Original Article

Hematological parameters of malnourished children after nutritional intervention: a randomized clinical trial

Parâmetros hematológicos de crianças desnutridas após intervenção nutricional: ensaio clínico randomizado

Parámetros hematológicos de niños desnutridos después de intervención nutricional: ensayo clínico aleatorizado

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Abstract

Objective: To assess hematological parameters of malnourished children after nutritional intervention with cashew nut flour.

Methods: This is a randomized, controlled, blind trial. The study was conducted from April to December 2017, in two Basic Health Units. The sample consisted of children under 5 years of age who met the inclusion criteria, 15 in the Intervention Group (cashew nut flour) and 15 children in the Control Group (carboxymethylcellulose flour), randomly allocated to the groups. The parameters of erythrocytes, hemoglobin and hematocrit (red blood cells) and leukocytes, neutrophils, segmented, eosinophils, monocytes and lymphocytes (white blood cells) parameters were analyzed. Blood collection was performed in two moments: the first before intervention implementation and the second after 32 weeks of use of cashew nut flour. To assess the sample normality and homogeneity, Shapiro-Wilk and Bartlett variance tests were used, respectively. The paired t-test was used within each group and, to assess possible associations between the Intervention and Control Groups and the level of leukocytes (below, normal and above), Fisher's Exact test and/or Fisher-Freeman-Halton test were used.

Results: There was an increase in the mean of the individual red blood cell count, especially in the hemoglobin patterns of malnourished children in the Intervention Group ($p<0.05$). The investigation also showed an intragroup difference in the hemoglobin parameter, both in the Control Group ($p=0.007$) and in the Intervention ($p<0.001$) as well as in the hematocrit parameter for both groups ($p=0.001$). Specifically in the white blood cells, after intervention, there was a significant decrease in leukocytes ($p=0.04$) and lymphocytes ($p<0.01$)

Conclusion: After intervention, the use of cashew nut flour improved the hematological parameters of malnourished children.

Brazilian Clinical Trial Registry (REBEC): U1111.1213.9219

Resumo

Objetivo: Avaliar parâmetros hematológicos de crianças desnutridas após intervenção nutricional com farinha da castanha de caju.

Métodos: Ensaio clínico randomizado, controlado, cego. O estudo foi realizado no período de abril a dezembro de 2017, em duas Unidades Básicas de Saúde. A amostra foi composta de crianças menores de 5 anos que preencheram os critérios de inclusão, sendo 15 no Grupo Intervenção (farinha da castanha de caju) e 15 crianças no Grupo Controle (farinha de carboximetilcelulose), alocadas nos grupos de forma randômica aleatória simples. Foram analisados os parâmetros de eritrócitos, hemoglobina e hematócrito (série vermelha) e de leucócitos, neutrófilos, segmentados, eosinófilos, monócitos e linfócitos (série branca). A coleta de sangue

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foi realizada em dois momentos: o primeiro antes da implementação da intervenção e o segundo após 32 semanas de utilização da farinha da castanha de caju. Para avaliação da normalidade e homogeneidade da amostra, utilizaram-se os testes de Shapiro-Wilk e de variância de Bartlett, respectivamente. Utilizou-se o teste T pareado dentro de cada grupo e, para avaliar possíveis associações entre os Grupos Intervenção e Controle e o nível de leucócitos (abaixo, normal e acima), utilizaram-se o teste exato de Fisher e/ou o teste Fisher-Freeman-Halton.

Resultados: Houve incremento na média das células individuais da série vermelha do hemograma, sobretudo nos padrões de hemoglobina de crianças desnutridas do Grupo Intervenção (p<0,05). A investigação também apontou diferença intragrupo no parâmetro da hemoglobina, tanto no Grupo Controle (p=0,007) como no Intervenção (p<0,001), bem como no parâmetro hematócrito para ambos os grupos (p=0,001). Especificamente na série branca, após a intervenção, evidenciou-se diminuição significativa nos leucócitos (p=0,04) e linfócitos (p<0,01)

Conclusão: Após intervenção, a utilização da farinha da castanha de caju melhorou os parâmetros hematológicos das crianças desnutridas.

Resumen

Objetivo: Evaluar parámetros hematológicos de niños desnutridos después de la intervención nutricional con harina da castaña de cajú.

Métodos: Ensayo clínico aleatorizado, controlado, ciego. El estudio se realizó en el período de abril a diciembre de 2017, en dos Unidades Básicas de Salud. La muestra se compuso por niños menores de 5 años que cumplieron con los criterios de inclusión, 15 en el Grupo Intervención (harina de castaña de cajú) y 15 niños en el Grupo Control (harina de carboximetilcelulosa), repartidas en los grupos de forma muestreo aleatorio simple. Se analizaron los parámetros de eritrocitos, hemoglobina e hematocrito (serie roja) y de leucocitos, neutrófilos, segmentados, eosinófilos, monocitos e linfocitos (serie blanca). La muestra de sangre se realizó en dos momentos: el primero antes de la implementación de la intervención y el segundo después de 32 semanas de utilización de la harina da castaña de cajú. Para la evaluación de la normalidad y la homogeneidad de la amuestra, se utilizaron los tests de Shapiro-Wilk y de varianza de Bartlett, respectivamente. Se utilizó la prueba T pareada dentro de cada grupo y, para evaluar posibles asociaciones entre los Grupos Intervención y Control y el nivel de leucocitos (debajo, normal y superior), se utilizó la prueba exacta de Fisher o prueba de Fisher-Freeman-Halton.

Resultados: Hubo un aumento en el promedio de las células individuales de la serie roja del hemograma, sobre todo en los estándares de hemoglobina de niños desnutridos del Grupo Intervención (p<0,05). La investigación también apuntó una diferencia intragrupo en el parámetro de la hemoglobina, tanto en el Grupo Control (p=0,007) como en la Intervención (p<0,001), así como en el parámetro hematocrito para ambos grupos (p=0,001). Específicamente en la serie blanca, después de la intervención, se evidenció una disminución significativa en los leucocitos (p=0,04) y linfocitos (p<0,01)

Conclusión: Después de la intervención, la utilización de la harina de la castaña de cajú mejoró los parámetros hematológicos de los niños desnutridos.

Introduction

Considered one of the world's leading and most worrying dilemmas, child malnutrition has given way to overweight and obesity. However, this increase in food intake does not mean that there is a contribution of vitamins and minerals and, as a consequence, pathologies associated with micronutrient deficit, such as anemia, have been evidenced, especially in children with low socioeconomic status. Micro and macronutrient deficiency due to an inadequate eating pattern in childhood is a worrying factor for health, as it contributes to the delay in growth and development and to the increase of hematological alterations.[1]

Evidence is accumulated that malnutrition is a serious public health problem associated with high morbidity and mortality rate and delayed infant psychomotor development.[2-4] In search of prevention and control of malnutrition in childhood, international organizations have implemented guidelines to reduce this problem, through healthy eating and exclusive breastfeeding practices. Among these measures, we highlight the use of dietary supplementation, used worldwide to combat nutritional deficits.[5,6]

Nutritional interventions that address food diversification, food fortification, infection control and nutritional supplementation provide actions for adequate weight gain and, consequently, prevention and control of malnutrition in children.[5,7] To include foods with adequate nutritional composition to improve the health status of malnourished people, is recommended to use dietary supplements, provided that all investigative techniques of the food are researched, to ensure safe and evidence-based use.[7]

An important example of food already thoroughly investigated for its beneficial properties to the body is cashew nut (*Anacardium occidentale* L.), an almond rich in proteins, lipids, carbohydrates, phosphorus, zinc, magnesium, fibers and unsaturated fat, whose properties help, among other purposes, in reducing the level of blood cholesterol. It is also worth noting that cashew nuts have 5.2 mg of non-heme iron in 100 g, and it is recommended, whenever possible, to ingest with other nutrients, such as vitamin C to improve bioavailability.[8,9]

In dietary interventions, the fundamental strategies to combat malnutrition are nutritional status assessment, through anthropometric measures, and micronutrient supplementation.[5] However, there are still uncertainties about the efficiency of interventions that use food supplementation to collaborate on treatment. Another question still unclear refers to the effects that the use of different foods and supplements has on blood markers of malnourished children.[6,7]

The importance of markers is observed in studies that show an association between malnutrition and impairment of immunity, since nutrient deficiency impairs biological processes such as leucopoiesis, compromising, respectively, the immune response and functional changes in the processes performed by leukocytes.[10-12] Moreover, iron deficiency anemia is more frequent in under 5 years of malnourished, due to the increase in organic demand for iron.[13]

Research proves that interventions that use dietary supplements have been shown to be effective in deficiency of micro and macronutrients in the diet of malnourished children.[6,14]

Considering the relevance of the theme for the overall improvement of malnourished children's health status, this research aimed to assess hematological parameters of malnourished children after nutritional intervention with cashew nut flour.

Methods

This is a randomized blind, controlled, longitudinal trial developed with children who received the intervention with cashew flour and children who received carboxymethylcellulose flour (placebo).

The data collection period was from April to December 2017, in two Basic Health Units of Imperatriz (MA), in northeastern Brazil.

This study included malnourished children according to the World Health Organization (WHO) malnutrition criteria and z score by weight × height for age and sex indicator,[15] born at term, under 5 years of age, of both sexes. Exclusion criteria were: children with severe malnutrition (z<3); users of psychotropic, antimicrobial or antineoplastic drugs; syndromes and who initiated an intervention to recover nutritional status. As a criterion of discontinuity, we opted for the inclusion of less than 75% of cashew nut flour consumption. The control of the following was assessed at home monthly by the researchers.

For peer pairing, the rule of having hematological parameters of red and white blood cells with the most similar values possible was obeyed. Then, after the first collection of blood data, each member of the pairs was randomized in intervention or control via coin toss. In total, the research included 30 eligible children, and the final analysis was performed with 15 children for the Intervention Group and 15 for the Control Group. Six participants out of 36 eligible (Figure 1) were excluded by withdrawal in the survey.

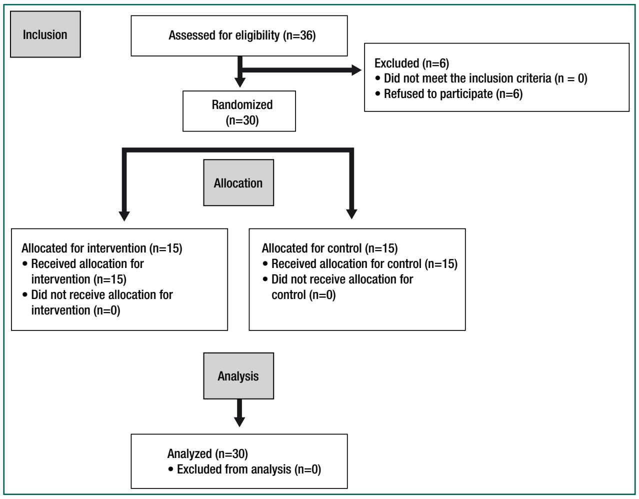

Figure 1. Projective inclusion, allocation and analysis of the research sample, as recommended by the CONSORT Statement

Before starting data collection, meetings were held for the actions and approach of all auxiliaries involved in the research. Data collection was initially performed in the Basic Health Units by scheduling and searching for children at home, through community health agents, after assessing the inclusion criteria.

For the intervention, cashew nut flour was used, which was submitted to physicochemical and microbiological analyses so that it could be administered to children without causing health risk. The results of analyses ensured that the product presented characteristic color, odor, taste and texture, in addition to the absence of fragments of parasites, insects, rodents and dirt in general.

Fifteen children used cashew nut flour in the amount of two tablespoons per day (36 g), which is equivalent to 1,872 mg of iron, fractionated in daily feeding (breakfast, lunch and dinner), during a period of 32 weeks.[16] This value was established after research in scientific articles on food supplementation/malnutrition.[15,17] Initially, participants received enough dietary supplement for 4 weeks. Then, monthly home visits were carried out to deliver the remaining sachets of cashew nut flour (for the next 4 weeks) and to count those used. The same process occurred with the Control Group participants who received carboxymethylcellulose flour (placebo). During the research period, children's legal guardians were asked not to offer other additional dietary supplements.

The main blood elements were selected, i.e.: erythrocytes (x10^6), hemoglobin (g/dL) and hematocrit (%) of the red blood cells; leukocytes (cells/mm^3), neutrophils (cells/mm^3), segmented (cells/mm^3), eosinophils (cells/mm^3), monocytes (cells/mm^3) and lymphocytes (cells/mm^3) of the white blood cells – all important indices in the screening of anemias and other infections. Hematological parameters were collected by a nursing technician, qualified in the practice of manipulating the collection and transport of samples to the clinical analysis laboratory. The blood samples collected used the BD Vacutainer® vacuum collection system, by means of venous puncture in the antecubital fossa. The 12-hour fasting blood laboratory analysis measured at baseline and at the end of the study included the red and white blood cell components.

Blood collection was performed in two moments, the first before intervention implementation and the second after 32 weeks of cashew nut flour use. On both occasions, children and their legal guardians were invited to the Basic Health Unit for blood collection in order to assess blood parameters.

Data were analyzed in IBM Statistical Package for Social Sciences (SPSS) for Windows, version 22.0, at 5% significance. After performing Shapiro-Wilk normality tests and Bartlett variance homogeneity, the paired Student's t-test was used within each group and independent Student's t-test among the groups. To assess possible associations between groups (intervention and control) and the level of leukocytes (below, normal and above), the Fisher-Freeman-Halton test was used.

The study was approved by the Institutional Review Board of the *Universidade Federal do Maranhão*, protocol 1,627,934 (CAAE (*Certificado de Apresentação para Apreciação Ética* - Certificate of Presentation for Ethical Consideration) 55979816.0.0000.5087).

Results

In the sample studied, there was a predominance of females in both groups, 53.33% in the Control and 73.33% in the Intervention. The groups were also similar about age: 2.46 years for the first and 2.93 years for the second. The assessment between groups showed that, after intervention, there was no statistical difference for the red blood cells, for the parameters of the sample studied. Specifically in the white blood cells, after intervention, a significant decrease in leukocytes (p=0.04) and lymphocytes (p<0.01) (Table 1) was evidenced between the groups.

Table 1. Differences in blood count in malnourished children between the Intervention and Control Groups

	Control Group	Intervention Group	p-value *
Erythrocytes, x10^6)	0.43±1.44	0.74±1.78	0.60
Hemoglobin, (g/dL)	0.84±1.04	1.13±0.72	0.38
Hematocrit, %	3.01±2.83	2.40±2.29	0.52
Leukocytes, cells/mm^3	-193±2.076	-1.753±2.630	0.04
Neutrophils, cells/mm^3	289±2.208	-654.67±2.554	0.14
Segmented, cells/mm^3	289±2.208	-654.67±2.554	0.14
Eosinophils, cells/mm^3	-103±400	-246±355	0.15
Monocytes, cells/mm^3	-78±243	-103±208	0.38
Lymphocytes, cells/mm^3	726±2.095	-765±1.039	< 0.01

n=30; Results expressed as ± standard deviation; *Student's t-test for independent samples

After intervention, within the groups, there was an increase in the mean of the individual red blood cell count, especially in hemoglobin patterns. There was an increase in erythrocytes, but it was not significant. There was a statistically signif-

Table 2. Blood count of malnourished children, before and after 32 weeks of intervention, within each group (Intervention and Control)

	Control Group			Intervention Group		
	Before	After	p-value*	Before	After	p-value *
Erythrocytes, x10^6	4.48±0.39	4.91±1.44	0.27	4.60±0.27	5.34±1.77	0.13
Hemoglobin, (g/dL)	11.93±0.45	12.77±1.00	0.007	12.11±0.84	13.24±0.87	<0.001
Hematocrit, %	35.87±1.30	38.87±2.66	0.001	37.47±2.36	39.87±2.72	0.001
Leukocytes, cells/mm^3	9.440±2.115	9.246±2.804	0.72	8.620±2.669	6.866±1.485	0.02
Neutrophils, cells/mm^3	4.161±1.604	4.450±1.885	0.62	3.957±2.456	3.302±1.366	0.34
Segmented, cells/mm^3	4.161±1.604	4.450±1.885	0.62	3.957±2.386	3.302±1.366	0.34
Eosinophils, cells/mm^3	394±173	291±64	0.33	373±75	126±88	0.02
Monocytes, cells/mm^3	499±159	420±214	0.23	501±197	397±144	0.05
Lymphocytes, cells/mm^3	3.964±1.809	4.691±1.376	0.20	3.805±954	3.039±748	0.01

n=30; Results expressed as ± standard deviation; *Student's t-test for dependent samples

icant difference within each group for hemoglobin in the Control (p=0.007) and in the Intervention Group (p<0.001). Although the gain profiles were identical, it cannot be said that the difference of the Intervention Group was greater. For white blood count assessment after intervention, there was a statistically significant intragroup difference in leukocytes (p=0.02), eosinophils (p=0.02), monocytes (p=0.05) and lymphocytes (p=0.01). In neutrophil dosage, although not significant, there was a decrease in the mean values (Table 2).

When assessing the individual leukocyte dosage, in the post-intervention phase with cashew nut flour, both the Control Group (73.3%) and the Intervention Group (93.3%) maintained the expected values for the normality pattern in the number of these cells (Table 3).

Table 3. Leukocyte level in relation to the group of children in the post-intervention phase

Group	Leukocytes after intervention			p-value*
	Below n(%)	Normal n(%)	Above n(%)	
Control	0	11(73.3)	4(26.7)	0.04
Experimental	1(6.7)	14(93.3)	0	

n=30; *Fisher-Freeman-Halton test

Discussion

The results obtained in the present investigation indicated an increase in the mean of the individual red blood cell count, especially in hemoglobin patterns, and except in erythrocytes, of malnourished children in the Intervention Group. It is also noteworthy that no similar studies were found in the literature on blood count assessment of malnourished children after nutritional intervention, this being the first randomized clinical trial that analyzed this effect.

The properties of cashew nut flour can exert positive effects on hematological parameters, directly and indirectly, in cells, considering its wide use for nutraceutical purposes.[18] Looking at nutritional composition, some vitamins (B, C and E) and minerals (Na, K, Ca, Mg, P, Fe, Cu and Se) are present in cashew nuts, but in low concentrations. The highest concentrations of these nutrients were identified in the pseudofruit (cashew). Antioxidant activity was also evidenced by allylic acids isolated from cashew nuts, which prevent the generation of superoxide radical inhibitory enzymes such as xanthine oxidase.[19] However, due to its low iron concentration it is not possible to affirm that cashew nut flour is significant for reducing the prevalence of iron deficiency anemia in malnourished children.

The high prevalence of iron deficiency worldwide has caused the WHO to recommend that this nutritional deficiency be combated with multiple measures and not only with drug iron supplementation; educational and environmental practices, clinical and biochemical assessment and fortification of iron foods were also mobilized.[17,20]

Although there was no difference between the Control and Intervention Groups in erythrocyte parameters, the statistically significant increase in hemoglobin and hematocrit was verified. Cashew nuts have a considerable content of several minerals, including iron, whose importance is related to the prevention of nutritional deficiencies.[8] The absorption mechanisms of non-heme iron from the diet use different proteins, such as the enzyme ferroreductase DCYTB, the transporter DMT1 and ferroportin.[9] Although this mechanism is well known, it should be considered that, in relation to the absorption of iron, other factors, linked to the individual and diet, need to be considered. Therefore, it cannot be affirmed that the amount of iron ingested in cashew nut flour in this study influences the nutritional need of the participating children.

In this perspective, a meta-analysis assessed the effect of iron-enriched foods on the mean hemoglobin concentration in children, identifying significantly higher hemoglobin elevation in anemic children who consumed iron-fortified foods, when compared to the group that received non-fortified food, which led to an increase in the hemoglobin and hematocrit parameters of these children, showing that fortification has positive results in nutritional status, especially in iron.[14,17] Still, there was a reduction in anemia in children who received multiple micronutrient powder in home fortification process.[20]

Furthermore, in a study that assessed the conformity of homemade food fortification strategies to provide iron and zinc among children aged 6 to 24 months for a period of 6 months, the experimental group used fortified complementary foods and the control, only nutritional education, showing that consumption of fortified complementary foods resulted in a significant increase in the mean hemoglobin in the Intervention Group compared to the Control Group, which received only dietary guidelines.[21]

An intervention study, in which one group received biscuits prepared with wheat flour fortified with iron and folic acid, and the other biscuits prepared with cowpea flour biofortified with iron and zinc, showed that, in both groups, there was a reduction in the prevalence of anemia, being higher in the group of biofortified cowpea flour.[21]

For white blood cell assessment, leukocyte count is directly related to subclinical inflammations, and it is not necessarily necessary to obtain altered results to verify effect over time. In the inflammatory reaction, leukocyte activation occurs, since, when activated, the production of other inflammatory markers begins.[10] In the individual leukocyte dosage, before intervention, in both groups, most of the children surveyed (86.7%) presented expected values for the normality pattern in the number of these cells (5,000 to 12,000/mm^3).

In this sense, a Spanish study demonstrated that the increase in the total concentration of white cells is a risk factor, regardless of morbidity and mortality, for stroke, coronary heart disease and peripheral arterial disease.[22] This finding, although not resulting from intervention, differs from the analysis in the present study, which showed a reduction in the values of leukocytes, lymphocytes and other cells after intervention, such as neutrophils, eosinophils and monocytes in the Intervention Group, when compared to reference values (5,000/mm^3 to 15,000/mm^3, 1,500/mm^3 to 4,000/ mm^3, 150/mm^3 to 400/ mm^3, 100/mm^3 to 300/ mm^3 and 100/mm^3 to 500/ mm^3, respectively).

Leukopenia is understood as a hematological manifestation of some organic, chronic or transient disorder. Pseudoleukopenia can occur in the early stages of infections, and then revert to leukocytosis. Global leukocyte counts may indicate leukocytosis, usually occurring in bacterial infections, and leukopenia; when the values are below the reference, it is suggested the existence of severe viral infections, which, in malnutrition, may be due to the change in the production of immune system cells.[23] Although the reduction of leukocytes was significant in the present study, post-intervention, these values remained within normal limits. It is important to emphasize that leukocytes participate directly in the immune response, and more specifically, lymphocytes play a central role in the adaptive immune response.

Supporting this statement, research reinforces that reduction in leukocyte and lymphocyte pattern in the presence of severe infections in childhood, as well as in the values of other cells assessed in the leukogram, may indicate strengthening of the immune system and the decrease results in fewer infections and inflammatory processes.[11]

Supplementation with cashew nut flour has important macro and micronutrients for the restoration of white blood cell production and its functions[8] and may have contributed to the reduction of these cells in the Intervention Group due to a greater contribution of these nutrients in the infant diet, when compared to the Control Group, which did not receive cashew nut flour. Corroborating this inference, an investigation on the effect of supplementation with B-complex vitamins in inflammatory processes demonstrated as a result that, after supplementation, there was an improvement in immunological functions, due to the mobilization of these vitamins to the sites of inflammation, functioning as a cofactor in the metabolite-producing pathways with immunomodulatory implications.[12]

Cashew flour is a regional component with a very broad nutritional value that contributes to the health status of those who consume it. It has B-complex vitamins in its composition, fundamental for the formation of white and red blood cells and, therefore, are essential to help in the increased production of blood and in the genetic material formation of each cell.[24]

The daily intake of cashew nut flour suggests some benefit in certain blood count parameters of malnourished children. However, it is necessary to consider the fact that the Control Group also presented improvements in the results, which does not cancel out the importance of research in the generation of evidence to support the clinical practice of health professionals.

This study has limitations, because it is a single-center study, the number of participants was relatively small. Thus, it is essential to expand the research of the effects of this product in populations with other diseases or chronic health conditions, with larger samples. Another question refers to the fact that the researchers did not follow the children by ingesting cashew nut flour, since the use was at home and the family may also have consumed the flour – and not only the child. The interaction between nutrients and food substances was also not investigated, so for future investigations, it is important to consider the aspects of bioavailability.

The positive encouraging results obtained with this investigation in relation to hematological parameters should be carefully contemplated, based on the findings of this research. Therefore, the professional recommendation for dietary intake of cashew nut flour for malnourished children should at first be 36g fractionated in the three main daily meals, as mentioned in the present investigation.

The promising findings of this research therefore reinforce the relevance for professionals' clinical practice on the importance of using nutritional interventions, which favor regional foods in the correction of nutrient-poor diets, and consequently contribute to healthy growth in childhood and the reduction of diseases. Moreover, it exhibits the relevance of interventional research with food supplementation for the target population, strengthened by the measurement of parameters involved in important organic function, such as blood count assessment.

Conclusion

After intervention, there was a statistically significant intragroup difference for hemoglobin and hematocrit in both groups, and the Intervention Group showed an increase in the mean of most cells individually, except for erythrocyte patterns. Among the groups, the Intervention Group participants showed an important decrease in the mean values of white blood cells surveyed, less in the neutrophils and segmented. Thus, the use of cashew nut flour improved the hematological parameters of malnourished children after intervention.

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Collaborations

Barroso RB, Silva AC, Santos FSS, Costa JRM, Santos LH, Pascoal LM, Neto MS, Costa ACPJ declare that they contributed to the project design, data analysis and interpretation, article writing, critical review of relevant intellectual content and final approval of the version to be published.

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