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TIDILAP: Treatment of iron deficiency in lipoprotein apheresis patients – A prospective observational multi-center cohort study comparing efficacy, safety and tolerability of ferric gluconate with ferric carboxymaltose

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Abstract

Objectives: Iron deficiency (ID) and iron deficiency anemia (IDA) are common findings in patients undergoing lipoprotein apheresis (LA). Different intravenous (iv) formulations are used to treat ID in LA patients, however guidelines and data on ID/IDA management in LA patients are lacking.

We therefore performed a prospective observational multi-center cohort study of ID/IDA in LA patients, comparing two approved i.v. iron formulations, *ferric gluconate (FG)* and *ferric carboxymaltose (FCM)*.

Methods: Inclusion criteria were a) serum ferritin <100 μg/L or b) serum ferritin <300 μg/L *and* transferrin saturation <20%. Patients received either FG (62.5 mg weekly) or FCM (500 mg once in ID or up to 1000 mg if IDA was present) i.v. until iron deficiency was resolved. Efficacy and safety were determined by repeated laboratory and clinical assessment. Iron parameters pre and post apheresis were measured to better understand the pathogenesis of ID/IDA in LA patients.

Results: 80% of LA patients treated at the three participating centers presented with ID/IDA; 129 patients were included in the study. Serum ferritin and transferrin levels were reduced following apheresis (by 18% ($p < 0.0001$) and by 13% ($p < 0.0001$) respectively). Both FG and FCM were effective and well tolerated in the treatment of ID/IDA in LA patients. FCM led to a quicker repletion of iron stores ($p < 0.05$), while improvement of ID/IDA symptoms was not different. Number and severity of adverse events did not differ between FG and FCM, no severe adverse events occurred.

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Conclusions: Our results suggest that FG and FCM are equally safe, well-tolerated and effective in treating ID/IDA in LA patients. These data form the basis for follow-up randomized controlled trials to establish clinical guidelines.

Keywords: Lipoprotein apheresis; Iron supplementation; Iron deficiency; Iron deficiency anemia; Ferric gluconate (FG); Ferric carboxymaltose (FCM)

1. Introduction

Iron deficiency (ID) and even more so ***iron deficiency anemia (IDA)*** are serious clinical complications that require swift treatment [1–3]. Whereas ID may be associated with impaired cognitive function, impaired physical performance and fatigue [1–3], IDA can lead to impaired cardiac function [2] and contributes to higher rates of hospitalizations and mortality [1]. ID is a symptom and not a diagnosis, which requires thorough history taking and examinations in order to identify the underlying cause and to hence provide specific causal treatment, rather than merely substituting iron. ID results from an imbalance between iron intake and iron loss (absolute ID), or between iron demand and iron availability (functional ID).

As previously shown, ID and IDA frequently occur in patients undergoing ***lipoprotein apheresis (LA)*** [4–6]. Precise identification of the individual cause of ID in LA patients is vital but demanding, since they present with several comorbidities such as diabetes mellitus, chronic kidney disease, coronary heart disease, cerebrovascular disease, peripheral artery disease. Consequently management often involves a polypharmaceutical regimen, including medications that might impair iron absorption such as proton pump inhibitors.

Both functional ID (insufficient iron availability due to a hepcidin-induced iron block preventing iron release from iron stores and intestinal iron adsorption) and absolute ID (depletion of iron stores in the bone marrow, liver and spleen due to increased blood loss, poor dietary intake) appear to contribute to the high prevalence of ID in LA patients. However the underlying pathomechanisms whereby LA leads to ID are not completely understood.

In this study we hypothesized that the development of ID in LA patients is due to a combination of some or all of the following reasons:

(1) Blood loss due to blood remaining in the apheresis lines and repeated blood withdrawals (absolute ID)
(2) Ferritin and transferrin loss though binding and removal with apheresis columns during LA (absolute ID) [5,6].
(3) Hemolysis during plasma separation or whole blood adsorption (absolute ID)
(4) Anticoagulation in patients with history of cardiovascular events (absolute ID) [5].
(5) Comorbidities (chronic kidney disease, diabetes etc.) (functional ID) [5].
(6) States of chronic inflammation (functional ID)
(7) Insufficient dietary intake and/or absorption (absolute ID/functional ID)

To date, there are no guidelines for iron supplementation in LA patients due to insufficient data and lack of controlled trials. There are no studies on the comparison of different forms of iron supplementation in LA patients [4].

Clinical experience shows that i.v. iron often appears to be superior compared to oral iron substitution in LA patients, which is consistent with our above hypothesized pathogenesis that ID/IDA in LA patients has a substantial functional component. Ferric gluconate (FG) and Ferric carboxymaltose (FCM) are two of the most widely used i.v. iron formulations in Germany to address ID/IDA in LA patients. FG is administered repetitively until repletion of iron stores whereas FCM, a novel formulation, can be administered more rapidly in larger doses due to high complex stability [7] hence leading to a faster correction of ID. However, it is not known if these apparently superior properties of FCM also translate into a clinical benefit for LA patients.

The aim of this prospective observational multi-center cohort study was to compare the efficacy, safety and tolerability of FG to FCM in the treatment of ID/IDA in LA patients.

2. Material and methods

This prospective observational multi-center cohort study was conducted at three apheresis centers in Germany without any industrial or private funding.

It was approved by the institutional review board of the Medical Faculty at the Technische Universität Dresden, Germany (EK 318092011). All patients gave written informed consent before enrollment.

2.1. Patients

Patients undergoing LA due to severe hyperlipidemia were recruited from three large German apheresis centers (the apheresis unit of the University Hospital Dresden, the ambulatory healthcare center Dr. Heigl and partners in Kempten-Allgäu and the dialysis and apheresis center Dr. Ramlow and partners in Rostock). Patients were screened