Can Iron Treatments Aggravate Epistaxis in Some Patients With Hereditary Hemorrhagic Telangiectasia?

Claire L. Shovlin, PhD, FRCP; Clare Gilson, MRes MRCP; Mark Busbridge, PhD; Dilip Patel, PhD; Chenyang Shi, MSc; Roberto Dina, MD, FIAC, FRCPath; F. Naziya Abdulla, BSc, MBBS; Iman Awan, BSc, MBBS

**Objectives/Hypothesis:** To examine whether there is a rationale for iron treatments precipitating nosebleeds (epistaxis) in a subgroup of patients with hereditary hemorrhagic telangiectasia (HHT).

**Study Design:** Survey evaluation of HHT patients, and a randomized control trial in healthy volunteers.

**Methods:** Nosebleed severity in response to iron treatments and standard investigations were evaluated by unbiased surveys in patients with HHT. Serial blood samples from a randomized controlled trial of 18 healthy volunteers were used to examine responses to a single iron tablet (ferrous sulfate, 200 mg).

**Results:** Iron tablet users were more likely to have daily nosebleeds than non–iron-users as adults, but there was no difference in the proportions reporting childhood or trauma-induced nosebleeds. Although iron and blood transfusions were commonly reported to improve nosebleeds, 35 of 732 (4.8%) iron tablet users, in addition to 17 of 261 (6.5%) iron infusion users, reported that their nosebleeds were exacerbated by the respective treatments. These rates were significantly higher than those reported for control investigations. Serum iron rose sharply in four of the volunteers ingesting ferrous sulfate (by 19.3–33.1 μmol/L in 2 hours), but not in 12 dietary controls (2-hour iron increment ranged from −2.2 to +.5.0 μmol/L).

**Conclusions:** Iron supplementation is essential to treat or prevent iron deficiency, particularly in patients with pathological hemorrhagic iron losses. However, in a small subgroup of individuals, rapid changes in serum iron may provoke endothelial changes and hemorrhage.

**Key Words:** Epistaxis, iron.

**Level of Evidence:** 4.

**INTRODUCTION**

Hereditary hemorrhagic telangiectasia (HHT) poses a substantial burden on otorhinolaryngological practice. Inherited as an autosomal dominant trait, HHT is caused by gene defects, most commonly in ENG, ACVRL1, or SMAD4, and leads to the development of nasal and gastrointestinal telangiectasia, in addition to visceral arteriovenous malformations (AVMs). Recurrent epistaxis (nosebleeds) is the hallmark of HHT, and results from fragile nasal telangiectasia, which are often lined by a single endothelial layer with no smooth muscles cells or pericytes, despite acting as conduits for blood at arterial pressure (see Supporting Fig. 1 in the online version of this article). Nosebleeds often occur daily, and can be associated with acute hemodynamic disturbances and reduced quality of life. Treatments include surgically based therapies such as cautery, laser photocoagulation, septal dermoplasty, and Young’s procedure, and medical therapies such as antioestrogens, tranexamic acid, and bevacizumab.

**OBJECTIVES**

1. To determine the efficacy of iron treatments in reducing nosebleeds.
2. To compare the effects of iron treatments with standard investigations.
3. To examine the response of healthy volunteers to a single iron tablet.

**METHODS**

A survey was conducted among HHT patients, and a randomized controlled trial was performed in healthy volunteers. Serial blood samples were used to measure changes in serum iron.

**RESULTS**

Iron tablet users were more likely to have daily nosebleeds than non–iron-users as adults, but there was no difference in the proportions reporting childhood or trauma-induced nosebleeds. Although iron and blood transfusions were commonly reported to improve nosebleeds, 35 of 732 (4.8%) iron tablet users, in addition to 17 of 261 (6.5%) iron infusion users, reported that their nosebleeds were exacerbated by the respective treatments. These rates were significantly higher than those reported for control investigations. Serum iron rose sharply in four of the volunteers ingesting ferrous sulfate (by 19.3–33.1 μmol/L in 2 hours), but not in 12 dietary controls (2-hour iron increment ranged from −2.2 to +.5.0 μmol/L).

**CONCLUSIONS**

Iron supplementation is essential to treat or prevent iron deficiency, particularly in patients with pathological hemorrhagic iron losses. However, in a small subgroup of individuals, rapid changes in serum iron may provoke endothelial changes and hemorrhage.

**Key Words:** Epistaxis, iron.

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ing to the severity of epistaxis, and many patients require more than one modality. Further treatment modalities are currently under evaluation in clinical trials.

The epistaxis that can be so difficult to manage in clinical practice also causes additional problems. HHT patients are commonly iron deficient and/or anemic because replacing iron lost through recurrent hemorrhage demands very high iron intakes, and it is difficult to meet the hemorrhage-adjusted iron requirement by dietary intake alone. The diverse detrimental consequences of iron deficiency include anemia and transfusional requirements that occur because iron deficiency restricts erythropoiesis, leading to low hemoglobin and reduced arterial oxygen content. The development of iron deficiency predicts development of high output cardiac failure for HHT patients with severe hepatic AVMs. Additionally, low serum iron is associated with venous thromboemboli, paradoxical embolic stroke through pulmonary AVMs, exuberant platelet aggregation to 5HT, and elevated coagulation factor VIII.

Treatment of iron deficiency and anemia for people with HHT is essential to prevent these complications. In the clinic, however, we were surprised by a small number of HHT patients who spontaneously volunteered that they could not use iron tablets or infusions to treat their iron deficiency because the iron treatments precipitated nosebleeds within hours. This prompted us to examine whether endothelial cells were modified by iron concentrations similar to those present in the bloodstream after iron tablets or infusions. Previous studies demonstrated toxicity at much higher iron concentrations, relevant to iron overload disorders or experimental endothelial models. Our recent work demonstrates that the more clinically relevant concentration of 10 μM iron generates rapid molecular and cellular changes in primary human endothelial cells, compatible with activation of DNA damage response pathways.

The goal of the current study was to explore whether such processes might be relevant to human recipients of iron tablets, particularly patients with HHT.

MATERIALS AND METHODS

HHT Surveys

The primary aims of the Imperial 2012 HHT survey were to capture acute responses to iron treatments, and to assess differences between patients using or not using iron, although the survey addressed multiple aspects of HHT, with a nonspecific participant information sheet that did not specify precise study foci. Relevant survey extracts are presented in Supporting Figure 2 in the online version of this article. All respondents were asked about aspects of the HHT phenotype including the use of iron tablets, and blood transfusions, before they were separately asked about intravenous iron. Respondents who stated they had HHT were directed to nonbiased follow-on questions regarding nosebleeds and iron tablets, infusions, and transfusions. For each treatment, tick box response options were: 1) "I do not get nosebleeds," 2) "I never noticed any difference in my nosebleeds," 3) "I think my nosebleeds were better," and 4) "I think my nosebleeds were worse." The survey closed in April 2013. Following interim assignment of HHT phenotypes and data analyses, all data were downloaded from SurveyMonkey in December 2015 for the purposes of the current report.

To provide a control group of nosebleeds responses to non-invasive investigations, similar questions were incorporated in a further survey, which asked whether the participant had completed the 2012 survey. Relevant extracts are presented in Supporting Figure 3 in the online version of this article. The second study remained open until April 2015, when 706 patients had completed the survey. Data were downloaded from SurveyMonkey in August 2015. The 460 responses from people who had also completed the 2012 survey were analyzed for the purposes of this study.

Iron Treatment Trial in Healthy Volunteers

Eighteen healthy volunteers (see Supporting Table I in the online version of this article) were randomly assigned to receive a 200-mg ferrous sulfate tablet containing 65 mg elemental iron, a dietary supplement (10 mL molasses containing ~2 mg iron), or no agent on each of 2 consecutive days. The eligibility criteria were males or females aged 18 to 80 years, who were not receiving iron supplements, had no needle phobias, and were able to provide informed consent (see Supporting Figs. 4 and 5 in the online version of this article). The trial recruited February to April 2012, and was conducted at the National Institute for Health Research/Wellcome Trust Imperial Clinical Research Facility, Hammersmith Hospital, London, United Kingdom. Study and sampling completion rates were 100%.

The primary outcome was the absolute serum iron at serial time points, to compare iron absorption after iron tablet or dietary supplements to diurnal variation. Additional study objectives were to obtain research samples to examine parameters of vascular injury, to be categorized by iron absorption status if feasible. To prevent any inadvertent study unblinding, 1) during the study, only c.g. was aware of randomization codes (generated by Urbania/k/Plus randomization); and 2) biochemical analyses by m.b. were not performed until 6 months after circulating endothelial cell (cEC) analyses had been completed by c.L.S., d.P., and c.s. Serum iron, transferrin saturation index (T/SI), and ferritin were then measured on Ci1600 Architect Analyzers (Abbott Diagnostics, Sligo, Ireland), and m.b. categorized the 18 participants as absorbers or nonabsorbers, based on serial changes, and blinded to experimental groups and outcomes.

On the day of sample collection, blinded to treatment group, hematologic variables, including total and differential leukocyte counts, were measured as part of a complete blood count, on XE Series Analyzers (Sysmex, Milton Keynes, UK). At all six time points, plasma and serum samples were stored, and blood monocytes were harvested to provide a source of DNA in cells anticipated to be exposed to either stable or transiently rising iron levels. Additionally, at the T = 0, T = 4.5, T = 7, and T = 24 hours time points, 10 mL of blood was processed using the designated CEC Enrichment & Enumeration Kit (Miltenyi Biotec, Bergisch Gladbach, Germany), following training in Bergisch Gladbach, and according to the published protocol. Further methodological details are provided in the Supporting Methods in the online version of this article.

Data Analyses

In the 2012 HHT survey, responses to questions about nosebleeds, telangiectasia, and AVMs permitted the assignment...
of HHT with confidence in 1,080 of the 1,433 survey respondents, using the algorithm in Hosman et al., which is based on the Curacao Criteria. For a further 174 participants, a diagnosis of HHT could not be assigned with complete confidence. To understand and minimize potential bias, data were analyzed both including (n = 1,288) and excluding (n = 1,080) this “likely HHT” group. Survey statistical analyses were performed using Stata IC version 12 (StataCorp, College Station, TX) and Prism version 6.0 (GraphPad Software, San Diego, CA). Categorical data were compared using $\chi^2$ analyses; two group comparisons by Mann-Whitney, and for three or more groups, $P$ values were calculated using Kruskal-Wallis with Dunn’s post-test correction applied.

The trial data were analyzed in Stata IC version 12, and Prism 6. No changes were made to over study numbers, and all data (six iron/TfSi time points, four circulating endothelial cell time points) on all 18 participants are reported. Single time point, two-group comparisons were performed using Mann-Whitney; three-group comparisons were performed using Kruskal-Wallis. Multiple time point, two- or three-group comparisons were performed using two-way analysis of variance. Serum ferritin changes were modeled using the 48-hour change as the dependent variable in linear regression.

**RESULTS**

**HHT Population Demographics**

The 2012 survey was completed by 1,467 international respondents, with the majority of respondents residing in the USA. One hundred seventy-nine had no suggestion of HHT–many had completed the survey as spouses, friends, or staff members. A total of 1,288 who stated they had HHT or were blood relatives of an HHT patient reported nosebleeds, telangiectasia in characteristic sites, and/or AVMs. Their median age was 55 years, and 732 (57.3%) were women. Six hundred one (46.6%) had pulmonary AVMs, 216 (16.8%) hepatic AVMs, 100 (8.5%) gastrointestinal HHT, and 105 (8.1%) cerebral AVMs, rates comparable to those reported in other HHT series. Nosebleeds affected 1,262 of 1,288 (98%), including 523 (40.6%) at least once daily, a further 405 (31.4%) weekly, and 183 (14.2%) at least once per year.

Of these 1,288 respondents, 837 (65.0%) had used iron tablets, 273 (21.2%) had received iron infusions, and 396 (30.8%) had received blood transfusions. One hundred five of 1,288 (8.1%) had been transfused on at least 10 different occasions. The majority of the 396 receiving blood transfusions had also received iron tablets (364 of 396, 91.9%). Similarly, 258 of 273 (94.5%) iron infusion users had received iron tablets, including 220 who answered a question about concurrent usage. When iron infusions were commenced, more than half of these respondents had their iron tablets stopped (137 of 220, 62.3%). Smaller proportions continued using iron tablets (92 of 220, 42%), or described varying patterns of cessation (13, 5.4%).

**Iron Treatments and HHT Nosebleeds**

Iron treatments are usually started in adult life, and at first sight, the iron-using group appeared to have more nosebleeds earlier in life, or in response to trauma (see Supporting Fig. 6 in the online version of this article). However, the population of 1,288 respondents was likely to include a small proportion of people without HHT, who would tend to have fewer nosebleeds, and use iron less frequently, therefore biasing the data. Responses to questions about nosebleeds, telangiectasia, and AVMs permitted the assignment of HHT with complete confidence in 1,080 respondents. When analyses were restricted to these 1,080 respondents, there was no difference in the proportion of iron users reporting nosebleed during childhood, or following trauma, compared to nonusers (Fig. 1A), indicating that less rigorous phenotyping would have introduced an important bias in this setting.

In the 1,080 individuals with a confident diagnosis of HHT, 781 (72.3%) reported current or previous use of iron tablets, and 261 (24.2%) had received intravenous iron. Iron tablet users were more likely to have daily...
nosebleeds than non–iron-tablet users (Fig. 1B). This was more pronounced in patients who also required intravenous iron infusions or blood transfusions (Fig. 1B), and would be expected, because frequent nosebleeds lead to iron deficiency and the need for additional iron intake.22

However, of the 732 iron tablet users reporting nosebleed associations, 35 (4.8%) reported that nosebleeds appeared to be worse after iron tablets. Similarly, of the 261 using intravenous iron, 17 (6.5%) reported that nosebleeds seemed worse after iron infusions. The proportion of those reporting nosebleeds that were worse after oral iron was similar after the subgroup of patients who also used intravenous iron was excluded (20 of 442, 4.5%).

To evaluate whether these reports may reflect methodological bias or reporting noise, the proportions were compared to the proportion of individuals reporting nosebleed changes in response to control investigations not expected to modify blood vessels or serum iron (Fig. 2). Only two individuals reported any changes in nosebleeds after control investigations (one after a blood test, one after being weighed). Using blood tests as a comparison, the proportion of those reporting nosebleeds who worsened after iron treatments was significantly higher for users of iron tablets ($\chi^2$, $P = .031$), and intravenous iron ($\chi^2$, $P = .0084$; Fig. 2).

Reported iron exacerbation of nosebleeds was restricted to a subgroup of HHT patients. Most iron-using participants reported no change in nosebleeds after iron treatments, whereas 56 of 732 (7.6%) using iron tablets and 34 of 261 (13.0%) using iron infusions reported nosebleed improvement. One iron tablet user reported both improvements and exacerbations on different occasions. We remained concerned that iron treatments appeared to sometimes augment the hemorrhagic losses they were required to replace.

**Rapid Rises in Serum Iron Levels Following Ferrous Sulfate (200 mg)**

To evaluate whether there could be a plausible link between oral iron ingestion and acute vascular changes leading ultimately to an HHT nosebleed, serum iron indices were evaluated in serial blood samples from the 18 healthy volunteers randomized to receive a single 200-mg ferrous sulfate tablet, a dietary iron supplement, or no agent (Fig. 3A).

Blinded biochemical assessments demonstrated sharp rises in serum iron concentrations to supranormal concentrations in four of the 18 study participants. When the study was unblinded, all four “absorbers” had received ferrous sulfate (Fig. 3A). Baseline serum iron had been comparable in the three groups (median values $= 17.1$ $\mu$mol/L in controls, 14.6 $\mu$mol/L in iron treatment group, and 12.5 $\mu$mol/L in the dietary supplement group, $P = .59$ by Kruskal-Wallis).

The sharpest rises in serum iron concentrations occurred within 2 hours of oral iron ingestion. Compared to the normal range for serum iron concentrations (7–27 $\mu$mol/L), the absolute 2-hour rises in the four iron absorbers averaged 28.2 $\mu$mol/L (range = 19.3–33.1 $\mu$mol/L). The changes in the remaining 14 nonabsorbers ranged from −2.2 to 5.0 $\mu$mol/L (mean = 0.8 $\mu$mol/L; Fig. 4A).

Serum iron concentrations remained high for several hours. Seven hours after ingestion of the iron tablet (at ~17:00 hours), the median values were 30.1 $\mu$mol/L in the iron-treated group compared to 15.6 $\mu$mol/L in controls, and 13.0 $\mu$mol/L in the molasses group ($P = .015$ by Kruskal-Wallis).

**Biological Sequelae**

The majority of circulating iron is sequestered by transferrin.23,28,53 The percentage of transferrin binding sites occupied by iron (Tf/TSI) is used in clinical practice as an index of iron deficiency and iron overload, with a normal range of 20% to 40%.23,28,53 The four healthy volunteers demonstrating sharp rises in serum iron also exhibited sharp rises in Tf/TSI concentrations, again to values substantially exceeding the normal range (Fig. 4A).

Participants displaying a higher rise in serum iron had greater increases in serum ferritin, considered to be an important marker of iron stores.23,28,53 By linear regression, for each micromole per liter greater increase in serum iron at 2 hours, the serum ferritin at 48 hours...
was 0.21 μg/L (95% confidence interval 0.002 to 0.41) higher ($P = 0.048$).

Circulating endothelial cells (cEC) are considered a marker of endothelial damage, have a normal range of <20/mL, and are substantially increased in several vascular diseases.\textsuperscript{54,55} In the 18 healthy volunteers, all cEC counts were normal at baseline (<20/mL), but rises were seen in a proportion of the study group. When the study was unblinded, cEC counts remained normal in all controls and iron-treated nonabsorbers. However, in the high iron absorbers there were transient rises in cEC counts (Fig. 4B).

**DISCUSSION**

Replacement of lost iron is an essential part of the management of patients with nosebleeds and other hemorrhagic iron losses. Current iron treatments have elemental iron contents far in excess of the usual dietary daily intakes, which rarely reach 20mg/day.\textsuperscript{22} This study demonstrates that for approximately 1 in 20 people with HHT, iron replacement treatments may aggravate nosebleeds. The study also provides a plausible link through biochemical and cellular studies.

The main strengths of the study are the capture of data from a very large iron-using population who can report vascular sequelae in real time, and the clinical trial that provides novel insights into responses to iron tablet ingestion. The main study weaknesses are that survey data are subjective, and observational data cannot demonstrate causality. Additionally, the iron treatment evaluations were performed in a control population (although this is relevant to wider groups of people using iron), and involved small study numbers.

The most common side effects from iron tablets are gastrointestinal, which often limit tolerance; the strongest data are from a 1966 trial\textsuperscript{56} and were recently summarized for easier access.\textsuperscript{22} The current data, using a...
population able to report vascular sequelae in real time, raise the additional challenging issue that for approximately one in 20 patients with HHT, iron treatments for anemia may also exacerbate HHT nosebleeds in a vicious circle. Mechanisms are likely to relate to the rapid changes in serum iron that can occur, as reported here and in other studies. Preliminary evidence is provided to suggest that the vascular endothelium may be a potential target. Because iron is recognized to cause oxidant and other endothelial injury, further examination is warranted.

These study findings need to be considered in conjunction with the substantial risks of untreated iron deficiency. Furthermore, for 7% to 13% of HHT patients, iron treatments were reported to improve nosebleeds. We suspect that on these occasions, nosebleeds had been aggravated by the high cardiac outputs required to maintain tissue oxygen delivery when patients were anemic, and that improvements (when cardiac outputs were reduced) offset any possible precipitant effects due to endothelial injury.

For clinical practice, these data raise questions about iron tablet dosages, particularly because factors regulating gastrointestinal iron absorption are better understood than when conventional strength iron tablets were introduced. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. Laryngoscope 2015;125:1269–1273.

CONCLUSION
In conclusion, iron treatments remain essential, but we suggest there is a rationale to consider reduced strength iron tablets, closer to the recommended dietary allowances of 8 mg/day, increasing to 18 mg/day for premenopausal females. These allowances are often unmet through dietary intake alone. Additionally, hepcidin/ferroportin-dependent mechanisms mean that iron deficient individuals generally absorb a higher proportion of ingested iron, and gastrointestinal absorption may be further enhanced in patients who are actively bleeding, or with cirrhotic liver diseases. In contrast, patients with chronic and/or inflammatory disease states with inappropriately elevated hepcidin have more limited gastrointestinal iron absorption, irrespective of ingested iron doses.

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BIBLIOGRAPHY


