



Editorial Article

Iron Deficiency Anemia in the 21st Century: Why is still too prevalent and what we can do as treatment?

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Anemia due to iron deficiency anemia is the most common anemia in the world and 5% and 2% of American women and men, respectively, have it [1]. Iron deficiency anemia is a form of anemia due to the lack of sufficient iron to create healthy red blood cells. It is caused by inadequate intake of iron, chronic blood loss, or a combination of both. It is quite prevalent in the World for years. We have noticed an increased of patients with this diagnosis in the community based practice as well as in the academic practice. We want to make knowledgeable the importance of prevention, early diagnosis, and management of the anemia in the 21st century despite the advancements of the medicine in particularly using the integrative medicine approach.

Iron has been used by physicians to treat a variety of ills throughout history. According to Nicholas Monarde, a 16th century physician in Seville, the applications of iron as a medicine included in the treatment of diseases are Alopecia, Acne, Vaginal discharges, and Tuberculosis within others [2]. Iron plays a role in anemia and has been used by many physicians, although we can see iron deficiency without anemia. Chlorosis, sometimes known as the “green sickness,” is no longer diagnosed. Clinicians considered it the most common of maladies, and it characterized by a hypochromic anemia that responded to iron therapy; we must conclude that the primary pathogenesis was that of iron deficiency. Hippocrates, Lange, Whipple made history for years about this [2]. There has been greater consensus about the effect of iron deficiency without anemia on deficits and attention spans leading to learning and problem solving difficulties in children [3]. This is critical to let the physicians know about this.

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Low iron bioavailability of the diet in developing countries, is the primary cause of iron deficiency anemia [4,5]; however, in advanced countries, decreased iron absorption and blood loss account for the more likely etiologies. Atrophic gastritis and malabsorption syndromes, especially celiac disease, are the responsible for reduced iron absorption [6]. Other causes are post surgical gastrectomy (partial or total), Bariatric Surgery, intra abdominal surgeries, and chronic blood loss from genitourinary, gynecological, or gastrointestinal tracts. Excessive menstruation is the most common etiology of iron deficiency anemia in premenopausal women [1]. It's quite common seen in my practice. We see women aged from teens until 50's with excessive regular or irregular menses running with anemia between 7 and 10gm/dL.

A global study [7] performed an evaluation of the change in micronutrient deficiency over time in the form of a composite indicator-the Hidden Hunger Index (HHI). They used an from the Nutrition Impact Model Study for anemia due to iron deficiency, vitamin A deficiency, and stunting (used as a proxy indicator for zinc deficiency). Africa was within the 20 global regions with the lowest HHI in 1995 but was also among the top 20 worst performers regarding a net change in HHI over the 16 year period studied. The reason is due to significant conflict and vulnerability to food insecurity due to climate changes. The impact of micronutrient deficiency holds representative and adverse consequences in the cognitive and physical development of the children as well as adverse effects on productivity and economic potential in later adulthood. So, nutritional deficiency as the cause of iron deficiency anemia is still a major public health issue linked to the socio economic status of the countries in this Century. We don't see this only in children; we see the elderly population affected too. A study was done at United Kingdom [8] with adults aged 65 years and over revealed that that population's life expectancy and health status is adversely affected due to nutritional deficiency anemia. The study encouraged to educate health care professionals as to what constitutes a healthy diet for the elderly population and gives practical guidance as to how to try and prevent the ever growing problem of malnutrition within this age group. Definitively, poor nutrition plays a significant role in the pathogenesis of iron deficiency anemia in the World no matter the age and the time.

Another study in Canada with the geriatric population [9] included all anemic patients over 60 years old who had erythropoietin measured between 2005 and 2013 at a single center. A total of 570 patients met the inclusion criteria. Linear regression analysis showed that erythropoietin levels in chronic kidney disease, anemia of chronic illness and anemia of unknown etiology were lower by 48%, 46%, and 27%, respectively, compared to iron deficiency anemia even after adjusting for hemoglobin and other comorbidities. They demonstrated that erythropoietin levels are inappropriately low in anemia of unknown etiology, even after adjusting for confounders. This statement suggests that decreased erythropoietin production may play a fundamental role in the pathogenesis of anemia of unknown etiology. It is imperative when we got that population with anemia to perform the appropriate blood levels of erythropoietin as well as the serum iron

levels. It's important to replace the iron storage if deficient before give epoetin alpha therapy to those patients because it won't work too.

So, we usually give oral preparations and supplementations when we diagnosed iron deficiency anemia, but in many cases, they do not respond well, and we need to use parenteral iron such as iron dextran or iron sucrose. The first parenteral infusions caused severe acute reactions and were unsuitable for use [10]. The development of iron dextran in 1954 caused that IV iron is given more quickly, but severe acute reactions still occurred infrequently. In 1964, the first report of 37 patients receiving a total dose infusion (single replacement dose) published in *Blood* [11], with one delayed reaction consisting of fever and chills without hypotension or wheezing. It was, however, another 16 years before the findings of the first prospective study in 471 patients published in *JAMA* [12]. While all patients responded and none died, three developed signs of anaphylaxis, leading the investigators to conclude that IV iron should reserve for those clinical situations in which oral iron could not use.

A study of C.Wang et al., [13] stated that rates of adverse reactions are lower than others. Although other study populations might have contributed to the observed differences, other differences in identifying and reporting anaphylaxis cases during clinical trials and during general clinical practice might also be pertinent. Practicing physicians might not classify less severe or atypical anaphylactic cases as anaphylaxis; thus, the sensitivity of the anaphylaxis algorithm used in their study was probably small. Others did not recommend comparing the crude incidence rates of anaphylaxis from their study with rates of other medications, especially if the following estimates based on different data sources or research methods. Interestingly, 5 of 444 patients identified with anaphylaxis in the study died within two days of anaphylaxis diagnosis (2 in iron dextran group, 1 in iron gluconate group, and 2 in ferumoxytol group).

Few prospective studies report the safety, ease, convenience and efficacy of complete or near complete replacement doses of IV iron administered in a single setting (total dose infusion over 15-60 minutes) [14-17]. One study in chronic heart failure and iron deficiency anemia [18] demonstrated that another parenteral iron formulation such as ferric carboxymaltose IV is very effective compound for total dose single infusions causing better health related quality of life and fewer hospitalizations. For subjects who have losses and absorption problems, a total dose infusion is a more convenient and less expensive method of replacing iron than oral preparations. Compared to the side effects present in the majority of people taking oral preparations, such as constipation, metallic taste, gastric cramping and robust green tenacious stool, the adverse events with IV iron are minor, infrequent and short lasting. So, IV iron is consequently moving rapidly forward in the treatment paradigm in the last decade. Published evidence supports a larger and earlier role for parenteral iron and raises the question of whether it should be frontline therapy in many conditions. It is more important than ever that inferences and conclusions on the relative safety of the available IV iron formulations based on credible data. Based on all prospective and retrospective studies, when iron

dextran is avoided the remaining formulations are safe, and probably much safer than most physicians realized.

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