Study of Ionized Magnesium and Calcium Levels in a Cohort of Patients with Septic Shock Treated with Standard Therapy and Antioxidants

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Abstract

Background: Septic shock is the most serious form of sepsis and can be due to several factors, such as hypovolemia, vascular hyporesponsiveness, myocardial dysfunction, or dysfunction of the circulation. Likewise, electrolyte levels have been associated with septic shock in intensive care units, although it has been underdiagnosed. Based on this, the purpose of the present work was to evaluate plasma ionic levels in patients with septic shock before and after treatment with different antioxidants.

Methods: Plasma ionic levels were measured (Na^+, K^+, Cl^- and ionized Ca^{2+} and Mg^{2+}) in 194 subjects, 129 healthy control patients, 14 patients with septic shock without treatment and 51 patients with septic shock under treatment with 4 different antioxidants (N-acetyl cysteine, melatonin, vitamin C and vitamin E).

Results: We found important differences when comparing the plasma ionic levels of K^+, Ca^{2+} and Mg^{2+} between the control group versus in both groups with sepsis at the time of hospital admission. In patients with septic shock, there is a decrease in the serum levels of ionized Na^+, K^+, Cl^- and Ca^{2+} and Mg^{2+}. Antioxidant treatment as an adjunct to the standard management of patients with septic shock increases the electrolyte deficit. The correction of the magnesium deficit also leads to an increase in serum calcium and potassium levels.

Conclusion: The management of antioxidant therapy in patients with septic shock within the first hours of admission can help to improve their ionic levels of Ca^{2+} and Mg^{2+}, mainly in patients with lung damage.

Clinical Trial gov registration: NCT03557229. Registered june 14, 2018. https://clinicaltrials.gov/ct2/show/NTC03557229?term=aISA+ALFREDO&draw=2&rank=1

Introduction

Sepsis and septic shock are public health problems worldwide and represent a high cost to health systems; three cases have been reported for every 1000 inhabitants and 2.6 cases for every 100 hospital discharges, of which 51% receive medical attention in an intensive care unit and 17.3% in an intermediate or coronary care unit [1]. Septic shock is the most severe form of sepsis and occurs when it is associated with hypotension and tissue hypo perfusion. Locally, during hypo perfusion some organs can be compromised due to the redistribution of flow from the splanchnic and peripheral circulation to other sites. Hypotension and hypo perfusion associated with septic shock can be due to various factors such as hypovolemia, vascular hyporesponsiveness, myocardial dysfunction, or dysfunction in the circulation. On the other hand, electrolyte levels associated with septic shock in intensive care units have been underdiagnosed. There are reports [2] that correlate serum magnesium levels (Mg^{2+}) with the admission of patients to the Intensive Care Unit (ICU), the duration of their stay in the ICU, the requirement and duration of mechanical ventilator support, and the final outcome of the patient (discharge/death) [3].

The incidence of hypomagnesemia is reported in 2% of the general population, between 10–20% in hospitalized patients, and 50–60% in patients in an intensive care unit [4]. The magnesium concentration in plasma is kept in a narrow range between 1.7 and 2.2 mg/dl (0.75–0.95 mmol or 1.5–1.9 mEq /L), this homeostasis of magnesium depends on the balance between its intestinal absorption and its renal excretion [5]. Another electrolyte recognized as a factor in sepsis is the calcium [6]. The calcium exists in three forms or fractions in plasma o serum: ionized (iCa, free calcium) only this fraction is physiologically active, quelated (bound to phosphate, bicarbonate, citrate) and bound to protein. The Vitamin D deficiency, "relative" hypoparathyroidism, vitamin D resistance, and 1α hydroxylase deficiency are proposed mechanisms for hypocalcemia in critically ill patients [7]. The normal plasma calcium concentration is between 8.5 and 10.4 mg / dl and practically does not vary with age during childhood and adolescence. Normal ionic calcium concentrations are between 4.4 and 5.2 mg / dl (1.1–1.3 mmol/l) [8]. Studies carry out in animals demonstrated that interleukin 1β induces hypocalcemia in association with a decrease in parathyroid hormone (PTH) and an increase in the expression of calcium-sensing receptors (CASR) in the kidneys and parathyroid [9, 10]. Furthermore, elevated levels of tumor necrosis factor (TNF-α) have also been

associated with hypocalcemia. Chernow et al. [11], reported an association between hypocalcemia and prolonged duration in the intensive care unit (ICU), as well as an increase in mortality. However, the diagnosis is complicated by limitations in the interpretation of total plasma calcium concentration. These limitations are primarily the result of the effects of hypoalbuminemia and acid-base balance disorders on total calcium concentration.

Therefore, the measurement of ionized calcium can be critical in determining the actual levels of calcium in an individual's serum. In this way, the recognition of serum electrolytes in patients of the Medical Intensive Care Unit (ICU) may be important, since it could be associated with the severity of the disease or with an increase in mortality and morbidity.

On the other hand, antioxidants have been defined as substances that, when present at low concentrations compared to an oxidizable compound, delay or prevent oxidative, so a large number of exogenous antioxidants have been used.

There are reports that indicate that supplementation with antioxidants helps oxygenation rates, with an increase in glutathione and a greater immune response [12]. This leads to a reduction in hospital stay and in intensive care units, in addition to a decrease in the rates of multi-organ dysfunction and in the rate of morbidity and mortality. However, there are few studies in this regard, which requires greater efforts to reinforce the benefits of antioxidant supplementation.

Based on the above, the purpose of this work was to assess the ionic levels of calcium and ionized magnesium, as well as sodium, potassium and chlorine in patients with septic shock in an intensive care unit, before and after treatment with different antioxidants such as n-acetylcysteine, vitamin C, melatonin, and vitamin E.

Material And Methods

A case-control clinical trial was conducted. Sixty-five patients > 18 years of age with septic shock in the last 24 hours, characterized by refractory hypotension and vasopressor requirement, despite sufficient fluid resuscitation (20 mL/kg of colloids or 40 mL/kg of crystalloids) to maintain blood pressure were included ≥ 65 mmHg with a lactate > 2 mmol/L and samples from 129 control patients. The Acute Physiology And Chronic Health Evaluation (APACHE) II and SAPS II scores were determined at admission, as well as the Sequential Organ Failure Assessment (SOFA) score. and MEXSOFA score of organ dysfunction, for each of the sections (Neurological, respiratory, hemodynamic, hepatic, hematological). The MEXSOFA is a validated score in a Mexican cohort that uses the same sections of the SOFA score with two modifications: the PaO2/FiO2 is changed to the SpO2/FiO2 and the neurological evaluation is eliminated. A MEXSOFA ≤ 9 points during the first hours of admission to the unit have a mortality of 14.8%, while in patients with a MEXSOFA ≥ 10 points they have a mortality of 40%.

Signed informed consent from each participant was obtained after full explanation of the purpose and nature of all procedures used in the research study, in accordance with the stipulated in the Declaration of Helsinki, modified by the Tokyo Congress, Japan. The research was approved by the Ethical, Biosecurity and Investigation Committees of the National Institute of Cardiology (Registration number: INCAR-DG-DI-ACEP-039-2021). The protocol was registered (TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT 03557229.

Blood samples were taken from all subjects upon admission to the ICU in sterile tubes with EDTA, with heparin, and in tubes with a gel polymer for serum separation. The serum was immediately separated by centrifugation and the determination of the serum electrolytes was performed (Sodium, potassium, chlorine, calcium and magnesium). The blood samples in the heparin-containing blood tubes were kept on ice and analyzed for ionized Ca^{2+} and Mg^{2+} levels using an electrolyte analyzer (Nova Biomedical, Waltham, Mass., USA). The Nova can analyze Na^{+}, K^{+}, Cl^{-}, ionized Ca^{2+}, and ionized Mg^{2+}. The analyzer provides calculated results for ionized Ca^{2+}, and ionized Mg^{2+}, normalized to a pH of 7.4, for samples with pH values between 6.9 and 7.8. It also mathematically adjusts all ionized Mg^{2+} results for ionized Ca^{2+} concentrations. A sample volume of 250µl is required for analysis. The analyzer was calibrated with its own calibration solution and was maintained according to the manufacturer's instructions. The results were expressed in millimoles per liter (mmol/L). In addition, blood

biometry, blood chemistry, liver function tests, c-reactive protein, procalcitonin, and venous and arterial blood gases were analyzed for each study subject.

Antioxidant supplementation

Patients were randomized and masked into 4 groups, to start treatment in the first 24 hours after admission to the ICU.

1) For the N-acetyl cysteine group, 2 effervescent tablets of 600 mg of N-acetyl cysteine (1200 mg) were administered every 12 hours by oral route or naso-enteral tube for five days.

2) For the melatonin group, melatonin was administered in 5 mg prolonged-release capsules, at a dose of 50 mg (10 capsules) orally or by naso-enteral tube for five days.

3) For the vitamin C group, 1-gram vitamin C tablets were used, which were administered every 6 hours by oral route or naso-enteral tube for five days.

4) For the vitamin E group, vitamin E (d-alpha tocopheryl acetate) capsules of 1200 IU equivalent to 1200 mg were used, which were administered every 24 hours for five days.

After each treatment, the same blood and electrolyte tests were performed.

Statistical Analysis

The SPSS 21 program was used for statistical analysis. The Student's t test was used to evaluate the differences between the mean values obtained between the groups. An ANOVA test was used to compare plasma ion concentrations. Pearson's chi2 test or Fisher's exact test was used for normal data. The Shapiro-Wilk test was used to determine whether the distributions of the variables were normal. Numerical data are shown as the mean ± SD, and nominal data were reported as percentages. A logarithmic transformation was applied for the ionized Mg^{2+} levels due to the non-normal distribution of the variables. The value of $p < 0.05$ was considered statistically significant.

Results

194 subjects were studied, 129 healthy control patients, 14 patients with septic shock without treatment and 51 patients with septic shock under treatment with antioxidants. The mean age of healthy patients was 35.4 ± 12.04, which showed a statistically significant difference compared to patients with sepsis without treatment 73.0 ± 10.49 ($p = 0.000$) and with treatment 64.16 ± 17.38 ($p = 0.000$), being older in these last two groups; Furthermore, there were no significant differences between the two groups with septic shock with and without treatment ($p = 0.096$). Similarly, in gender and BMI, no statistically significant differences were found between the three study groups. When comparing our two groups with septic shock, we found significant differences in the APACHE II score ($p = 0.039$) and in the malnutrition risk assessment ($p = 0.020$) (Table 1). When comparing only our group of patients with septic shock with the different antioxidant treatments, we did not find significant differences in any parameter.

Table 1
General characteristics of the study subjects and divided according to treatment

	Healthy control (n = 129)	Untreated Sepsis patients (n = 14)	Sepsis patients with treatment (n = 51)	P	Sepsis patients divided according to treatment (n = 51)				
					Vitamin C (n = 14)	Vitamin E (n = 13)	n-acetylcysteine (n = 11)	Melatonin (n = 13)	P
Women (%)	46.2	50	49.23	0.001	30.8	64.3	54.5	46.3	0.949
Age (years)	35.4 ± 12.04	73.0 ± 10.49	64.16 ± 17.38	0.937	63.14 ± 21.33	65.66 ± 16.02	62.36 ± 20.25	65.15 ± 12.65	0.653
Weight (kg)	74.04 ± 13.56	70.57 ± 15.26	70.06 ± 18.81	0.251	67.0 ± 20.29	75.92 ± 20.89	67.09 ± 19.52	70.0 ± 14.68	0.342
Size (mts)	1.59 ± 27.9	1.64 ± 0.09	1.65 ± 0.100	0.001	1.62 ± 0.09	1.67 ± 0.11	1.67 ± 0.13	1.67 ± 0.78	0.001
BMI(kg/m^2)	28.96 ± 16.4	25.90 ± 4.56	25.73 ± 6.81	0.331	25.18 ± 7.09	26.87 ± 6.24	23.44 ± 4.35	27.13 ± 8.93	0.741
SAPS II	----	44.14 ± 17.85	36.61 ± 13.79	0.311	36.64 ± 12.79	45.53 ± 15.72	36.45 ± 11.74	39.53 ± 13.93	0.384
APACHE II	----	18.07 ± 6.45	15.84 ± 5.85	0.221	14.14 ± 5.66	19.46 ± 5.59	13.09 ± 5.00	16.38 ± 5.56	0.039
SOFA	----	9.07 ± 3.09	7.75 ± 2.58	0.108	7.64 ± 2.34	8.76 ± 3.13	6.81 ± 3.12	7.61 ± 1.38	0.221
NUTRIT	----	5.21 ± 1.25	3.80 ± 1.70	0.005	3.57 ± 2.02	4.46 ± 1.76	3.18 ± 1.40	3.92 ± 1.44	0.020
DM (%)	----	21.4	19.6	0.882	14.3	15.4	9.1	38.5	0.415
HT (%)	----	42.9	37.9	0.708	21.4	46.2	45.5	38.5	0.685
COPD (%)	----	----	9.8	0.229	7.1	23.1	----	7.7	0.175
AMI (%)	----	7.1	3.9	0.617	----	----	9.1	7.7	0.701

BMI: Body mass index, DM: Diabetes mellitus, HT: hypertension, COPD: chronic obstructive pulmonary disease, AMI: acute myocardial infarction

It should be mentioned that, at the time of hospital admission, the most frequent site of infection was the pulmonary system (48.3%), followed by the gastrointestinal system (17.3%) (Table 2).

Table 2. Site of infection of subjects with sepsis

	N (%)
Pulmonary	30 (48.39)
Gastrointestinal	17 (27.42)
Nephrourinary	7 (11.29)
CNS	2 (3.23)
Skin	2 (2.33)
Gastrointestinal and renal	2 (2.33)
Pulmonary and CNS	1 (1.61)
Pulmonary and gastrointestinal	1 (1.61)

Subsequently, the ionic levels were analyzed in our 3 study groups: controls, patients with sepsis under treatment, and patients with sepsis without treatment. (Table 3). According to the results, we found significant differences when comparing the plasma ionic levels of K^+, Ca^{2+} and Mg^{2+} between the control group versus in both groups with sepsis at the time of hospital admission. At the end of 48 hours under treatment with the different antioxidant drugs, we observed significant differences in all plasma ion values of patients with sepsis compared to controls, except for chlorine levels.

Table 3. Ionic levels at hospital admission and discharge.

	hospital admission						hospital discharge				
	Control	No Treatment	With Treatment	P1	P2	P3	No Treatment	With Treatment	P1	p2	p3
Levels of Na^+	139.21±5.23	140.03±11.18	134.10±11.68	0.792	0.096	0.004	140.74±9.83	135.63±7.481	<0.001	0.088	0.001
Levels of K^+	6.48±3.23	4.25±0.869	4.16±0.554	<0.001	0.706	0.000	4.21±0.572	4.15±0.555	0.001	0.718	<0.001
Levels of Cl^-	108.27±8.90	111.06±8.085	106.71±8.044	0.240	0.089	0.257	110.21±7.117	105.39±14.41	0.202	0.089	0.222
Levels of Ca^{2+}	1.16±0.98	1.09±0.060	1.10±0.097	0.001	0.486	0.001	1.12±0.086	1.12±0.087	0.008	0.948	0.008
Levels of Mg^{2+}	0.68±0.043	0.63±0.115	0.63±0.141	0.003	0.915	0.043	0.66±0.098	0.65±0.119	0.001	0.588	0.001

P1: control vs sepsis without treatment

P2. Sepsis without treatment vs sepsis with treatment

P3. control vs sepsis with treatment

When performing the analysis comparing only the septic shock groups, with and without antioxidant treatment, we did not find statistically significant differences, at the beginning and end of the treatment, in the plasma levels of the study ions. In the same way, ionic levels were compared between the groups under treatment with the different antioxidants, and between the patients with each one of the antioxidants, before and after it (Table 4); however, we did not find a significant difference either.

Table 4
Plasma ion levels at admission (initial) and after of treatment (final)

	Untreated sepsis patients	**Patients with sepsis and with treatment**				
	(n = 14)	Vitamin C (n = 14)	Vitamin E (n = 13)	n-acetylcisteine (n = 11)	Melatonin (n = 13)	p
Na + initial	140.03 ± 11.18	135.26 ± 10.11	131.98 ± 15.58	134.41 ± 6.54	134.70 ± 13.08	0.504
Na + final	140.84 ± 9.83	137.48 ± 8.54	135.57 ± 6.98	135.55 ± 6.37	133.75 ± 7.97	0.232
p	**0.828**	**0.269**	**0.498**	**0.591**	**0.759**	
K + initial	4.25 ± 0.86	4.23 ± 0.61	4.20 ± 0.61	4.08 ± 0.62	4.12 ± 0.51	0.956
K + final	4.21 ± 0.57	4.31 ± 0.30	4.16 ± 0.66	4.01 ± 0.70	4.09 ± 0.52	0.700
p	**0.890**	**0.618**	**0.755**	**0.725**	**0.898**	
Cl- initial	111.06 ± 8.08	108.34 ± 7.24	104.27 ± 9.63	105.93 ± 4.26	108.05 ± 8.88	0.264
Cl- final	110.21 ± 7.11	101.84 ± 26.65	107.26 ± 4.97	105.85 ± 4.62	106.94 ± 5.65	0.588
p	**0.712**	**0.314**	**0.406**	**0.953**	**0.668**	
Ca2 + initial	1.09 ± 0.06	1.12 ± 0.82	1.08 ± 0.13	1.08 ± 0.06	1.12 ± 0.10	0.622
Ca2 + final	1.12 ± 0.08	1.11 ± 0.11	1.13 ± 0.08	1.12 ± 0.08	1.12 ± 0.05	0.965
p	**0.224**	**0.620**	**0.148**	**0.162**	**0.976**	
Mg2 + initial	0.63 ± 0.11	0.60 ± 0.19	0.63 ± 0.11	0.61 ± 0.09	0.66 ± 0.13	0.868
Mg2 + final	0.66 ± 0.09	0.65 ± 0.12	0.67 ± 0.11	0.62 ± 0.13	0.63 ± 0.10	0.876
p	**0.221**	**0.378**	**0.330**	**0.804**	**0.487**	

Despite not finding significant differences in our patients with sepsis and treatment, we were able to observe a physiological response. In patients treated with vitamin C, an increase in the levels of Na^+, K^+ and Mg^{2+} was observed, as well as a decrease in the post-treatment levels of Cl^-. When comparing these values with the control group, we found a statistically significant difference in all the aforementioned ions ($p \leq 0.001$). In patients post-treated with vitamin E, we observed an increase in the levels of Na+, Cl^-, Ca^{2+} and Mg^{2+}. When compared with our control group, ionized calcium presented a significant difference before treatment ($p = 0.013$), but after treatment, this difference was lost ($p = 0.378$); in the case of chlorine, there were no differences versus control before and after treatment. For patients treated with n-acetylcysteine, the most important parameter was ionized calcium, with an increase after treatment. When compared to control patients, there was a significant difference before treatment ($p = 0.008$), but it was lost after treatment ($p = 0.129$). In the case of treatment with melatonin, the most important differences were observed in chlorine and magnesium, since both decreased after treatment, however, only magnesium had a significant difference when compared to the control group, before and after treatment. Subsequently, we made a correlation between the ionic levels before and after the treatment according to the site of infection with respect to the control subjects (Table 5). For patients with lung infection, there was a significant difference in the pretreatment K^+ ($p = 0.038$) and Mg^{2+} pretreatment ($p = 0.039$) and post treatment ($p < 0.001$) values. In patients with urinary tract infection, an increase in calcium levels was found after treatment ($p = 0.047$) and in patients with pulmonary + CNS + gastrointestinal infection there was a significant difference in pretreatment magnesium levels ($p = 0.028$).

Table 5
Correlation between ionic levels according to the site of infection between cases vs controls

	Na + initial	Na + final	K + initial	K + final	Cl- initial	Cl- final	Ca2 + initial	Ca2 + final	Mg2 + initial	Mg2 + final
Pulmonary (n = 26)	0.616	0.266	**0.038**	0.457	0.657	0.443	0.845	0.257	**0.039**	**< 0.001**
Pulmonary + CNS (n = 1)	0.315	0.933	0.932	0.780	0.114	0.369	0.431	0.788	0.204	0.391
Gastrointestinal (n = 17)	0.461	0.517	0.280	0.936	0.835	0.090	0.916	0.732	0.432	**0.004**
Nephrourinary (n = 7)	0.530	0.671	0.523	0.265	0.241	0.881	0.109	**0.047**	0.183	0.793
Pulmonary + Gastroint (n = 1)	0.927	0.899	0.054	0.350	0.316	0.840	0.845	0.788	0.359	**0.031**
SNC (n = 2)	0.447	0.939	0.425	0.460	0.407	0.231	0.664	0.919	0.744	0.872
Skin + Soft tissue (n = 2)	0.705	0.847	0.357	0.069	0.740	0.922	0.790	0.983	0.816	0.277
Pulm + CNS + Gastro (n = 2)	0.240	0.888	0.150	0.893	0.449	0.555	0.731	0.430	**0.028**	0.112

Finally, the ionic levels were analyzed according to the SOFA score, categorized as mild, moderate and severe, in pre-treatment and post-treatment (Table 6). We found a progressive increase in ionic levels from mild to severe of Na^+, K^+ and Cl^-, both pre-treatment and post-treatment; and decreased in ionized calcium and magnesium prior to treatment. In patients with severe SOFA score, after treatment, we found a significant increase in the levels of chlorine (p = 0.008) and ionized magnesium (p = 0.001).

Table 6
Ionic levels according to the SOFA score

	Mild	Moderate	Severe	P
Na + Pretreatment	134.70 ± 7.05	133.66 ± 11.36	137.36 ± 12.74	0.472
Na + Post treatment	140.92 ± 9.26	135.55 ± 9.33	176.10 ± 20.68	0.520
K + Pretreatment	3.64 ± 0.42	4.21 ± 0.51	4.24 ± 0.73	0.129
K + Post treatment	3.99 ± 0.47	4.13 ± 0.57	4.23 ± 0.55	0.615
Cl- Pretreatment	104.78 ± 0.03	107.34 ± 0.08	108.47 ± 0.10	0.628
Cl- Post treatment	89.04 ± 4.36	107.94 ± 6.75	107.81 ± 5.02	**0.008**
Ca2 + Pretreatment	1.12 ± 0.03	1.09 ± 0.08	1.10 ± 0.10	0.796
Ca2 + Post treatment	1.12 ± 0.02	1.11 ± 0.09	1.13 ± 0.08	0.695
Mg2 + Pretreatment	0.64 ± 0.14	0.63 ± 0.01	0.62 ± 0.12	0.974
Mg2 + Post treatment	0.53 ± 0.06	0.62 ± 0.09	0.70 ± 0.12	**0.001**

Discussion

In this work we analyze plasma ionic levels in patients with septic shock before and after treatment with different antioxidants. After a treatment with 4 types of antioxidants (n-acetyl cysteine, melatonin, vitamin C and vitamin E, we found a change in ionic levels, mainly in ionized magnesium.

Different studies have tried to establish the electrolyte alterations associated with septic shock, particularly in the length of stay in an ICU, however, the studies are still very scarce.

There are reports where Mg^{2+} deficiency, together with other electrolyte abnormalities, coexists in up to 40% of patients [13]. Various factors can contribute to hypomagnesemia in patients with septic shock, such as: decreased absorption caused by impaired gastrointestinal activity, malnutrition, diabetes mellitus, hypokalemia and hypocalcemia [14], hyperaldosteronism, renal tubular disorder, use of drugs such as amphotericin, cisplatin, cyclosporine, diuretics, proton pump inhibitors, and aminoglycoside antibiotics of which some are used during the management of septic shock and others may be being applied prior to septic shock due to cancer or other conditions.

Thus, several reports indicate that hypomagnesemia is associated with a higher mortality rate [13, 15, 16]. In our study, we found low levels of magnesium compared to control subjects in both groups of patients with sepsis; After treatment with different antioxidants, there was an increase in the serum levels of ionized magnesium, however, these values did not reach the levels of the control subjects. The presence of hypomagnesemia can lead to neurological disorders such as diffuse muscle spasms, lethargy, ataxia, nystagmus, twitching, tetany, or seizures. At the muscular level, there may be weakness of the respiratory muscles, hypoventilation, dysphagia and dysphonia; while at the cardiovascular level there may be a prolongation of the P-R and Q-T segments, atrial and ventricular arrhythmias, as well as congestive heart failure. On the other hand, we also observed alterations in the levels of other serum electrolytes such as sodium, potassium and calcium. There are reports that indicate that the decrease in magnesium levels may be accompanied by a reduction in the levels of K^{+} (hypokalemia) and Ca^{2+} (hypocalcemia) [17, 18]. This is because part of calcium metabolism is controlled by the activity of parathyroid hormone (PTH), which seems to be the site of action of magnesium for modulation of calcium balance, since serum magnesium deficiency inhibits the action of PTH in bone, directly preventing calcium release [19, 20]; furthermore, PTH secretion is prevented, since magnesium is a cofactor of the adenylate cyclase enzyme in parathyroid tissue. It has been observed that when hypokalemia occurs, there is the presence of hypomagnesemia in 40%; Likewise, when hypocalcemia is present, hypomagnesemia is present in 22%. [17, 20, 21]. On the other hand, when there is a decrease in potassium levels (hypokalemia), it is known that Mg^{2+} participates in the flow of Na^{+} and K^{+} in the cell membrane, since it acts as a cofactor in the Na-K ATPase, generating an electrochemical gradient and therefore an alteration in the membrane potential that can cause changes in excitability and / or irritability at the neuromuscular level.

Our results show a clear decrease in the serum levels of Na^{+}, K^{+} and Ca^{2+} with respect to the control subjects. In the different treatments with antioxidants, we found an increase in the levels of these electrolytes despite not finding a statistically significant increase. These differences were independent of the type of treatment given. This may be due to different reasons, including the number of patients with septic shock, the time between the initial and final sampling, and therefore the time of treatment with antioxidants. However, despite the foregoing, a physiologically important change was observed in the serum levels of the studied ions. Therefore, it is important to correct magnesium levels, to maintain adequate levels mainly of calcium and potassium in patients with septic shock.

Finally, when carrying out the analysis of the electrolytes studied before and after the treatment with antioxidants, according to the SOFA score, an important change was observed mainly in the subjects with severe scores in Na^{+} and Mg^{2+} levels. This indicates that, the greater the severity of the damage, the antioxidant therapy, regardless of what it is, causes an improvement in the patient, mainly in the levels of magnesium, which, as mentioned above, is an ion that participates in the regulation of other electrolytes and that can help improve the patient's condition.

This study leads to propose that in patients admitted with septic shock, medical management should consider, in addition to standard therapy, antioxidant therapy and specific electrolyte monitoring. The importance of determining magnesium in the basal state allows defining the deficit, which leads to septic shock. The determination of ionized magnesium could be a useful biomarker to include during the study and follow-up of patients in extreme severity

Conclusion

Serum levels of ionized Na^+, K^+, Cl^- and Ca^{2+} and Mg^{2+} were analyzed in control patients with septic shock in an intensive care unit. In patients with septic shock, there is a decrease in the serum levels of ionized Na^+, K^+, Cl^- and Ca^{2+} and Mg^{2+}. Antioxidant treatment as an adjunct to the standard management of patients with septic shock increases the electrolyte deficit. The correction of the magnesium deficit also leads to an increase in serum calcium and potassium levels.

This preliminary result makes it possible to propose multicenter clinical trials with a greater number of cases to confirm the importance of monitoring and surveillance of these ions in the comprehensive therapy of septic shock.

Declarations

Ethics approval and consent to participate: Signed informed consent from each participant was obtained after full explanation of the purpose and nature of all procedures used in the research study, in accordance with the stipulated in the Declaration of Helsinki, modified by the Tokyo Congress, Japan. The research was approved by the Ethical, Biosecurity and Investigation Committees of the National Institute of Cardiology (Registration number: INCAR-DG-DI-ACEP-039-2021). The protocol was registered (TRIAL REGISTRATION: ClinicalTrials.gov Identifier: NCT 03557229.

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Authors' contributions

AAA: Design of the work and interpretation of data and helped draft the manuscript. **MES**: Participated in the study design and manuscript revision. **GCA**: Assistant in the collection and analysis of samples. **JFG**: Assistant in the collection and analysis of samples. **RCS**: Selection and determination of patients. **IPT**: Interpretation of data. **CHG**: Interpretation of data and manuscript revision. **YTP:** Sample processing. **GFA**: Sample processing. **RGA**: Strategy design and drafted manuscript.

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