Journal of Pharmaceutical Care & Health Systems
ISSN: 2376-0419

Yu, et al., J Pharma Care Health Sys 2015, S4
DOI: 10.4172/2376-0419.S4-002

Commentary Open Access

Iron Liposome: A more Effective Iron Supplement for Sports Anemia and Anemia of Inflammation

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Received date: November 18, 2015; **Accepted date:** November 30, 2015; **Published date:** December 07, 2015

Abstract

Anemia is such a serious global health problem that it has aroused the focus of the world. Anemia is characterized by decreased number of red blood cells (RBC), lower haemoglobin concentrations or even altered RBC morphology. Due to the critical role of iron in the production of haemoglobin and RBC, iron-deficiency is often accompanied with anemia. In general, it is recommended to supplement iron formulations when iron is deficiency in anemia patients. However, sports anemia and anemia of inflammation (AI) cannot be treated with traditional iron supplements because the iron cannot be absorbed adequately resulting from the decreased expression of iron uptake and exported proteins in duodenum. Therefore, new types of iron supplements should be designed to prevent or treat iron deficiency in sports anemia and AI. Iron liposome is a new type of iron supplement that can be absorbed without the limitation of iron uptake and export proteins. Iron liposome has the superiority of liposome that can cross the duodenum through membrane fusion, membrane diffusion or phagocytosis. This review mainly covers the advantage and usage of iron liposomes in the prevention and treatment of sports anemia and AI. This will shed light on the application of iron liposomes in clinic in future.

Keywords: Iron deficiency anemia; Sports; Inflammation; Iron liposome; Absorption

Introduction

Anemia is a serious global health problem, and its prevalence had reached 32.9% and accounted for 8.8% of the total disability in 2010 [1]. Anemia patients suffer from fatigue, weakness, difficulty in concentrating, decreased cognitive performance or poor work efficiency. They are frequently encountered in the emergency department. Clinical characterization of anemia showed the decreased number of red blood cells (RBC), lower haemoglobin concentrations or even altered RBC morphology. Because approximate 80% of the iron demand in human body is used for haemoglobin synthesis to supply the production of 200 billion new erythrocytes every day [2], the anemia are usually accompanied by iron deficiency. It is reported that significant iron-deficiency can lead to iron deficiency anemia (IDA), which is very common in children younger than 5 years old. IDA has been associated with cognitive and behavioral delays in children and has been considered as a major contributor to the global burden of disease [3-5]. Therefore, anaemia has aroused the world-wide attention. There are quite a few other conditions that can induce anaemia such as chronic disease, sports and inflammation [1,6]. In particular, sports anaemia and anemia of inflammation (AI) display iron deficiency, which cannot be improved with traditional iron supplements, this enhanced the difficulty in its prevention and treatment in clinic. It is critical to investigate the causes and strategy for dealing with sports anemia and AI.

Sports Anaemia and Iron Deficiency

Iron is the most abundant trace element in the world that plays important roles in oxygen transport, energy metabolism, electron delivery chain and the cofactor for enzymes in biosynthesis [7]. Despite the long history of fundamental observations about iron metabolism and the significance of iron nutrition, the molecular mechanisms involved in iron metabolism are just being defined in recent two decades [7]. Iron is mainly absorbed at the duodenum (1–2 mg of dietary iron per day) and released into the circulation system; macrophages also phagocytose senescent erythrocytes and recycle the iron (20–25 mg of iron per day) into the blood, which contributes to the majority of the iron in plasma [8]. Insufficient iron absorption from diet in the duodenum and inappropriately high levels of hepcidin can cause IDA, which is a serious health issue all over the world [7,8].

High intensity of sports can develop into anaemia, which is known as sports anaemia [9]. Sports anaemia mainly describes the athletes, and they are characterized by iron deficiency with difference from IDA. Because of the insufficient iron absorption, sweat loss of iron and blood loss though foot strike haemolysis or gastrointestinal blood loss [10,11], the iron in the plasma cannot meet the demand of the human body. Moreover, hepcidin levels were significantly elevated at the early stage after exercises [9,12]. Increased levels of hepcidin could bind to iron exporter-Ferroportin 1 (FPN1) in enterocytes and macrophages, induce its internalization and degradation, thus the levels of FPN1 protein on the membrane were decreased which induce the decline of iron efflux from enterocytes and macrophages into the plasma [13,14]. Therefore, iron levels are decreased in the serum, which affects the work performance of iron-deficient athletes. How to elevate the iron levels in human become an important issue, and iron supplementation

is proposed to be one effective way to increase iron levels and elevate the performance of athletes with sports anemia.

Anaemia of Inflammation and Iron Deficiency

Anaemia of inflammation (AI), also called anaemia of chronic disease, is caused by an underlying inflammatory disease such as inflammatory bowel disease (IBD) and a typically normocytic anaemia [15,16]. Chronic inflammatory of human body is reported to induce anaemia of chronic kidney disease resulted from the iron deficiency and decreased erythropoietin (EPO) affected by hepcidin [6].

Hepcidin plays an important role in the pathology and progression of AI. In the status of inflammation, hepcidin is increased. The increased hepcidin induced the degradation of FPN1 in enterocytes and macrophages, then inhibits the efflux of iron into the blood through absorption by duodenum and iron release from macrophages [17]. Therefore, AI was also characterized by low serum iron concentrations, low serum ferritin levels, reduced saturation of transferrin and impaired release of iron from storage, which results in a lack of iron delivery to the developing red cells despite adequate iron stores [15,18]. It indicates that patients with AI need treatment with iron supplements.

However, the systemic iron stores are not depleted in AI patients. Traditional oral iron supplements commonly used in clinical practice cannot be efficiently absorbed and transported into the plasma due to the deficiency of FPN1 protein on the membrane of enterocytes [11]. Moreover, the absorbed iron accumulates in organs because FPN1 expression was decreased and iron exported was impaired. In turn, more iron supplementation was administrated, which not only injures the mucosa of the upper gastrointestinal tract but also aggravates the burdens or iron contents in organs without relief of iron deficiency in serum. Therefore, it is necessary to find new strategies for iron supplementation or formulation for AI.

Traditional Iron Supplements

Both sports anaemia and AI are characterized with iron deficiency. It comes to the mind that they should get treatment of iron supplementation. The World Health Organization (WHO) recommends a daily dose of 60 mg iron per intake to minimize the adverse effects and facilitate compliance [4]. Iron supplements can be delivered intramuscularly, intravenously, or orally [11,19], and oral administration is preferred and more convenient. For example, a women endurance athlete repeatedly suffered from iron deficiency anemia would get the prophylactic supplementation of ferrous sulphate [20].

The most commonly used iron supplements are inorganic. Comparing with ferric supplements with poor absorption, ferrous salts was considered more effective, cost-effective and bioavailable [4]. The regularly used iron supplements in clinic include ferrous sulphate, ferrous sulphate with mucoproteose, ferrous glycine sulphate, iron protein succinylate, ferrous gluconate and ferrous fumarate [4,21]. However, only ferrous sulphate with mucoproteose is the best tolerated iron supplement with extended-release [4]. Most of the other oral iron supplements will cause mucosal injury in the gastrointestinal tract, and high iron intake will produce iron overload in some people, which cause cell toxicity and side effects such as constipation, abdominal discomfort, nausea, respiratory morbidities and an increased risk of infection [4,21,22]. What is more, ferrous sulphate with mucoproteose cannot be applied to sports anemia and AI patients because they have difficulties of iron absorption due to the deficiency of FPN1 protein in enterocytes. Therefore, it is urgently needed to explore new types of iron formulations.

Liposome-Encapsulated Iron is a New Type of Iron Formulation with High Absorption Efficiency

Liposomes have a cell membrane-like phospholipid bilayer structure and are usually produced in the form of lipid microcapsules with aqueous phase cores. As intelligently designed carriers for the delivery of bioactive molecules, iron liposomes have been designed and applied in pharmaceutical synthesis.

Ferric ammonium citrate (FAC), one form of ferric iron, cannot be absorbed by duodenum effectively. Especially in sports anemia and AI patients, because the expression of iron exporter-FPN1 was decreased in duodenum enterocytes and macrophages, it becomes more difficult for FAC to be absorbed and released from macrophages into the plasma even if FAC is absorbed by duodenum. However, the prepared liposomes encapsulated with FAC can be successfully and efficiently absorbed into the circulatory system through duodenum and relieved the iron deficiency status in animal models of sports anemia and AI [11,18]. Compared with ordinary iron supplements (FAC and heme iron), iron liposomes can obviously increase the iron levels and haemoglobin concentrations in serum so as to alleviate the anemia in murine models of sports anemia and AI. FAC encapsulated in liposome solved the low absorptive deficiency of FAC when the iron absorption was restricted due to the decreased expression of FPN1. Iron liposomes have high efficiency of absorption is mainly because they can enter the body easily through membrane fusion, membrane diffusion or phagocytosis and enter the blood circulation directly, which can avoid passing through protein-mediated transport pathways and is different from the uptake and transport of FAC by duodenum [18].

As is known, extraneous iron will cause oxidative stress lipid peroxidation. Attractively, iron liposomes did not aggravate the oxidative stress at the same time of increasing iron levels in serum, which is the main superiority to FAC and heme iron supplementation [11,18]. Moreover, iron liposomes are unilamellar vesicles and mostly nanosized particles, they also have physical stability and gradual released properties [18]. Furthermore, they have no toxicity and minimal side effects to the body than unencapsulated iron reagents.

It should be mentioned that, for clinic, AI patients also have severe inflammation and other accompanying diseases, so they should get other therapies except supplementation of iron liposome. For some competitive athletes with sports anemia, the iron deficiency might be a host-defense response to underlying injury or infection [23,24]. In such kind of conditions, it should firstly determine which type of microorganism causes the iron reduction, because some bacteria will grow more happily with iron and iron supplements will exacerbate the disease of sports anemia.

Perspectives

Iron is abundant in the earth's crust, but IDA is a big health issue in many parts of the world, which is mainly due to the poor efficiency of absorption and low bioavailability of iron. From animal experiments, it demonstrates that iron liposome is a new form of iron supplement with high efficiency of absorption and low side effects compared with the traditional iron supplements. Iron liposomes have many

advantages: they are physically stable, non-toxic, gradually released, non-immunogenic targeted drug carriers. Especially, they can reduce drug dosages in clinical applications due to their ability to improve drug absorption and reduced toxicity [11,25]. Therefore, iron liposome can be used in prevention and treatment of sports anemia and AI and oral administration of liposomal drugs has broad application prospects. However, there is a long way to apply iron liposomes on human beings, such as optimal dose for both safe and effective, the optimal duration, the optimal mode of delivery and important interactions between iron and other micronutrients (especially zinc) raised by WHO. In summary, iron liposome is a prospective and more effective iron formulation for sports anemia and AI, which gives us a new strategy for designing iron supplements to prevent and treat anemia effectively with less side effects.

Acknowledgement

This was supported by the National Natural Science Foundation of China (30871260) and the Natural Science Foundation of Hebei Province (C2012205082 and C2012205068).

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This article was originally published in a special issue, entitled: **"Global Burden of Disease",** Edited by Nagwa Ibrahim