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Article Review

Iron deficiency anemia: clinical, diagnostic and therapeutic aspects

Anemia ferropriva: aspectos clínicos, diagnósticos e terapêuticos

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ABSTRACT: Iron deficiency anemia occurs due to iron deficiency and is considered the most common nutritional deficiency in the world. It can be triggered by iron malabsorption, low iron intake and blood loss, affecting mainly risk groups and presenting its characteristic symptoms. The objective of the present study is to carry out an integrative bibliographic review in relation to its clinical, diagnostic and therapeutic aspects, associating it with risk groups, describing relevant points of the pathology, presenting adopted exams and describing therapeutic methods for the treatment. A literature review was carried out in publications of the type original scientific articles found through electronic databases SciELO, PUBMED, BVS, LILACS, Medline and GOOGLE ACADÊMICO, in English and Portuguese, published between 2006 and 2020, using criteria for inclusion and exclusion . 20 publications were found, of which 9 were included following the aforementioned criteria. Iron-deficiency anemia is considered an obstacle to public and global health because it affects fragile social strata in emerging countries. It is believed that adhering to healthy lifestyle habits, along with State support, can improve this problem and thus reduce the rate and prevalence of the disease.

KEY WORDS: Iron-Deficiency; Diagnosis; Therapeutics.

RESUMO: A anemia ferropriva ocorre por deficiência de ferro e é considerada a mais comum das carências nutricionais do mundo. Pode ser desencadeada pela má absorção de ferro, baixa ingestão do mineral e perda sanguínea, acometendo, sobretudo grupos de risco e apresentando seus sintomas característicos. O objetivo do presente estudo é realizar uma revisão bibliográfica integrativa em relação aos seus aspectos clínicos, diagnósticos e terapêuticos associando a grupos de risco, descrever pontos relevantes da patologia, apresentar exames adotados e descrever métodos terapêuticos para o tratamento. Foi realizada uma revisão de literatura em publicações do tipo artigos científicos originais encontradas por meio de bases eletrônicas SciELO, PUBMED, BVS, LILACS, Medline e GOOGLE ACADÊMICO, nas línguas inglesa e portuguesa, publicados entre 2006 e 2020, utilizando critérios para inclusão e exclusão. Foram encontradas 20 publicações, das quais 9, foram incluídas seguindo os critérios supracitados. A anemia ferropriva é considerada um empecilho à saúde pública e mundial, por acometer camadas sociais fragilizadas em países emergentes. Acredita-se que aderir hábitos de vida saudáveis, juntamente com o apoio do Estado, podem melhorar esta problemática e assim diminuir o índice e a prevalência da doença.

PALAVRAS CHAVES: Anemia ferropriva; Diagnóstico; Terapêutica.

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INTRODUCTION

The most common nutritional deficiency is iron deficiency affecting primarily developing countries, so anemia is defined as a state of concentration in which hemoglobin is below the reference values, and may be needy and in this context, be caused by deficiency of one or more nutrients, such as iron, zinc, vitamin B12. Iron deficiency anemia, is considered the most common nutritional deficiency in the world, the causes being: poor absorption of the mineral iron, low intake of foods rich in iron, acute blood loss associated with trauma and chronic blood loss (nose and hemorrhoids may be visible in stool). Among the groups most susceptible to developing Iron Deficiency Anemia are children under five years of age, lactating and women of childbearing age[1,2].

In Brazil there is no survey of the prevalence of iron deficiency anemia, but some studies have conceptualized that approximately 4.8 million preschool children develop this pathology. Iron deficiency anemia has some nonspecific clinical signs which may be present in others types of anemia but the most commons signs reported by patients are muscle weakness, mucous skin discolouration, cephalea, dizziness, vertigo, dyspnea, irritability, attention deficit and psychomotor disabilities[3].

Iron depletion is characterized by the decrease of the concentration of the reserve present in bone marrow, spleen and liver associated with the serum ferritin, in which it evaluates the storage of iron present in the body. It emphasizes the importance of keeping attention to it due to the serum ferritin concentration that may suffer from the presence of liver diseases, inflammatory and infectious processes[2,3].

The iron deficiency anemia is conceptualized by a major public and world health problem for it consists of a nutritional problem that consequently affects people living in developing countries who are in poverty. Due to the great problem that this pathology causes in the life of an individual, studies qualify that the primary therapy in the first stage of the development of the disease is the implementation of ferrous sulfate orally, where the therapeutic dose of elemental iron recommended for the treatment of children is on average 20 mg, of infants 15 mg and adults 65 mg for a period where it is sufficient to normalize the necessary concentration of iron for the body, where the durability of the treatment is according to the individual and the intensity of iron deficiency[4].

In addition to the nutritional deficiency factor caused by the difficulty in access to adequate food caused, among the other reasons, by the socioeconomic status of vulnerable families, vitamin deficiency factor caused by vegetarian and/or vegan diets. As the main source of B12, iron and others vitamins and minerals essentials to homeostasis are obtained through food intake of animal origin, diets with this characteristic, when performed erroneously, can lead to a deficiency that can lead to iron deficiency anemia. Studies demonstrate the vegetarians an vegans despite having access to iron, vitamin C, B12 via vegetable foods, need a nutrition with a greater presence of this nutrients, but how they do not get enough, they have a lower amount of vitamin B12 and iron stocks, which can lead in the long term a low in hemoglobin and consequently anemia especially in women and children.

Another important factor to be commented on is inflammation-related Anemia. In addition to absolute iron deficiency, a significant cause of iron deficiency anemia is iron deficiency anemia resulting from non-mobilization of iron stocks and no absorption of it, often observed in conditions of chronic inflammation, neoplastic diseases and others underlying medical conditions. In these contexts, the chronic inflammatory response induces increased production of interleukins, particularly interleukin-6 (IL-6), which stimulates hepatic synthesis of hepcidin. This polypeptide performs a central role in regulating the iron metabolism, acting to block the intestinal iron absorption and iron release from intracellular stocks leading to a state of functional iron deficiency anemia. Thus, understand the pathophysiological mechanisms underlying anemia from chronic disease is crucial to an comprehensive and effective approach in the diagnosis a treatment of iron deficiency anemias specially in patients with complex chronic medical conditions[7,8,9,10].

Given the relevance of this pathology, considering its prevalence, injuries and impacts it is necessary to carry out a literature review on this anemia, specially related to its clinical, diagnostic and therapeutic aspects in order to promote scientific bases that can contribute to knowledge of students and health professionals who experience in their routines the significant occurrence of this anemia providing more information for the entire population.

MATERIALS AND RESEARCH METHODOLOGY

This work is an integrative literature review, having as guiding questions: What are the clinical forms and clinical picture of this disease? What laboratory methods are adopted in practice for diagnosis, therapeutic monitoring and prognosis? What are the main findings that can conclude a clinical-laboratory diagnosis? What are the main therapeutic methods adopted in clinical practice for a possible treatment of iron deficiency anemia?

Being developed through electronic bases: Scientific Eletronic Library Online – Biblioteca Cientifica Online (SCIELO), Público/Editora Medline (PubMed), Biblioteca Virtual em Saúde (BVS), Medline (Medical Literature Analysis and Retrieval System Online), LILACS (Literatura Latino- Americana e do Caribe em Ciências da Saúde) and Google acadêmico. Through a previous consultation in the Descritores em Ciências da Saúde (DeCS) Finder, advanced search, the following descriptors were determined for research: “Iron deficiency anemia”, “diagnosis”; “clinical aspects” “therapeutic”.

The inclusion criteria are based on publications of the types, scientific articles, publications in newspapers, provided that they are available in Portuguese and English, containing full text, published between 2006 and 2022 and presented compatibility to the theme and proposed objectives. And the exclusion criteria were productions that did not meet the proposed theme and the guiding questions of the research, which did not meet the inclusion factors, as well as review articles, letter to the editor, and articles of opinions and incomplete texts.

The results obtained were organized in chronological order of publication in Table 1.

Table 1 - Document analysis of the data obtained

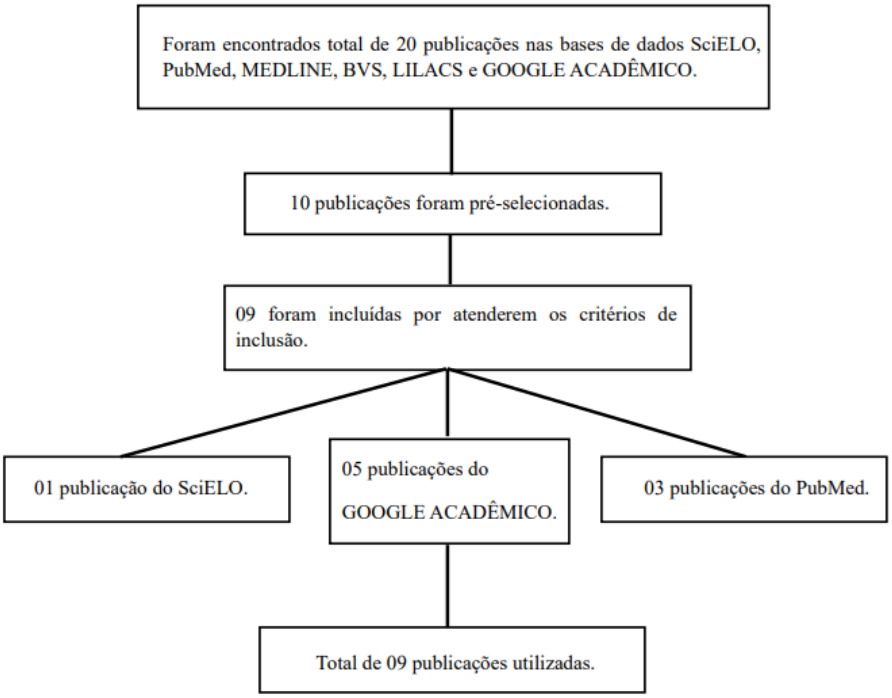
Title of publication	YEAR	Results	Database	Author
Anemia e estado nutricional de crianças em creches de Guaxupé.	2008	Study with male and female children evaluating serum iron dosages and transferrin saturation indexes.	PUBMED	Camillo et al., 2008[11]
Anemia ferropriva e fatores associados em gestantes assistidas em hospital de referência do Estado de Pernambuco.	2012	Study with 611 pregnant women taking into account the anemic and non-anemic, evaluating the economic conditions and the race of each of them, and evaluating the weight.	Scholar Google	Silva, 2012[12]
Anemia ferropriva na infância: estratégias para prevenção e tratamento.	2012	Studies conducted in Brazil demonstrated the effectiveness of iron supplementation, a great strategy pointed out was to invest in health education. Effective treatment for the disease of ingestion of compounds with iron orally.	Scholar Google	Ferraz, 2012[13]
Anemia e deficiência de ferro em crianças: associação com consumo de carne vermelha e aves.	2013	Study with 263 children, where 11.2% had anemia, 22% iron deficiency and 3.7% iron deficiency anemia, evaluating the consumption of poultry and red meat.	PUBMED	Moshe et al., 2013[14]
Anemia ferropriva: diagnóstico e tratamento.	2017	This study aimed to demonstrate the symptoms and clinical signs presented by patients and an effective treatment for iron deficiency anemia.	Scholar Google	Yamagishi et al., 2017[15]
Iron deficiency anemia revisited.	2019	Iron deficiency anemia is a global health problem, affecting especially children and women. Its etiology is variable and may have as a risk factor the reduction of iron intake, malabsorption and increased demand for this mineral. Oral and therapeutic methods are highly effective in the therapeutic purposes of pathology.	PUBMED	Cappellini et al., 2019[16]
Estudo de correlação da anemia ferropriva, deficiência de ferro, carência nutricional e fatores associados.	2021	Iron deficiency anemia stands out for being considered one of the greatest nutritional deficiencies, obtaining the possible diagnosis of this is performed by blood count, the hematimetric indexes.	Scholar Google	Mortari et al., 2021[17]
Anemia ferropriva na infância: diagnóstico e tratamento.	2021	A study comparing anemia with poverty and precarious public services, thus citing the programs carried out in the state through public policies.	Scholar Google	Da Silva, Benchaya, 2021[18]
Fisiopatologia, diagnóstico e tratamento da anemia ferropriva.	2021	Anemia is a pathological process in which the concentration of hemoglobin is below the reference values, iron deficiency anemia caused by iron deficiency. It is the one with the highest incidence of other anemias.	SCIELO	Brito et al., 2021[19]

Source: Elaborated by the authors themselves.

RESULTS

After using the databases cited during the study methodology associated with the inclusion factors established, 20 publications were selected, where after performing an analysis under them, were pre-selected 9 publications that were evaluated by the inclusion and exclusion criteria because they fit the objectives proposed by the study as shown in Figure 1.

Figure 1 - Flowchart of the inclusion and exclusion criteria.



Source: Elaborated by the authors themselves.

Table 1 shows the evaluation of the data obtained from the integrative literature review.

Camillo et al., conducted a study with 211 children, where being noted in their test results that the presence of 49.76% were female and 50.23% were male, even if the hemoglobin averages were within normal values consequently 33 children from 6 to 36 months, 2 children from 36 to 60 months and 1 child from 60 to 72 months had low values, being the average of 33 children lower than the others. Children aged 6 to 36 months showed that serum iron dosage and transferrin saturation index were lower than the reference value and lower than the other children[11].

Anemia is equivalent to the decrease in the number of erythrocytes per unit volume of blood and the amount of hemoglobin present in it, thus anemia is defined as the hemoglobin concentration below the reference value (14.0 to 18.0 g/dL for men;12.0 to 16.0 g/dL; less than 11 g/dL for pregnant women and less than 13.5 g/dL for children up to 12 years), there are different types of anemias, among them: deficiency anemia, such as iron deficiency, megaloblastic, pernicious, sideroblatic and aplastic; and hemolytic anemias among them: sickle cell anemia and thalassemias. Iron deficiency anemia stands out for its higher prevalence in relation to the others, and is characterized by iron deficiency within the body leading to reduction of hemoglobin[11].

Silva conducted a study with 611 pregnant women, of which 29.9% were anemic. It was noted that about 36.1% of the pregnant women were considered anemic and had low ferritin, and 26.5% of the non-anemic pregnant women had low levels of ferritin. When assessing economic conditions, it was observed that 42.4% received less than half a salary. In relation to race, pregnant women who have white or black color presented higher prevalence when compared to those of brown color[12].

Ferraz et al., demonstrated in their trials conducted in Brazil the effectiveness of iron supplementation as therapeutic, with 4 to 6 mg/kg/day of elemental iron and, in some cases, the use of chelate glycinate iron as a more effective alternative in view of less adverse effects. In addition, an important strategy was to invest in health education as a means of increasing adherence to treatment and the correct use of medications[13].

Moshe et al., presented a study with 263 healthy children. According to the study, hemoglobin levels were related to the age of the child. The mean hemoglobin level was lower in children aged 1.5 to 3 years than children aged 3 to 6 years. There was no significant discrepancy between male and female sex. It was seen that 11.2% of the population studied had anemia, 22% had iron deficiency and 3.7 already had iron deficiency anemia. When assessing the consumption of foods that have iron, 97% of children who reported that they consumed birds at least once a week. It was possible to evaluate that children with extremely low (rare) red meat consumption were four times more likely to have iron deficiency compared to children who consume two to three times a week[14].

In addition, according to the authors, enteroparasites infections may favor the occurrence of anemic, the spooliative capacity of parasites, that is, the absorption of nutrients causes hemorrhages in the mucous membranes and this is considered a primordial factor for the development of iron deficiency anemia. Diseases caused by enteroparasites are prominent throughout Brazil, being found in both rural and urban areas, the dissipation

of enteroinfections is due to the precariousness of basic sanitation in a given region, non-existent hygiene practices and houses in unhealthy places[14].

According to studies carried out by Yamagishi et al., the laboratory diagnosis of Iron Deficiency Anemia is performed using simple and easily accessible tests to any laboratory, but its interpretation must be carried out with great attention so that it cannot release inauthentic result, it should be noted the research of hidden blood in the stool to analyze blood loss through the fecal bolus, elderly people usually have small bleeding in the gastrointestinal tract due to the appearance of ulcers, or even the appearance of gastrointestinal neoplasms which can lead to possible iron deficiency anemia, which is imperceptible to the naked eye, and due to this, hidden blood in the stool is searched to identify the origin of anemia[15].

Still according to the essay of Yamagishi and cols. symptoms of Iron Deficiency Anemia include: headache, cutaneous discoloration, eating perversion, attention deficit, learning difficulties, weakness and psychomotor disabilities. When developed the eating perversion, patients report the desire to eat unconventional foods such as: raw rice, paper, rubber, earth, starch among others. During the first years of life a poor diet that does not provide the necessary minerals and vitamins can trigger a state of malnutrition in the patient, which thus favors a greater risk of infectious diseases, parasitic and intestinal thus causing a progressive increase in infant mortality rates[15].

Cappellini et al., pointed out that iron deficiency anemia is a worldwide disease. In his study, he emphasized that iron deficiency anemia is a pathology with multifaceted etiology and presented examples of populations with comorbidities that influence the onset of the disease. Finally, it demonstrated that oral and parenteral therapeutic methods are highly effective in the therapeutic purposes of pathology[16].

According to Mortari and cols. iron-deficiency anemia stands out from other existing anemias because it is one of the major problems to public health in the world, in which this nutritional deficiency occurs in three stages:

1st depletion of the iron reserve in the body;

2nd levels of ferritin and hemoglobin are decreased;

3rd drop in hemoglobin levels, being considered the most severe stage.

Table 2 shows the main changes in biochemical dosages and parameters relevant to erythrogram[17].

Table 2 - Stages of iron depletion and biochemical changes and erythrogram

PARAMETERS	1st STAGE	2nd STAGE	3rd STAGE
Hemoglobin	Normal	Decreased	Decreased
MCV	Normal	Normal	Decreased
Serum Iron	Decreased	Decreased	Decreased
Ferritin	Normal	Decreased	Decreased
TIBC	Normal	Increased	Increased

Subtitle: MCV: Mean corpuscular volume TIBC: Total Iron Binding Capacity.
Source: Adapted from Mortari et al*.,* 2021.

According to Mortari and cols., anemia caused by the presence of excessive bleeding arises when the loss of circulating red blood cells is greater than the generation of new red blood cells (erythropoiesis). The most common cause for this event is excessive bleeding. During excessive bleeding the body captures water from the tissues to keep the blood vessels full-bodied and, with this, the concentration of hematocrit present in the total volume of blood is decreased. The anemia developed through a hemorrhage is reversible because it has a correction established by the bone marrow by increasing the production of red blood cells. When blood loss is considered chronic, bleeding can occur in any part of the human body, and the most common, reported by patients, nosebleeds and hemorrhoids, however, small bleeding can occur and are classified as hidden. If bleeding lasts for a long time, there may be significant blood loss. This type of bleeding can occur in disorders such as: ulcers in the stomach and large intestine, polyps in the large intestine or even the appearance of a neoplasm in the large intestine, kidney tumors and tumors in the urinary bladder (where individuals report blood loss in urine)[17].

Da Silva et al., conducted a comparative study relating the cases and prevalence of anemia with poverty and precariousness of public services in Brazil, citing programs such as Bolsa Família, Fome Zero and even the Sistema Único de Saúde (SUS). According to the research, it was noted a difficulty of public programs focused on social aid and health in raising awareness and guiding the population about the importance of supplementation and the dangers of irregular iron administration, problems related to the adverse effects of medicines, especially in children. In addition, social vulnerability and poverty are closely related to malnutrition and the emergence of diseases such as anemia[18].

Finally, according to Brito and cols. anemia is equivalent to the fall in the number of erythrocytes per unit volume of blood and the concentration of hemoglobin, so anemia is defined as the hemoglobin concentration below the reference values (reference values: 14.0 to 18.0 g/dL for men; 12.0 to 16.0 g/dL for women; 11 to 16.0 g/dL for pregnant women and children under the age of 12). There are different types of anemias, including needy anemias such as ferropriva, megaloblástica, perniciosa, sideroblática and aplásica; and hemolytic anemias among them sickle cell anemia and thalassemias. Iron deficiency anemia

stands out for its higher prevalence in relation to the others, and is characterized by iron deficiency within the body leading to reduction of hemoglobin[19].

DISCUSSION

In iron deficiency anemia, the diagnosis is made through laboratory tests such as blood count, in which indicates and evaluates the decrease in hemoglobin, low in hematimetric indexes (MCV, MCH and MCHC), through the blood smear can be observed changes in erythrocytes, with respect to size and coloration where cells are microcytic and hypochromic, and changes in forms may also be present, with poikilocytosis, usually having the presence of codocytes or red blood cells in target, leptocytes and elliptocytes. In the biochemical analyses, serum iron dosage is performed, associated with complementary tests: ferritin, transferrin and transferrin saturation index (TSI), are performed to establish a possible diagnosis of iron deficiency anemia[1].

A diagnosis of Iron Deficiency Anemia is relatively easy in most cases, the degree of anemia can be variable and can be intense, the characteristics present in Iron Deficiency Anemia are microcytic (erythrocytes with small sizes) and hypochromic (reduction in the hue of red blood cells, with the increase of the central halo), MCV (mean corpuscular volume) may be within normality, but it may change remaining very close to the lower limit or still reduced, showing whether in the latter case, a microcytosis. As the reduction of hemoglobin there is also a reduction in tone, and may be associated with a reduction of MCH (Mean Corpuscular Hemoglobin)[1].

The leukocyte series most often does not undergo changes, but in relation to platelets, some patients have platelets or thrombocytosis (number of platelets are higher than the reference value), or may be close to the maximum value established, the reference values for platelet counts generally comprise 150,000 to 450,000/mm³ particularly when in Iron Deficiency Anemia blood loss occurs[1].

Regarding biochemical dosages, transferrin concentration is increased, consequently affecting reduced transferrin saturation (children under 7 years 40-100 µg/dL, men 65-175 µg/dL and women 50-170 µg/dL). The concentration of ferritin is decreased and the concentration of transferrin is increased and this consequently affects the reduced saturation index of transferrin (less than 15%)[1].

Correlating anemia with public health, indicators report that there is a conjuncture between iron deficiency anemia, poverty and malnutrition and poverty social phenomenon mitigated through public policies implemented by the State through programs such as Bolsa Família, Fome Zero e Sistema Único de Saúde (SUS). The State exercising its role in health, must have the obligation to install the Programa Nacional de Suplementação Medicamentosa de Ferro (PNSMF), in which the target audience are children between 6 and 18 months, pregnant women, infants and women aged[18].

Studies conducted in Brazil showed that iron supplementation (3 mg to 5mg/kg/day) for a sufficient period to normalize hemoglobin values as indicated, reduced the prevalence of iron deficiency anemia in children aged 12 and 18 months. Thus, other strategies should be considered, such as investing in health education, providing knowledge of hygiene/food handling, improving living conditions and basic sanitation. For the treatment of the disease, it is indicated to perform the administration of compounds with iron orally, where the most indicated is ferrous sulfate. The use of the medication should be maintained for a period of at least 4 to 5 months so that it is possible to replace the iron stock in the body[13].

The response to the treatment of iron deficiency anemia can be observed by counting reticulocytes that increase with the improvement of the clinical picture and hemoglobin begins to rise after two weeks of treatment[19].

The best option for iron replacement is oral due to therapeutic effectiveness, gastrointestinal tolerance and minimal risk of toxicity, in Brazil are marketed and available ferrous salts, ferripolymaltose and carbonyl iron, the recommended dose of elemental iron for the treatment of iron deficiency anemia is 3 mg to 5mg/Kg/day for a period that can normalize the hemoglobin value or even obtain the value of 15ng/mL for children and 30 ng/mL for adults of serum ferritin, due to this it is emphasized that the period for success may vary depending on the intensity of each individual. Values above 200 mg are not recommended due to the action of the intestinal mucosa preventing the absorption of iron. Another way to be successful during treatment is to maintain a balanced diet rich in iron, foods that are considered rich are: red meat, fish, chicken, egg yolk, beans, dark-colored vegetables such as watercress, arugula, spinach, kale and broccoli[18].

However, in specific cases, oral supplementation is insufficient, such as in patients undergoing bariatric surgery, gastrectomy or gastroplasty, severe anemia (other than the response of oral treatment) and absolute intolerance of the patient to oral treatment (nausea and incoercible vomiting). In these situations, supplementary parenteral treatment with Iron Oxide Saccharate and/or Ferric Carboxymaltose is indicated. Iron Oxide Saccharate is indicated mainly for gastrointestinal absorption disorders. Its use is given by dilution in 0.9% sodium chloride solution and administered by slow injection or infusion in a single dose maximum tolerated of 7mg iron/ kg body weight, with a minimum infusion time of three and a half hours. If the total dose required for the treatment of the patient exceeds the maximum single dose, the administration should be fractional, not exceeding the total dose of 500mg of iron20.

Ferric Carboxymaltose is safer and causes less hypersensitivity reactions due to lower bioreactivity when compared to Saccharate, making it ideal for patients with iron intolerance or patients in urgent need of replacement. However, its use is not recommended in children due to the lack of data in trials in this population during medication testing. Its administration is given in two ways: by intravenous infusion of maximum dose of 1,000mg of iron (20 mL) per day or 20mg of iron (0.4 mL) per kg of body weight. It should be diluted in 100 ml to 200 ml 0.9% sodium chloride solution, with infusion time of minimum 6 to 15 minutes. Or by intravenous injection (bolus) with a maximum dose of 1,000 mg of iron by means of undiluted solution[20].

We emphasize the existence of an update in therapy, adopted so far by countries: United States, France and England. In comparison with the mentioned above therapy, performed by the Ministry of Health, there are few differences, especially regarding feeding and supplementation by iron oxide[21].

CONCLUSION

Iron deficiency anemia, caused by iron deficiency is considered a major public health problem causing negative factors to the population, studies showed that children in preschool and pregnant women have a higher prevalence of developing the pathology. The insufficient consumption of dietary supplements containing iron and the lack of information of the population about the pathology has increased the rates of anemic people, thus leading to doubts regarding the measures implemented to ensure the physical, mental and social well-being of the population. Nowadays, due to the progress of laboratory tests for the diagnosis of pathologies that present specific changes, they have become more efficient for the discovery of diseases. Iron dosage, ferritin and transferrin dosage together with blood count and clinical manifestations are of paramount importance to detect the pathology and start treatment.

Adhering to the correct supplementation of iron-rich foods such as red meat, beans, broccoli, kale, spinach and adhering to guidelines on a healthy diet are measures that should be increased along with drugs provided by the State as ferrous sulfate, ferripolimaltose and carbonyl iron and with this, it is believed that after the implementation of these interventions can improve issues related to public health, thus reducing the index and prevalence of the disease.

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