Hemochromatosis Treatment by Venipuncture Through History

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Abstract

Hemochromatosis is a hereditary disease caused by the mutation of genes responsible for regulating iron metabolism in the body. The mutation results in increased absorption of iron from food, which is then deposited in various organs and tissues. Due to the excessive decomposition of iron, organs, most commonly liver, heart and pancreas are damaged. The standard therapeutic procedure for the treatment of hereditary hemochromatosis is phlebotomy or venipuncture, which removes excess iron from the blood. The therapeutic procedure is carried out until the iron level returns to the reference interval. Ancient, three thousand years old bloodletting skills are still used to this day. It was considered that the bloodletting establishes a good balance of bodily fluids referred to as eucrasia. Venipuncture was used to treat various diseases, with different amount of blood released, from half a liter to two liters, and sometimes even more. Venipuncture was applied not only for the treatment of existing diseases, but also as a preventive measure. To date, the use of therapeutic venipuncture has remained the gold standard for the treatment of hereditary hemochromatosis.

The aim of this paper is to present a historical review of venipuncture or phlebotomy as a therapeutic procedure for the treatment of hemochromatosis.

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Introduction

There are various expressions used to describe the procedure of therapeutic blood sampling, venipuncture, phlebotomy, venesection and bloodletting. A widely used expression across the English-speaking world is “phlebotomy”, derived from the Greek word “phleb”, which stands for “vein”, and “tōmos” which means “incision”. Phlebotomy is the process of opening a vein by incision in order to take blood for therapeutic treatment or diagnosis. One of the first people who recognized the importance of veins and arteries was the Chinese Emperor known as the Yellow Emperor or Huang-Di (who ruled China in the 27th century BC). His famous remark was that “everything in the blood is under the control of the heart” (1).

The ancient skill of bloodletting dates back to about three thousand years ago. Ancient Greeks, Egyptians, the peoples of Mesopotamia, the Maya and the Aztecs all knew the practice of blood-shedding, or bloodletting, as a treatment for diseases. This practice began with the Egyptians 1000 years before Christ and was...
Hemochromatosis

Primary hemochromatosis is a hereditary disease caused by HFE gene mutation on chromosome 6. This is the most common autosomal recessive hereditary disease of the Caucasian population in Northern European countries, with prevalence in Europe reported as 1:300. It is equally represented amongst both male and female populations. Sickness rarely occurs in the African and African American population, as well as in the Asian population. Men develop a clinical picture more often than women, about 10 times more often, the reason for this being the loss of iron in women during periods, birth and breastfeeding. Hereditary hemochromatosis is divided into four subtypes, and only type 1 is clinically important. A total of 85-90% of patients with confirmed diagnosis of hemochromatosis are homozygotes for mutation C282Y (Y/Y genotype), while about 5% are heterozygotes for mutations C282Y, H63D and / or S65C. In individuals who did not demonstrate mutation C282Y, and who are heterozygotes for S65C and / or H63D, the possibility of developing a clinical picture of inherited hemochromatosis is extremely low (5,6).

Diagnoses of hemochromatosis include laboratory diagnostics, radiological diagnostics and histological treatment. The clinical picture of hemochromatosis includes tiredness, hyperpigmentation (bronze skin color), loss of libido in men, diabetes, joint pain, cirrhosis of the liver and cardiomyopathy.
Laboratory diagnostics show elevated levels of serum iron and ferritin as well as increased transferrin saturation index.

**Applying venipuncture in the treatment of hemochromatosis**

Hemochromatosis was first described in Paris in 1865 by Armand Trousseau, a French physician, who outlined the disease as a set of symptoms involving diabetes, skin pigmentation, and liver cirrhosis. Trousseau did not name the disease (2).

Davis and Arrowsmith are attributed with the first report on the treatment of hemochromatosis which showed the value of venipuncture. In their report, they state that repeated venipunctures can remove harmful iron. To confirm the diagnosis of hemochromatosis, they carried out a liver biopsy. The first patient was a 69-year-old woman. Between March 1947 and February 1949, 40 liters of blood were drawn from this patient. According to their report, all patients treated by bloodletting showed a general improvement (7).

In 1954, Davey, Foxell and Kamp reported the case of a man at the age of 55 who was hospitalized in October 1950. The patient complained of abdominal pain that had lasted for 2 years, increased tiredness and gray and black pigmentation of the face, neck and upper arm. His liver was enlarged, spleen was not palpable, and free intra-abdominal fluid was found. He had not suffered from previous illnesses except for colon cancer surgery in 1936. He drank plenty of beer daily. The tested urine showed glucose in the urine. Skin biopsy showed iron deposits, especially around the sweat glands. The patient was treated with repeated venesections. Over the course of two years, 31 liters of blood were drawn from the patient. Heavy anemia developed, although the patient showed subjective and objective improvement. The patient was last registered in 1954 when his symptoms were pain in the joints. A report was published, claiming that venesection is an effective hemochromatosis treatment method (8). In 1965, a group of authors (Block, Moore, Wasi and Haiby) investigated a cohort of patients with hemochromatosis. In their research, a liver biopsy was performed prior to venesection, the findings of which suggested that liver lesions arise due to abnormal absorption of iron despite a normal diet (9). In an article published in 1969, Dr. R. Williamson reported that over a period of 5 years, the mortality of patients treated with repeat venesection was 11%, while the mortality of untreated patients was more than 60% (10).

Untreated hemochromatosis can result in death due to cardiac complications. Heart damage is manifested as cardiomyopathy, arrhythmia and heart failure. A period of 12 months is required to restore normal liver function and up to 30 months to fully recover from angina. Continuous and controlled therapy (venipuncture) is needed to restore normal parameters (12).

An early diagnosis of hereditary hemochromatosis has a tremendous significance in preventing the development of diabetes mellitus as well as hepatocellular carcinoma. Niederau et al. claim that patients who received timely therapy prior to the onset of cirrhosis did not develop hepatocellular carcinoma later. Early treatment with venipuncture prevents the formation of cirrhosis and attention should therefore be focused on early diagnosis of hereditary hemochromatosis (13).
A research conducted by a group of authors in Norway shows that the treating of hereditary hemochromatosis by venipuncture leads to a change in the level of some trace elements, including increased absorption of toxic elements such as copper. (14).

**Conclusion**

Therapeutic venipuncture or phlebotomy is the golden standard for the hemochromatosis therapy. In the procedure, 500 ml of blood containing 200 to 250 mg of iron is extracted. Standard procedures prescribe periodic venipuncture, approximately once a week, with the letting of 400-500 ml of blood, during the first 3 years, followed by 400-500 ml every 1-3 months. Venipuncture is carried out until the levels of iron and ferritin drop to the lower limit of the normal reference interval. Venipuncture can be performed on younger patients 2-3 times a week. The aim is to achieve ferritin values below 50 ng / ml and a ferritin saturation index under 50% in serum. Most patients can tolerate quite well a week of undergoing the procedure, which should be performed until hematocrit falls below 37%. To monitor the therapeutic response, it is recommended to check serum saturation and serum ferritin levels every 2 to 3 months (15).

Treatment of primary hemochromatosis by venipuncture is a safe and effective way of removing blood in order to reduce iron levels. Treatment is a lengthy process, usually lasting several years until iron values return to normal. Venipuncture improves the overall condition of the patient, alleviates the symptoms of fatigue, pain, and skin pigmentation. Regular therapy prevents liver complications, heart disease and diabetes (16).

Despite the advances in technology, bloodletting as a therapeutic procedure has survived to this day as a controlled, supervised, safe and efficient treatment option. In this procedure, it is important to follow all the guidelines for proper blood drawing. The role of medical laboratory personnel in diagnosing and monitoring primary hemochromatosis is vital. Laboratory tests allow the physician to make a proper diagnosis and evaluate the overall medical condition during the course of disease monitoring.

**References**