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Women with Red Hair Report A Slightly Increased Rate of Bruising, but Have Normal Coagulation Tests

Edwin B. Liem, M.D.^{*}, Sandra C. Hollensead, M.D.[†], Teresa V. Joiner, B.S.N.^{††}, and Daniel I. Sessler, M.D.^{**}

^{*}Assistant Professor, *OUTCOMES RESEARCH* Institute and Department of Anesthesiology, University of Louisville.

[†]Associate Professor, Medical Director of Hematology and Coagulation Laboratories, Department of Pathology and Laboratory Medicine, University of Louisville.

^{††}Research Coordinator, *OUTCOMES RESEARCH* Institute, University of Louisville.

^{**}Vice Dean for Research and Associate Vice President for Health Affairs, Director *OUTCOMES RESEARCH*TM Institute, Interim Chair and Lolita & Samuel Weakley Distinguished Professor of Anesthesiology, University of Louisville.

Abstract

There is an anecdotal impression that redheads experience more perioperative bleeding complications than those with other hair colors. We, therefore, tested the hypothesis that perceived problems with hemostasis could be detected with commonly used coagulation tests. We studied healthy female Caucasian volunteers, 18 to 40 years, comparable in terms of height, weight, and age, with natural bright red (n = 25) or black or dark brown (n = 26) hair. Volunteers were questioned about their bleeding history and the following tests were performed: complete blood count, prothrombin time/international normalized ratio, activated partial thromboplastin time, platelet function analysis (PFA-100), and platelet aggregation using standard turbidimetric methodology. Agonists for aggregation were adenosine diphosphate, arachidonic acid, collagen, epinephrine, and two concentrations of ristocetin. The red-haired volunteers reported significantly more bruising, but there were no significant differences between the red- and dark-haired groups in hemoglobin concentration, platelet numbers, prothrombin time/international normalized ratio, or activated partial thromboplastin time. Furthermore, no significant differences in platelet function, as measured with the PFA-100 or with platelet aggregometry, were observed. We conclude that if redheads have hemostasis abnormalities, they are subtle.

Correspondence to: Daniel I. Sessler.

Address correspondence to Daniel I. Sessler, M.D., *OUTCOMES RESEARCH* Institute, 501 E. Broadway, Louisville, KY 40202. Telephone: 502-852-2553. Fax: 502-852-2610. E-mail: ssessler@louisville.edu. On the world wide web: www.or.org.

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These results have been presented in part at the annual meeting of the American Society of Anesthesiologists, San Francisco, October, 2003.

Implications: Hemostatic abnormalities that have been reported for redheads, but we were unable to identify any abnormality using routine clinical coagulation testing.

Keywords

Anesthesia; Melanocortin; Platelets; Surgery; Coagulation

Introduction

The phenotype of nearly all red-haired individuals can be traced to distinct mutations of the melanocortin-1 receptor (MC1R) gene (1). The human MC1R is expressed on the surface of melanocytes and is a key regulator of intracellular signaling to the melanin biosynthetic pathway governing pigment formation, with excess pheomelanin production leading to the red hair phenotype. Red hair is thus an easily identifiable human phenotype that can be traced to a distinct genotype (*MC1R* mutation). Anecdotal clinical observations suggest that redheads differ in their anesthetic requirements, respond differently to analgesics, and suffer from increased bleeding tendencies in the perioperative period (2,3).

Recent studies have provided increasing scientific support for some of these observations. For example, red-headed volunteer subjects require 19% more desflurane to suppress movement in response to a noxious stimulus than do subjects with dark hair (4). Similarly, in rats with a *MC1R* mutation, the minimum alveolar concentration (MAC) of volatile anesthetics is slightly larger than in wild-type rats (5,6). Redheads are more sensitive to thermal pain than women with dark hair and are resistant to the analgesic effects of subcutaneous lidocaine (6). Recent studies by Mogil *et al.* (7) and Dahan *et al.* (8) suggest a role for the *MC1R* gene in female-specific pain modulation.

Reid and Trotter (3) compared bleeding time, whole blood coagulation time, thromboplastin generation (9), platelet count, and platelet adhesiveness after addition of adenosine 5' diphosphate (ADP) (10) in red-haired versus dark-haired men. The only significant difference they observed was in the whole blood coagulation time, which was slightly increased in redheads (9.9 ± 1.2 versus 8.3 ± 1.2 minutes), but the results for both groups were still within the normal range (3).

Coagulation test methodologies have improved considerably since that study, and current tests, such as platelet aggregometry (11-14), PFA-100 (15,16), prothrombin time (PT), and activated partial thromboplastin time (aPTT), provide more intense sensitivity and specificity than were previously available. We, therefore, tested the hypothesis that the clinical observations of impaired hemostasis in redheads can be attributed to differences in coagulation that are detectable with commonly used clinical coagulation tests.

Methods

With institutional approval and written informed consent, we recruited healthy Caucasian women between 18-40 years (ASA I) with natural bright red or dark (black or dark brown) hair for this independent study. Only females were recruited because studies suggest that at least some of the observed physiological differences associated with red hair are female-specific (7,8).

Our sample-size estimate was based on a two-sided, unpaired *t*-test, using institutional normative data for platelet aggregometry with five agonists. This estimate suggested that 15 volunteers per group would provide an approximately 80% power for detecting a 20% reduction in platelet aggregation. Because the initial results were equivocal, the Data Safety and Monitoring Committee elected to add at least 10 additional volunteers to each group. In fact, we inadvertently enrolled one extra volunteer in the dark-haired group, thus leaving us

with 25 volunteers with red hair and 26 with dark hair; results from all subjects were included in our analysis.

Our volunteers were recruited from Greater Louisville, Kentucky, an urban area with a population approaching one million. We considered study subjects to be Caucasian if they were mainly of northern European descent as indicated by self-report. The ovarian cycle can affect both the levels of coagulation factors (17) and platelet function (18). We therefore restricted studies to the first 10 days of the participants' menstrual cycles unless they were using hormonal contraceptives.

Exclusion criteria included chemical hair treatment (coloring and highlighting), any history of medical or psychiatric problems, any history of chronic pain problems, possible pregnancy, body mass index $> 30 \text{ kg/m}^2$, recreational drug use, and medication usage other than oral contraceptives. Specifically excluded were persons who, within the previous 10 days, had taken herbal medications, aspirin, nonsteroidal antiinflammatory drugs, and any other drugs that affect the coagulation system.

Protocol

Each volunteer completed a written questionnaire containing the following questions:

1. Do you have a history of easy bruising (i.e. spontaneous bruising, without trauma or with minimal trauma) and, if so, how long and where?
2. Do you have a history of frequent nosebleeds (duration, frequency, and severity)?
3. Have you had any abnormal bleeding following dental extractions or other dental work (what type of dental work, severity of bleeding)?
4. Have you had abnormal bleeding following major or minor surgery (type of surgery, date, severity of bleeding)?
5. Have you ever required a blood transfusion (reason, number of units)?
6. Do you have a family history of bleeding? (relationship, type of bleeding)?
7. Do you have a family history of abnormal blood clotting (i.e. pulmonary embolus, thrombophlebitis, heart attack, etc.)?

Thirty ml venous blood was taken from each volunteer *via* a 21-gauge needle. Great care was taken to withdraw the sample slowly, thus avoiding unnecessary activation of coagulation mechanisms. Measurements of hemoglobin, hematocrit, and platelet count were performed on EDTA anticoagulated whole blood samples, using the Abbott Cell-Dyn 4000 (Abbott Park, IL) automated complete blood count analyzer. A clinical laboratory technician who was unaware of the volunteer's hair color, reviewed platelet morphology on a Wright-Giemsa stained peripheral blood film. The blood samples were also analyzed for PT / international normalized ratio (INR), aPTT, platelet aggregometry and platelet function analysis (PFA-100) testing. All testing was performed within 2 hours of collection.

Both the PT and aPTT were performed by an automated photo-optical clot detection assay using the Dade Behring Blood Coagulation System (Dade Behring, Newark, DE). Blood samples were drawn into a 3.2% sodium citrate tube containing a 9:1 ratio of blood to anticoagulant. Samples were centrifuged for 180 seconds at 8500 RPM (StatSpin Express 2, Iris Norwood, MA) to obtain platelet poor plasma (platelet count $< 10 \times 10^9/\text{L}$) for both the PT and aPTT. The thromboplastin used for the PT was Innovin (Dade Behring, Newark, DE) with an international sensitivity index of 0.93. The INR was calculated (normalized) by the blood coagulation system instrument using the international sensitivity index and the geometric mean of the PT reference range. The aPTT reagent was Dade Actin FSL (Dade Behring, Newark,

DE). Both assays were performed according to manufacturer's directions. Reference ranges for the PT and aPTT were previously established from healthy volunteers as 9.5-11.7 seconds for the PT and 25.0-33.7 seconds for the aPTT.

Platelet aggregometry remains the gold standard for functional testing of platelet aggregation; however, it is used infrequently because of the cost, time, and high level of technical proficiency required for the analysis. We performed optical platelet aggregometry using standard turbidimetric aggregation methodology. Although platelet function tests using platelet rich plasma are commonly performed at many institutions, the concentration of agonists (particularly ADP) and interpretation of results are specific to each institution (11). The assays were done by one of two analysts, each unaware of the volunteers' hair color, using the same aggregometer and identical methodology. Platelets form aggregates when stimulated by agonists, thereby reducing the number of free platelets. The turbidity of the solution, which decreases as more platelets aggregate, was assessed by light transmittance.

For platelet aggregometry, whole blood was drawn into 4 glass tubes with silicon-coated interior (B-D Vacutainer, Franklin, NJ) containing 3.2% citrate with a blood to anticoagulant ratio of 9:1. The sample was kept at room temperature and tested within two hours of collection. Platelet rich plasma was prepared by centrifuging 3 of the tubes at 150 x g (1000 RPM Mistral Centrifuge, Sanyo Gallenkamp PLC / MSE, Chicago, IL) at room temperature for 5 minutes. The platelet-rich plasma was removed from the cells with a plastic pipette into a capped plastic tube. Samples were diluted as necessary to obtain a platelet count of 200,000-300,000/mm³. For dilution purposes and to establish a baseline turbidimetric reading, platelet poor plasma (<10.0x10⁹/L or 10,000/mm³) was prepared by centrifuging the fourth tube for 180 seconds at 8500 RPM (StatSpin Express 2, Iris Chatsworth, CA) at room temperature.

Platelet aggregation assays were performed using the Bio Data PAP-4 (Bio Data Corp., Hirscham, PA). The aggregating agents used in the platelet aggregation studies, ADP, collagen, epinephrine, arachidonic acid, and ristocetin, were chosen because they are the most commonly used agonists clinically (11):

1. ADP (Bio Data Corp., Hirscham, PA) This agonist stimulates platelet cohesion, i.e., platelets adhering to other platelets. ADP is stored in the platelet dense granules and is considered a mild platelet agonist. Two G-protein-coupled purinergic receptors (P2Y₁ and P2Y₁₂) contribute to platelet aggregation initiation by ADP (11). The concentration of ADP used for the platelet aggregation studies was 2x10⁻⁵ M, which is considered a large concentration. At this concentration, a monophasic (single broad wave) curve is produced, which represents an "all or none" platelet response (12, 13).
2. Collagen (Bio Data Corp., Hirscham, PA) Collagen activates platelets by inducing release of ADP, and *in vivo* it stimulates the interaction of platelets with subendothelial stroma. Two major platelet receptors for collagen have been identified. The receptor GPIIb/IIIa (α₂β₁ integrin) contributes to platelet adhesion, and the receptor GPVI induces platelet signaling and thromboxane formation (11). The concentration used for testing was 0.2 mg/ml. After the addition of collagen to platelet rich plasma, complete aggregation occurs as a single wave, corresponding to the release of contents of platelet granules (13).
3. Epinephrine (Helena Laboratories, Beaumont, TX) Epinephrine stimulates arachidonic acid metabolism and is considered a weak agonist for platelet aggregation, because like ADP, it has aggregation dependent secretion (11). The receptor on platelets for epinephrine is the α₂-adrenergic receptor. The concentration used was 3x10⁻⁴ M. In 20-30% of healthy people, decreased aggregation with epinephrine is found (14). Therefore, the finding of decreased aggregation to

epinephrine, but with normal aggregation to other agonists, must be correlated with clinical history.

4. Arachidonic Acid (Bio Data Corp., Hirscham, PA) Arachidonic acid is a free fatty acid that induces platelet aggregation and thromboxane production by the platelets and is used to detect platelet aggregation defects due to medication. Thromboxane is a strong inducer of platelet aggregation, causing rapid and irreversible platelet aggregation (13). Nonsteroidal, antiinflammatory drugs and aspirin will inhibit platelet aggregation induced by arachidonic acid. A concentration of 0.5 mg/ml was used. The platelet aggregation test was repeated if arachidonic acid failed to elicit > 50% platelet aggregation and the volunteer was reminded to ingest no prescription or over-the-counter medications prior to the repeat study.
5. Ristocetin (Fisher Scientific International Inc. - Pacific Hemostasis, Hampton, NH) Ristocetin is an antibiotic that induces platelet aggregation when incubated with plasma containing von Willebrand factor. It is used in platelet aggregation studies to determine the presence and function of GPIb-IX-V complex on platelets and von Willebrand factor in the platelet rich plasma (11). Ristocetin presumably mimics the activity of a subendothelial constituent that enhances platelet adhesion. The agonist is used to primarily detect von Willebrand disease and Bernard-Soulier syndrome, in which aggregation with ristocetin may be reduced or absent. Two concentrations were used: 1.5 mg/ml and 0.5 mg/ml. Decreased aggregation with the larger concentration will be seen with von Willebrand disease in all types; however, a normal aggregation tracing may be found in moderate von Willebrand deficiency (Type I). The study is often combined with other tests for von Willebrand disease, including factor VIII activity levels, von Willebrand activity (ristocetin cofactor), and von Willebrand antigen. The smaller concentration of ristocetin is used to screen for von Willebrand disease type IIb, in which aggregation occurs in the patient plasma, but is absent or minimal in healthy subjects (14).

The PFA-100 allows rapid evaluation of platelet function by exposing platelets to high shear flow conditions. The assay was performed on the Platelet Function Analyzer (Dade Behring, Neward, DE) using whole blood from a 3.2% sodium citrate tube. An 800- μ l sample of whole blood was pipetted into the sample reservoir of the reaction cartridge. The instrument aspirates whole blood from the reservoir through a capillary reservoir into a membrane coated with collagen, which acts as the initial matrix for platelet attachment. In addition, the membrane is coated with either epinephrine or ADP. The PFA-100 determines the time from the start of the test until a platelet plug occludes the aperture and reports that time interval as the closure time. Reference ranges for the closure time for each cartridge were established from healthy volunteers, who also underwent platelet aggregation testing on the same day (method as described above). Only values obtained for volunteers showing normal platelet aggregation were included in the PFA-100 reference range. Reference range for the closure time < 162 seconds for the collagen/epinephrine cartridge and < 103 seconds for the collagen/ADP one.

Data Analysis

Demographic and morphometric data for the volunteers with red or dark hair were compared using unpaired, two-tailed *t* tests. Prevalence of hormonal contraceptive use and the results of the questionnaire were analyzed using Chi-square testing. Laboratory results were analyzed using unpaired, two-tailed *t* tests. Results are presented as means [95% confidence intervals]; *P* < 0.05 was considered statistically significant.

Results

Volunteers with red and dark hair had comparable heights, weights, and ages. Results of the questionnaire indicated that 7 of the 25 redheads versus 2 of the 26 dark-haired volunteers reported a history of easy bruising ($P = 0.014$). No significant differences were found in the responses to the remaining questions from the yes/no questionnaire. In fact, no other abnormalities were noted in the questionnaire results for either group (Table 1).

There were no significant differences between the volunteers with red and dark hair in terms of hemoglobin concentration, platelet numbers, PT/INR, or aPTT. Furthermore, the percent of platelet aggregation was similar with the five agonists (Table 2) and the PFA-100 results did not differ between the hair color groups.

Discussion

The red-haired volunteers reported significantly more bruising. A limitation of the questionnaire, though, was that we were unable to blind investigators (or the subjects!) to hair color. Although the questionnaire was self-administered, we cannot fully exclude investigator bias or evaluate the extent to which our bias may have influenced participants' responses. However, the volunteers were not informed of our study hypothesis, which makes this particular bias less likely. A potentially confounding factor was the use of hormonal contraceptives. Coagulation factor levels (17) and platelet function (18) may be affected by hormone replacement therapy. However, with the number of volunteers in this study, no significant difference in the use of hormonal contraceptives could be detected between the groups.

Another limitation of questionnaires was the fact that people may vary greatly in their recognition and response to the bruising symptoms. Thus, people who always bruise excessively may assume this is normal because they have experienced it frequently. In contrast, normal individuals who bruise only rarely may grow concerned about even a single bruise associated with minor trauma. Many normal healthy people consider their bleeding and bruising excessive (19), whereas those with mild to moderate abnormalities may not recognize symptoms as abnormal (20). Given the infrequency of hemorrhagic disorders in the population and the frequent false-positive rates in the normal population, the predictive value of a history of bruising is small.

We were unable to detect any significant differences in coagulation testing between the two groups. Our results provided adequate power to detect changes in platelet aggregation. For ADP, arachidonic acid, collagen, and epinephrine, there was 90% power for detecting at least a 20% difference in platelet aggregation between the dark-haired and redheaded groups. For 1.5 mg/ml ristocetin, there was 90% power to detect a 7% difference in aggregation between the dark-haired and red-haired groups. Although the difference approached statistical significance when 1.5 mg/ml ristocetin was used as the agonist, the actual difference in values is unlikely to be clinically important.

We therefore conclude that if red hair is associated with clinical abnormalities in hemostasis, they are subtle and not detected by commonly used coagulation tests. Our conclusion — using modern and sensitive coagulation tests — was thus similar to that of Reid and Trotter (3) using tests available in 1973. An important difference, though, is that we evaluated women rather than men because many of the clinical consequences of *MC1R* mutations seem to be restricted to women (7,8).

Coagulation factors and adequate platelet function are hardly the only elements required for adequate hemostasis. Excessive bruising and bleeding may be a manifestation of acquired or

inherited defects in the blood vessels or skin. Human MC1R is mainly expressed on the surface of melanocytes and keratinocytes, but these receptors are also expressed on endothelial cells (21). It remains unknown whether MC1R dysfunction affects structural integrity of the skin or blood vessels. We considered performing template bleeding times, as these might reflect microvascular function, while *in-vitro* assessment of platelet function does not. However, template bleeding times have fallen into disfavor as a preoperative hemostatic screening tool and are not predictive of bleeding in patients typically encountered in clinical practice (22). The PFA-100 has thus replaced the template bleeding time in many centers as a preoperative screening test for platelet function.

MC1R expression has also been found on macrophages (23), lymphocytes, and neutrophils (24). The main ligand of MC1R, α -MSH, appears to have antiinflammatory influences, which are likely exerted through inhibition of inflammatory mediator production and inflammatory cell migration (25). MC1R dysfunction might, therefore, modulate inflammatory processes. Inflammation contributes to the thrombotic response through both cellular and humoral mechanisms (26). It, thus, remains possible that clinically important effects of MC1R dysfunction on coagulation may only be unmasked within the context of a generalized inflammatory response — which is often provoked by surgery.

In summary, redheads in this study reported slightly more bruising. However, we were unable to find objective evidence for an underlying coagulopathy using commonly performed clinical screening tests: coagulation factor and platelet function test results were comparable in red-haired and dark-haired women.

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Table 1.

Volunteer Characteristics.

	Red Hair N=25	Dark Hair N=26	P
Age (years)	27 [25 - 29]	27 [25 - 29]	0.900
Height (cm)	164 [161 - 167]	163 [160 - 166]	0.659
Weight (kg)	61 [58 - 64]	61 [58 - 66]	0.609
Body Mass Index (kg/m ²)	22 [21 - 23]	23 [21 - 24]	0.357
Hormonal Contraceptive (n)	14 (56%)	10 (38%)	0.210
Easy Bruising (n)	9 (36%)	2 (7%)	0.014

Results are presented as means [95% confidence intervals] for demographics or number of volunteers (percentage of total group) for hormonal contraceptive use and questionnaire results.

Table 2.**Laboratory Results.**

	Red Hair	Dark Hair	P
Hemoglobin (g/dl)	13.7 [13.5 - 14]	13.3 [13.1 - 13.7]	0.15
White Blood Cells (thou/mm ³)	6 [5.5 - 6.5]	6.1 [5.5 - 6.7]	0.77
Platelets (10 ³ /mm ³)	270 [243 - 296]	272 [249 - 294]	0.92
PT (sec)	10.3 [10.1 - 10.5]	10.4 [10.2 - 10.6]	0.46
PTT (sec)	30.6 [29.5 - 31.7]	30.2 [29.5 - 30.9]	0.52
INR	0.98 [0.96 - 1.01]	0.98 [0.96 - 1.01]	0.98
Platelet Aggregometry (%)			
ADP	86 [81 - 92]	92 [87 - 97]	0.16
Arachidonic acid	88 [83 - 93]	92 [89 - 96]	0.19
Collagen	78 [73 - 83]	78 [73 - 84]	0.92
Epinephrine	86 [80 - 93]	90 [86 - 94]	0.35
Ristocetin 1.5 mg/ml	87 [83 - 91]	93 [89 - 97]	0.06
Ristocetin 0.5 mg/ml	3.5 [1.1 - 6.0]	3 [1.7 - 4.3]	0.74
Platelet Function Analysis (PFA-100) (sec)			
Collagen/Epinephrine	120.3 [107.3 - 133.4]	120.8 [110.8 - 130.9]	0.95
Collagen/ADP	82.4 [77.1 - 87.7]	86.3 [80.1 - 92.6]	0.35

Data presented as means [95% confidence intervals]. PTT = activated partial thromboplastin time, PT = prothrombin time, INR = international normalized ratio, ADP = adenosine 5'-diphosphate