Dietary supplement use and nosebleeds in hereditary haemorrhagic telangiectasia – an observational study

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1. Introduction

Patients with hereditary haemorrhagic telangiectasia (HHT) provide an intriguing real-life model to evaluate potential precipitants of haemorrhage. Due to a causative mutation most commonly in an ENG, ACVR1L or SMAD4 gene, HHT leads to the development of vascular abnormalities, particularly visceral arteriovenous malformations, and smaller nasal and gastrointestinal telangiectasia (1,2). Patients with HHT can report nosebleeds (epistaxis) in real time, and the magnitude of their nasal haemorrhagic losses are such that iron deficiency anaemia commonly results, permitting objective evaluations (3).

Understanding nosebleed precipitants is also important in the overall management of people with HHT. Despite a battery of potential interventional,
surgical, and medical approaches (4). HHT patients are commonly iron deficient and/or anaemic because replacing iron lost through recurrent haemorrhage demands very high iron intakes (3). In a recently surveyed international group, 273 of 1,288 (21.2%) had received iron infusions and 396 (30.8%) had received blood transfusions, 105 (8.1%) on at least 10 occasions (5). Additionally, arterial rate bleeds can cause acute haemodynamic disturbances (3,4,6,7); epistaxis severity is a major predictor of reduced quality of life (8-11); and epistaxis is the primary outcome measure in nine of ten clinical trials of new therapeutic agents recruiting in HHT (12).

Understanding what provokes HHT nosebleeds at particular times offers insights into haemorrhagic precipitants, and potential strategies to limit healthcare demands, improve quality of life, and optimise clinical trial design. HHT nosebleeds are highly variable, and generally difficult to predict. However, in recent studies by our group, HHT patients reported that nosebleeds could be precipitated by certain food groups (3,4,6,7); epistaxis severity is a major predictor of reduced quality of life (8-11); and epistaxis is the primary outcome measure in nine of ten clinical trials of new therapeutic agents recruiting in HHT (12).

2. Materials and Methods

2.1. Ethics

The study was given a favourable Ethics opinion by the London Wandsworth Research Ethics Committee (11/H0803/8), and all participants gave written informed consent.

2.2. Survey methodology

Based on previous experience from pilot study numbers, an unselected group of 50 patients with HHT attending our tertiary care clinic were recruited into a blood sample and questionnaire-based study during two study periods to coincide with recruiter availability, April-September 2011, and March-May 2013. Inclusion criteria were a definite diagnosis of HHT using the Curaçao Criteria (15) and not residing in the same household as another study participant. Within this period, ~180 eligible patients were approached by letter or in person. All recruited participants recorded nosebleed severity by the validated Epistaxis Severity Score (ESS) (16). This rates nosebleed severity on a scale of 0-10, with the minimal important difference recently identified as 0.71 (17). Dietary supplement intake was assessed in an unbiased manner on the final page of the validated European Prospective Investigation into Cancer and Nutrition (EPIC) Food Frequency Questionnaire (18). Participants were asked “Have you taken any vitamins, mineral, fish oils, fibre or other food supplements during the past year?” and then asked to detail the brand, strength, amount and frequency (6 frequency options were provided).

2.3. Haematological evaluations

Blinded to epistaxis severity scores and supplement use, full blood count, prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen concentrations, and biochemical analyses were measured as part of routine clinical care. Blood samples were obtained by a professional phlebotomist in the early to mid-afternoon, and centrifuged to obtain platelet-rich plasma (PRP) and platelet poor plasma (PPP). Blinded to supplement use and other blood results, PRP was used to determine platelet aggregation to freshly-prepared adenosine diphosphate (ADP), by a Helena Aggregometer.

2.4. Statistical analysis

Statistical analyses were performed using GraphPad Prism 6 (GraphPad Software, San Diego, CA). Participants were categorised by supplement use as described in the text. Where there were three categories (e.g. no supplement use, iron supplement, and non iron supplement use) or no supplement use, fish oil and non fish oil supplement use) p values were calculated using Kruskal Wallis. Where there were two categories (e.g. supplements use, or no use of supplements), p values were calculated using Mann Whitney.

3. Results and Discussion

The 50 study participants ranged in age from 18 to 72 (median 53) years with an even gender distribution. Haemoglobin ranged from 5.9 to 17.8 (median 14.1) g/dL, with higher values in participants with hypoxaemia (low blood oxygen levels) induced by pulmonary arteriovenous malformations (19) that affect at least 50% of people with HHT (20).

Of the 50 participants, 24 (48%) had used dietary supplements in the previous year. Twelve of the HHT-affected study participants used iron supplements which would be fully appropriate given their high iron requirements, but 18/50 (36%) also used between 1-3 non-iron containing supplements (Figure 1). There were no evident gender differences, but compared to the 26 study participants using no supplements (median age 53, IQR 40, 63 years), there were trends for iron supplement users to be younger (median age 47, IQR 39.5, 62.3 years) and non-iron supplement users to be older (median age 58.5, IQR 49.5, 66 years).
severity scores did not differ between users of fish oils and any other group (data not shown). However, subtle differences emerged examining indices related to platelets in blood from fish oil users compared to non users of fish oils. Platelet counts were lower in supplement users ($p=0.037$, Figure 4A), while serum fibrinogen, which can act as a circulating protein for platelet aggregation (Figure 4B), also tended to be lower in fish oil supplement users ($p=0.07$). For a subgroup of 11 patients, ‘selected’ based purely on dates of attendance at clinic when the study was in progress, platelet aggregation studies were undertaken and provided provocative, preliminary findings: Within this very small sample, although there was no apparent difference in platelet aggregation to ADP between iron/
other vitamins, and non supplement users (Figure 4C), the one individual using fish oil demonstrated markedly reduced platelet aggregation to ADP (Figure 4C).

The strengths of the study were the use of validated questionnaires to capture epistaxis severity and dietary supplement intake, and the evaluation of a patient population able to recognise and report their haemorrhagic losses in a quantifiable manner. It is clearly a small study that should be repeated in larger HHT cohorts, and the observational nature means it is difficult to infer causality, but we believe it does allow helpful conclusions to be drawn.

First, it was surprisingly common for people with HHT to use dietary supplements. The non-iron supplements were generally instituted by the patients themselves. The supplements were not recorded on communications to us, and we suspect, were not recognised within standard clinical care pathways.

Second, the supplements which were self-prescribed included fish oils with recognised anti-platelet activity. The study participants appeared to demonstrate subtle differences in platelet activity, although differences in epistaxis scores did not emerge in the small cohorts. High proportions of HHT patients avoid therapeutic antiplatelet and anticoagulant agents, often on medical advice (26). It is not known whether any potential antiplatelet activity for example, from Omega-3 compounds (22-25), would be sufficient to exacerbate HHT nosebleeds in the subgroup of individuals who report that their HHT nosebleeds are exacerbated by aspirin and/or clopidogrel (26). We are however, unaware of any medical recommendation for their use in haemorrhagic disorders, and in the clinic, find patients to be surprised and concerned that these "healthy supplements" may act as natural blood thinners.

Third, within this small observational sample, despite having worse nose bleeds, iron supplement users had higher serum iron than non iron users, and were able to maintain their baseline haemoglobin and red cell indices. This would support data from other sources suggesting oral iron absorption is appropriate in people with HHT (i.e. enhanced in iron-deficiency (3)). It may be of concern however, that for five iron users, serum iron concentrations were at least twice the upper limit of normal (Figure 2B), in keeping with recent data from a healthy volunteers study (5). One in 20 HHT iron users report nosebleeds are worse after iron treatments (5,27), and recent data suggest one plausible biological explanation through activation of endothelial DNA damage response pathways by 10 µM iron (28), an order of magnitude lower than examined in recent iron toxicity studies (29,30).

In conclusion, this study highlights how frequently people with HHT self-medicate with dietary supplements that may influence nosebleed (epistaxis) severity and platelet function. The scale of use, and potential of "natural health supplements" to exacerbate nosebleeds has not been appreciated previously in HHT. We suggest management of people with HHT and other haemorrhagic disorders should include a discussion of dietary supplements, and particularly the fish oil supplements that have recognised antiplatelet activity (22-25). For individuals with troublesome haemorrhage or iron deficiency, a trial of cessation of non-iron containing supplements may be indicated unless there has been clear benefit from their use.

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