number that will be utilized in lieu of personally identifiable information for all research data provided to statisticians. Documents such as signed informed consent and other paper files will be kept in a locked cabinet that only the PI and her staff have access to in a secure Baylor College of Medicine office building. These files will be maintained in storage for 3 years after completion of the study.

IIIH. Statistical methods

i. All planned analyses will be descriptive in nature. Summary statistics such as mean, standard deviation, and 95% confidence intervals will be reported. No formal hypothesis testing will be performed.

IIII. Harms

Significant harms related to the study intervention are not anticipated considering the planned intervention is a commonly prescribed medication that can also be obtained over the counter. The participants may experience discomfort related to common side effects of iron administration including unpleasant taste, nausea, abdominal pain, dark stools, constipation, and/or diarrhea. Participants and their families will be made aware that accidental or intentional iron overdose is a serious potential effect and will be advised to keep iron pills away from small children for the duration of the study. It is possible that subjects randomized to the alternate day intervention may have a slower resolution of iron deficiency anemia. Serious adverse events following initiation of iron supplementation during the study period will be reported to the IRB. Gastrointestinal side effects and adherence will be tracked and will be compared between study groups.

IIIJ. Auditing

After the first subject is enrolled, compliance personnel will audit pharmacy, laboratory and consenting procedures for proper conduct and documentation. Additional audits may occur without warning as warranted by the initial review or spontaneously.

IV. Ethics and dissemination

IVA. Research ethics approval

The protocol, informed consent form, participant education materials, and participant questionnaires and any subsequent modifications will be approved by the Institutional Review Board (IRB). Subsequent to initial review and approval, the IRB will review the protocol at least annually.

IVB. Protocol amendments

Any modifications of the study protocol which substantially impact the patient safety, study objectives, study design, patient population, sample sizes, or significant administrative changes will be approved by the IRB prior to implementation.

IVC. Consent/assent

Patients who meet the inclusion criteria in the outpatient or inpatient service will be invited to participate in the study. Study personnel will explain the purpose of the study and provide an information sheet regarding the study. The voluntary nature of the study will be emphasized. An informed consent form will be obtained from a parent/legal guardian of participants <18 years. Participants who are 18 years old or older will sign their own consent form. Information regarding the study in age-appropriate language will be provided to the participant if less than 18 years old and assent will be obtained from the participant.

IVD. Confidentiality

There is a minimal risk of loss of confidentiality, but all efforts will be made to protect subject privacy and confidentiality. Upon enrollment in the study, participants will be assigned a study ID number. Identifying data will be linked to the study ID number in a separate data set. All data will be entered electronically and housed in Texas Children's Hospital REDCap. REDCap is a self-managed, secure, web-based data support system. The data is backed up offsite nightly and hosted in a secure environment maintained by Information Resources. This password protected study database will include a subject's personal identifiers and all Protected Health Information (PHI) such as medical history. All personnel who will be accessing the data will be trained in REDCap and have individual user ID and passwords. Subjects will have a study ID number that will be utilized in lieu of personally identifiable information for all research data provided to statisticians. Documents such as signed informed consent and other paper files will be kept in a locked cabinet that only the PI and her staff have access to in a secure Baylor College of Medicine office building. These files will be maintained in storage for 3 years after completion of the study.

IVE. Costs/payments

i. Clinical Costs: Patients will be undergoing laboratory evaluation and treatment for abnormal uterine bleeding and iron deficiency anemia. These are not research costs but clinical costs which would be incurred whether or not the patient participated in the study. Subjects/subjects' insurance will be responsible for the costs of the tests/analyses and clinical visits during participation in the study. The only additional laboratory test that will be obtained through the study that is not standard of care is a serum iron study panel to be obtained at 4 weeks. This will be covered by research costs and not charged to the patient or patient's insurance. The cost of the prescribed iron medication will be covered as part of the study.

ii. Patient payments: A pill box worth $15 will be provided at study enrollment. A $13 parking voucher will be provided at enrollment and at 3 subsequent follow up clinic visits for a total of $52. Total compensation for participation will therefore be $67 over a 6 month period.

IVF. Declaration of interests

The authors of this study have no conflicts of interest to report.

IVG. Access to data

The principal investigator will have access to all trial data. The PI will provide access to additional approved co-investigators as needed during study analysis.

IVH. Ancillary/post-trial care

Ancillary and post-trial care will be provided by the patient's primary gynecologist as needed.

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