The case for iron supplementation for blood donors

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In this AABB issue of *Medical Laboratory Observer*, we present four articles on distinct, important issues facing blood bankers.

- "The case for iron supplementation for blood donors," pages 10-12, reviews relevant literature to argue forcefully that such supplementation not only benefits donors but helps to maintain the blood supply and the quality of the product.
- "Competency assessment for a Massive Transfusion Protocol: managing cross-training demands," pages 14-16, offers one institution's experience as a model for ensuring that the best possible procedures are in place for emergent events in the trauma setting and otherwise.

The Continuing Education test on page 21 is drawn from those two articles.

In addition, we present two informative and useful sidebar articles:

- "Re-homing blood banking equipment to help tackle the world transfusion crisis" (pages 18-19) asks blood banks to consider helping their counterparts in resource-challenged nations by donating equipment that would otherwise be discarded.
- "Using a quality management system to implement best practice standards for phlebotomy processes" (page 20) offers advice on how to prevent errors that occur during the collection and handling of blood specimens.

- MLO

Studies have shown that frequent blood donors have a higher likelihood of absent iron stores or iron-deficiency anemia compared to reactivated and first-time donors. Blood donors provide life-saving blood products, but in doing so they risk suffering adverse consequences. A decline in serum ferritin, and eventually hemoglobin levels, has been seen in frequent donors. Increasing the donation time interval or raising the minimum donation hemoglobin level are strategies that could address this, but implementing them would reduce the available blood supply. It has also been shown that without oral iron supplementation, increasing the donation time between donations would not allow donor hemoglobin and iron levels to recover in most cases. Oral iron supplements have been observed to maintain mean serum ferritin levels in donors compared to the declining mean serum ferritin of a placebo group, and serum ferritin levels are a measure of iron storage status. This literature review aims to show that by providing oral iron supplementation, the blood community would protect both its donors and its blood supply.

Continuing Education

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LEARNING OBJECTIVES

Upon completion of these articles, the reader will be able to:

1. **Describe the state of the maintenance of the current donated blood supply and statistics in current donor populations.**
2. **Identify types of health outcomes in the donor population and discuss recommendations concluded from the RISE study related to iron supplementation of donors.**
3. **Define the characteristics of a massive transfusion protocol and the blood products used at each stage, according to MidHudson Regional Hospital protocol.**
4. **Describe the competency assessment used by MidHudson Regional Hospital for an MTP in terms of the objectives used to assess and the procedural steps of the competency exam.**

Low hemoglobin and the blood supply

Blood-collecting agencies are typically focused on maintaining a safe and adequate blood supply. While there has been a reduction in transfusion-transmitted diseases, the essential details of blood supply management and effective collection techniques have often been overlooked.[1] According to the 2013 AABB Blood Collection, Utilization, and Patient Blood Management Survey, 6,847,000 successful allogeneic blood donations occurred that year in AABB facilities. First-time donors accounted for 32.3 percent of donors, which means that repeat donors were overwhelmingly the most abundant source of total donations.[2] Low hemoglobin levels remain the largest cause of donor deferral (48.8 percent of deferrals).[3] With the goal of maintaining an adequate blood supply while still prioritizing volunteer donors' health and safety, studies have been done to assess different aspects of donor management.[4] Several approaches to modify the donation process have been studied to address the issue of donor iron depletion, but no single approach has been shown to be the best option.[1] Because iron supplementation does not negatively affect the number of available blood

donations, iron supplementation has been encouraged to improve donor health.[4]

After blood donation, there is an expected drop in donor hemoglobin. However, two other conditions can also occur. These conditions are subclinical, but they are important to identify whether the donor has iron deficiency anemia.[5] Cable et al described these conditions as absent iron stores (AIS) and iron deficient erythropoiesis (IDE).[6] A donor was defined as having AIS if he or she had a plasma ferritin of less than 12 ng/mL. IDE was detected if the donor's log of the ratio of soluble transferrin receptor (sTfR) to ferritin was greater than or equal to 2.07. Ferritin is the storage form of iron, so the body's ferritin level is an indicator of iron stores and can be used to determine if stores are decreased, except during times of inflammation.[7]

Iron depletion and iron deficiency are observed more commonly in frequent donors as opposed to first-time or infrequent donors. Currently in the United States (and some other countries) the hemoglobin donation minimum is 12.5 g/dL. In other countries, the minimum-donation hemoglobin is based on whether the donor is male (13.5 g/dL) or female (12.5 g/dL). It has been suggested that frequent donors should have a higher minimum hemoglobin than first-time or infrequent donors to avoid iron loss complications.[8]

The U.S. Food and Drug Administration (FDA) has established donation intervals to allow the donor's body time to achieve its pre-donation hemoglobin level. According to Custer et al,[9] donors who begin with a higher hemoglobin level at their first donation are more apt to return to their pre-donation hemoglobin level at the time of their next donation. In the Custer study, in one-half of the first-time donation males and one-third of first-time donation females, hemoglobin levels recovered within eight to 16 weeks upon returning for another donation. Donors who returned after 36 weeks seemed to return to baseline more closely than those who waited 24 to 36 weeks to donate again. Overall, the majority of donors did not fully recover by the end of the study, but the longer the interval between donations, the closer donors came to achieving hemoglobin recovery.

Studies have shown that deferring a donor increases the chance that he or she will not attempt to donate again, especially if deferred when donating for the first time.[10] The impact of donor resilience to deferral correlates with the number of donations in the previous year before the deferral occurred. The more frequent the donation, the more likely the donor will return after the deferral.[10]

A task force led by the FDA Blood Product Advisory Committee and the AABB examined the options to avoid disrupting the available blood supply while still protecting the health of donors. The concern with increasing the hemoglobin minimum and donation intervals is that donors will fail to return to donate, and thus the resulting blood supply may be compromised. Because of this concern, no new formal policies have been put in place.[11] The AABB recommended that donors be provided with information about the effects of iron deficiency after donation to avoid any significant changes in the donor pool. It also recommended targeting menstruating females and frequent donors. Iron replacement therapy was listed as one of the actions to take for those at risk for iron depletion.[12]

The use of iron supplementation has been shown to be beneficial for donors.[13] Iron supplementation can help replenish what is lost during donation even if the donor's hemoglobin is adequate. When blood donors are deferred due to low hemoglobin levels and given oral iron supplements, they are more likely to return to donate.[13] Iron supplements can help maintain or increase donor ferritin and hemoglobin levels, thus benefiting the health of donors, avoiding donor deferral, and improving the quality of the blood supply.[13] A review of the relevant literature, which follows, bolsters the argument for the addition of iron supplementation to the blood donation process to achieve the aforementioned benefits.

Classifying iron deficiency

Iron deficiency presents itself in three stages. The first stage is iron depletion. Donors with iron depletion have decreased ferritin, normal RBC morphology, soluble transferrin receptor (STfR), and normal hemoglobin levels as their iron stores are emptied. The second stage is iron-deficient erythropoiesis. The donor's ferritin is decreased, STfR is increased, and RBC morphology and hemoglobin levels are normal. The bone marrow no longer has sideroblasts, and there is not enough iron to put in the heme protoporphyrin ring. The third stage is iron deficiency anemia. Ferritin levels remain decreased; STfR is increased; microcytic, hypochromic RBC morphology develops; and hemoglobin levels are decreased, all due to iron loss.[7] As a donor progresses through the stages of iron deficiency, he or she may begin experiencing symptoms including cognitive changes, restless leg syndrome, fatigue, pica, and increased work time for tasks.[1]

To establish baseline values of study participants, the REDS-II Donor Iron Status Evaluation (RISE) study measured plasma ferritin, STfR, venous hemoglobin levels, and fingerstick hemoglobin and hematocrit values.[4] The study collected samples for the same testing at the donor's final visit and attempted to test during interim visits.[6] These tests can be used to identify whether a donor is in one of the three stages of iron deficiency. A donor may possess the donation-qualifying hemoglobin but be considered to have a subclinical iron deficiency, which would not be detected with measuring the donor hemoglobin alone.[14] Other studies use a combination of the same tests as well as serum iron and transferin.[13-16] To track participants, most studies conduct pre-donation testing, testing at different intervals, and testing at the last donation or conclusion of the study. These intervals include every donation, every tenth donation, or at set day or weekly timelines.[15-17]

Each study defined and categorized its donors to determine which donors were at risk for iron deficiency. First-time donors (FT) are donors who have never donated before. Reactivated donors (RA) are donors who have not donated blood in two years before the start of the study. Frequent donors were described as men who have donated three or more and women who have donated two or more times in the last year.[4] Kiss et al chose donors who had donated once before, but not within the last four months.[16] Another classification for donors is those who gave two-unit red cell apheresis donations.[18]

Studying supplementation

Iron supplements may be given at each donation to help blood donors avoid or recover from iron deficiency. Studies have utilized multiple forms of supplements including

ferrous gluconate, ferrous fumarate, ferrous bisglycinate, iron (II)-glycine-sulfate-complex, and ferrous sulfate.[15-18] Iron supplementation can cause gastrointestinal as well as other adverse side effects. Some of the side effects including bloating, abdominal cramping, vomiting, nausea, hyperactive bowel sounds, black stools, constipation, and metallic taste in mouth. Kiss et al gave participants 325 mg of oral ferrous gluconate. Approximately nine percent of iron takers dropped out of the study, compared to one percent of those not taking iron who dropped out. If adverse effects were experienced, participants were advised to drop down to using supplements every other day. There was a 92.5 percent compliance rate.[16]

It has been indicated that taking ascorbic acid with iron supplements helps the body absorb and utilize iron. One study[19] administered to donors either 200 mg of ferrous fumarate, 200 mg of ferrous fumarate with 100 mg ascorbic acid, or 200 mg ferrous fumarate with 500 mg ascorbic acid to be taken once a day between meals. Ascorbic acid did not seem to have an effect on participants' side effects, and none of the study's participants withdrew.

Bryant et al[13] administered 325 mg of ferrous sulfate when donors were deferred due to low hemoglobin. The instructions were to take one tablet 30 minutes before bed while drinking half a glass of water. If a donor formed intolerance or had a previous adverse effect to ferrous sulfate, 325 mg of ferrous gluconate were given. The trial had a 68 percent compliance rate, with the most commonly reported adverse effect being constipation. Five percent of participants who began taking ferrous sulfate and nine percent who began taking ferrous gluconate were not tolerant to either form and stopped taking the supplements.

Magnussen and Ladelund[15] gave donors 330 mg of ferrous fumarate with 60 mg of ascorbic acid. If the donor complained of adverse effects, he or she was switched to ferrous bisglycinate. Donors were instructed to take supplements with water before bed. Supplement frequency was decreased if side effects were seen. Radtke et al[18] administered iron (II)-glycine-sulfate-complex because the majority of this form is released in the duodenum, with the goal being fewer observed side effects in donors. They classified a participant as compliant when 90 percent of the capsules were taken.

Evaluating the donor population

To protect blood donors from becoming anemic and to assist those who are subclinically anemic, the donor population needs to be evaluated.[13] Frequent blood donors and women most commonly have low hemoglobin and/or iron deficiency anemia.[15] The RISE study discovered that the more units donated in the past two years, the stronger the likelihood that the donor had AIS or IDE. In frequent donating males, AIS was observed in 16.4 percent and IDE in 48.7 percent. Frequent donating females had 27.1 percent AIS and 66.1 percent IDE.[4] The RISE study also noted that in donors who took iron supplements, the supplements helped protect them from AIS and IDE. The study also estimates that it takes about three to four months for lost RBCs to be replaced by the bone marrow based on the odds ratios for AIS and IDE at 14 weeks becoming insignificant.[6] It has been shown that donor hemoglobin recovery times are more than eight weeks in donors who do not take iron supplements and are iron-depleted. These donors can take more than 168 days to recover. Increasing the interdonation interval would compromise blood supplies and would not allow donors to fully recover.[16]

If donors and physicians are educated about AIS and IDE, both can be proactive. Studies have shown that after a deferral, only 36 percent of donors contacted their general practitioner. After completing a survey, 98 of 295 donors who had a low ferritin level had been to the doctor, and 50 percent of those participants began iron supplementation. Physician visits do not typically involve a conversation about whether the patient is a blood donor, and if so, screening for low ferritin levels. Both donors and physicians need to be made aware of the importance of monitoring donors for iron deficiencies.[20]

An algorithmic approach was studied by Magnussen and Ladelund using both hemoglobin and ferritin measurements.[15] Based on the donor's results, an outreach team provided iron supplementation and, if needed, a referral to a doctor. Hemoglobin and ferritin levels were measured in each donor. Donors were allowed up to four donations per year. Each subsequent donation was based on the previous donation hemoglobin level. If the donor's hemoglobin was above 12.5 or 13.5 g/dL in females and males respectively, they could donate, and if not, a new sample was analyzed. If a donor's ferritin was less than 60µg/L, iron supplements were offered. Hemoglobin levels were measured with every donation and ferritin level were measured initially and after every 10th donation due to cost. Based on this algorithm, the hemoglobin levels of the donor should increase, but the ferritin levels would take longer to increase before the next donation. Helping to keep the donor healthy also benefits the blood supply, because each unit will also have a higher hemoglobin value.

The value of iron supplementation

There is an increasing prevalence of AIS and IDE in male and female blood donors with increasing donation frequency. It is more effective to retain those who presently donate blood, rather than recruiting first-time donors. Therefore, donor safety and preserving a sufficient blood supply is vital. Iron supplementation programs have not been implemented or had well-defined guidelines, yet iron supplementation could help avoid the reduction in frequent blood donors. Blood centers need to investigate dispensing iron supplements, and their medical directors need to advocate protecting donors—thereby protecting the blood supply and increasing the retention of regular donors.

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Blood banking by the numbers

7,000
Is the number of units of platelets needed daily in the U.S.

10,000
Is the number of units of plasma needed daily in the U.S.

21 million
Is the number of blood components transfused each year in the U.S.

3 pints
Is the amount of blood used in an average red blood cell transfusion.

100 pints
Is the amount of blood used for a single car accident victim.

13.6 million
Is the number of whole blood and red blood cell units collected in the U.S. in a year.

6.8 million
Is the number of blood donors in the U.S. in a year.

10 pints
Is the average amount of blood in an adult body.

1 pint
Is the average amount of blood in given during a donation.

42
Is the number of days after collection within which most donated red blood cells must be used.

5
Is the number of days after collection within which donated platelets must be used.

- Source: http://www.redcrossblood.org/learn-about-blood/blood-facts-and-statistics