

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

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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 $\mu\text{mol/L}$ in 2 hours), but not in 12 dietary controls (2-hour iron increment ranged from -2.2 to $+5.0$ $\mu\text{mol/L}$). High iron absorbers demonstrated greater increments in serum ferritin at 48 hours, but transient rises in circulating endothelial cells, an accepted marker of endothelial damage.

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.

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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).^{1,2} Recurrent epistaxis (nosebleeds) is the hallmark of HHT^{1–4}, and results from fragile nasal telangiectasia, which are

often lined by a single endothelial layer with no smooth muscle cells or pericytes, despite acting as conduits for blood at arterial pressure⁵ (see Supporting Fig. 1 in the online version of this article). Nosebleeds often occur daily, and can be associated with acute hemodynamic disturbances^{1,3,4,6,7} and reduced quality of life.^{8–12} Treatments include surgically based therapies such as cauterization, laser photocoagulation,¹³ septal dermoplasty,¹⁴ and Young's procedure,¹⁵ and medical therapies such as antioestrogens,¹⁶ tranexamic acid,^{17,18} and bevacizumab

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(Avastin).^{19,20} Therapeutics are generally graded according to the severity of epistaxis,²¹ 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.²² The diverse detrimental consequences of iron deficiency^{23–26} include anemia and transfusional requirements that occur because iron deficiency restricts erythropoiesis,²⁷ leading to low hemoglobin,²⁸ and reduced arterial oxygen content.^{29,30} The development of iron deficiency predicts development of high output cardiac failure for HHT patients with severe hepatic AVMs.³¹ Additionally, low serum iron is associated with venous thromboemboli,³² paradoxical embolic stroke through pulmonary AVMs,³³ exuberant platelet aggregation to 5HT,^{33,34} and elevated coagulation factor VIII.³²

Treatment of iron deficiency and anemia for people with HHT is essential to prevent these complications.³⁵ 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^{36–40} or infusions.^{41,42} Previous studies demonstrated toxicity at much higher iron concentrations, relevant to iron overload disorders or experimental endothelial models.^{43,44} Our recent work demonstrates that the more clinically relevant concentration of 10 μ M iron generates rapid molecular and cellular changes in primary human endothelial cells, compatible with activation of DNA damage response pathways.⁴⁵

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.^{22,46–48} 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 nosebleed responses to non-invasive investigations, similar questions were incorporated in a further survey,^{49,50} 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).⁵¹ 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 Urbaniak/Plous 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 (TfSI), 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 leucocyte 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 RNA in cells anticipated to be exposed to either stable or transiently rising serum 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

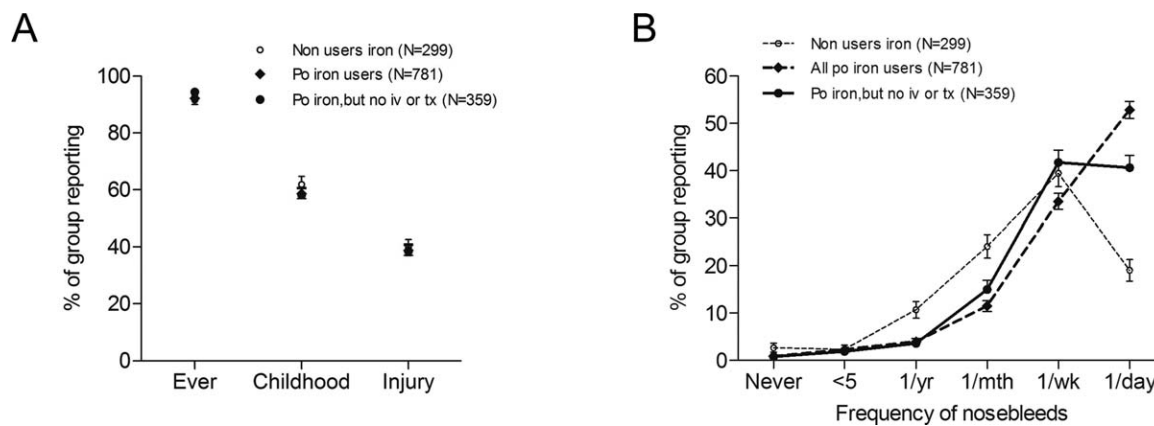


Fig. 1. Nosebleed frequency in study respondents, categorized by iron use. (A) Percentage (%) of the 1,080 respondents in whom hereditary hemorrhagic telangiectasia could be confidently assigned, reporting any nosebleed ever, nosebleeds in childhood, or nosebleeds in response to trauma or injury. Open circles indicate the 299 patients who had never used iron tablets, diamonds indicate the 781 users of iron tablets, and filled circles indicate the 359 who had used iron tablets without intravenous iron or blood transfusions. Mean and standard error are indicated. (B) Percentage (%) of groups reporting no nosebleeds ever (“never”), <5 in lifetime, or nosebleeds at least once per year, once per month, once per week, or once per day. Symbols are as in A.

of HHT with confidence in 1,080 of the 1,433 survey respondents, using the algorithm in Hosman et al.⁴⁸ which is based on the Curaçao Criteria.⁵² 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 χ^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/TySI 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%), includ-

ing 523 (40.6%) at least once daily, a further 405 (31.4%) weekly, and 183 (14.2%) at least once per.

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

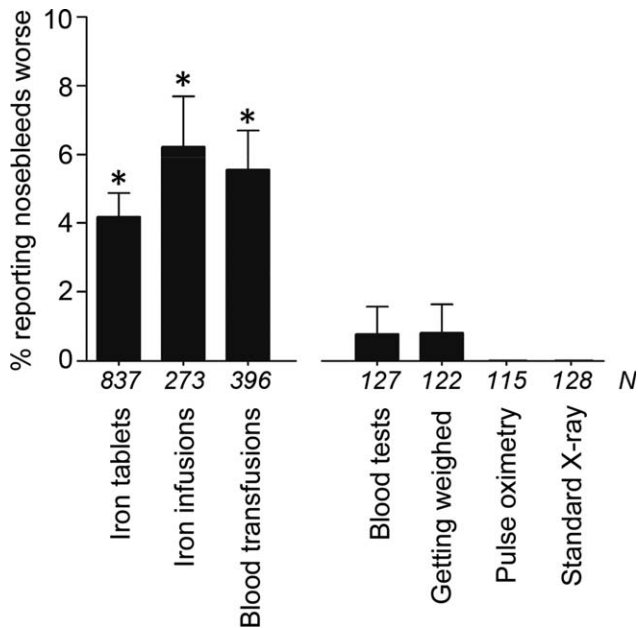


Fig. 2. Reported exacerbation of nosebleeds after treatments and investigations. Percentage (%) of patients reporting that iron tablets, infusions, or blood transfusions exacerbated nosebleeds compared to a subgroup of 460 reporting responses to the control investigations in the second survey. N indicates number of respondents reporting responses for the treatment or investigation. * $P < .05$ compared to equivalent responses in control investigations. Note that the iron and transfusion data are from all 1,288 participants with confident and likely hereditary hemorrhagic telangiectasia (HHT), as this group was more comparable to the control survey population, although the proportions reporting exacerbation by iron treatments were marginally lower than in the 1,080 participants with rigorously defined HHT (see text).

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 (χ^2 , $P = .031$), and intravenous iron (χ^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 $\mu\text{mol/L}$ in controls, 14.6 $\mu\text{mol/L}$ in iron treatment group, and 12.5 $\mu\text{mol/L}$ in the dietary supplement group, $P = 0.59$ 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 $\mu\text{mol/L}$), the absolute 2-hour rises in the four iron absorbers averaged 28.2 $\mu\text{mol/L}$ (range = 19.3–33.1 $\mu\text{mol/L}$). The changes in the remaining 14 nonabsorbers ranged from -2.2 to 5.0 $\mu\text{mol/L}$ (mean = 0.8 $\mu\text{mol/L}$; 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 $\mu\text{mol/L}$ in the iron-treated group compared to 15.6 $\mu\text{mol/L}$ in controls, and 13.0 $\mu\text{mol/L}$ in the molasses group ($P = 0.015$ 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 (T/SI) 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 T/SI 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

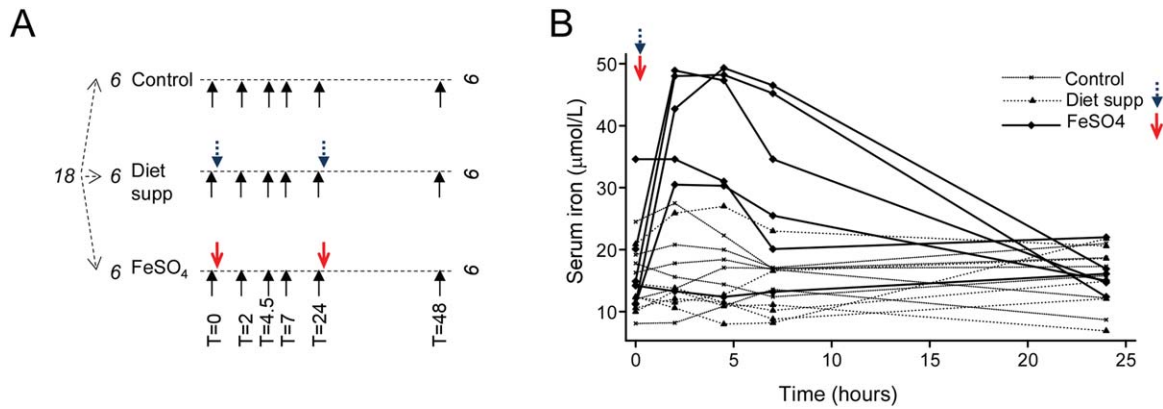


Fig. 3. Iron treatment trial. (A) Study protocol. Black arrows indicate time of blood samples, red arrows indicate the time of administration of ferrous sulfate (FeSO_4) 200 mg, and blue dotted arrows indicate the time of administration of the dietary supplement (Diet supp; molasses). (B) Serum iron concentrations (normal range = 7–27 $\mu\text{mol/L}$) in the 18 healthy volunteers before ($T = 0$) and after ingestion of ferrous sulfate (solid lines), molasses (dotted lines), or no agent (dashed lines). Note all four rapid increases were in individuals receiving ferrous sulfate.

was 0.21 $\mu\text{g/L}$ (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 $<20/\text{mL}$, and are substantially increased in several vascular diseases.^{54,55} In the 18 healthy volunteers, all cEC counts were normal at baseline ($<20/\text{mL}$), 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.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 trial⁵⁶ and were recently summarized for easier access.²² The current data, using a

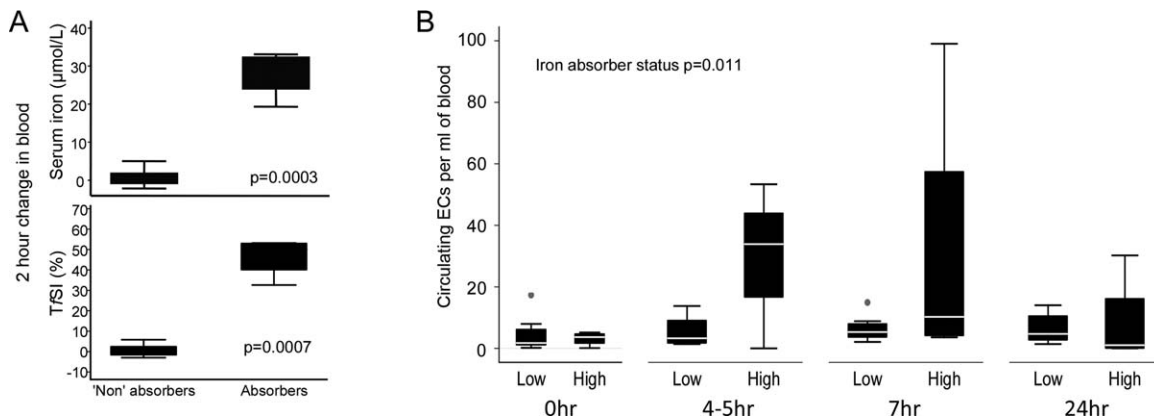


Fig. 4. Biomarkers in iron treatment trial. (A) Change in serum iron (upper graph) and transferrin saturation index (TfSI, lower panel) in the first 2 hours after iron administration, categorized by absorber groups. Boxplots display interquartile range and 2 standard deviations. Probability values for iron absorber status were calculated by two-way analysis of variance using $T = 0$ and $T = 2$ hours data. (B) Circulating endothelial cells (ECs; viable $\text{CD34}^+\text{CD45}^-\text{CD146}^+$ cells) in the iron treatment and control groups, categorized by iron absorption status. Boxplots display median, interquartile range, and 2 standard deviations; dots at extremes represent outliers. At each of the 4-5 and 7-hour time points, one of the molasses group also demonstrated circulating EC rises (data not shown).

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.^{36–42} 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,^{43–45} further examination is warranted.

These study findings need to be considered in conjunction with the substantial risks of untreated iron deficiency.^{23–35} 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,^{29,33,57–60} 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^{27,28,53,61} than when conventional strength iron tablets were introduced >50 years ago.⁵⁶ Single dosages of tablets available over the counter at leading pharmacies provide ≥ 65 mg of elemental iron, compared to recommended dietary allowances of 8 mg/day, increasing to 18 mg/day for premenopausal females.²⁵ These allowances are often unmet through dietary intake alone.^{22,25,26,62–64} 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,⁶¹ or with cirrhotic liver diseases.⁶⁵ 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.^{53,66}

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 allowance. More frequent administration of lower individual iron dosages may be helpful for individual HHT patients reporting that their nosebleeds increase after commencing or escalating iron treatments for anemia.

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BIBLIOGRAPHY

- Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev* 2010;24:203–219.
- McDonald J, Woderchak-Donahue W, VanSant Webb C, Whitehead K, Stevenson DA, Bayrak-Toydemir P. Hereditary hemorrhagic telangiectasia:

- genetics and molecular diagnostics in a new era. *Front Genet* 2015; 6:1.
- Rimmer J, Lund VJ. Hereditary haemorrhagic telangiectasia. *Rhinology* 2015;53:129–134.
- Hoag J, Terry P, Mitchell S, Reh D, Merlo C. An epistaxis severity score for hereditary hemorrhagic telangiectasia. *Laryngoscope* 2010;120:838–843.
- Braverman IM, Keh A, Jacobson BS. Ultrastructure and three-dimensional organization of the telangiectases of hereditary hemorrhagic telangiectasia. *J Invest Dermatol* 1990;95:422–427.
- Yin LX, Reh DD, Hoag JB, et al. The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2015. doi: 10.1002/lary.25669. [Epub ahead of print].
- Hunter BN, Timmins BH, McDonald J, Whitehead KJ, Ward PD, Wilson KF. An evaluation of the severity and progression of epistaxis in hereditary hemorrhagic telangiectasia 1 versus hereditary hemorrhagic telangiectasia 2. *Laryngoscope* 2015. doi: 10.1002/lary.25604. [Epub ahead of print].
- Folz BJ, Tennie J, Lippert BM, Werner JA. Natural history and control of epistaxis in a group of German patients with Rendu-Osler-Weber disease. *Rhinology* 2005;43:40–46.
- Loaec M, Moriniere S, Hitier M, Ferrant O, Plauchu H, Babin E. Psychosocial quality of life in hereditary haemorrhagic telangiectasia patients. *Rhinology* 2011;49:164–167.
- Geirdal AO, Dheyauldeen S, Bachmann-Harildstad G, Heimdal K. Quality of life in patients with hereditary hemorrhagic telangiectasia in Norway: a population based study. *Am J Med Genet A* 2012;158A:1269–1278.
- Merlo CA, Yin LX, Hoag JB, Mitchell SE, Reh DD. The effects of epistaxis on health-related quality of life in patients with hereditary hemorrhagic telangiectasia. *Int Forum Allergy Rhinol* 2014;4:921–925.
- Ingrand I, Ingrand P, Gilbert-Dussardier B, et al. Altered quality of life in Rendu-Osler-Weber disease related to recurrent epistaxis. *Rhinology* 2011;49:155–162.
- Mahoney EJ, Shapshay SM. Nd-YAG laser photocoagulation for epistaxis associated with hereditary hemorrhagic telangiectasia. *Laryngoscope* 2005;115:373–375.
- Harvey RJ, Kanagalingam J, Lund VJ. The impact of septodermoplasty and potassium-titanyl-phosphate (KTP) laser therapy in the treatment of hereditary hemorrhagic telangiectasia-related epistaxis. *Am J Rhinol* 2008;22:182–187.
- Richer SL, Geithoff UW, Livada N, et al. The Young's procedure for severe epistaxis from hereditary hemorrhagic telangiectasia. *Am J Rhinol Allergy* 2012;26:401–404.
- Yaniv E, Preis M, Hadar T, Shvero J, Haddad M. Antiestrogen therapy for hereditary hemorrhagic telangiectasia: a double-blind placebo-controlled clinical trial. *Laryngoscope* 2009;119:284–288.
- Gaillard S, Dupuis-Girod S, Boutitie F, et al. Tranexamic acid for epistaxis in hereditary hemorrhagic telangiectasia patients: a European cross-over controlled trial in a rare disease. *J Thromb Haemost* 2014;12:1494–1502.
- Geithoff UW, Seyfert UT, Kubler M, Bieg B, Plinkert PK, König J. Treatment of epistaxis in hereditary hemorrhagic telangiectasia with tranexamic acid—a double-blind placebo-controlled cross-over phase IIIB study. *Thromb Res* 2014;134:565–571.
- Karneizis TT, Davidson TM. Efficacy of intranasal bevacizumab (Avastin) treatment in patients with hereditary hemorrhagic telangiectasia-associated epistaxis. *Laryngoscope* 2011;121:636–638.
- Brinkerhoff BT, Choong NW, Treisman JS, Poetker DM. Intravenous and topical intranasal bevacizumab (Avastin) in hereditary hemorrhagic telangiectasia. *Am J Otolaryngol* 2012;33:349–351.
- Lund V, Howard D. A treatment algorithm for the management of epistaxis in hereditary haemorrhagic telangiectasia. *Am J Rhinol* 1999;13:319–322.
- Finnamore H, Le Couteur J, Hickson M, Busbridge M, Whelan K, Shovlin CL. Hemorrhage-adjusted iron requirements, hematincs and hepcidin define hereditary hemorrhagic telangiectasia as a model of hemorrhagic iron deficiency. *PLoS One* 2013;8:e76516.
- Lopez A, Cacoub P, Macdougall IC, Peyrin-Biroulet L. Iron deficiency anaemia. *Lancet* 2015. pii: S0140-6736(15)60865-0. doi: 10.1016/S0140-6736(15)60865-0. [Epub ahead of print].
- McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anemia, WHO Vitamin and Mineral Nutrition Information System, 1993–2005. *Public Health Nutr* 2009;12:444–454.
- Center for Disease Control: Iron Deficiency United States, 1999–2000. *MMWR Wkly* 2002;51:897–899.
- The World Health Report 2002: Reducing Risks, Promoting Healthy Life. Geneva, Switzerland: World Health Organization; 2002.
- Fairbanks VF, Beutler E. Iron deficiency. In: Beutler E, Lichtman MA, Coller B, et al., eds. *Williams Hematology*. 6th ed. New York, NY: McGraw-Hill; 2001:447–470.
- Shander A, Goodnough LT, Javidrooz M, et al. Iron deficiency anemia-bridging the knowledge and practice gap. *Transfus Med Rev* 2014;28:156–166.
- Pittman RN. Oxygen transport. In: Regulation of Tissue Oxygenation. 2011. Available at: <http://www.ncbi.nlm.nih.gov/books/NBK54103>. Accessed January 10, 2016.
- Santhirapala V, Williams LC, Tighe HC, Jackson JE, Shovlin CL. Arterial oxygen content is precisely maintained by graded erythrocytotic responses in settings of high/normal serum iron levels, and predicts

- exercise capacity. An observational study of hypoxaemic patients with pulmonary arteriovenous malformations. *PLoS One* 2014;9:e90777.
31. Buscarini E, Leandro G, Conte D, et al. Natural history and outcome of hepatic vascular malformations in a large cohort of patients with hereditary hemorrhagic telangiectasia. *Dig Dis Sci* 2011;56:2166–2178.
 32. Livesey JA, Manning RA, Meek JH, et al. Low serum iron levels are associated with elevated plasma levels of coagulation factor VIII and pulmonary emboli/deep venous thromboses in replicate cohorts of patients with hereditary haemorrhagic telangiectasia. *Thorax* 2012;67:328–333.
 33. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. *PLoS One* 2014;9:e88812.
 34. Woods HF, Youdim MBH, Boullin D, Callender S. Monoamine metabolism and platelet function in iron-deficiency anaemia. In: *Iron Metabolism*. CIBA Foundation Symposium 51 (new series). Amsterdam, the Netherlands: Elsevier; 1977:227–248.
 35. Shovlin CL. Circulatory contributors to the phenotype in hereditary hemorrhagic telangiectasia. *Front Genet* 2015;6:101.
 36. Hutchinson C, Al-Ashgar W, Liu DY, Hider RC, Powell JJ, Geissler CA. Oral ferrous sulfate leads to a marked increase in pro-oxidant nontransferrin-bound iron. *Eur J Clin Invest* 2004;34:782–784.
 37. Dresow B, Petersen D, Fischer R, Nielsen P. Non-transferrin-bound iron in plasma following administration of oral iron drugs. *Biometals* 2008;21:273–276.
 38. Lin L, Valore EV, Nemeth E, Goodnough JB, Gabayan V, Ganz T. Iron-transferrin regulates hepcidin synthesis in primary hepatocyte culture through hemojuvelin and BMP2/4. *Blood* 2007;110:2182–2189.
 39. Schumann K, Solomons NW, Romero-Abal ME, Orozco M, Weiss G, Marx J. Oral administration of ferrous sulfate, but not of iron polymaltose or sodium iron ethylenediaminetetraacetic acid (NaFeEDTA), results in a substantial increase of non-transferrin-bound iron in healthy iron-adequate men. *Food Nutr Bull* 2012;33:128–136.
 40. Breuer W, Herschko C, Cabantchik ZI. The importance of non-transferrin-bound iron in disorders of iron metabolism. *Transfus Sci* 2000;23:185–192.
 41. Scheiber-Mojdehkar B, Lutzky B, Schaufler R, Sturm B, Goldenberg H. Non-transferrin-bound iron in the serum of hemodialysis patients who receive ferric saccharate: no correlation to peroxide generation. *J Am Soc Nephrol* 2004;15:1648–1655.
 42. Van Campenhout A, Van Campenhout C, Lagrou A, Manuel-y-Keenoy B. Iron-induced oxidative stress in haemodialysis patients: a pilot study on the impact of diabetes. *Biometals* 2008;21:159–170.
 43. Chan S, Chen MP, Cao JM, Chan GC, Cheung YF. Carvedilol protects against iron-induced microparticle generation and apoptosis of endothelial cells. *Acta Haematol* 2014;132:200–210.
 44. Kartikasari AE, Georgiou NA, Visseren FL, van Kats-Renaud H, van Asbeck BS, Marx JJ. Endothelial activation and induction of monocyte adhesion by non transferrin-bound iron present in human sera. *FASEB J* 2006;20:353–355.
 45. Mollet IG, Patel D, Govani FS, et al. Low dose iron treatments induce a DNA damage response in human endothelial cells within minutes. *PLoS One* 2016;11:e0147990.
 46. Silva BM, Hosman AE, Devlin HL, Shovlin CL. Lifestyle and dietary influences on nosebleed severity in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2013;123:1092–1099.
 47. Devlin HL, Hosman AE, Shovlin CL. Antiplatelets and anticoagulants in hereditary hemorrhagic telangiectasia. *N Engl J Med* 2013;368:876–878.
 48. Hosman AE, Devlin HL, Silva BM, Shovlin CL. Specific cancer rates may differ in patients with hereditary haemorrhagic telangiectasia compared to controls. *Orphanet J Rare Dis* 2013;8:195.
 49. Elphick A, Shovlin CL. Relationships between epistaxis, migraines, and triggers in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2014;124:1521–1528.
 50. Patel T, Elphick A, Jackson JE, Shovlin CL. Does paradoxical emboli of particulate matter through pulmonary arteriovenous malformations precipitate migraines? *Thorax* 2015;70(S3):A3.
 51. The efficacy and safety of iron supplementation. Available at: <http://clinicaltrials.gov/show/NCT01590134>. Accessed January 10, 2016
 52. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet* 2000;91:66–67.
 53. Ganz T. Hepcidin and iron regulation, 10 years later. *Blood* 2011;117:4425–4433.
 54. Miltenyi Biotec. cEC enrichment and enumeration kit. Available at: <https://www.miltenyibiotec.com/~media/Images/Products/Import/0002000/IM0002014.ashx>. Accessed January 10, 2016.
 55. Rowand JL, Martin G, Doyle GV, et al. Endothelial cells in peripheral blood of healthy subjects and patients with metastatic carcinomas. *Cytometry A* 2007;71A:105–113.
 56. Hallberg L, Ryttinger L, Solvell L. Side-effects of oral iron therapy. A double-blind study of different iron compounds in tablet form. *Acta Med Scand Suppl* 1966;459:3–10.
 57. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J* 1993;70:357–362.
 58. Mehta PA, Dubrey SW. High output heart failure. *QJM* 2009;102:235–241.
 59. Porter WB, Watson JG. The heart in anaemia. *Circulation* 1953;8:111–116.
 60. Hebert PC, Van der Linden P, Biro G, Hu LQ. Physiologic aspects of anaemia. *Crit Care Clin* 2004;20:187–212.
 61. Kautz L, Jung G, Valore EV, Rivella S, Nemeth E, Ganz T. Identification of erythroferrone as an erythroid regulator of iron metabolism. *Nat Genet* 2014;46:678–684.
 62. Thane CW, Bates CJ, Prentice A. Risk factors for low iron intake and poor iron status in a national sample of British young people aged 4–18 years. *Public Health Nutr* 2003;6:485–496.
 63. Nelson M, Erens B, Bates B, Church S, Boshier T. *Low Income Diet and Nutrition Survey—Food Standards Agency*. London, UK: Stationary Office; 2007.
 64. Finnamore HE, Whelan K, Hickson M, Shovlin CL. Top dietary iron sources in the UK. *Br J Gen Pract* 2014;64:172–173.
 65. Tan TC, Crawford DH, Franklin ME, et al. The serum hepcidin:ferritin ratio is a potential biomarker for cirrhosis. *Liver Int* 2012;32:1391–1399.
 66. Schmidt PJ. Regulation of iron metabolism by hepcidin under conditions of inflammation. *J Biol Chem* 2015;290:18975–18983.