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Folic Acid and Iron Supplementation in Children with Insufficient Diets in a Developed Country, a Randomised Controlled Trial

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Abstract

Background: In developed countries, dietary intake of pre-schoolers is sometimes inadequate. Not because of insufficient provisions, but due to picky eating and behavioural feeding problems. Micronutrient deficiency could be a result, but is most of the time difficult to detect due to failing laboratory evaluations. Iron deficiency is the most common detected nutritional deficiency in children; other deficiencies may be present but are also hidden because they cannot always be found in routine evaluations. We therefore studied the supplementation of a single or two micronutrients in clinical and laboratory outcomes.

Methods: A double blind randomised controlled trial was performed in children aged 1-5 years with a suspicion of micronutrient deficiencies; expressed in picky eating and clinical complaints like recurrent infections or tiredness. They were supplemented with either iron alone or iron in combination with folic acid.

Results: 83% of the children showed inadequate dietary iron intake and 48% inadequate folic acid with the 3 day food recall evaluation. Clinical parameters like tiredness, the number of infections or antibiotic use improved in almost all children after supplementation in both groups. Combined iron and folic acid supplementation did not have an additive effect compared to iron supplementation alone. Laboratory parameters like hemoglobin levels, Mean Corpuscular Volume, Red cell Distribution Width and ferritin levels improved in all children.

Conclusions: Despite inadequate dietary intake, folic acid supplementation has no additive effect on iron supplementation alone in a developed country.

Keywords

Folic acid deficiency [MeSH], Iron deficiency, Infection [MeSH], Hemoglobin(s) [MeSH], Respiratory infections

Introduction

Iron deficiency leads to microcytic red blood cells and is the most common nutritional deficiency in children. In developing countries up to 50% is known with an anaemia caused by iron deficiency [1]. In the United States the prevalence of anaemia in childhood is decreasing from 7.9% in 1981 to 3.6% in 1994 [2]. During childhood, dietary iron is the main source for iron stores. Deficiencies are frequently caused by inadequate qualitative and/or quantitative dietary intake [3,4].

In developed countries, these deficiencies can also occur in the general population, not due to low-income, but to inadequate intake in childhood. Dietary habits of most children aged 1 to 4 consist of high consumption of milk and other products low on iron [3]. Combined with their high growth velocity [5] and picky eating as a normal stage in childhood it results in a larger risk for micronutrient deficiencies like iron and folate [4]. At the age of 2, about 50% of the children are to some extent picky eaters [6]. Studies have shown only few picky eaters develop a micronutrient deficiency [6]. Micronutrient deficiencies are difficult to detect due to little early symptoms. Of all micronutrient deficiencies, iron deficiency is detected most frequently by laboratory abnormalities like decreased hemoglobin levels, ferritin and Mean Corpuscular Volume (MCV).

As a symptom of this time period, several children suffer from a specific disorders like tiredness or recurrent infections without a known cause. When they are evaluated physically and by laboratory examination, causes like immunologic or hematologic disorders can be ruled out. Usually, from a large group the causes of the clinical problems remain unclear.

We hypothesize that the clinical picture of recurrent infections in childhood can be caused by insufficient dietary iron intake, even though laboratory research is not always conclusive.

We investigated an iron deficiency as a possible cause for a group of children with recurrent infections without another known cause.

Methods

Patients

Children between the age of 1 and 5 years with picky eating and clinical complaints like recurrent viral respiratory infections

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and/or subjective complaints of tiredness were included in a period of 2 years. Picky eating was defined as children who consume an inadequate variety of foods through rejection of a substantial amount of foods that are familiar (as well as unfamiliar) to them. Laboratory research for immunological or haematological disorders was conducted according to our protocol [7]. When abnormalities at laboratory research (hemoglobin < 6.6 or immunologic disorders like absent immunoglobulin values) were found, the patient was excluded. Children who had conditions like congenital anaemia, hemoglobin disorders or any chronic illness causing the iron deficiency were excluded. Also, when they used iron supplementation net prescribed by the researchers, they were excluded. During the first visit, children were examined for physical abnormalities and length and weight were measured. Standard deviation scores from growth charts were calculated for each child using Growth Analyser (version 3.5. Application Ed. Dutch Growth Foundation, PO Box 23068, 3001 KB, Rotterdam, The Netherlands). Parents were asked to answer a questionnaire about their child's health, number of infections, are they tired compared to other children, and interfering parameters like medication and vitamins. During the second visit length, weight and hematologic values were measured and parents were requested to answer the questionnaire again (with additional questions about side effects).

The patients were included at the pediatric outpatient clinic of a general hospital, Enschede, The Netherlands. The parents of the patients filled out the questionnaires at home, and they were collected at the outpatient clinic by the main researcher. The main (blinded) researcher also performed the measurements for growth and laboratory research. Another researcher had no patient contact and evaluated the blinded data.

Iron status

Of all patients, hematologic parameters (hemoglobin levels, MCV, hematocrit, reticulocytes and ferritin) were determined. Hemoglobin levels below 6.6 mmol/l (10.5 g/dl) were defined anemic. MCV levels below 70 (children between 1 and 2 years) or below 75 (children between 2 and 4 years) were defined as too low [8]. Parents were asked to prospectively to keep up a 3 day food questionnaire. Iron and folic acid intake were calculated based on this 3 day food questionnaire using Eetmeter (version 1.4.0.0., Voedingscentrum, Netherlands). Deficient diets were defined as an iron intake below 7 mg/day and a folic acid intake below 85 mcg/day (age 1 to 4) or 150 mcg/day (age 4 to 5).

To evaluate if there was only an iron deficiency or also a folate deficiency, a double blind randomised controlled clinical trial was performed at these patients, since a folate deficiency is difficult to detect. They were randomised using Wissenschaftliche Tabellen (Geigy, p167) to receive either folic acid solution (400 µg) once a day for the intervention group or placebo solution for the control group consisting of caramelized sugar water. The bottles were blinded by the pharmacist of the hospital. After ending the study, the code was released by the pharmacist. All children received 3 mg/kg ferrofumarate in a solution in 2 doses daily. Parents gave their child the supplements for 3 months (11-16 weeks).

Statistical analysis and ethics

All parents gave their written consent and the study was approved by the ethical committee of the hospital (Medisch Spectrum Twente) seated at Enschede, the Netherlands. The METC-number was P02-070. The power was calculated of 22 patients for each group, for an expected change of 1 mmol/l in hemoglobin level. With an expected loss of control, we included 25 patients in each group.

Analysis was performed with SPSS version 11.5 (SPSS Inc., Chicago, USA). Group descriptives and the questionnaire were analysed with a Chi-square test and for growth and laboratory values independent sample t-tests were used. Regression analysis was performed to correct for the time between the 2 visits.

The level of significance was set for $p < 0.05$.

Results

Group descriptives

A total of 50 patients were included with picky eating, unexplained recurrent respiratory infections and/or tiredness. No immunologic disorders were found. Of these 50 patients; 31 were tired compared to children of their age and 43 suffered from recurrent infections (Table 1). 27 patients were both tired and suffered from infections.

For the iron-folate trial, 50 children (32 boys, 18 girls) were included, but due to absence at the second visit, too long periods between two visits (> 16 weeks) or incorrect use of medication, 9 patient were excluded afterwards for the trial. Of the 41 children, 18 (12 boys, 6 girls) received iron alone and 23 (14 boys, 9 girls) received iron in combination with folic acid.

No significant differences were found between patient descriptives of both groups. No apparent signs of malnutrition were found on growth parameters in all patients.

Iron status

In the group of 41 children, food recall analysis showed insufficient iron intake in 83% of the children and insufficient folic acid intake in 48%. Of these 41 patients, we searched for signs of iron deficiency with laboratory examination. Since patients with haemoglobin < 6.6 mmol/l were excluded, there were no obvious signs for anaemia present. In 12 patients there were one or more signs present for iron deficiency expressed in low MCV, ferritin or elevated Red cell distribution width (RDW) (Table 1). When iron was substituted, we found a hemoglobin increase of more than 1 g/dL in 18 patients. 6 of these 18 patients were already detected with one or more laboratory signs of iron deficiency, the others showed no abnormalities in their initial laboratory values. Since half of the children received iron and folate supplementation, we only analyzed the patients who received iron supplementation for the iron deficiency parameters. When we would use the parameters of all children, we could not differentiate between the effects of iron or folate supplementation. We saw all laboratory parameters improved significantly except for the ferritin levels (Table 2). This could be due by decreased numbers, since the ferritin levels were not measured in all patients.

Clinical effect of iron supplementation

All patients received iron supplementation, with or without folic acid supplementation. 23 patients filled out 2 completed questionnaires about the clinical symptoms of their child before and after the trial. After supplementation, 20 out of 23 patients improved in clinical parameters. Tiredness disappeared completely at 12 of the 15 tired patients. The incidence of infections decreased in 9 of the 19 patients with recurrent infections (data not shown). The antibiotic use decreased from 0.9

Table 1: Group descriptives and signs for iron deficiency (n = 50).

Boys vs girls	32 vs 18
Mean age (years)	2.8
Patients with recurrent infections	19 of 23 (83%)
Patients with tiredness	15 of 23 (65%)
Hb < 6.6 (mmol/L)	0 of 41 (0%)
MCV below target range for age	5 of 41 (12%)
Ferritin < 12 (ug/L)	5 of 16 (31%)
RDW > 15 (%)	3 of 25 (12%)
At least 1 sign of iron deficiency	12 of 41 (29%)
Insufficient dietary iron intake	34/41 (83%)
Insufficient dietary folic acid intake	20/41 (48%)

Table 2: Effect of 3 months of iron supplementation in normocytic patients (n = 18).

	T = 0	T = 3 months	P-Value
Hemoglobin level (mmol/L)	7.34	7.86	0.000
Hematocrite (L/L)	0.35	0.37	0.001
MCV(fl)	75.8	77.2	0.013
RDW (%)	14.0	13.6	0.049
Ferritin (ug/L)	16.5	40.8	0.095
Tired compared to other children (%)	64.7	11.8	0.070

Table 3: Mean group descriptives and outcomes for part of the randomized controlled trial (n = 41).

	Iron and folic n = 23	Iron n = 18	p-value
Boys vs. Girls	14 vs. 9	12 vs. 6	0.70
Age in years	2.8	2.7	0.83
Weight in kilogram on 1st visit (SD)	14.5 (3.1)	14.3 (3.8)	0.87
Weight gain in 3 months (kg)	0.58 (0.6)	0.83 (0.6)	0.11
Length in centimetres on 1st visit (SD)	94.1 (11.1)	93.7 (10.9)	0.92
Length growth in 3 months (cm)	2.54 (1.4)	2.54 (1.2)	0.98
Hemoglobin level in mmol/l (SD)	7.4 (0.5)	7.3 (0.5)	0.56
Mean increase hemoglobin level (SD)	0.31 (0.5)	0.50 (0.5)	0.18
MCV level in fl. (SD)	76.2 (2.0)	75.6 (3.0)	0.47
Mean increase MCV in fl (SD)	1.27 (1.88)	1.36 (2.25)	0.90
Ferritin level in ug/l	38 (19)	16 (9)	0.04*
Mean increase ferritin level in ug/l (SD)	13 (13)	24 (27)	0.36

treatments per child before to 0.3 treatments per child after 3 months of iron supplementation. 8 children stopped using antibiotics in the 3 months of iron therapy, while 4 patients continued using it.

In this group we evaluated side effects of iron therapy like nausea, stool frequency, stool consistency, abdominal pain or change in stool pattern. There were no significant changes in abdominal symptoms before and after 3 months of iron supplementation, except for the colour of the stools.

Folic acid versus placebo

After 3 months supplementation, growth parameters (absolute and standard deviation scores), hematologic parameters and information about subjective health improved significantly in both groups, without significant differences in the extent of change between the two groups (Table 3). The rise of hemoglobin levels, MCV and ferritin tend to be increased more in the iron group, though not significant. The ferritin level in this group was also lower at the start of the study compared to the control group. No side effects were reported in both groups.

Discussion

We hypothesized that the clinical picture of recurrent infections in childhood can be caused by insufficient dietary iron intake, even though laboratory research is not always conclusive.

We investigated an iron deficiency as a possible cause for a group of children with recurrent infections without another known cause. First, laboratory evaluation was performed. We searched for indirect signs of iron deficiency which was found at 29% of our patients (low MCV, ferritin or elevated RDW but haemoglobin > 6.6 mmol/l).

For infants with low MCV values and a presumptive diagnosis of iron deficiency, a therapeutic trial with iron can be diagnostic [9]. When iron supplementation produces a hemoglobin rise greater than 1 g/dL, an iron deficiency was present. In our patients, there was a mean rise of 0.81 g/dL. 18 of the 41 (44%) patients had a rise of at least 1 g/dL after supplementation, irrespective of their hemoglobin value at start, suggestive for an iron deficiency.

The clinical improvement showed impressive numbers; 20 out of 23 patients improved in their level of energy and/or presenting less infections. This, of course, was a subjective opinion according to the parents. In what extent a placebo effect contributed to this phenomenon was not investigated. However, the parents searched for medical attention because of unexplained recurrent infections and/or fever with no therapy available at that moment. The majority of the children found a relieve in their symptoms for that time period.

These numbers indicate that we should be aware that there can still be an insufficient dietary iron intake, even though laboratory findings do not show clear signs of iron deficiency. We should ask about the actual iron intake at patients. This study emphasises the importance for dietary intake in childhood and supports the finding of a micronutrient deficiency in this age group.

Folate deficiencies are difficult to detect, therefore clinical improvement during/after supplementation was used as a marker for presence of a deficiency. Additional increase in hemoglobin level or clinical improvement (less infections or tiredness) was expected in the folic acid group due to optimal ingredients for DNA replication. The results in this small study do not support this hypothesis. Therefore, a folate deficiency was not present in these children, or had no clinical consequences.

In contrast to other studies in pregnant women, children and adolescents in developing countries [10-12] we cannot reproduce an additive effect of adding folic acid to iron supplementation on hemoglobin level and MCV during a study period of 3 months. Also, no clinical improvement (reduction of tiredness and infections) was seen. We think the absence of additional folate effect could be ascribed to the food pattern in the developed countries, though our study population showed impressive numbers of insufficient diets. Probably these diets were not insufficient for long enough periods to have clinical consequences

Conclusion

Our data showed that children with picky eating, unexplained recurrent infections and/or tiredness with adequate hemoglobin levels could still have symptoms from an iron deficiency. 44% of the children increased significantly with respect to their hemoglobin after iron supplementation. 87% of the children improved clinically, though this was a subjective view of the parents. Possible causes for this finding were 83% of the pre-schoolers who had inadequate iron intake. Adding folic acid to iron supplementation does not significantly improve hematologic parameters, number of infections or tiredness in the pre-schoolers, compared with iron supplementation alone.

For now, we should still focus on stimulating and improving dietary intake in this age group since a high percentage of the children have an inadequate intake.

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