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Effect of Vitamin A and Zinc Supplementation on the Hematological Values of School children

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ABSTRACT

Introduction: According to the World Health Organization, childhood and gender-related anemia is a global issue that is dealt with via adequate prevention, treatment, and screening. It is estimated that anemia affects about 50% of the children under the age of 5 and 25% of children aged 6–12 years worldwide.

Objective: To evaluate the effect of vitamin A and zinc supplementation on the hematological values of schoolchildren.

Methods: This was an experimental prospective study, which was carried out in an educational center in Zulia State, Venezuela. The population included 202 schoolchildren, 80 of which were selected from the municipality of Maracaibo, Zulia State. The population was divided into three subgroups: Group 1 consisted of 29 children receiving vitamin A + zinc, Group 2 consisted of 25 children receiving vitamin A, and Group 3 consisted of 26 children receiving zinc. A bioclinical, biochemical, and nutritional evaluation were performed pre- and post- supplementation. An ANOVA test was applied to the mean values before and after supplementation. Percentage values were compared with Fisher's test.

Results: There was a high frequency of eutrophic male children (55%). Group 2 (n = 25 children), supplemented only with vitamin A, had better results regarding low hemoglobin levels (12.54 ± 0.64), followed by the group supplemented with only zinc (12.12 ± 1.05).

Conclusion: The study demonstrates the benefits of vitamin A and zinc supplementation in reducing the signs of anemia in the children studied.

Keywords: *anemia; supplementation; vitamin A; zinc; hemoglobin*

INTRODUCTION

Anemia is one of the most important public health problems in developed and developing countries. The 2011 World Health Organization (WHO) reports indicate that more than 2,000,000,000,000 people have iron deficiency representing almost 25% of the world's population. It occurs in 800,000,000 individuals, and 273,000,000 of them are children. Worldwide, it is estimated that about 50% of children under the age of 5 and 25% aged 6–12 years suffer from this condition (WHO, 2015; Dreyfuss et al., 2000). Anemia has a multifactorial origin, and its possible causes are iron deficiency, infectious or chronic diseases, genetic defects, and deficiencies of folate, cobalamin, and vitamin A (VA) (Righetti et al., 2012; WHO/PAHO, 2017).

Developing countries in Africa, Asia, Latin America, and the Caribbean have consistently reported the highest prevalence of anemia among children under three years of age (60.0%–78% of children under three) with the highest peaks being observed in southern African countries such as Angola, Botswana, Cameroon, Gambia, and Maputo, and in Latin American countries such as Bolivia, Peru, Ecuador, and Venezuela (Landaeta-Jiménez, 2018).

According to international agencies, hunger has recently increased slowly and gradually in Latin America and the Caribbean, although it remains below 7%, and has slowed down or declined in many middle-income countries where the economy has slowed or contracted, including Venezuela. In Venezuela, food insecurity is an important factor in determining undernutrition in the population, since it increases it in all its forms. The same can be observed for hidden hunger, affecting the most vulnerable populations, which are children, pregnant women, and the elderly, with a greater impact on the poorest (Landaeta-Jiménez, 2003).

Micronutrient deficiency (MND), known as "hidden hunger," is the most common form of malnutrition in the world. It includes iron, iodine, and VA deficiency, which mainly affect children and women. It is estimated that >2,000,000,000 individuals worldwide suffer from various deficiencies (Grandy, 2010).

MND is a global issue with important public health consequences. When its prevalence is high, it negatively affects the country's economy, because it considerably increases the overall burden of disease, which is estimated numerically as deaths and years of life lost due to disability, and therefore, its prevention is essential. It is estimated that >2,000,000,000,000 people worldwide have deficiency in one of the following micronutrients: iron, VA, iodine, and zinc (Zn). These are considered the most important indicators of micronutrient deficiency rates and their effects on health (Fao, 2019).

In Venezuela, the prevalence of iron deficiency in preschoolers, schoolchildren, and adolescents vary between 9% and 34.66% (Zimmermann and Hurrell, 2007; WHO, 2011). There are several causes of iron deficiency, for example, inadequate intake, inadequate absorption, or increased demand due to growth. The prevalence of anemia typically ranges from 14.92% to 78% (Osório, 2002; Mora, 1998). Although the most common causes of anemia are related to multifactorial and micronutrient undernutrition (especially foods deficient in iron, folic acid, B12, and VA), anemia occurs as a result of long-term infectious or inflammatory processes or chronic blood depletion (Jaffe and Entrena, 1993).

There is worldwide evidence that the measures for the control of anemia have succeeded in preventing its complications, which hinder the physical and mental development of children. In addition to specific treatment with iron, these interventions include a strategy of supplementation with multimicronutrients, which has been shown to be effective in reducing anemia (Black et al., 2008). The most effective interventions for reducing stunting, micronutrient deficiency, morbidity, and mortality in young children are VA supplementation, therapeutic Zn supplementation, and the use of micronutrient powders (Tanumihardjo, 2018).

VA is shown to improve hemoglobin (HGB) concentrations and increase the efficacy of iron supplementation. Its mechanisms are not yet fully elucidated, but it is suggested that it acts on transferrin receptors that affect the mobilization

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of iron stores and increase their absorption, stimulate erythrocyte protectors in the bone marrow, and reduce susceptibility to infections (Gibson et al., 2008). VA plays an essential role in the functioning of the human body in supporting immune function, vision, eye health, and reproduction (Siyame et al., 2013). Moreover, there is evidence that plasma Zn is a strong predictor of HGB, regardless of iron levels (Garnica, 1981; Labbaye et al., 1995).

It should be noted that one of the Sustainable Development Goals 2 (SDG 2) is to eradicate the global burden of micronutrient deficiency, improve maternal health, and reduce infant mortality (Labbaye et al., 1995), a challenge for many countries, mainly developing ones (Sabbahi et al., 2018).

Considering the aforementioned information, our research was framed to evaluate the effect of VA and Zn supplementation on the hematological values of schoolchildren.

METHODS

This was an experimental, prospective, descriptive, and comparative study. The population consisted of 202 schoolchildren of both sexes belonging to an educational center in the State of Zulia, Venezuela, and attending the National Bolivarian School "Catatumbo," located in the Amparo Sector, Municipality of Maracaibo, State of Zulia, located in the Amparo Sector, Cacique Mara parish, from September to July 2016. A total of 122 schoolchildren (40 girls and 82 boys) were excluded from the total population because they did not meet the inclusion criteria, which were as follows: Prior informed consent by the child's parents or legal representatives; being of Venezuelan nationality; and being asymptomatic without active infectious processes. Children aged <6 years and >12 years who presented clear clinical signs of active infectious processes and related conditions and children who had received nutritional therapy or vitamin and mineral supplements two months before the first blood sample was taken were excluded.

The sample size consisted of 80 children, with an average age at the beginning of the study of 8.06 ± 14 years, who were classified as eutrophic at the anthropometric-nutritional evaluation, obtained from the evaluation according to size for age (S/A), weight for age (W/A), and weight for size (W/S) (Fundacredesa, 1993) described in the letters of the Venezuela Project and in a longitudinal study of the Caracas metropolitan area carried out by a clinical nutritionist (Lopez and Landaeta, 1991).

The study complied with the provisions of the international ethical standards established by the WHO for human research and the Declaration of Helsinki (World Medical Association Declaration of Helsinki. 52nd General Assembly Edinburgh, 2000). The clinical evaluation was carried out by a pediatrician who also performed the deworming process through the administration of a single dose of anthelmintic (Abendazol) provided by the Health Unit of Maracaibo. A dietary interview was conducted directly with the child's mother or legal representative responsible for their feeding. The 24-hour reminder method was applied before and after supplementation. Adequate quality control was used in blood sampling to obtain accurate and reliable results. Complete hematology analyses were performed in the first hours of the day before and after the study by a specialized bioanalyst. The children were under fasting conditions when the tests were performed. The blood sample (5 mL) was collected from a forearm vein by peripheral venous puncture in two tubes, one of which contained an anticoagulant for the determination of hematological parameters: HGB, hematocrit (HTC), and erythrocyte indices, which were measured in an automated electronic hematological counter Sysmex K-800 based in Kobe, Japan. The values recommended by the WHO were taken as reference values for HGB classification. In children aged 6–12 years, the threshold value for determining anemia was 11.5 g/dL. The degree of anemia was classified as mild (<11.0 g/dL in children aged <6 years and up to 8 years and 11.5 g/dL in children aged 8–14 years), moderate (<10 g/dL) and severe (<7 g/dL); all data were corrected for altitude (WHO, 2011; Siyame et al., 2013).

Reference HTC values in children aged 5–15 years were 37%–47% (WHO, 2015). Children were randomly divided into three groups: Group 1 consisted of 29 children and were supplemented with VA (SD) + multivitamin and Zn; Group 2 consisted of 25 children and were supplemented with only VA (SD); and Group 3 consisted of 26 children and were supplemented only with Zn.

The Zn-supplemented group of 26 schoolchildren were given liquid Zn sulfate (dose: 12.5 mg) continuously for 80 days. Zn doses per child/day of 12.5 mg (12.5 cc) were administered, which is considered an acceptable and tolerable supplementation dose between 12 and 23 mg/day for children aged 4–13 years (Gracia et al., 2005; Jiménez, 2005). Zn sulfate was given to the children in the morning before the first meal of the day (breakfast) to ensure absorption. The group supplemented with VA + Zn consisted of 29 schoolchildren, who received VA (single dose: 100,000 IU) + Zn (12.5 mg of Zn sulfate, continuously for 80 days of treatment). The data were analyzed with the SAS statistical software. Normal distribution tests were applied for the variables. Results were expressed as number (n), percentages (%), and mean ± standard deviation (SD) as appropriate. Mean values between groups were compared before and after supplementation with an ANOVA test. A value of $p < 0.05$ was considered statistically significant. Percentage values were compared with Fisher's test (Brown et al., 2002; Armitage and Berry, 1993).

RESULTS

TABLE 1: Mean hematologic variables in study participants according to the groups, before and after intervention

Variables	Group 1 (n = 29) VA+Zn		Group 2 (n = 25) VA		Group 3 (n = 26) Zn	
Hematological	Before	After	Before	After	Before	After
HGB	11,48±0,70	11,98±0,88	11,49±0,79	12,54±0,64	11,35±0,74	12,12±1,05
HCT	36,94±2,52	38,84±2,98	36,88±3,06	41,02±2,45 **	36,18±2,10	38,72±3,21
MCV	92,46±4,78	86,30±6,3	90,84±4,06	84,54±5,69	91,90±6,05	85,52±6,06
MCHC	28,74±1,94	26,79±2,24	28,32±1,44	25,80±2,19	28,83±2,47	26,78±2,03

Source: Results yielded from the study in different groups. Expressed as mean ± standard deviation.

Analysis of results

The group of eutrophic children included 80 children. The results showed a high frequency for male children aged 6.06 ± 12.6 years (55%) and female children (45%). The average age of the girls was 8 years and 9 months and of the boys was 8 years and 5 months, which is within the school population (6–12 years). The average weight of the children was 25.21 kg, and the average height was 125.75 cm. The results of weight and average height were similar for both sexes at the beginning and after supplementation, with no significant differences between sexes.

Hematological analyses were performed before and after supplementation by means of the extraction of a 5 mL blood sample to show whether there was any variation in the biochemical results of the schoolchildren. It was demonstrated that all the schoolchildren studied presented HGB levels below 11.49 ± 0.79 g/dL before being supplemented with multivitamin, VA, and Zn, showing according to the classification a degree of mild anemia (<11.0 g/dL in children aged <6 and 8 years and 11.5 g/dL in children aged 8–14 years) according to WHO 2001 (Lopez and Landaeta, 1991). HTC values were found to be below 36.94% ± 2.52% before being supplemented, being considered below 37%–47%, which are normal values for children aged 5–15 years (Comité Nacional de Hematología, 2017).

It is important to emphasize that HGB is an iron protein in red blood cells that carries oxygen throughout the body. HTC is a measure of the proportion of red blood cells in the blood. Therefore, a low HGB or HTC value is a sign of anemia (Comité Nacional de Hematología, 2017). The WHO estimated that 700,000,000–800,000,000 individuals around the world population are anemic, with rates of 2%–8% in industrialized countries; and that indicators in the underdeveloped world are alarming. Although the causes of anemia are multifactorial, the most frequent cause of iron deficiency is nutritional deficiency coupled with a deficit of other important micronutrients (WHO, 2015).

It was observed that all the study groups of children before supplementation presented a HGB value <11.49 ± 0.79, this being classified according to the classification (<11.5 g/dL for children aged 8–14 years) as mild anemia according to WHO, 2001 (Lopez and Landaeta, 1991). Group 2 (n = 25) supplemented only with VA achieved better HGB results (12.54 ± 0.64), followed by the group supplemented with only Zn (12.12 ± 1.05). Despite the fact that they started with values considered as low (11.49 ± 0.79 and 11.35 ± 0.74, respectively), these two groups achieved normality (12.54 ± 0.64 and 12.12 ± 1.05, respectively) after supplementation.

In relation to HCT levels, all groups showed levels considered as low (<36.94 ± 2.52) according to the classification (37%–47% normal values for children aged 5–15 years old) (Castejon et al., 2004). Group 2 (n = 25) supplemented only with VA achieved normal HCT values after supplementation (41.02 ± 2.45).

Taking the hematological results of HGB in blood as a reference value (López and Landaeta, 1991), we observed that the occurrence of anemia in girls was higher (71%) than in boys (68%); in Groups: 1 (VA + Zn) and group: 2 (VA).The results of the graph show that the group of boys improved their HGB levels after supplementation of VA + Zn and VA alone, going from 100% to 50% improvement in HGB. On the contrary, the group of girls had a better HGB performance when they were supplemented with only VA and only Zn, going from 71% to 21% and from 86% to 36% improvement in HGB, respectively. In relation to the levels of HTC, it was observed that they were <37% for all groups before supplementation in an important percentage according to classification (Castejon et al., 2004), and that after supplementation these values improved >37% of the children studied, which is considered as normal. These results are contradictory, and hence, further research is required.

DISCUSSION

Anemia is a global public health problem that may be related to many causes, including deficiency of VA and other micronutrients. VA deficiency alters iron mobilization. However, studies are inconclusive, considering the interaction between iron and VA metabolisms and that VA deficiency can cause anemia (Mazariegos et al., 2016).

No effect on mean corpuscular volume (MCV) and mean corpuscular hemoglobin concentration (MCHC) values was observed, may be because Zn becomes an alternative metal substrate for ferrochelatase during periods of Fe deficiency or non-utilization (anemia), which increases the formation of Zn protoporphyrin (ZnPP), i.e., the heme group contains Zn instead of Zn-Fe, so it is not used for HGB synthesis (Sermini, 2017).

Chhagan, M.K et al. (2010), in a community trial study of prophylactic vitamin A supplements alone or multiple micronutrient supplements, and another group supplemented with VA + Zn, administered to three cohorts of children starting at 6 months and continuing up to 24 months, found that the group of children without infection had improved HGB levels, decreasing the number of children with anemia following VA supplementation alone from 76.6% to 59.4%. These values were surpassed by the group supplemented with multivitamins. These results are very similar to those found in the cohort group where children with anemia decreased after VA supplementation alone from 76.5% to 58.8%, this value being surpassed by the group of children with anemia receiving multivitamin supplementation including Zn and VA, which decreased from 83% to 58.5%. These results are similar to the study conducted after VA supplementation where the children improved their HGB levels, decreasing anemia in both girls and boys, observing similar results to those obtained after Zn supplementation only in girls, while in boys a decrease of 50% in anemia was observed after VA + Zn supplementation (Chhagan et al., 2010).

In a study conducted by Alarcon K. et al. (2004) in children, in the iron Zn VA group, children aged 6–12 months received a single dose of 100,000 IU VA as retinol palmitate and 1-year-old children received 200,000 IU. The dose of Zn was 3 mg × kg 1 × d 1 of Zn sulfate providing 0.7 mg × kg 1 × d 1 of elemental Zn. In children receiving iron, VA and Zn after 18 weeks of treatment, the mean (SD) increase in HGB and Zn group was 24.0 to ± 9.95 g/L, and in the iron, Zn and VA group, it was 23.8 to ± 7.72 g/L. HGB increased in groups supplemented with iron and Zn and group supplemented with iron, Zn, and VA. Of the 22.5% of anemic children at the end of the iron, Zn, and VA supplementation treatment, only 9.4% of the children remained anemic. The study yielded the number of children who improved their HGB levels and therefore their anemia state after supplementation of VA alone, Zn alone, and VA+ Zn. Results do not clearly state which micronutrient had a better effect: whether VA alone, Zn alone, or VA+ Zn.

Chen, K. et al (2016) selected 186 anemic preschool-aged anemic children aged 3–6 years. They were randomly divided into two groups: Group 1 received albendazole alone, Group 2 received a 60000 μg VA capsule combined with 400 mg single dose albendazole. After 6 months of treatment, they showed that albendazole alone and albendazole + VA administration showed improvement in anemia (Chen et al., 2016). The HGB levels of the children in Group 2 at 3 and 6 months were statistically higher than those of the children in Group 1, reducing the number of children with anemia at 3 months of treatment to 56.7% and at 6 months to 38.3%. These results were similar to the study where the group of girls after supplementation with VA alone managed to reduce their anemia from 71% to 21%, but the same effect occurred in the group supplemented with Zn alone, as well as a similar effect in the group of children supplemented with VA + Zn.

Al-Mekhlafi et al. (2014) studied 126 boys and 124 girls aged 7–12 years with a mean age of 10 years, who received VA supplementation. The prevalence of anemia was higher among children aged ≤10 years, than children aged >10 years, and the findings indicated that changes in HGB and other indices of iron status after three months were significantly higher in children supplemented with VA compared to those supplemented with placebo. At 3 months of VA treatment, HGB levels improved from 47.2% to 27.2%, thus decreasing the anemia (Al-Mekhlafi et al., 2014). A similar effect was observed in the group of girls supplemented with VA alone, but also with Zn alone. In contrast to these findings, a previous study found no effect of weekly VA supplementation on HGB concentration among schoolchildren in rural and urban areas of East Java, Indonesia (Soekarjo et al., 2004). This could be due to the short duration and low dose of VA (10,000 IU) used. The benefits of VA supplementation appear to be most pronounced among anemic children (Mwanri et al., 2000). However, the interaction of VA with other micronutrients is still under debate. Most of the effects of VA on Zn have been demonstrated in animal models (Baly et al., 1984; Duncan and Hurley, 1978). Human trials have failed to show a consistent relationship between Zn and VA.

CONCLUSION

Micronutrients, including vitamin A and zinc, play an important role in iron metabolism and thus in HGB, HTC, MCV, and MCHC levels. Our study showed a beneficial effect of a single dose of vitamin supplement in reducing the effect of anemia in the children studied, and for Zn as well. Based on these results, further research related to this study is recommended to identify the prevalence of anemia in children in order to develop micronutrient supplementation programs to address this public health problem in our children.

Appendices: Table A.1. Mean hematologic variables in study participants according to the groups, before and after intervention

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest. Source of financing own resources.

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