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Iron deficiency and its management in patients undergoing lipoprotein apheresis. Comparison of two parenteral iron formulations

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Abstract

Objectives: There is evidence of *iron deficiency* (ID) in patients treated with lipoprotein apheresis. Aim of this study was to assess ID in apheresis patients and to study its management comparing safety and efficacy of two approved intravenous (i.v.) iron formulations.
Methods: Inclusion criteria were defined as a) serum ferritin < 300 μg/l and transferrin saturation < 20%, b) ferritin < 100 μg/l. Both iron deficient alone and ID anemic (IDA) patients were included. Other causes for anemia were ruled out by thorough history-taking and examination/blood tests. Patients were treated with six different lipoprotein apheresis methods: DALI, Liposorber D, TheraSorb LDL, HELP, MONET and Lipidfiltration. 50 patients were randomized to either ferric carboxymaltose (FCM, 500−1000 mg as single shot infusion over 20 min) or ferric gluconate (FG, 62.5 mg once weekly).
Results: 50 of 67 patients of our Lipoprotein Apheresis Center showed iron deficiency. Both i.v. iron formulations studied were equally safe (no serious adverse events (SAEs), 6 patients/group showed adverse events (AEs)) and both effective (clinically and with respect to laboratory data) in lipoprotein apheresis patients, however FCM led to a more rapid and steeper rise of iron parameters.
Conclusions: ID and IDA are common findings in lipoprotein apheresis patients. The pathogenesis remains yet poorly understood and is probably multifactorial. Differential diagnosis of ID/IDA is as essential as differential therapy. Handled with care, older i.v. iron preparations like FG appear to be safe and effective in lipoprotein apheresis patients. However, novel formulations like FCM can be administered rapidly at higher doses due to high complex stability, allowing faster filling of iron stores.

Newer laboratory parameters (Reticulocyte-He, low/medium/high fluorescence reticulocytes (LFR/MFR/HFR)) assessing iron status may be helpful in early detection of ID and in monitoring iron replacement therapy.

Keywords: Lipoprotein apheresis; Iron deficiency; Iron deficiency anemia; Reticulocytes; Ferric carboxymaltose; Ferric gluconate

1. Introduction

Worldwide, *iron deficiency* (ID) belongs to the most common nutritional deficiencies [4]. In Europe prevalence is about 10%, in third world countries >50% of women of childbearing age [2]. Worldwide about 25% of all humans suffer from ID [2]. *Iron deficiency anemia* (IDA) is the most common anemia with about 80% [2].

There is evidence of ID in patients treated with lipoprotein apheresis [1]. However, data is scarce and hence there are no guidelines for iron replacement therapy in lipoprotein apheresis patients. Pathogenesis of ID/IDA in lipoprotein apheresis patients appears to be multifactorial with both functional and absolute ID [1,3].

Using conventional iron parameters (iron, serum ferritin, transferrin saturation (TSAT)), accurate laboratory diagnosis of ID and monitoring iron replacement therapy can be demanding, especially in functional ID which is often prevalent in multimorbid patients like our study population. Here new diagnostic approaches may be helpful. In this study we determined the content of reticulocyte hemoglobin (Ret-He,

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diminished content indicates functional ID, rises quickly after iron replacement) as well as low, middle and high fluorescence reticulocytes (LFR, MFR, HFR) and the immature reticulocyte fraction (IRF) as early markers of ID [5–7]. Ret-He and HFR have been proposed as predictors of ID and provide means of early identification of non-responsiveness to i.v. iron therapy [5–7].

1.1. Objectives

Aim of this study was to assess ID/IDA in lipoprotein apheresis patients and to study its management by comparing two approved intravenously administered iron formulations: ferric gluconate versus ferric carboxymaltose.

2. Material and methods

We conducted a two-arm study assessing iron deficient patients undergoing lipoprotein apheresis at baseline and after 4 and 8 weeks of intravenous iron administration: patients were randomized to either ferric gluconate or ferric carboxymaltose.

Sodium Ferric gluconate (FG, Ferrlecit®, Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany) is a ferric iron carbohydrate complex containing elemental iron (1 ampule = 5 ml = 62.5 mg iron) in an alkaline aqueous solution with about 20% sucrose in water. 62.5 mg iron as FG was administered once weekly after each apheresis session as an infusion (diluted in 0.9% saline over 20 min) until iron parameters exceeded those defined as inclusion criteria.

Ferric Carboxymaltose (FCM, Ferinject®, Vifor International, St. Gallen, Switzerland) belongs to the newer i.v. iron formulations that can be administered rapidly at higher dosages. In ID alone, 500 mg was given once only as short infusion (diluted in 0.9% saline over 20 min) after completion of apheresis treatment. In IDA iron demand was calculated using the Ganzoni equation (Total Iron Deficit = Weight {kg} × (Target Hb − Actual Hb) {g/dl} × 2.4 + Iron stores {mg}). Up to 1000 mg of iron can be administered in one single session. Hence, if iron demand exceeded 1000 mg, 1000 mg was given in week 1 and the remaining iron in week 2.

2.1. Patients

50 patients with iron deficiency treated with lipoprotein apheresis for severe hypercholesterolemia were enrolled.

There were no clinical signs for bleeding. A thorough history was taken as to concomitant disease and their last check-up consultations (colonoscopy, gastroscopy, gynecological/urologic examination, chest X-ray, ultrasound, test for occult blood), and blood tests were performed for differential diagnosis of anemia.

Inclusion criteria were defined as serum ferritin < 100 μg/l or ferritin < 300 μg/l and transferrin saturation < 20%. Since there are no guidelines for iron replacement therapy in lipoprotein apheresis, rationale for these cut off values was gained by data from cardiology patients (FAIR-HF trial [8]), especially since the majority of our patients have cardiac insufficiency, and guidelines in nephrology [25].

Blood was withdrawn before apheresis treatment at baseline and after 4 and 8 weeks, assessing iron status and a full blood count. Symptoms of iron deficiency were determined at baseline and after 6 weeks. AEs were monitored carefully.

The study was approved by the ethics committee of the University of Dresden. Patients gave written informed consent before commencement of the study.

2.2. Lipoprotein apheresis

Six different lipoprotein apheresis methods were applied: (1) DALI (Fresenius Medical Care GmbH, Bad Homburg, Germany), (2) Liposorber D (Kaneka Pharma Europe N.V., Wiesbaden, Germany), (3) TheraSorb LDL (antibodies, Miltenyi Biotec GmbH, Bergisch Gladbach, Germany), (4) HELP (B. Braun Melsungen AG, Melsungen, Germany), (5) MONET (Fresenius Medical Care GmbH, Bad Homburg, Germany), (6) lipidfiltration (LF; DIAMED Medizintechnik GmbH, Cologne, Germany). DALI and Liposorber D are whole blood systems, whereas the others treat plasma. All of the lipoprotein apheresis methods are extra-corporeal systems, based on three main principles: precipitation (HELP), filtration (Lipidfiltration, MONET) and adsorption (DALI, Liposorber D, TheraSorb LDL). For details of the apheresis methods refer to Ref. [13].

2.3. Clinical chemistry

Serum ferritin, transferrin and iron were measured on the Modular Analytics System by Roche using transferrin, ferritin or iron reagents (Roche, Mannheim Germany); iron was measured photometrically (ferro-zine-reaction), transferrin and ferritin analyses are antibody based. Complete blood count and reticulocyte hemoglobin (Ret-He), low fluorescent reticulocytes (LFR), middle fluorescence reticulocytes (MFR), high fluorescence reticulocytes (HFR) and the immature reticulocyte fraction (IRF) were quantified from EDTA whole blood on the XE5000 hematology analyzer of Sysmex (Sysmex, Kobe, Japan). Folic acid and Vitamin B12 were measured on the Immulite 2000 (Siemens, Erlangen, Germany) using the respective reagents. CRP, LDH, haptoglobin and TSH were measured on the Modular Analytics System (Roche, Mannheim, Germany) using the respective reagents.

2.4. Statistics

All statistical analysis and reporting were performed using the IBM-Software SPSS Statistics (version 20).

In general and for a detailed overview, ordinal and other categorical (i.e. classified) parameters have been