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Therapeutic erythrocytapheresis versus phlebotomy in the initial treatment of hereditary hemochromatosis – A pilot study

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Abstract

Hereditary Hemochromatosis (HH) is a genetic disorder of iron metabolism, resulting in excessive iron overload. Currently, phlebotomy is the standard effective treatment that prevents progression of tissue damage. Aim of the therapy is to reach ferritin levels between 20 and 50 $\mu g\, l^{-1}$. In patients with total iron stores of more than 30 g, intensive treatment by means of weekly phlebotomies during 2–3 years is required to reach this aim.

More recently mechanical removal of erythrocytes through therapeutic erythrocytapheresis (TE) has become a new therapeutic modality. By means of TE, up to 1000 ml erythrocytes per session can be removed, depending on patient characteristics, compared to 250 ml erythrocytes per phlebotomy. Thus, TE potentially offers a more efficient method of removing iron overload with less procedures in a shorter treatment period.

In a pilot study between 2002 and 2005, results from a group of HH patients treated with TE ($N = 6$) were compared to the results of a historical control group of HH patients ($N = 6$) treated with phlebotomy. The results showed a reduction of almost 70% in both the total number and the duration of treatments in the TE group. Although, the procedure costs compared on the basis of a single TE session were higher, the total costs for the whole treatment were comparable or cheaper with the use of TE. Future prospective studies are needed to compare both therapies in a randomized setting.

Keywords: Hereditary Hemochromatosis (HH); HFE-gene; Phlebotomy; Therapeutic Erythrocytapheresis (TE)

1. Introduction

HH is a common genetic disorder in which the iron absorption is increased from the normal 1–2 mg/d to 4 mg/d. After many years this increase can lead to deposition of excessive amounts of iron in parenchymal cells, resulting in impaired organ

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function, especially with regard to the liver, pancreas, heart, joints and pituitary gland.

The gene involved in the most common form of HH was discovered in 1996 and is called the HFE-gene [1]. The most common mutations responsible for clinical manifestation of the disease are a substitution of cysteine with tyrosin at position 282 (C282Y), or a substitution of histidine with aspartic acid at position 63 (H63D) [1–3]. The prevalence of homozygotes varies globally between 0.25% and 0.50%. The prevalence of heterozygotes varies between 10% and 15% of the population. In 1–20% of the homozygote carriers, clinical manifestations of HH develop during their lifetime. The prevalence among the heterozygote carriers is much lower, as only 0.13% develops clinical manifestations [4–6].

Clinical manifestations are diverse and not always specific for HH. The most common initial symptoms are asthenia (46%), arthralgia (44%) and aminotransferase increase (45%) [7]. In an advanced stage of the disease, the clinical manifestations include various degrees of hepatomegaly (95%), cirrhosis, hepato-cellular carcinoma, congestive heart failure (15%), diabetes mellitus(30–65%), destructive arthropathy (25–50%), hypogonadotrophic hypogonadism, impotence, arrhythmias and excessive skin pigmentation [8].

One of the earliest manifestations of disturbed iron metabolism is an increase in the plasma iron concentration with a concomitant increase in the transferrin saturation (TS).

2. Treatment

Once HH is diagnosed, the therapy is simple, straightforward and effective since it is based on the removal of the excess of body iron by removing blood. The effect of the therapy is monitored by the iron saturation and ferritin levels. Initial therapy starts by trying to normalize the serum ferritin concentration to $\leqslant 50\ \mu g\ l^{-1}$ and/or the transferrin saturation to 50% or less. After achieving these target levels, the initial treatment is followed by a lifetime maintenance treatment in order to preserve these target levels of the iron concentration, as mentioned above [9].

Up to now the standard treatment to achieve this result is phlebotomy, which is a simple and effective, but time-consuming, therapy. The frequency of phlebotomy, which can be performed up to once or twice a week, is determined by the hematocrit, the hemoglobin concentration, the degree of iron overload, the presence of organ dysfunction, and the limitations imposed by other conditions such as coronary heart disease [10]. In severe cases (ferritin higher than 1000 μg/l) the patient starts blood letting treatments once or twice a week, whereby usually 500 ml of whole blood is removed. This equals approximately 250 mg of iron. Weekly phlebotomies for a period of 1–2 years (a total of 50–100 phlebotomies) may be required. After the serum ferritin concentration and transferrin saturation are normalized, the maintenance therapy is continued with phlebotomies every 2–6 months during the remaining lifetime of the patient. Despite all safety criteria, many adverse events occur during this treatment such a vasovagal reactions, hematomas, fatigue and injuries of the vascular wall. After a whole blood donation of 500 ml, one-third of healthy blood donors develop one or more adverse events, such as bruises (23%), sore arm (10%), fatigue (8%) and vasovagal reactions (7%) [11]. When presented for treatment with phlebotomy, HH patients often already have concomitant diseases that would put them at a greater risk of complications while undergoing blood letting compared to regular blood donors. Up to today there are at least two published cases of fatal complications after phlebotomy treatment in HH patients [12,13].

Phlebotomy cannot be used in patients with severe cardiac disease, anemia, or hypoproteinemia. For these patients, chelation therapy provides the only means of effectively removing iron. At this moment the only commercially available iron chelator is deferoxamine. However, this therapy is known for its potentially even more serious local and systemic side-effects [10].

In the last 15 years, automated therapeutic erythrocytapheresis (TE) became available, which seems to offer a good alternative for HH treatment [14–24]. During a single TE procedure up to 1000 ml of red blood cells can be removed, equalling 800 mg of iron, depending on the estimated circulating blood volume. Thus, almost up to four times more iron can be removed per treatment, compared to conventional treatment with phlebotomy. A TE procedure preserves the valuable blood components of the patient, such as plasma proteins, platelets, clotting factors and leucocytes, which make this approach also a viable option for patients with hypoproteinemia or thrombocytopenia. During a TE procedure the patient receives compensation for the removed volume by saline or protein solu-