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Quality deviations in magnesium chloride-based food supplement capsules

Desvios de qualidade em cápsulas de suplemento alimentar à base de cloreto de magnésio

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ABSTRACT

Introduction: Magnesium plays various roles in metabolism necessary for homeostasis, and supplementation becomes necessary when the satisfactory amount cannot be obtained through diet. Therefore, quality control becomes essential to ensure product safety through tests based on current legislation. **Objective:** To evaluate the quality of dietary supplements based on magnesium chloride, marketed in the form of capsules from four nationally distributed brands, sold in pharmacies. **Method:** The description of the samples was performed by extracting information from the labels and observing visual aspects with the naked eye. Physical-chemical quality control tests were used: average weight, disintegration, assay, and content uniformity as described in the current official compendium. **Results:** According to the labeled information, the content of the samples ranged from 450 mg to 600 mg of magnesium chloride. Visually, the casings of three samples were transparent, while one was opaque, filled in two samples. The content consisted of powder with variable coloration ranging from white to yellowish, with coarse and aggregated particles. The tests revealed that only sample A did not comply with the official compendium in terms of weight. In the disintegration test, all samples disintegrated within the established time. Only samples A and C achieved the specified content. None of the samples met the content uniformity limit. **Conclusions:** All analyzed samples showed some nonconformity related to content, suggesting an urgent need for specific oversight in the production of this type of product.

KEYWORDS: Nutraceuticals; Quality Control; Sanitary Supervision

RESUMO

Introdução: O magnésio desempenha diversas funções no metabolismo necessárias à homeostasia. Quando não se consegue obter a quantidade satisfatória por meio da alimentação, é preciso fazer a suplementação. O controle da qualidade do produto, feito por meio de ensaios baseados na legislação vigente, é fundamental para garantir a segurança. **Objetivo:** Avaliar a qualidade do suplemento alimentar à base de cloreto de magnésio, comercializado na forma farmacêutica cápsulas, de quatro marcas de abrangência nacional, comercializados em farmácias. **Método:** A descrição das amostras foi realizada a partir da extração de informações de conteúdo dos rótulos e da observação dos aspectos visuais à vista desarmada. Utilizou-se os testes de controle de qualidade físico-químico: peso médio, desintegração, doseamento e uniformidade de conteúdo, conforme descrito no compêndio oficial vigente. **Resultados:** Segundo as informações rotuladas, o conteúdo das amostras variava de 450 mg a 600 mg de cloreto de magnésio. Visualmente, os invólucros de três amostras eram transparentes e o outro, opaco, totalmente preenchidos em duas amostras. O conteúdo era um pó de coloração variável entre branca e amarelada e partículas grosseiras e agregadas. A realização dos ensaios evidenciou que, no parâmetro peso, apenas a amostra A não estava em conformidade com o compêndio oficial. No teste de desintegração, todas as amostras desintegraram no tempo estabelecido. Apenas as amostras A e C alcançaram o teor especificado. Nenhuma

das amostras atendeu ao limite de uniformidade de conteúdo. **Conclusões:** Todas as amostras analisadas apresentaram alguma inconformidade relacionada ao conteúdo, o que sugere uma urgência na implementação de fiscalização específica na produção desse tipo de produto.

PALAVRAS-CHAVE: Nutracêuticos; Controle de Qualidade; Fiscalização Sanitária

INTRODUCTION

Magnesium is an alkaline earth metal which, in its ionic form, is the fourth most present cation in the body, widely distributed in various parts and in fundamental organelles, such as mitochondria and the endoplasmic reticulum[1]. The concentration of this micronutrient in the bloodstream is influenced by the dynamic balance between intestinal absorption, bone storage and renal excretion and transport, so that its homeostasis can be affected by the use of medication, age, alcoholism and genetic defects[2].

Thus, magnesium contributes to cellular homeostasis and organ physiology, as it regulates important cellular activities such as oxidative phosphorylation, energy production, protein, and nucleic acid synthesis, as well as participating as a cofactor in enzymatic reactions, especially those involving adenosine triphosphate (ATP)[3].

According to the Resolution of the Collegiate Board (RDC) of the National Health Surveillance Agency (Anvisa) No. 269, of September 22, 2005, a daily intake of 260 mg is recommended for adults[4], which can be achieved by consuming grapes, avocados, whole grains, oilseeds, and potatoes[5].

Hypomagnesemia is associated with muscle weakness, tremors, convulsions, arrhythmias, hypertension, and disturbances in the concentration of other ions such as calcium and potassium[6]. Magnesium-based dietary supplements are a strategy for acquiring the necessary amount of this micronutrient, especially for the elderly and alcoholics, so they come in a variety of formulations, in the form of inorganic salt and organic compounds[7]. One of the presentations is magnesium chloride, recognized for its satisfactory bioavailability[8], usually in capsule pharmaceutical form which, in theory, should meet quality control standards and specifications.[9]

In order to contribute to the population's access to safe and quality food supplements, reduce the asymmetry of information in this market, and facilitate sanitary control and risk management of these products, the Resolution of the Federal Pharmacy Council (CFF) No. 661, of October 25, 2018, defines food supplements as: products for oral intake, presented in pharmaceutical forms, intended to supplement the diet of healthy individuals with nutrients, bioactive substances, enzymes or probiotics, alone or in combination[10].

The quality control of medicines and pharmaceutical supplies is based on good manufacturing practices and includes carrying out tests and release procedures to ensure that the materials released for marketing and distribution conform to standards of purity, quality, and efficacy, so as not to put patients at risk[11].

It is therefore expected that technically prepared supplements will be in accordance with the quantitative values set out on their labels, corroborating the supply of a certified product, even though it is a formulation exempt from registration[12] and therefore free to market. The aim was therefore to assess the quality of magnesium chloride-based food supplements sold in the pharmaceutical form of capsules available on the market.

METHOD

We analyzed four samples of magnesium dietary supplement capsules from different manufacturers obtained from pharmacies in Cuité and Campina Grande, both in Paraíba (PB).

For the purposes of sample description, information on the content of magnesium chloride and elemental magnesium and other components was taken from the sample label. Visual aspects were also observed with the naked eye.

The average weight of the capsules was checked as described in the Brazilian Pharmacopoeia[13]. Twenty full capsules were weighed individually on a Marte Shimadzu AY220 scale (Kyoto, Japan), then all the contents were removed from the inside of the capsules and the 20 empty units were weighed individually. Calculations were then made to determine the average weight of the contents of each sample, obtained from the difference in the mass of the filled and empty capsules. The standard deviation and coefficient of variation were then calculated. To construct the control charts, variation limits of ± 7.5% were applied, considering that all the samples had an average weight of over 300 mg. As an acceptance criterion, no more than two units outside the specified limits can be tolerated in relation to the average weight of the contents but none can be above or below twice the indicated percentages.

The disintegration test was carried out as described in the Brazilian Pharmacopoeia[13]. A Nova Ética disintegrator was used, consisting of a system of baskets and tubes, a compartment for the immersion liquid and a thermostat[14]. The capsules were placed individually in the basket tubes. Water at 37 ± 1ºC was used as the immersion liquid, and the observation time was 45 min. After this period, all the capsules had to be completely disintegrated or only fragments of the shell remained.

To determine the uniformity of unit doses, the weight variation method was applied, as described in the Brazilian Pharmacopoeia[13]. The amount of magnesium per unit was estimated from the individual mass of the contents of ten capsules, as described when determining the average weight and the dosage result, assuming homogeneous distribution of the active component between the capsules and obtaining the amount of active

component in each capsule. The results were expressed as an acceptance value (VA).

Magnesium was measured in triplicate, as described in the Brazilian Pharmacopoeia, in complexometric titrations for magnesium[13]. Exactly 0.5 g was weighed, diluted in 50 mL of water, any undissolved excipients were kept suspended, 10 mL of ammonium chloride buffer pH 10.0 and a few drops of eriochrome black T SI were added. This was followed by titration with 0.05 M SV disodium edetate, standardized according to the Brazilian Pharmacopoeia, until the color changed from violet to blue. Each mL of 0.05 M SV disodium edetate is equivalent to 1.215 mg of magnesium.

RESULTS AND DISCUSSION

The magnesium chloride-based food supplement samples were described in terms of their labeling and appearance. We observed different variations in the weights and concentrations of magnesium described on the package labels (Chart 1).

As described on the labels, the magnesium chloride-based samples ranged in mass content from 450 mg to 600 mg of magnesium chloride, and from 75 mg to 219.7 mg in elemental magnesium (Chart 1).

Chart 1. Labeled information of magnesium chloride-based food supplement capsule samples.

Substance	Sample			
	A (mg)	B (mg)	C (mg)	D (mg)
$MgCl_2$	500.0	600.0	450.0	500.0
Elemental Mg	130.0	219.7	130.0	75.0

Source: Prepared by the authors, 2023.

Looking at the physical appearance of the capsules tested, it can be seen that samples A and C did not have completely filled capsules, unlike sample D, which apparently had compacted contents. The wrappings of sample B were made of opaque material and it was impossible to see how they were filled. Therefore, the correct filling of each casing is a stage that must be carried out with caution, since it can influence the behavior of other parameters, such as changes in average weight, dosage, and dose uniformity[15].

The powder found in the capsules of samples A and C was white in color, with fine particles. Sample B had a yellowish powder, with relatively coarse and aggregated particles, visibly with low flow characteristics. Sample D had a white powder with relatively coarse particles (Figure 1).

Thus, in order to guarantee an adequate and regular filling in each capsule, the powder needs to have good fluidity; however, the behavior of its flow is determined by the intrinsic and extrinsic properties of the material, such as: size, shape, roughness, porosity, and chemical characteristics[16].

When analyzing the composition declared on the product labels (Chart 2), sample A and sample B showed magnesium chloride and magnesium oxide as components of the formulation, in addition to the food supplement. In addition, the samples had excipients with diluent, lubricant, sliding, and moisturizing functions, as detailed in Chart 2.

The data obtained in the pharmacopoeial tests to determine average weight, disintegration time, content and uniformity of content are shown in Table 1.

The average weight values obtained and shown in Table 1 ranged from 397 mg (sample A) to 529 mg (sample B), and the

Source: Prepared by the authors, 2023.

Figure 1. Appearance of capsules and content of magnesium chloride-based food supplement samples from four different brands.

percentage variation in the individual masses ranged from 2.98% for sample D to 10.07% for sample A.

To construct the control charts (Figure 2), we applied the rule from the Brazilian Pharmacopoeia[13], which establishes an acceptable weight variation for hard gel capsules containing doses of more than 300 mg of ±7.5%, with two out of every 20 capsules being able to exceed this limit but never exceeding it twice.

Sample A was the only one that did not comply with the recommendations of the Brazilian Pharmacopoeia[13], as it exceeded the permitted variation limits. Samples B, C and D were within the permitted variation limits. It is worth noting that samples A and B had an average mass (Table 1) well below the dosage shown on the formulation label (Chart 1).

Figure 2 shows the behavior of samples A, B, C and D of magnesium chloride food supplement capsules in graph form, making it clear that sample A did not meet the specification of the official Brazilian pharmaceutical compendium, with eight units outside the limits of ± 7.5%, and of these, three units were outside twice the limit (± 15%). Of the samples analyzed, sample D showed the least variation.

The relative standard deviation (RSD) expresses the dispersion of samples in relation to the mean, and its use in the pharmaceutical industry has multiple applications, one of which is to describe the variability in the concentration of the active pharmaceutical ingredient in a mixture[17]. In practice, the lower the standard deviation, the more homogeneous the data, and therefore the more accurate[18] .

Chart 2. Labeled composition of magnesium chloride capsule samples.

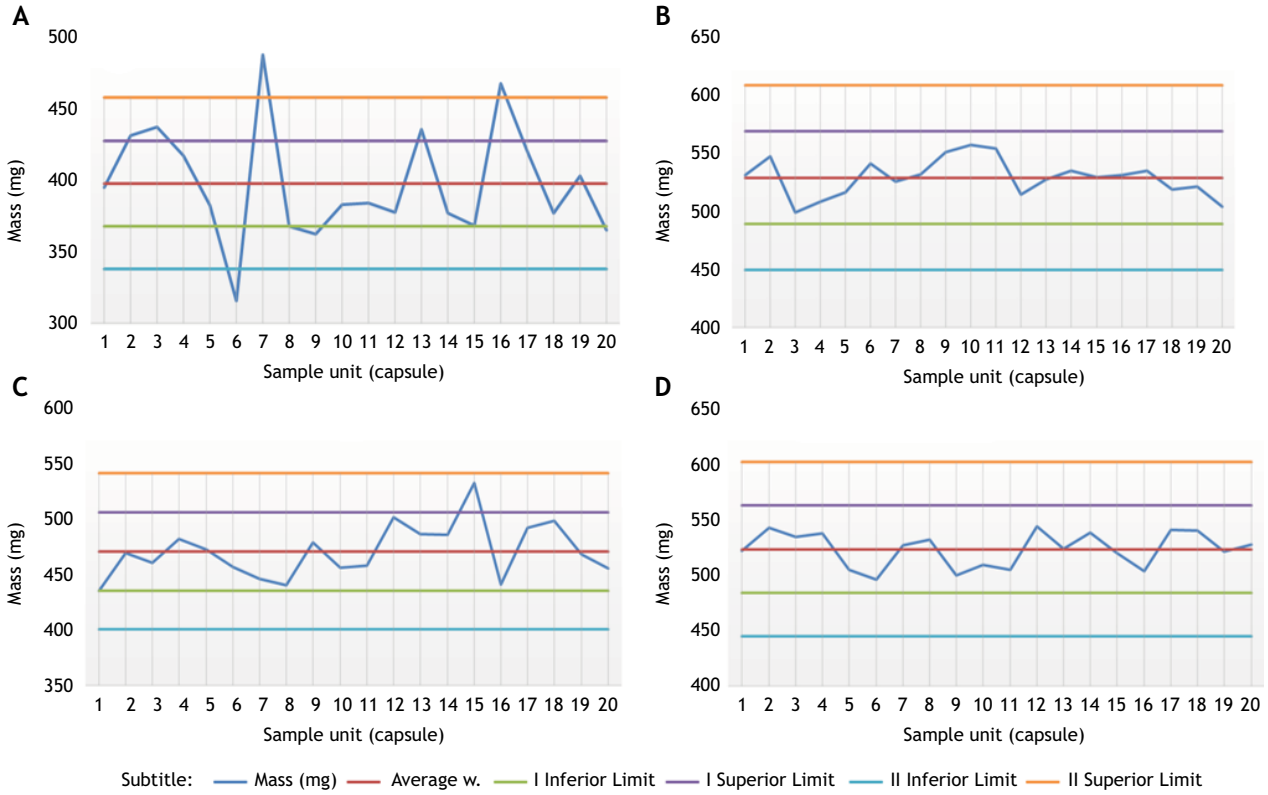
Component	Property	Sample			
		A	B	C	D
Magnesium chloride	Mineral supplement	X	X	X	X
Magnesium oxide	Mineral supplement	X	X		
Microcrystalline cellulose	Diluent	X			
Magnesium stearate	Lubricant	X			
Silicon dioxide	Sliding	X			
Maltodextrin	Diluent			X	
Glycerin	Moisturizing			X	
Starch	Diluent				X

Source: Prepared by the authors, 2023.

Table 1. Results of physical-chemical quality tests of magnesium chloride-based food supplement capsule samples.

Test	Sample							
	A		B		C		D	
Average weight								
Mass (mg)	397		529		471		523	
RSD (%)	10.07		3.04		5.19		2.98	
Result	Disapproved		Approved		Aprovado		Approved	
Desintegration								
Time (min)	13’45”		26’31”		12’00”		7’30”	
Result	Approved		Approved		Approved		Approved	
Dosage								
Content (%)	96.31		57.44		84.87		13.35	
RSD (%)	0.6		0.6		0.0		6.9	
Result	Approved		Disapproved		Approved		Disapproved	
Unit dose uniformity								
Stage	1°	2°	1°	2°	1°	2°	1°	2°
VA	29.05	21.18	45.37	53.65	19.86	22.05	86.05	85.95
Result	Disapproved		Disapproved		Disapproved		Disapproved	

Source: Prepared by the authors, 2023.
RSD: Relative standard deviation; VA: Acceptance value.



Source: Prepared by the authors, 2023.

Figure 2. Graph of average weight variation of magnesium chloride-based food supplement samples.

A study[15] looked at whether there was an association between the RSD for the weight variation test and the dose uniformity test in capsule quality control. The authors aimed to establish a maximum internal tolerance for capsule weight variation. To do this, they tried to identify an acceptable RSD value for weight that would indicate a warning of possible dose deviations, considering its satisfactory homogeneity. The tests indicated that a weight variation with an RSD of more than 4.0% could result in preparations which, if submitted to the dose uniformity by content test, would not pass the test.

Thus, taking the above data into account and analyzing the data in Table 2, samples A and C had RSD values of more than 4%. This indicates that, if submitted to the dose uniformity test by content, there is a high possibility of failing the test.

Disintegration is a crucial stage in ensuring maximum bioavailability of the drug in most solid pharmaceutical forms[19] and, in general terms, consists of submersing the material in an immersion medium, observing defined experimental conditions, in order to measure its disintegration time[20]. The Brazilian Pharmacopoeia 6th edition[13] describes the specifications for the disintegration test of capsules, recommending that the maximum time allowed for total disintegration is 45 min.

The disintegration test data is shown in Table 1. All the samples met the official specifications. The capsules of samples A and B disintegrated before the maximum time recommended by the Brazilian Pharmacopoeia[13] but the powder remained compact inside the baskets.

Sample D had the shortest disintegration time (7' 30"), which can be attributed to the presence of starch as an excipient, unlike the other samples. Starch is one of the polymeric carbohydrates widely used in capsule production because, due to its physical and chemical properties, it has various applications, especially as a diluent, binder and disintegrant[21]. Sample B had the longest disintegration time (26'31") and was composed only of the magnesium chloride and magnesium oxide mineral supplements, with no other excipients.

The application of this test is of great importance because the consequent dissolution of the drug after disintegration is a key point for intestinal absorption when solid pharmaceutical forms are administered orally[22]. The dosage test makes it possible to verify the content of a substance present in a given pharmaceutical presentation. It is therefore classified as an extremely important test in quality control, since it makes it possible to confirm that the dosage written on the label is consistent with its composition[23].

The dosage results showed a variation in magnesium content from 13.35% (sample D) to 96.31% (sample A). According to Anvisa, the tolerance rule established in RDC No. 360, of December 23, 2003, of plus or minus 20% in relation to the value declared on the nutritional label is also applicable to food

supplements[24]. In this sense, samples B (57.44%) and D (13.35%) had levels lower than the tolerated limit (± 20%), according to the supplement legislation.

For sample A, although the average mass obtained was lower than the amount of magnesium chloride declared on the label, the dosage test showed a content within the acceptable range for supplements (± 20%), which can be attributed to the presence of magnesium oxide in the formulation. Sample B had a content of less than 80%, which was to be expected as it had an average weight below the amount stated on the label. Sample D had a much lower content than expected, indicating probable fraud.

These results can be attributed to failures in the inspection and manufacture of these supplements as they are products exempt from registration according to Anvisa's RDC No. 240 of July 26, 2018[25].

The administration of a substance with an active ingredient concentration above or below the concentration stated in the formula may represent a risk of intoxication or therapeutic inefficiency for the patient[14,26]. Failure to comply with the requirements set out in official compendia can characterize situations of alteration and adulteration, making the product unfit for consumption and subject to health inspection.[27]

According to the Health Surveillance Secretariat Ordinance No. 32 of January 13, 1998[28], which defines and classifies vitamin and/or mineral supplements, these foods are used to supplement the daily diet of a healthy person in cases where their intake from food is insufficient or requires supplementation. They must contain a minimum of 25% and a maximum of 100% of the recommended daily intake (RDI) of vitamins and/or minerals, in the daily portion indicated by the manufacturer, and cannot replace food or be considered an exclusive diet.

The unit dose uniformity test makes it possible to assess the amount of drug in individual units of the batch and check that this amount is uniform in the units tested. This is an important parameter to ensure that the correct doses are administered, as each unit in a batch of a drug must contain the appropriate amount of the active ingredient that is close to the declared amount[14]. In addition, Anvisa's RDC No. 243 of July 26, 2018, stipulates that nutrient-source ingredients in food supplements must fully meet the specifications of identity, purity and composition[29] and, as verified in this study, there were flaws in the composition in terms of content and/or uniformity of content in all the samples analyzed.

The results obtained in the uniformity test for unit doses of magnesium chloride food supplement capsules are shown in Table 1.

For the unit dose uniformity test on magnesium chloride food supplement capsules, the VA ranged from 21.18 (sample A) to 86.05 (sample D), all of which were outside the established criteria. According to the Brazilian Pharmacopoeia[13], for hard gelatine capsules with a dosage > 25 mg and a ratio of active ingredient x average weight > 25%, the method used is weight variation. The VA for the first stage is carried out with ten capsules and the value of L1 is 15, as all the samples evaluated exceeded the value of L1, a new VA was calculated using 30 capsules and the value of this second stage must not be greater than L1 and the amount of active component of any individual unit is less than (1 - L2 × 0,01)M or greater than (1 + L2 × 0.01)M, with L2 equal to 25 and M corresponding to the reference value to be used according to T (average of the limits specified in the individual monograph for the quantity or potency declared, expressed as a percentage). The VA obtained by the 30 samples exceeded the permitted value.

None of the samples analyzed showed homogeneity and uniformity of distribution of magnesium chloride in the individual doses. Samples B and D showed content values well below what is recommended and dose uniformity values well above the limit (L1), proving the lack of uniformity of the batch, after the second stage of analysis with another 20 units, which proved the lack of uniformity of the batch tested.

The uniformity of the content of a solid formulation can be affected by various stages of the production process, including particle size distribution, the excipients used and the proportionality between mixing time and speed. It is therefore urgent to use tests to verify the efficiency of the homogenization of a powder mixture, since its uniformity reverberates in the bioavailability and efficacy of the formulation[30].

Chart 3 summarizes the results of the magnesium supplement capsule samples in relation to the quality specifications evaluated, revealing that most of the samples showed a deviation in quality in two of the four parameters evaluated, with emphasis on the non-conformity of four samples in terms of uniformity of content and two in terms of magnesium content.

Table 2. Comparison between the labeled information on dietary supplements based on magnesium chloride and values obtained in the magnesium dosing test (n = 3).

Sample	Labeled quantity (mg)		Magnesium found in the dosage		
	Magnesium chloride	Elementary magnesium	Magnesium (mg)	%	RSD
A	500.0	130.0	125.2	96.31	0.6
B	600.0	219.7	126.2	57.44	0.6
C	450.0	130.0	110.3	84.87	0.0
D	500.0	75.0	10.0	13.35	6.9

Source: Prepared by the authors, 2023. RSD: Relative standard deviation.

Chart 3. Summary of quality results of analyzed magnesium supplement capsules.

Test	Sample			
	A	B	C	D
Average weight	X			
Disintegration				
Dosage		X		X
Content uniformity	X	X	X	X
General situation	Disapproved	Disapproved	Disapproved	Disapproved

Source: Prepared by the authors, 2023.

Similar problems were reported in a study with samples of oyster calcium capsule supplements, evaluated for minimum quality standards involving determination of average weight, disintegration, dosage, and uniformity of content, all samples showed non-conformity in two or three of the four parameters analyzed[31].

Another important observation is that the product analyzed falls into the "non-prescription" category according to Anvisa's RDC No. 242 of July 26, 2018[32], which requires quality maintenance as a user safety mechanism.

The findings of this research corroborate the understanding that the variety of food supplements offered commercially in the face of the scarcity of studies related to specific quality control for these products encourages the scientific community and health surveillance bodies to make it possible to identify fraud and adulteration in order to prevent quality deviations that compromise consumer health, as well as to improve quality assurance and provide safer and more effective products.

CONCLUSIONS

The data obtained showed that samples A and B had lower average weights than stated on the label and were incompatible with the quality specifications, while sample A did not comply with the acceptable variation limits. In the dosage test, samples A and C met the limits accepted by the legislation (± 20%). In the disintegration test, all the samples met the requirements in terms of the time needed for complete disintegration. None of the samples showed homogeneity and uniformity of magnesium distribution, and there are no parameters for assessing equivalence between the samples, since each one has different labeled content, ranging from 450 to 600 mg.

It should also be pointed out that the exemption from health registration should not make product quality aspects more flexible. It is therefore essential to invest in regulations capable of dealing with the characteristics of this market, in order to protect the health of the population without hindering the development of the sector and the population's access to these products.

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Authors' Contribution

Alves MS - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. Diniz ÍFS - Analysis, data interpretation, and writing of the work. Souza JBP - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the work. All the authors approved the final version of the work.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.