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Comparison Of The Efficacy And Safety Of Succrosomial Iron And Elementar Iron Supplementation To Treat Iron Deficiency And Iron Deficiency Anemia In Preschool Children (3-6 Years): Protocol Of A Randomized Clinical Trial.

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Abstract
Children are particularly vulnerable to iron deficiency and its consequences. The estimated prevalence of anemia in the world population is about 40%. According to WHO, 47% of preschool children and 25% of school-age children suffer from iron deficiency anemia. Results of ongoing studies indicate that iron deficiency and anemia in children may impair their further development, both neurological and motor. The treatment of choice for iron deficiency and iron deficiency anemia is prolonged administration of oral iron preparations. Iron ions not absorbed from the intestine determine frequent adverse effects, which become a reason to abandon therapy with the prolongation of supplementation. Our study was designed to compare the efficacy of succrosomal and elemental iron supplementation in the treatment of iron deficiency and iron deficiency anemia in children aged 3-6 years by evaluating iron metabolism parameters. We also planned to assess the side effects of the studied supplements, the efficacy of the therapy with a single daily dose and the analysis of the occurrence and subsidence with the supplementation of clinical symptoms of iron deficiency or iron deficiency anemia in children aged 3-6 years. This is the single-center randomized comparative study. A total of 100 patients were planned to be enrolled in the study. Iron supplementation will be administered for 12 weeks. The primary aim of the study is to demonstrate that the effect of the application of succrosomal iron preparation is not worse than in the case of the application of elemental iron. The secondary objectives are to evaluate the adverse effects of the compared preparations, the efficacy of iron supplementation administered in a single daily dose and assess the occurrence and treatment-related resolution of iron deficiency symptoms and iron deficiency anemia in the study population.

Key words: Anemia, iron, iron deficit, children, supplementation

Introduction

Children are particularly vulnerable to iron deficiency and its consequences. A clinically latent iron deficit initially develops in deficiency conditions, followed by microcytosis with normal hemoglobin concentration, and the final stage is anemia [1]. The estimated prevalence of anemia in the world population is about 40% [2]. Almost 80% of all cases are iron deficiency anemia [3]. It is estimated that 1.224 billion people worldwide suffer from it [4]. According to WHO, 47% of preschool children and 25% of school-age children suffer from iron deficiency anemia [5]. Iron requirement during this period is high and difficult to cover with diet. Results of ongoing studies indicate that iron deficiency and anemia in children may impair their further development, both neurological and motor [6,7,8]. The treatment of choice for iron deficiency and iron deficiency anemia is prolonged administration of oral iron preparations. The bioavailability of commonly used products is limited [9,10]. Iron ions not absorbed from the intestine determine frequent adverse effects, which become a reason to abandon therapy with the prolongation of supplementation. Studies conducted on tissue models indicate that intestinal absorption of succrosomal iron is nearly 3.5 times higher than previously used preparations [11]. In studies conducted to date, the efficacy of succrosomal iron is comparable, with a favorable safety profile. Available studies indicate that using a lower dose of the preparation allows achieving a similar therapeutic effect with fewer reported side effects. So far, no studies have been published comparing the efficacy of succrosomal iron supplementation with elemental iron in children.

Study design

Hypotheses posed

The study was designed to compare the efficacy of succrosomal and elemental iron supplementation in the treatment of iron deficiency and iron deficiency anemia in children aged 3-6 years by evaluating iron metabolism parameters. The primary objective is to demonstrate that the effect of succrosomal iron in the study population is no worse than the standard recommended elemental iron.

We also planned to assess the side effects of the studied supplements, the efficacy of the therapy with a single daily dose and the analysis of the occurrence and subsidence with the supplementation of clinical symptoms of iron deficiency or iron deficiency anemia in children aged 3-6 years.

Material and methods

Study site and randomization procedure

The single-center randomized comparative study will be conducted at the 2nd Department of Pediatrics of the Medical Center for Postgraduate Education of the Central Clinical Hospital of the Ministry of Internal Affairs and Administration in Warsaw. Patients will undergo block randomization. The study compares two groups of patients: those supplementing with succrosomal iron (Group 1, study group) and those receiving elemental iron (Group 2, control group). It is planned to analyze the response to treatment in subgroups: patients diagnosed with isolated iron deficiency and iron deficiency anemia.

Study group

Sample size

Anticipating future statistical analysis and patients lost to follow-up, a total of 100 patients were planned to be enrolled in the study.

Inclusion criteria

- Age 3 to 6 years
- Iron deficiency assessed by hematological parameters according to WHO standards
- Iron deficiency anemia detected by hematological markers according to WHO standards

Exclusion criteria

- Severe anemia (hemoglobin -2 SD from the age-standard)
- Iron deficiency due to probable blood loss
- Anemia due to other causes, including genetic disorders (e.g., thalassemia, hemolytic anemia, etc.)
- Intravenous iron administration or blood transfusion within the past three months
- Current acute infection (time criterion)

- History of intestinal malabsorption
- Coexisting chronic diseases except for asthma and allergies
- Intolerance to orally administered preparations regardless of the cause
- Prematurity with birth age <35 Hbd
- Low birth weight <2500 g
- Child from a multifetal pregnancy
- Obesity (BMI > 90 pc according to WHO percentile grid)
- Iron supplementation (time criterion)

Randomization and blinding

The study participants will be randomly assigned to one of two groups - a succrosomal iron supplement group or an elemental iron supplement group. A diagnosis of iron deficiency or iron deficiency anemia in a child cannot be left untreated, so the placebo control group is waived. It is assumed that an even distribution of patients diagnosed with iron deficiency and iron deficiency anemia is achieved using block randomization within the groups. Because of the need to calculate the individual dose of treatment, blinding will be done only for patients.

Intervention

Iron supplementation will be administered for 12 weeks. Weight-adjusted iron will be administered daily in a single daily dose.

Study design

Study participants will undergo a systematic evaluation. The initial assessment will include a physical examination and laboratory tests: peripheral blood count, reticulocyte count, serum ferritin and iron levels, TIBC, transferrin, transferrin saturation, CRP.

Follow-up evaluation after 4, 8, and 12 weeks was scheduled. Each assessment included a physical examination and laboratory tests: peripheral blood count, reticulocyte count, serum ferritin and iron concentration, TIBC, transferrin, transferrin saturation, CRP.

Duration of study

The planned duration of iron supplementation in all patients is 12 weeks. The study is designed to end three months after the inclusion of the last participant. Shortening the time of observation of individual patients could occur in the lack of improvement or worsening of hematological status during the observation or occurrence of adverse events, preventing further participation in the study.

Endpoints of the study

The primary aim of the study is to demonstrate, based on the assessment of the change in hematological parameters, that the effect of the application of succrosomal iron preparation in the population of preschool children with diagnosed iron deficiency or iron deficiency anemia is not worse than in the case of the application of elemental iron.

The secondary objectives are to evaluate the adverse effects of the compared preparations, the efficacy of iron supplementation administered in a single daily dose and assess the occurrence and treatment-related resolution of iron deficiency symptoms and iron deficiency anemia in the study population.

Upon completion of the study, the collected data will be summarized and statistically analyzed.

Reporting of adverse reactions

According to the current WHO definition, an adverse reaction is defined as any untoward symptom or condition associated with using an investigational product in a patient.

Adverse effects occurring in connection with supplementation of the compared iron preparations, their frequency and severity, will be analyzed based on questionnaire data. Severe and health- or life-threatening side effects of therapy to participants will be reported according to local requirements and practice.

Dropout

A subject who develops circumstances that make it impossible to continue in the study will be dropped from the study. This applies particularly to the serious adverse events development, the lack of therapy effectiveness, or unsatisfactory patient compliance.

Withdrawal and discontinuation

You have the right to refuse to participate in the study or to withdraw from it at any time. Patients who do not complete the study, regardless of the reason, will not be included in the statistical

analysis. Withdrawal due to adverse reactions to therapy is a separate category. All adverse reactions observed during the conduct of the study will be included in the final analysis, regardless of whether or not they affected the conduct of supplementation according to the study protocol.

Discussion

Iron deficiency is the most common single nutritional deficiency worldwide. The most common form of anemia is iron deficiency anemia, affecting 20% of the population [12]. It results from systemic iron deficiency and is its final stage [13]. Certain populations are particularly vulnerable to iron deficiency and the anemia caused by it, including children. The prevalence of isolated iron deficiency in children is estimated to be 27-48%, depending on the country [14-17]. Iron deficiency anemia affects approximately 5% of children [16-24], but is estimated to be much more common [15,25,26].

We chose to study a population of children aged 3-6 years with a diagnosis of iron deficiency or iron deficiency anemia because of the high prevalence of the condition in this group. In addition, the registration indication for succrosomal iron includes patients older than three years of age.

To date, there have been no studies comparing the efficacy of supplementation of different oral iron preparations. Therefore, we intend to compare the efficacy of succrosomal iron supplementation with the current standard, elemental iron, in the study we designed. The use of block randomization will allow us to obtain an even distribution of patients with iron deficiency and iron deficiency anemia in the study groups. Because of the need to calculate the individual dose of preparation, blinding will only be done on patients.

In our study, the diagnoses of iron deficiency and iron deficiency anemia will be established based on WHO criteria. The diagnosis of isolated iron deficiency is made based on the measurement of plasma ferritin concentration. The values taken as the norm vary from author to author. Some investigators consider a concentration of <10 ug/l as the lower limit of the norm [14,15]. However, most analyses take a concentration of <12 ug/l as the lower limit of normal [16,22]. Because of this, in our work we will qualify iron deficiency as a decrease in plasma ferritin concentration below 12 ug/l. Ferritin belongs to the group of positive acute phase proteins - its concentration should be analyzed in conjunction with inflammatory markers. In our study, as in other authors, the presence of inflammation will be excluded by measuring the concentration of C-reactive protein (CRP).

Iron deficiency anemia is diagnosed when the hemoglobin level is two standard deviations below what is considered normal. In children, normal hemoglobin concentrations vary according to gender and age. In the population of preschool children, normal values are identical for both sexes.

According to WHO, in the population of preschool children, anemia is diagnosed with a hemoglobin concentration <11 g/dl. The sole determination of hemoglobin concentration is not sensitive and specific enough to diagnose iron deficiency anemia. MCV, MCH, MCHC, TIBC and ferritin concentration should also be determined. On the other hand, according to the American Academy of Pediatrics guidelines, a complete iron assessment in a given patient should include the measurement of hemoglobin, ferritin, hemoglobin in reticulocytes (CHr) and soluble receptor for transferrin type 1. CHr is considered the most decisive and most sensitive marker of systemic iron deficiency [8,27]. The parameter reflects the pool of iron available to young RBC forms in the bone marrow. It is independent of inflammation and validated in children, but it is unavailable in most laboratories in Polish conditions. CHr will not be evaluated in our work, but it seems that a surrogate parameter for CHr may be MCH, which will be determined in all patients [28]. The soluble receptor for transferrin type 1 concentration reflects iron deficiency at the cellular level. The parameter has only been determined in adults, we do not have a range of standards, and we will not evaluate it.

Considering the above, in the planned study we will diagnose iron deficiency anemia based on the finding of decreased hemoglobin <11 g/l and ferritin <12 ug/l (with negative CRP) with additional assessment of MCV, MCH, MCHC and TIBC.

After completion of supplementation of the compared iron preparations, based on the analysis of the change in hematological exponents in the study groups, we expect at least an equal increase in hematological exponents.

Oral iron supplementation is recognized as effective and safe management. The current regimens are based on administering an individually calculated daily dose in two or three parts. In isolated iron deficiency the recommended dose of elemental iron is 1-2 mg/kg b.w., in anemia 4-6 mg/kg b.w. Intestinal absorption of iron from most oral preparations is 10-15%. Limited absorption forces the administration of higher doses to achieve the intended therapeutic effect. Unabsorbed iron ions are probably responsible for side effects of the therapy [29,30,31]. Currently, lower daily doses are proposed to be administered at one time [32]. This treatment is supposed to be equally effective, with a lower risk of side effects and better patient compliance. In most patients, the recommended duration of therapy sufficient to saturate body iron reserves is three months. In iron deficiency, systemic reserves are used up first, followed by tissue reserves, so that the pool available for hematopoiesis remains unchanged for as long as possible. With supplementation, normalization of hematological parameters occurs rapidly - an increase in reticulocytosis can be observed after 7-10 days and complete normalization of hemoglobin concentration after several weeks of therapy. The reserve pool, measured by plasma ferritin concentration, is rebuilt on average after three months, therefore the total time of supplementation in our study will be 12 weeks with three assessments of iron metabolism exponents before the end of supplementation. Some patients discontinue supplementation prematurely due to side effects. The efficacy of such therapy is temporarily limited. On the other hand, once the reserve iron pool is replenished, iron administration does not benefit the patient and may be harmful. Iron supplementation in patients without established deficiency may be potentially toxic [33, 34]. In our study, the total duration of supplementation will be 12 weeks. A follow-up evaluation of patients after 4, 8 and 12 weeks of treatment is planned. A 1 g/dl increase in hemoglobin after two weeks of supplementation is considered an adequate response to treatment. Cyclic evaluation of patients in the project aims to trace the dynamics of changes in hematological parameters in the study groups and evaluate the adverse effects of supplementation.

We will compare the efficacy of succrosomal iron with elemental iron in patients aged 3-6 years with diagnosed iron deficiency and iron deficiency anemia because of the high prevalence of the condition in this group and the limited efficacy of therapy with commonly used preparations. The too short duration of supplementation is responsible for the failure of standard therapy in most cases [35]. Side effects of chronically taken iron supplements for some patients are the reason for premature discontinuation of therapy. The results of studies conducted so far with the use of succrosomal iron indicate that it is at least as effective as the previously used preparations, and the side effects are less frequent and less severe [36]. Intestinal absorption of most iron preparations is 10-15%. Achieving the intended therapeutic effect requires administering the higher dose of the preparation to the patient, the greater the deficit found initially. Iron ions not absorbed from the gastrointestinal tract are responsible for side effects. It has been shown that in contrast to previously used products, succrosomal iron is absorbed along the entire length of the intestine [36, 37]. Transport of iron ions occurs not only via the conventional pathway using a protein transporter in the membrane of the enterocyte but also via the transcellular and intercellular route [38]. When used in the succrosomal formulation, encapsulation of iron in microcapsules limits the release of iron ions in the intestinal lumen and promotes the formulation of an additional reserve pool available for increased demand within the enterocytes. In patients with refractory anemia resulting from chronic kidney disease, the use of succrosomal iron was comparably effective as repeated intravenous iron injections [39]. In patients with anemia secondary to malabsorption after bariatric surgery, succrosomal iron administration was as effective as intravenous iron preparations [40].

Available data do not indicate the occurrence of serious or life-threatening adverse effects after the use of oral iron preparations, but their intake is not free of side effects. Gastrointestinal symptoms such as abdominal pain, vomiting, or constipation

are the most common, and tooth discoloration or rash may also occur [41]. Iron supplementation with succrosomal iron is associated with fewer side effects, and they are less severe than previous therapies [42]. Serious, life-threatening side effects have also not been observed.

The need for iron supplementation in patients diagnosed with iron deficiency remains undisputed. Our study is aimed not only to evaluate and compare the efficacy and safety of supplementation with two iron preparations. We would also like to demonstrate the effectiveness of therapy with a single daily dose, which will certainly improve patient compliance. Analysis of questionnaire data concerning possible symptoms of iron deficiency or iron deficiency anemia in children included in our study will allow us to bring closer the clinical manifestation of these conditions.

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