Iron Chelation for Iron Overload Secondary to Transfusions of Packed Red Blood Cells

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H&O Could you give some background on iron overload?

JC Iron is an essential element in many proteins and enzymes, and a key component of many biochemical processes. Although iron is necessary for life, accumulation of excess iron in the body is potentially harmful because iron can also catalyze the formation of injurious reactive oxygen species. Therefore, the total quantity of iron in the body must be tightly regulated. Since humans have no physiologic mechanism for active elimination of excess body iron, total body iron is controlled almost exclusively by the rate of iron absorption from the duodenum.

The concentration of iron in the human body is normally maintained at approximately 50 mg/kg of body weight in men and approximately 40 mg/kg of body weight in women, and is distributed among functional (e.g., red blood cells [RBCs]), transport, and storage compartments. Iron overload is defined by the Spanish Society of Blood Transfusion and the Spanish Society of Haematology and Haemotherapy as ferritin levels greater than 1000 μg/L on 2 or more consecutive measurements within 15 days, or a liver iron concentration greater than 7 mg Fe/g of dry tissue, measured by liver biopsy or by magnetic resonance imaging. The National Comprehensive Cancer Network suggests initiating iron chelation therapy after transfusion of 20 to 30 units of RBCs or in those whose serum ferritin level is greater than 2500 ng/mL.

H&O Who is at risk for iron overload?

JC Accumulation of excess body iron can result from prolonged excessive ingestion of dietary iron or iron-containing supplements, chronic liver disease, some hereditary disorders of iron metabolism (such as hemochromatosis, which causes excessive absorption of dietary iron), and chronic transfusion therapy for anemia in patients with ineffective erythropoiesis, ineffective hemoglobin production, or chronic hemolysis, such as those with β-thalassemia, sickle cell disease, or myelodysplastic syndromes. Regular transfusion is the main available treatment for many patients with severe, chronic anemia, and it can be lifesaving. Patients receiving regular RBC transfusions, however, unavoidably and invariably develop cumulative iron overload and therefore are at risk for iron toxicity.

Iron toxicity develops when free iron in tissues leads to organ dysfunction and damage. Iron toxicity is associated with substantial morbidity and increased mortality, which are directly related to the degree of iron overload. Because symptoms of iron toxicity may not appear until substantial organ damage has occurred, a high degree of awareness is necessary to identify patients at risk.

Transfusion departments should establish mechanisms that guarantee the early detection of iron overload, and appropriate monitoring, control, and reporting to the relevant health authorities. In a study that was recently published in Blood Transfusion, my colleagues and I found a significant discrepancy between what is recommended by current guidelines and the standard of care exercised by the health care providers at our institutions. Monitoring and evaluation of patients receiving multiple transfusions should be a common practice in transfusion departments in order to detect the population at risk of iron overload.

H&O How quickly does iron overload occur?

JC Accumulation of free iron in tissues characteristically occurs over decades in patients with hereditary disorders...
of iron metabolism, but may take place within a few years in transfusion-dependent patients.

One unit of RBCs contains approximately 200 mg of heme iron, more than 100 times the quantity absorbed from the diet daily. A patient with transfusion-dependent anemia requiring 2 units of RBCs per month would receive 24 units per year—or approximately 100 units over 4 years. This results in an accumulation of 20 g of iron after 4 years, which is 7 times greater than the normal total mass of body iron. Accordingly, the number of RBC transfusions is a predictor of iron overload.

**H&O What are the risks of iron overload?**

**JC** The most serious adverse effect of iron overload in the heart is sudden death from heart failure. In the past, children with β-thalassemia major who did not receive chelation therapy developed left ventricular hypertrophy and cardiac conduction disturbances before the age of 10 years, and ventricular arrhythmias and refractory myocardial failure at approximately 15 years of age. Two clinical trials published in the *New England Journal of Medicine* in 1994—one by Olivieri and the other by Brittenham—found that systemic iron load is the main prognostic factor for determining the clinical course of these patients: patients whose ferritin levels were below 2500 μg/L during the follow-up period had a heart disease–free survival rate of 91% after 15 years of follow-up, vs a heart disease–free survival rate of 21% in patients with ferritin measurements greater than 2500 μg/L. In addition, the survival rate at 25 years of age in patients with liver iron concentration levels greater than 15 mg Fe/g of dry weight was 32%, whereas no deaths occurred in patients with levels below 15 mg Fe/g of dry weight.

**H&O Does iron overload caused by transfusions of packed RBCs lead to the same short-term and long-term complications that primary hemochromatosis does?**

**JC** In transfusional iron overload, free iron from erythropoagocytosis of transfused RBCs accumulates in macrophages after iron storage proteins become saturated. This free iron is subsequently transported to and deposited primarily in parenchymal cells of the liver, heart, pancreas, and endocrine tissues—particularly the anterior pituitary in patients with thalassemia and transfusional iron overload. Lipid peroxidative products are also formed; peroxyl radicals have a longer half-life than hydroxyl radicals, and these reactive oxygen species have a greater capacity for chronic cell toxicity and DNA damage. Excess iron accumulation in tissues results in a number of adverse clinical outcomes and an associated increase in morbidity and mortality that correlates with the degree of iron toxicity.

**H&O What specific problems does iron overload cause in the liver?**

**JC** The liver is the organ with the greatest capacity to store iron. Because of this, it is generally the first organ affected by iron overload. Iron deposition in the liver may cause rapid development of portal fibrosis and cirrhosis. Portal fibrosis has been demonstrated in children younger than 3 years. The initial signs of iron deposition in the liver (hepatomegaly or elevated liver enzymes) may be absent or mild in some cases, however. Additionally, the concentration of iron in the liver is an expression of iron deposition in tissues. The main sequelae of excess iron deposition are fibrosis/cirrhosis and hepatocellular carcinoma.

**H&O Which patients receiving RBC transfusions need chelation therapy?**

**JC** Patients on RBC transfusion support should be considered candidates for chelation therapy if they are older than 2 years; are expected to liver longer than 1 year; have received over the past year more than 20 units of packed RBCs if an adult or 10 units of packed RBCs if a child; and have documented iron overload.

**Suggested Readings**


