Comparing Care of the Primary and Secondary Hemochromatosis Patients

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ABSTRACT

Hemochromatosis is an imbalance of excessive serum iron and is a life-threatening condition if left untreated. Due to different causes, primary and secondary hemochromatosis have different patient care considerations for the infusion nurse. Understanding the pathophysiology and how the body absorbs iron is imperative for providing the highest quality care. Since primary (hereditary) hemochromatosis originates from a gene mutation, and secondary (acquired) from excessive intake, the treatment and education must be adjusted accordingly to deliver successful outcomes for both diagnoses.

Key words: acquired hemochromatosis, deferasirox, deferiprone, deferozamine, ferritin, hemochromatosis, hereditary hemochromatosis, iron, iron chelators, primary hemochromatosis, secondary hemochromatosis, therapeutic phlebotomy

Iron absorption in the healthy individual is precisely matched with iron losses.[1] When this balance is interfered with, allowing for an excess of iron, hemochromatosis results. Primary hemochromatosis, also referred to as hereditary hemochromatosis (HH), occurs when an individual absorbs too much iron due to a genetic mutation. Acquired, or secondary hemochromatosis, is produced by excess of iron intake. It is important for the infusion nurse to understand hemochromatosis pathophysiology in the development and implementation of the patient's plan of care due to the variation in causes; primary and secondary hemochromatosis are treated dissimilarly, requiring different and specific nursing considerations.[2] If it is left untreated, inappropriate absorption of dietary iron and iron deposits in the parenchymal organs can be life-threatening.[1]

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HEREDITARY OR PRIMARY HEMOCHROMATOSIS

For type 1, the typical population exhibiting the mutated gene includes Northern Europeans, with an age of presentation between 40 and 60 years (males, 10 years earlier). Menstrual blood loss in women and maternal iron loss during pregnancy are thought to be the cause of delayed presentation of HH.[3] Fletcher and Powell[4] noted in their study that there is a strong association of symptomatic HH in patients with heavy alcohol intake. More than 40% of affected HH patients consumed at least 100 g of ethanol daily. This excess of intake accentuates the iron overload, increasing the chance of developing cirrhosis of the liver.[4]

Juvenile or type 2 (A and B) hemochromatosis occurs at the onset in childhood, causing a decrease or absence of sex hormone production by the age of 20 years. Death by the age of 30 years can occur if the individual is untreated. Type 3 presents at around 30 years old and is referred to as transferrin receptor 2 gene hemochromatosis causing hepcidin deficiency. Occurring primarily in males, type 4 (A and B), ferroportin disease, is similar to type 1, appearing primarily in males ages 40 to 60 years and women after menopause. With this final type, hepcidin is normal, affecting mostly the spleen.[2]

ACQUIRED OR SECONDARY HEMOCHROMATOSIS

In cases where hemochromatosis is acquired, the patient has taken a massive or excessive intake of iron supplements,

received blood transfusions, or suffers from anemias. β-Thalassemia, sideroblastic, and acute hemolytic anemias cause enhanced erythroid drive, reducing peptide hormone hepcidin (HEPC) release. This hormonal drop leads to excessive absorption of iron in the intestines.[1] The most common cause of secondary hemochromatosis is chronic transfusion therapy, because each unit of packed red blood cells (RBCs) contains approximately 200 to 250 mg of iron as a component of the red heme pigment.[5]

Pathophysiology

Oxygen requires iron to bind to erythrocytes for transport, increasing oxygen-carrying capacity. Iron is also necessary for energy metabolism and in neurotransmitter homeostasis.[6] There are 2 forms of iron, heme and non-heme. Heme is obtained from hemoglobin (Hb) and myoglobin in meats, poultry, seafood, and fish. Plant foods, such as grains, beans, fruits, vegetables, nuts, and seeds, provide non-heme iron.[7] Gastric and ascorbic acid promote absorption of non-heme iron. Understanding the sources of iron is important when caring for and teaching hemochromatosis patients about their diet.[1]

Iron is primarily stored in the liver, including surplus amounts, and is released and mobilized when needed.[8] The iron ion, ferrous ($Fe2^+$), is stored as ferritin and released into blood plasma by ferroportin. Ferric ion ($Fe3^+$) is oxidized from $Fe2^+$ and bound to plasma transferrin for transport throughout the body. HEPC is liver derived and blocks intestinal absorption of iron, inhibiting iron release from stores. When ferroportin is bound to HEPC, the result is inhibition of iron transport (Figure 1).[1] Normal serum levels of iron for adult males is 65 to 177 μg/dL and for females is 50 to 170 μg/dL. Serum ferritin levels are used to provide an indirect measurement of total body iron stores, with 15 to 200 μg/L as a normal range.[9]

Many factors contribute to the increase or decrease of HEPC, which then affects the ferritin levels. Alcohol, HFE gene mutation (as in HH), hemolysis, and release of tumor necrosis factor (TNF-α) cause a decrease in HEPC, while hydrogen peroxide (H_2O_2), anemia, interleukin 6 (IL-6), lipopolysaccharides (LPS), bone morphogenic proteins (BMPs), and small mothers against decapentaplegic (SMAD) proteins will increase hepcidin. Hypoxia may trigger either response.[10]

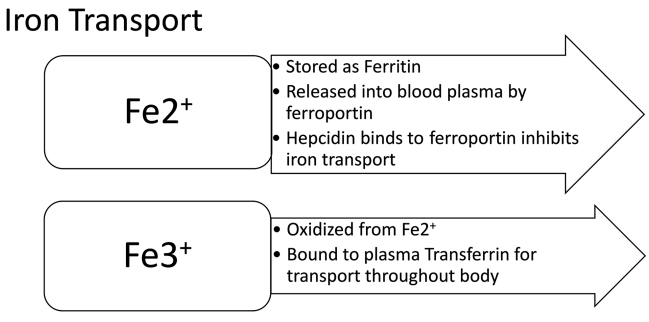

Figure 1 The iron ions, $Fe2^+$ oxidizes $Fe3^+$. HEPC is liver derived, blocks intestinal absorption of iron, and inhibits iron release from stores.[1] *Abbreviations: $Fe2^+$, ferrous; $Fe3^+$, ferric ion; HEPC, peptide hormone hepcidin.*

There are no active excretory mechanisms for iron. In the normal individual, the body recycles 90% of available iron, losing small amounts from exfoliation of skin and gastrointestinal cells. Iron levels are modulated by absorption via the duodenum and proximal jejunum. Anemia stimulates erythropoietin (EPO) secretion by the kidney, triggering erythroblasts to enter the erythropoietic differentiation mechanism. As erythroferrone (ERFE) secretions increase, hepatic hepcidin production is lowered to promote iron balance.[11]

The strongest stimulator of iron absorption is erythrocyte production in the bone marrow. When the body stores of iron are low or the erythropoietic rate is high, iron absorption increases. Chronic hypoxia (stimulates EPO production) and pregnancy increase iron absorption. When there are excessive toxic serum iron levels in the body, oxygen radicals damage cells, leading to multiple organ failure. Since there is no intrinsic mechanism to remove excess amounts of iron, hemochromatosis becomes life-threatening if left untreated.[1]

Initial varying symptoms are fatigue, right upper quadrant abdominal pain, arthralgia, heart palpitations, loss of libido, impotence, and hair loss.[3] The classic triad of symptoms exhibited with hemochromatosis include hyperpigmentation, hepatic cirrhosis, bronze skin pigmentation, and diabetes mellitus (DM). The distinctive gray-to-brown cutaneous discoloration can be viewed on the face, dorsal hands, forearms, and inguinal area.[12] DM is a result of iron overload to the pancreas.[2]

HH is most commonly caused by a homozygous mutation of hemochromatosis gene (HFE) C282Y (on chromosome 6) and is classified as type 1. With HH, iron saturation is nearly 100%, therefore no transferrin is available to mobilize the unused iron, resulting in elevated serum ferritin levels.[9]

Testing and Diagnosing HH

When testing serum chemistry, transferrin saturation (TS) levels and liver enzymes need to be included. If the TS is ≥45% (300 μg/L in men, 200 μg/L in women), hemochromatosis is questioned but not a definitive diagnosis. A thorough history should include the possible excess ingestion of iron supplements, multiple blood transfusions, and anemias to exclude acquired hemochromatosis. If HH is suspected, then the patient requires genetic testing for the C282Y mutation or other variations. When ferritin levels reach 1000 μg/L, a liver biopsy is indicated unless hepatic fibrosis in the absence of excessive alcohol consumption is evident. A magnetic resonance image provides an estimate iron concentration within the liver and allows for the most sensitive imaging modality for the diagnosis of HH. Once the patient is confirmed to have HH, genetic testing of family members is encouraged.[3]

Treatments

Therapeutic phlebotomy reduces high serum levels of iron, providing symptom relief and subsequently reducing the risk of potential organ damage.[9] This repeated withdrawal

of RBCs decreases the iron present in the Hb, stimulating erythropoiesis, which mobilizes iron stores in organs, and eliminating excess.[2]

For initial treatment of HH, or the depletion phase, therapeutic phlebotomy is prescribed weekly or biweekly to withdraw 500 mL (or 1 unit) of blood, maintaining a ferritin level between 50 and 100 μg/L. After every 10 to 12 phlebotomies (every 3 months or more often), a ferritin level is obtained. It is imperative that the Hb and hematocrit (Hct) levels are monitored to ensure 80% of the initial or 20% of the prior level is maintained.[3] The treatment goal is to decrease serum ferritin levels 30 μg/L on average with each phlebotomy of 350 to 800 mL of RBCs. The total number of procedures necessary depends on the iron reserve status and is highly variable. For larger volumes (>500 mL), it is recommended that 30% of the volume be replaced with an isotonic solution.[2]

During the maintenance phase, 2 to 6 phlebotomy treatments per year with serum ferritin levels drawn every 6 months is recommended. Continued monitoring of Hb and Hct before treatments prevents reducing the Hb to <80% of the starting value. Phlebotomy treatments continue until the serum ferritin levels remain below the upper limit of normal value. For most patients with HH, this is a lifetime commitment.[2]

If the hemochromatosis patient's liver status continues to deteriorate, a liver transplant will be required. Liver fibrosis, cirrhosis, or patients with hepatocellular carcinoma (HCC) are more likely to continue into total liver failure. To objectively determine the extent of organ failure, the Model for End-Stage Liver Disease (MELD) scale is implemented. The MELD score is an objective assessment tool in which a calculated score of 6 denotes low risk and 40 denotes a grave prognosis. The higher the number, the more urgent the case. This allows those with the most advanced failure the greater priority for donor livers. Once a liver transplant occurs, the patient will still require phlebotomy treatments because the mutated gene has not been altered.[3]

Iron chelators are the standard treatment for secondary hemochromatosis (Table 1). Unfortunately, each can have major adverse effects, some similar to those of hemochromatosis (elevation of liver enzymes, gastrointestinal disorders, and arthralgia). Phlebotomy is also an option, especially for those not tolerating pharmacologic therapies. These medications are usually not used for HH unless phlebotomy is not appropriate or possible due to severe heart failure, no intravenous access, or severe anemia.[2]

Deferoxamine is the preferred prescribed initial iron chelator for long-term use. Administered by continuous cutaneous infusion via a battery-powered pump, it has been shown to prevent complications of iron overload, specifically with β-thalassemia.[16] Continuous injection is required due to the drug's short plasma half-life.[17]

Other than the above-mentioned adverse effects, therapy is limited by cost, and the necessity for a parenteral route despite its inconvenience, discomfort, and neurotoxicity.[16] Once the treatment is withdrawn, most drug toxicity resolves.[17]

Deferasirox is the latest drug therapy approved for treating iron overload. Older patients with myelodysplastic syndrome, renal or hepatic disease, and low platelet counts have demonstrated a higher predisposition for adverse effects. Surveillance of serum creatinine levels, serum transaminases, bilirubin, and complete blood counts should be completed regularly during therapy. To prevent complications, patients should avoid using aluminum-containing antacids.[17]

When the serum ferritin levels are not adequately reduced, deferiprone is used in conjunction with deferoxamine. Monitoring neutrophil counts routinely is necessary due to the incidence of agranulocytosis and neutropenia with this therapy.[17]

TABLE 1

List of Commonly Prescribed Iron Chelators[a]

Medication	Indications	Administration	Adverse Effects
Deferoxamine[b]	Thalassemia	IM 500 mg every 4-12 hours (preferred method for all patients not in shock); SC as a mini-infusion 20-40 mg/kg/d over 8-12 hours IV 40-50 mg/kg/d over 8-12 hours	Retinal and auditory neurotoxicity
Deferiprone[c]	Used in conjunction with deferoxamine when ferritin levels not adequately reduced	PO 25 mg/kg 3 times a day	Neutropenia and agranulocytosis
Deferasirox[d]	Latest to be FDA-approved; 10% of patients have adverse events	PO once a day (granules or tablet)	Diarrhea, headache, nausea, abdominal pain, increased serum creatinine, increased liver enzymes, rash, fatigue and arthralgia

Abbreviations: FDA, US Food and Drug Administration; IM, intramuscular; IV, intravenous; PO, by mouth; SC, subcutaneous.
[a]Data from Rombout-Sestrienkova et al.[2]
[b]Data from Pfizer manufacturer website.[13]
[c]Data from ApoPharma manufacturer website.[14]
[d]Data from Novartis manufacturer website.[15]
The above doses of each medication should be adjusted according to each patient's response.[16]

Nursing Considerations

The infusion nurse needs to understand the impact that the diagnosis of hemochromatosis has on the patient. Dietary changes need to be made, and daily routines need to incorporate frequent intake of medication or phlebotomy treatments. These are life-changing, disruptive, expensive, and inconvenient considerations that occur simultaneously when patients are experiencing uncomfortable symptoms.[2]

Dietary considerations for the hemochromatosis patient include the avoidance of vitamin C supplements because of the accelerated mobilization of iron, saturating circulating transferrin, causing elevation of pro-oxidant and/or free radical activity. Red meat with its high content of iron should be eliminated from the patient's diet. Alcohol is not to be consumed.[8] The cumulative effect of alcohol intake and iron overload causes an increased oxidative stress and progression of hemochromatosis.[2]

To avoid anemia, if Hb is <80% (Hct must be at least 30%), then phlebotomy treatment should be postponed.[2] Avoid using peripherally inserted central catheters, midline and tunneled catheters, or implanted ports for therapeutic phlebotomy. If a central line is the only option due to difficulty with peripheral access, then frequent flushing with normal saline may be necessary to maintain line patency.[9] The practitioner determines the appropriate catheter size, venipuncture site, and rate of removal. Estimation of withdrawn blood is done incrementally observing the collection bag or using a scale versus syringes for more accurate measurements. Vacuum bottles to improve blood flow are used in some institutions along with processes for the prevention of fatal air embolisms. AABB-approved bags can be used but are more expensive and have a 16-gauge needle.[9]

Any instructional phlebotomy protocol ought to include the basic steps as in any procedure. Verifying the patient by name, birth date, and health record number is completed before confirming the health care provider's specific phlebotomy treatment order, including the amount of volume to remove and the amount, type, and rate of fluid to concurrently infuse. A completed assessment of vital signs and serum levels of Hb, Hct, and ferritin is reviewed before the procedure to ensure that the patient is stable enough for a treatment.[9]

Once the phlebotomy has commenced, patients should be monitored for common side effects such as fatigue, fainting, pain at the venous access site, hematoma, and anemia. When removing the catheter, pressure needs to be applied to avoid the incidence of hematoma formation. If a hematoma is suspected, additional pressure and ice to the site are recommended.[9] Providers ought to follow documenting and reporting recommendations outlined in the *Infusion Therapy Standards of Practice* for adverse events associated with phlebotomy treatments.[18]

In the United States, blood obtained during the phlebotomy is not routinely preserved for future donation. Some facilities are following European practices that do not discard the iron-rich blood. Concerns of increased risk of infection from high-iron blood products are the primary reason that hemochromatosis blood is not used for donation infusion.[19]

Patient education postprocedure includes remaining in a reclined position immediately for several minutes before rising slowly to an upright position. An increase in fluid intake for the next few hours with avoidance of alcohol and caffeine intake needs to be stressed. Also, refraining from smoking for 30 minutes needs to be discussed when applicable. As with any discharge instructions, it is important to provide verbal and written instructions with symptoms of when to call their health care provider.[9]

CONCLUSION

The infusion nurse has unique access in caring for the hemochromatosis patient, enhancing patient knowledge and confidence in dealing with his or her disease. Understanding the cause of hemochromatosis is imperative to providing the appropriate care and education to the patient. Promoting proper procedures, ensuring patient safety, and improving patient outcomes comprise the key roles of the infusion nurse. Once a differential diagnosis for his or her specific variation of hemochromatosis is achieved, the specific plan of care can be accomplished by collaborating with the interdisciplinary team and empowering the patient to improve his or her own health.

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