Comparison of the effect of ferrous sulfate and ferrous gluconate on prophylaxis of iron deficiency in toddlers 6-24 months old: A Randomized Clinical Trial

Abstract

Background: Iron deficiency is the most common micronutrient deficiency affecting nearly one-third of the population and is the leading cause of anemia worldwide. n this study, we evaluated the effectiveness of ferrous gluconate and ferrous sulfate supplements to identify the best iron supplement with the most effective and the least side effects in toddlers 6-24 months old.

Methods: A randomized, single-blind clinical trial was performed. A total of 120 healthy toddlers aged 6 to 24 months old (two groups of 60) entered the study. Toddlers receiving ferrous sulfate (FS group) and ferrous gluconate (FG group) supplements. Blood indices such as hemoglobin & ferritin levels were evaluated at baseline and 6 months post-supplementation.

Results: The FG group that received ferrous gluconate chelate iron showed approximately 2.4 g/dl higher Hb level in comparison to the FS group with ferrous sulfate supplementation 6 months post-supplementation (12.51±0.58 g/dL vs. 10.10±0.83, $p = 0.045$). Side effects were significantly more common in the FS group than the FG group (43.3 % vs. 16.7 %, $P \leq 0.001$.

Conclusion: The present study shows that educating mothers to feed toddlers with breast milk and iron supplements, including ferrous sulfate and ferrous gluconate, can be helpful in the prophylaxis of iron deficiency. Our results show that ferrous gluconate can be used in cases where ferrous sulfate causes unacceptable side effects.

Introduction

Iron deficiency anemic (IDA) is the most common micronutrient deficiency affecting nearly one-third of the population and is the leading cause of anemia worldwide (1). World Health Organization (WHO) estimates that close to 30-40 % of the world's population are anemic and approximately half of them suffer from IDA (2).

Iron deficiency among infants and toddlers in the United States has a 13.5 % prevalence in the general population. However, only 1/3 of children with iron deficiency also have anemia (3). Iron deficiency and IDA remain a global concern. Iron is the most common nutritional deficiency among children in developing countries. In industrialized countries, despite a significant reduction in the prevalence of IDA, it is still a major cause of anemia in young children (4). More important than anemia, however, is the long-term effects of neurobehavioral development and some irreversible effects (3).

The risks of anemia in children begin during pregnancy. Maternal anemia during pregnancy is associated with an increased risk of low birth weight and maternal and child mortality. Iron is needed to produce newborn red blood cells in the first months after birth (5).

Since iron stores are usually depleted around 6 months (6), iron-fortified foods are recommended, which include meats, iron-containing products, and iron-fortified foods such as grains (7). Current guidelines for iron supplements for children are based on the assumption that the iron in the body that is present at birth and in breast milk is sufficient for the first 6 months of life (8).

Oral iron supplements are the first line of supplementation for IDA (9). Protocols for dose and duration of treatment are well defined. Adults with anemia are treated with 200-100 mg of elemental iron given in divided doses (9). In some people, lower doses may be used for fewer side effects. Children need a liquid solution (3-5 mg/Kg) (10). The gold standard is ferrous sulfate (FS) oral iron therapy (11). Other effective compounds include iron fumarate, gluconate, carbonyl iron, and iron-polysaccharide compounds. Given the important role of iron in the body and the high prevalence of iron deficiency in developing countries and the importance of prophylaxis of iron deficiency in toddlers aged 6 to 24 months old, in this study, we reviewed and compared ferrous gluconate (FG) and FS supplements to identify the best iron supplement with the most effective and the least side effects.

Methods

A randomized, single-blind clinical trial was performed; enrolling toddlers aged 6–24 months old. After obtaining informed consent, a total of 120 healthy toddlers aged 6 to 24 months old (two groups of 60) entered the study.

Based on the type of iron supplement received, toddlers categorized into 2 groups: group 1 (FS group), toddlers receiving 12 mg/day ferrous sulfate supplementation, and group 2 (FG group), toddlers receiving 85 mg/day ferrous gluconate supplementation.

All subjects were healthy and had a similar and healthy diet. Toddlers with iron deficiency or iron deficiency anemia, overweight, malabsorption, or any other gastrointestinal disorders were excluded from the study. In order to standardize the nutrition of toddlers, nutritional instructions were prepared and delivered to the mothers of toddlers. This nutritional guideline included protein, carbohydrate, lipids, iron, and vitamins (in the form of powdered milk). To ensure how much the mothers followed the mentioned nutritional guidelines, a questionnaire with 3 options was prepared: everything, nothing, or about half of what was served. In the end, only toddlers who followed the nutritional guidelines were included in the study.

To measure blood indices (Coulter Electronics, Ltd., UK), including hemoglobin (Hb), hematocrit (Hct), red blood cells (RBCs), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW) and serum ferritin (Dade Behring, Inc., Newark, DE, USA), five ml of blood samples were collected in the EDTA tubes. The above indices were in the normal range for all toddlers included in the study.

The samples were collected at baseline (at the beginning of the study) and 6 months post-supplementation. Healthy toddlers without anemia were randomly assigned to daily supplements with FS or FG chelate iron (15 mg of elemental iron) for 6 months. In fact, 60 toddlers took FS and another 60 toddlers took FG for 6 months. Mothers were advised to inject iron drops into the back of infants' mouths between feedings and then give them some water to prevent darkening of the teeth. Toddlers participating in the study were followed up on a monthly basis in terms of prescribed supplements and possible side effects.

After taking iron supplements (6 months post- supplementation), blood samples were taken from the toddlers again and their blood indices were evaluated. In addition, some side effects of iron supplementation, including anorexia, restlessness, diarrhea, vomiting or constipation in toddlers, were also evaluated.

The statistical significance of the differences in Hb, Hct, RBC, MCV, MCH, MCHC, RDW and ferritin level between FS and FG groups was calculated using Pearson's $\chi 2$ test or Fisher's exact test. The mixed-effects linear regression model was carried out to assess effects of receiving FS & FG on Hb and ferritin level during the study.

Mixed-effects linear regression model was carried out to assess the effects of supplementation on Hb and ferritin level after receiving FS & FG, adjusting by age, gender, ferritin, and Hb level at baseline using Multivariate analyses.

SPSS software (version 16, Chicago, IL) was used for statistical analysis. If the p-value is 0.05 or lower, the result is considered significant.

This study was approved by the Ethics Committee (ethical committee code number: IR.ARAKMU.REC.1398.016). The trial was registered at Registry of Clinical Trials as IRCT20190902044674N1.

Results

The mean ± SD age was 12.4 ± 3.3 months for the FS group and 12.3 ± 2.6 months for the FG group. A total of 120 toddlers, 61 (50.8 %) females and 59 (49.2 %) males were included in this study, which were divided into two groups of 60 subjects (Table 1). toddlers were randomly allocated to two treatment groups: 60 toddlers received FS and 60 toddlers received FG. There were no cases of discontinuation of iron supplements (FS and FG) due to unfavorable side effects or gastrointestinal disorders. No significant differences were observed in mean age, between the two groups (Table 1).

No significant effect was observed in RBCs count ($p = 0.230$), RDW ($p = 0.260$), and ferritin level ($p = 0.130$) between the groups (Table 2). Six months after supplementation, the FG group that received ferrous gluconate chelate iron showed approximately 3 μg/l higher ferritin level in comparison to the FS group with ferrous sulfate supplementation, $p = 0.130$ (Table 2). This is while at the same time, the FG group that received ferrous gluconate chelate iron showed approximately 2.4 g/dl higher Hb level in comparison to the FS group with ferrous sulfate supplementation, $p = 0.045$ (Table 2).

The adjusted Hb level 6 months post- supplementation was observed to be 10.10 g/dl (95% CI: 7.66–12.4) in the FS group, and 12.51 g/dl (95% CI: 11.10– 15.31 in the FG group, based

on the model revealed in Table 3. No significant effect was detected in the ferritin level (Table 4).

28 out of 60 toddlers (46.7 %) in the FS group and 48 out of 60 toddlers (80 %) in the FG group had no side effects from taking iron supplements. Thirty-two out of 60 toddlers (53.3 %) in the FS group and twelve out of 60 toddlers (20 %) in the FG group had one of the following side effects for one or more days (Table 5). Side effects were significantly more common in the FS group than the FG group (43.3 % vs. 16.7 %, $P \leq 0.001$; Table 5). Six toddlers in the FS group and two toddlers in the FG group had more than one symptom.

Discussion

Our results showed that 6 months post- supplementation with 12 mg/day of ferrous sulfate supplementation or 85 mg/day ferrous gluconate supplementation had a positive effect on blood indices, Hb, Hct, RBCs, MCV, MCH, MCHC, RDW, and serum ferritin concentration in toddlers.

This study demonstrated that both ferrous sulfate and ferrous gluconate supplements are effective in the prevention of IDA in toddlers. However, ferrous gluconate was more effective than ferrous sulfate.

Furthermore, ferrous gluconate supplementation was more efficient for maintaining a higher Hb level 6 months after supplementation than ferrous sulfate. On the other hand, FG group that received ferrous gluconate supplementation indicated a higher Hb level in comparison to the FS group with ferrous sulfate supplementation. Continuation of the observed effect after 6 months of ferrous gluconate supplementation may be described by the effect of a diet that may provide enough bioavailable iron to maintain iron status and iron-related blood indices.

In a study about the effect of supplementation with ferrous sulfate and iron bis-glycinate chelate on ferritin concentration in schoolchildren with iron deficiency in Mexican by schoolchildren without anemia after a fortification intervention, the authors found supplementing with ferrous sulfate or iron bis-glycinate chelate for 3 months, had a positive effect on increasing ferritin level in schoolchildren with low iron stores, and this effect persisted 6 months after supplementation (12). In our study, there were no differences in the odds of having low iron storages between the ferrous sulfate and ferrous gluconate

supplementation at 6 months post- supplementation. Therefore, it can be concluded the higher ferritin level at 6 months post-supplementation in the FG group versus the FS group had no clinical implication. The results of this study are valuable as little information is available on iron deficiency prophylaxis in toddlers. Studies in adults on iron deficiency prophylaxis have also yielded conflicting results (13).

Santos *et al*. confirmed the effectiveness of the iron supplements including iron salts and ferrous bisglycinate chelate on a weekly basis to overcome iron deficiency and IDA (14). Hurrell *et al*. reported that infants and young children with iron deficiency absorb less ferrous fumarate supplement than FS supplement (15). Ortiz *et al*. administered oral iron(III) polymaltose complex and oral ferrous sulfate to pregnant women with IDA and demonstrated favorable efficacy in the treatment of IDA during pregnancy, with a significant increase in Hb, 3 months post treatment (16).

In a study about the efficacy and safety of IDA prophylaxis with FG and iron polymaltose complex in healthy infants after a fortification intervention, the authors found supplementing with the supplements listed for 6 months, prevent IDA in infants and FG seems to be more effective but less tolerable (17).

This study showed that the side effects of ferrous gluconate were less than ferrous sulfate. Therefore, ferrous gluconate can be used in cases where ferrous sulfate had undesirable side effects. Jaber *et al*. reported that adverse effects such as vomiting, diarrhea, and constipation were significantly more common in the iron polymaltose complex group than in FG group (17).

In conclusion, the present study shows that educating mothers to feed toddlers with breast milk and iron supplements, including ferrous sulfate and ferrous gluconate, can be helpful in prophylaxis of iron deficiency. As a result, ferrous gluconate with higher efficacy and better tolerability can be a good replacement for ferrous sulfate. In addition, ferrous gluconate has fewer side effects and further increases hemoglobin levels and iron stores.

Conflicts of interest:

The authors declare no conflict of interest.

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