JPPT | Prospective, Observational Study

Impact of Acid Suppression Therapy on Iron Supplementation in the Pediatric Intensive Care Unit

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OBJECTIVE We assessed the impact of acid suppression therapy (i.e., ranitidine or proton pump inhibitors) on iron supplementation and its ability to maintain or alter laboratory values that are commonly associated with anemia.

METHODS This was a prospective, observational trial. The primary outcome was changes in serum iron levels from baseline. Secondary outcomes were changes in hemoglobin (Hgb) and hematocrit (Hct), transfusions, and maintenance of an alkalotic gastric pH.

RESULTS Thirty-four patients (mean 24 ± 43 months) met inclusion criteria. The serum iron levels increased to 50.9 ± 24.6 mcg/dL by day 3. The mean difference from baseline was 1.5 mcg/dL (95% CI, 1.14–1.98, p = 0.0056). Gastric pH increased to 4.68 ± 1.49 on day 5. The mean Hgb and Hct increased on day 5 to 10 ± 1.06 g/dL and 29.6% ± 3.27%, respectively. The mean difference of Hgb was 1.15 g/dL (95% CI, 0.51–1.78, p = 0.0009). The mean difference of Hct was 3.04% (95% CI, 1.11–4.97, p = 0.0032).

CONCLUSIONS The use of antacids along with oral ferrous sulfate supplementation did not affect the absorption of iron. Serum iron, Hgb, and Hct all showed statistically significant increases despite combined antacid and iron therapy. Thus, despite use of antacids, combination use showed increases in iron absorption.

ABBREVIATIONS H_2RA, histamine type-2 receptor antagonist; Hct, hematocrit; Hgb, hemoglobin; IV, intravenous; PICU, pediatric intensive care unit; PPI, proton pump inhibitor

KEYWORDS anemia; antacid; dietary supplements; drug interactions; iron; proton pump inhibitor; ranitidine

J Pediatr Pharmacol Ther 2021;26(4):366–371

DOI: 10.5863/1551-6776-26.4.366

Introduction

Iron deficient anemia is a common diagnosis seen in hospitalized pediatric patients often due to iatrogenic causes. Anemia may be present in 33% of patients on admission to the PICU and 41% of patients during the PICU stay.[1] Potential causes for anemia include chronic anemia, underlying disease, as well as blood loss.[1]

Patients who are diagnosed with iron deficient anemia are commonly treated with oral iron supplementation due to the benefits it provides. Although anemia may be treated with red blood cell transfusion, the risks of transfusion include transfusion-transmitted infection, acute hemolysis, and immunosuppression.[1] Some of the benefits pediatric patients with iron deficient anemia may see from iron supplementation include the following: improved immune function, anemia avoidance, achievement of developmental milestones, maintaining normal age cognitive function, as well as possibly preventing fatigue, shortness of breath, and poor work performance.[2,3]

The effects of acid suppression therapy on iron supplementation as well as iron absorption have been debated for many years. In order to reduce ferric iron to its more soluble ferrous form, it is theorized that an acidic medium (i.e., gastric secretion, pH of ≤ 2.5) is needed.[4] The conversion of ferric iron to its more soluble ferrous form by the acidic gastric secretions allows for increased duodenum absorption as well as allow the iron to form various complexes that result in increased solubility and uptake.[4-6] Clinically, proton pump inhibitor (PPI) administration has demonstrated decreases in iron absorption in iron-deficient patients.[5,7] Also, evidence has been documented showing that chronic histamine type-$_2$ receptor antagonist (H_2RA) or PPI use may lead to anemia in patients with anemia risk factors.[8] However, in healthy adults, a short duration of PPI therapy does not decrease iron absorption,[9] and in patients who have Zollinger-Ellison syndrome, long-term use of a PPI or H_2-receptor antagonists did not result in iron deficiency.[10]

In children who are admitted to the PICU, American Society of Health-System Pharmacists (1999) guidelines on stress ulcer prophylaxis support the prophylactic use of PPIs or H_2RAs because 50% of children in the PICU on mechanical ventilation develop upper gastrointestinal lesions; lesions may develop in 60% of children within 1

Table 1. Hemoglobin and Hematocrit Cutoff Levels That Defined the Presence or Absence of Anemia*

Patient Characteristics	Cutoff	
	Hgb Level, g/dL†	Hct, %
Age		
<6 mo	9.5	31
6 mo–6 yr	10.5	33
7–12 yr	11.0	34
>12 y		
Female	12.0	37
Male	14.0	42

Hct, hematocrit; Hgb, hemoglobin

* Anemia was defined as Hgb level (primary indicator) or Hct (secondary indicator).[14]

† Cutoff for Hgb level shown for white children; in black children, Hgb level cutoff was defined as 0.5 g/dL less than values shown.

day and 90% of children within 3 days.[11-14] In our institution, children who are admitted to the PICU commonly receive stress ulcer prophylaxis (oral or IV) with a PPI or H_2RA and an oral iron supplement for iron deficiency anemia. However, there is limited clinical information about the effects of PPIs and H_2RAs on iron status in critically ill children.

We hypothesized that iron absorption would not be inhibited by antacid use and hemoglobin (Hgb) and hematocrit (Hct) would still increase. This prospective, observational single-blind trial was conducted to determine whether or not patients iron stores are maintained or altered while receiving either oral/IV ranitidine or a PPI along with oral ferrous sulfate supplementation (oral or post-pyloric) during their PICU stay.

Materials and Methods

Study Design. This was a prospective, observational, trial to assess the effect of acid suppression therapy on oral iron supplementation and laboratory values that are associated with anemia. The trial was performed in the 14-bed PICU of the University of South Alabama Children's and Women's Hospital. Physicians, physician assistants, nurses, and pharmacists monitored the patients, drew laboratory tests, and recorded adverse events that were associated with the interventions. The primary indicators of anemia were serum iron and Hgb levels, and the Hct was used as an additional indicator of the presence or absence of anemia (Table 1).

Outcomes. The primary indicators of anemia used were serum iron, Hgb, and Hct based on the following definitions of anemia for age in Table 1. The primary outcome was changes in serum iron levels from baseline. Secondary outcomes that were evaluated were changes in Hgb and Hct, number of red blood cell transfusions, and maintenance of an alkaline gastric pH (pH ≥ 2.5).

Participants. Patients included in the study were patients aged < 18 years who were admitted to the PICU, had ≥ 1 blood draw per day, received an iron supplement (via oral or nasogastric), had acid suppression therapy (H_2RA or PPI), and consented to participate through 1 or both legal guardians and verbal patient assent for patients aged > 6 years. Patients were excluded for history of chronic anemia, chronic kidney disease, glucose-6-phosphate dehydrogenase deficiency, hemochromatosis, use of nonsteroidal anti-inflammatory drugs, consumption of ≥ 1 pint of cow's milk per 24 hours, *Helicobacter pylori* infection within the previous 6 months, short bowel syndrome, gastrointestinal bleed, gastrointestinal ulcer requiring transfusion or causing hemodynamic instability, bleeding from nasogastric tube or rectum, or small bowel resection.

Study Procedures. Patients were grouped on the basis of physician preference to treatment with: 1) iron supplement (ferrous sulfate) plus an H_2RA (ranitidine) or 2) iron supplement (ferrous sulfate) plus a PPI (omeprazole or lansoprazole). A majority of patients were already on the antacid of choice prior to enrollment in the study and initiation of iron supplementation. Each patient was assigned an identification number separate from his or her hospital admission record number in order to maintain confidentiality. Ferrous sulfate was administered by mouth, nasogastric tube, or percutaneous endoscopic gastronomy tube. Ferrous sulfate (1 mg/kg/dose, maximum 200 mg/day) was given every 8 hours. Ranitidine (4–8 mg/kg/day) was given IV or orally every 6 to 12 hours; esomeprazole (fixed dose: < 20 kg = 10 mg, ≥ 20 kg = 20 mg and > 12 years of age = 40 mg) or lansoprazole (7.5 mg infants ≥ 3 months, 15 mg ≤ 30 kg or 30 mg > 30 kg) was given IV or orally once daily.

Daily medication administration records were reviewed to evaluate the prescribed regimens. Gastric pH was monitored before the initiation of iron therapy (pretreatment) and on iron therapy day 5 when the patient remained in the PICU. Gastric secretions were sampled and tested 30 minutes before administration of ferrous sulfate preparation. Gastric pH was obtained via the Gastroccult (Beckman Coulter, CA) test from secretions collected through nasogastric tubes that have been previously placed based on physician attending orders a priori of the investigational study.

Complete blood count and baseline iron panels (i.e., serum iron, ferritin, and reticulocyte count) were drawn before starting iron and acid suppression therapy. Hemoglobin, Hct, and serum iron tests were repeated at least 3 days after starting ferrous sulfate. Patient demographics, informed consent/assent, type of acid suppression therapy, ferrous sulfate dose and route, and adverse drug reactions were recorded.

Statistical Analysis. Data analysis was performed with statistical software (SAS version 9.4, SAS Institute, Inc, Cary, NC). Descriptive statistics were determined

Table 2. Characteristics of Patients (N = 34) Included in the Study of Acid Suppression Therapy and Iron Supplements in the Pediatric Intensive Care Unit

Characteristic	Value
Sex, n (%)	
Female	19 (56)
Male	15 (44)
Age, mean ± SD, mo	24 ± 43
Weight, mean ± SD, kg	11 ± 11
Race, n (%)	
White	18 (53)
Black	13 (38)
Asian	1 (3)
Hispanic	1 (3)
Other or unknown	1 (3)
Admission diagnosis, n*	
Respiratory failure/distress	14
Respiratory syncytial virus	7
Status epilepticus	2
Pneumonia	9
Sepsis	1
Cerebral edema	1
Hyponatremia	1
Hydrocephalus	1
Craniotomy	1
Supraventricular tachycardia	1
Adrenal hypertrophy	1
Hernia	1
Pulmonary hypertension	1
Gastroenteritis	1
Epidural hematoma	1

* Some patients had multiple diagnoses.

for pre-treatment characteristics between groups. A quantile-quantile plot was performed for serum iron, Hgb, and Hct to evaluate normality before performing the paired *t* test. Logarithmic transformation was used for the serum iron results because of absence of normality in the quantile-quantile plot. Treatment effects on serum iron, Hgb, and Hct were evaluated with paired *t* test. The general linear model with repeated measures analysis of variance and mixed effect model with repeated measures were used to test the effect of a treatment at different times including the main effects within and between subjects and interaction effects between factors including age, weight, sex, race, acid suppression, blood transfusion, and gastric pH. Hemoglobin level and Hct from pre-treatment to post-treatment were extrapolated, and the next most recent Hgb level or Hct was taken. Between-subject tests and within-subject effects were evaluated for the dependent variables (serum iron, Hgb, Hct) vs the independent variables (gender, ethnicity, blood transfusions). Statistical significance was defined at the 95% CI for relative risk equivalent to $p < 0.05$.

Table 3. Antacid Therapy, Iron Supplements*, and Transfusions Given to Patients (N = 34) in the Pediatric Intensive Care Unit

Parameter	Patients, n (%)
Type of antacid therapy received	
Iron + H_2 antagonist	25 (74)
Iron + PPI + H_2 antagonist	5 (15)
Iron + PPI	4 (12)
Blood transfusion while taking iron supplement	17 (50)
Alkaline gastric pH	21 (63)

H_2, histamine type-2; PPI, proton pump inhibitor

* Iron supplement dosage, 1 mg/kg/dose given 3 times per day (total dose range: 2–119 mg).

Results

The 34 patients included in the study were mostly white or black with an average age of 2 years (Table 2). Most patients received iron and an H_2RA (ranitidine), half of the patients received a blood transfusion, and most patients maintained an alkaline gastric pH throughout the study (Table 3). By 5 days post-treatment, there were significant increases in the serum iron level from baseline (43.2–50.9 mcg/dL), Hgb level (8.9–10 g/dL), and Hct (26.4%–29.5%) and non-significant decreases in gastric pH (4.9–4.7) (Figure 1). The median ferritin did not change significantly from baseline (112–132 mcg/L). The median reticulocyte count was 1.52% to 1.58% prior to and after iron therapy, respectively. Overall, only 3 patients had low reticulocyte counts (1 prior iron therapy only, 2 prior to and after iron therapy).

The primary outcome of serum iron level from the paired *t* test showed a mean difference post-treatment of 1.50 mcg/dL (95% CI, 1.14–1.98, $p = 0.0056$). Second-

Figure 1. Mean pre-treatment and post-treatment results.

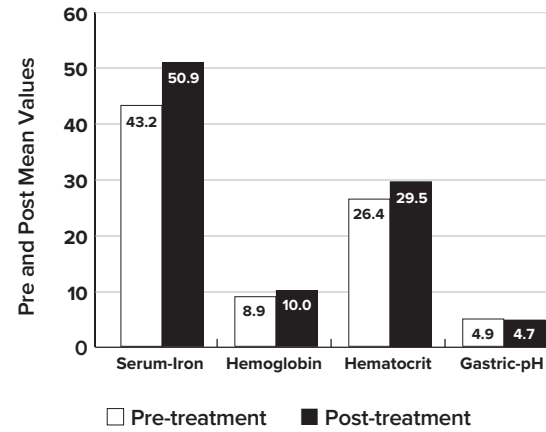


Figure 2. Change in serum iron levels over time.

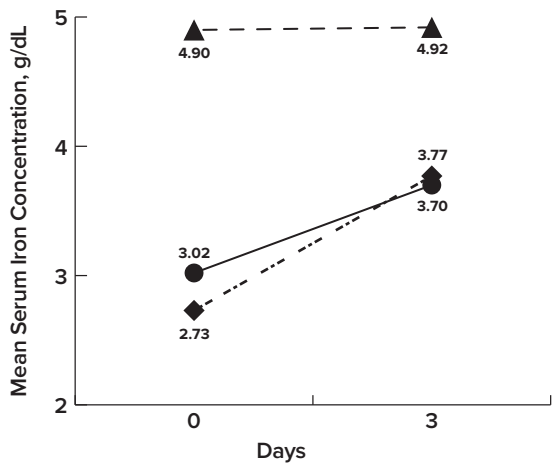
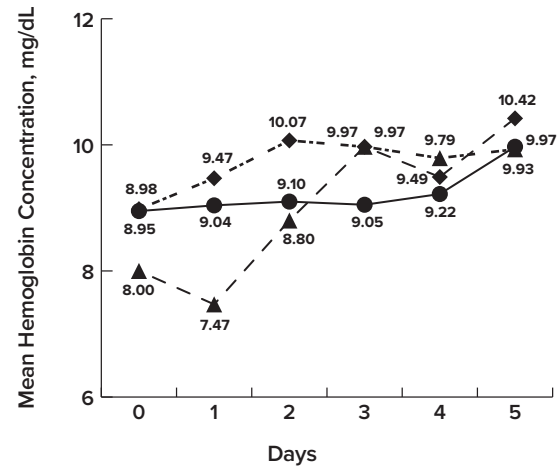


Figure 3. Change in hemoglobin over time.



H_2RA, histamine type-$_2$ receptor antagonist; PPI, proton pump inhibitor

– - –◆– - –, Iron + PPI + H_2RA; — —▲— —, Iron + PPI; —●—, Iron + H_2RA

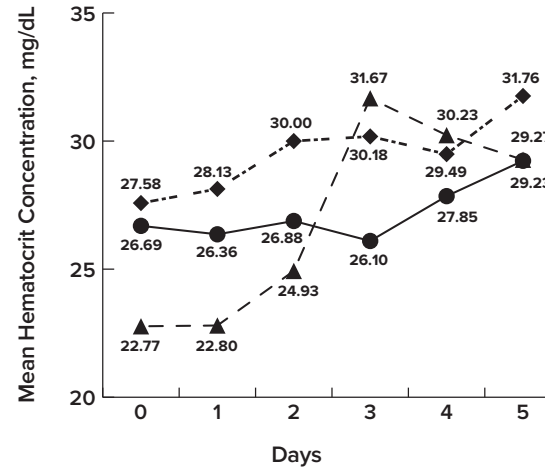
ary outcomes of Hgb and Hct also showed significant changes. Gastric pH decreased to 4.68 ± 1.49, the mean Hgb increased to 10 ± 1.06 g/dL, the mean difference of Hgb from pre-treatment was 1.15 g/dL (95% CI, 0.51–0.1.78, p = 0.0009), the mean Hct increased to 29.6% ± 3.27%, and the mean difference of Hct was 3.04% (95% CI, 1.11–4.97, p = 0.0032). All results except for gastric pH were statistically significant with p values < 0.05. Figure 1 shows the change in serum iron, Hgb from day 3, and Hct, and gastric pH from baseline to day 5 in all treatment groups.

The between-patients test, which compared all patients on iron, indicates that the effects of weight, acid suppression, blood transfusion, and gastric pH were statistically significant (p = 0.0004, p < 0.0001, p = 0.0003, and p = 0.0260, respectively). The within-subjects test, which compared 1 patient on iron, indicates that the main effect of time (baseline vs day 3) was not significant (p = 0.2651), and the interactions listed above were not significant except for time*gastric pH (p = 0.0010) at α = 0.05.

The results of the general linear model and mixed model are shown in Figures 2 to 4. Figure 2 depicts how the serum iron means change over time among 3 different acid suppression groups. However, the interaction was not statistically significant at 0.05. Figures 3 and 4 depict how the Hgb and Hct means changed over time among 3 different acid suppression groups; however, the interaction was not statistically significant (p = 0.7364 and p = 0.4378, respectively at 0.05).

The blood transfusions were a confounding factor accounted for in the models for changes (pre-treatment and post-treatment) in serum iron, Hgb, and Hct using the general linear model. But the changes (post-treatment vs pre-treatment) in Hgb and Hct were not statistically significant because the variable "time" was not significant in Hgb and Hct (p = 0.2335 and p = 0.6227, respectively).

Figure 4. Change in hematocrit over time.



H_2RA, histamine type-$_2$ receptor antagonist; PPI, proton pump inhibitor

– - –◆– - –, Iron + PPI + H_2RA; — —▲— —, Iron + PPI; —●—, Iron + H_2RA

Discussion

The present results showed that serum iron level, Hgb level, and Hct were able to increase despite concomitant antacid therapy in hospitalized children. Iron

Table 4. Factors Associated With Outcomes of Treatment With Antacids and Iron Supplements in Patients (N = 34) the Pediatric Intensive Care Unit

Test Variable	Factor	p value*
Between patients		
Serum iron level	Body weight	≤ 0.003
	Acid suppression	≤ 0.0001
	Blood transfusion	≤ 0.003
Hgb level	Blood transfusion	≤ 0.02
Hct	Blood transfusion	≤ 0.05
Within patients		
Serum iron level	Time (0 vs 3 days)	NS
Hgb level	Time (0 vs 5 days)	NS
	Time and sex	≤ 0.03
	Time and blood transfusion	≤ 0.01
Hct	Time (0 vs 5 days)	NS
	Time and sex	≤ 0.03
	Time and blood transfusion	≤ 0.003
Generalized linear and mixed models		
Serum iron level vs time	Acid suppression	NS
Hgb level vs time	Acid suppression	NS
Hct vs time	Acid suppression	NS

Hct, hematocrit; Hgb, hemoglobin; NS, not significant

* $p > 0.05$.

absorption still occurred when a patient was taking any combination of antacids: H_2RA alone, PPI alone, or a combination of an H_2 antagonist and PPI, similar to previous results.[9,10] Patients receiving antacid therapy had mean gastric pH of 4.7, which was higher than normal gastric pH. Nevertheless, iron was absorbed despite the higher gastric pH associated with antacid therapy. The only between-subject factors that showed any increase on the change in serum iron level, Hgb level, and Hct from pre-treatment to day 3 or 5 were body weight (serum iron level), acid suppression (serum iron level), and receipt of a blood transfusion (serum iron level, Hgb level, and Hct) (Table 4). Iron supplementation did not decrease or avoid the necessity of blood transfusions. Based on the statistical models, the blood transfusions did not appear to affect the overall change in serum iron, Hgb, and Hct from baseline.

Limitations of the present study included the small number of patients, no analysis of diet as a confounder, route of administration (orally vs nasogastric or oral gastric), short time period, inclusion of patients from only 1 institution and no control group to compare to. It was difficult to have a control group not on any antacid in our PICU because stress ulcer prophylaxis is our standard of care for the PICU patients especially if they are on mechanical ventilation. In addition, assigned therapy (H_2RA vs PPI vs both) was determined by physician preference, which may have skewed the results. It is possible that iron would have been absorbed to a greater extent without antacid therapy, but our primary goal was to demonstrate that iron is absorbed despite antacid therapy. We were unable to enroll enough patients who were not on any antacid therapy while in the PICU. Moreover, we attempted to control for confounders such as blood transfusions and gastric pH using a statistical test. However, there is still a possibility that blood transfusions could have affected our results as well as the gastric pH. From our study, we were unable to determine if there was a parallel relationship between increasing gastric pH and decreasing extent of iron absorption.

In summary, the use of oral or IV ranitidine and a PPI alone or in combination, with oral ferrous sulfate resulted in iron absorption. Iron supplementation resulted in increased serum iron levels, Hgb levels, and Hct despite concurrent antacid therapy. A larger, long-term comparative study may be warranted to validate the present results.

Article Information

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Disclosures. Dr. Chung has relationship with MobilCare. Other authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. All authors had full access to all data and take responsibility for the integrity and accuracy of the data analysis. Editorial support was provided by the Dean's Office, University of South Alabama College of Medicine. American College of Clinical Pharmacy provided student travel support for preliminary presentation of results.

Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by both the University of South Alabama and Auburn University. All patients and/or parents/caregiver(s) provided written informed consent and/or assent (as applicable) at enrollment.

Acknowledgments. The authors thank Richard Geiler for his contribution to the development and initiation of this project when he was a student. Thanks to Cassie Woodall for her tireless work in the PICU and recruitment of patients for this study. The authors thank John V. Marymont, Mary I. Townsley, and Elly Trepman for editorial support.

Submitted. April 14, 2020

Accepted. November 10, 2020

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