The Effect of the Excretion of Calcium, Magnesium, and Phosphate on the Serum Levels of These Substances in Newborns Who Therapeutic Hypothermia for Hypoxic Ischemic Encephalopathy

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Research Article

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Abstract

Background: Hypocalcemia, hypomagnesemia, and hyperphosphatemia are common electrolyte disturbances in perinatal asphyxia(PA). Different reasons have been proposed for these electrolyte disturbances. This study investigated the effect of the urinary excretion of calcium(Ca), magnesium(Mg), and phosphorus(P) on the serum levels of these substances in babies who were treated using therapeutic hypothermia for hypoxic ischemic encephalopathy(HİE) caused by PA. This study sheds light on the pathophysiology that may cause changes in the serum values of these electrolytes.

Method: This study included 21 healthy newborns(control group) and 38 patients(HİE group) who had undergone therapeutic hypothermia due to HİE. Only infants with a gestational age of 36 weeks and above and a birth weight of 2000 g and above were evaluated. The urine and serum Ca, Mg, P, and creatinine levels of all infants were evaluated at 24, 48, and 72 hours.

Results: The lower serum Ca value and the higher serum P value of the HİE group were found to be statistically significant compared to the control group. There was no significant difference in serum Mg values between the groups. However, hypomagnesemia was detected in five patients from the HİE group. The urine excretions of these substances, which were checked at different times, were found to be significantly higher in the HİE group compared to the control group.

Conclusion: This study determined that the urinary excretion of Ca, Mg, and P has an effect on the serum Ca, Mg, and P levels of infants with HİE.

Introduction

Despite advancing technology and treatments, perinatal asphyxia (PA) and one of its consequences, hypoxic-ischemic encephalopathy (HIE), continue to be significant health problems in neonatal patients. Moderate and severe HIE is seen in 1 to 3 out of every 1000 live births in developed countries [1,2], and its frequency in Turkey is 2.6 out of every 1000 live births [3]. Therapeutic hypothermia (TH) is a treatment method proven to reduce mortality and morbidity in full-term and near-term babies with moderate and severe HIE [4].

PA is known to cause acute kidney injury [5], and studies have also shown that PA can cause hypocalcemia, hypomagnesemia, and hyperphosphatemia [6–8]. This suggests that the urinary excretion of these substances can affect the serum calcium (Ca), magnesium (Mg), and phosphorus (P) levels of infants that have undergone TH due to HIE. It is possible that tubular dysfunction due to PA may affect the excretion and serum levels of these elements. To the best of our knowledge, this study is the first of its kind, and thus fills a gap in the literature, it will help us understand the relationship between renal involvement and serum electrolyte concentrations.

We aimed to evaluate the effect of Ca, Mg and P tubular excretions on the development of hypocalcemia, hypomagnesemia and hyperphosphatemia in patients who underwent TH for Grade 2–3 HIE.

Materials And Methods

This prospective study included 38 infants (HIE group) who underwent TH for the treatment of HIE between January 10 and August 10, 2019, in Kayseri City Hospital's Neonatal Intensive Care Unit and 21 healthy newborns (control group).

The newborns diagnosed with HIE were grouped according to modified Sarnat&Sarnat clinical staging criteria. As determined by clinical and laboratory data, whole-body TH treatment was applied to patients who met the diagnostic criteria for Stage 2 and 3 HIE using a TH Arctic Sun 5000 (produced by Medivance, Inc. of Louisville, Colorado) device. TH was started within the first six hours of the infant's life. Body temperatures were monitored using a rectal probe. The infant was cooled rapidly, and their temperature was kept at 33.5 ± 0.2°C for 72 hours. Their temperature was then raised by 0.25° C/hour to be between 36.5 and 37.5°C within 12 hours.

Along with the prenatal, natal, and postnatal histories of the patients included in the study, serum and spot urine Ca, Mg, P, and creatinine were measured consecutively for three postnatal days (24, 48, and 72 hours postnatal). Serum Ca, Mg, P, creatinine,

and spot urine Ca, Mg, P, and creatinine levels were measured with a Cobas 8000 (Cobas c702) device using a Roche kit; the colorimetric method was used for serum and spot urine Ca and Mg, and the photometric ultraviolet method was used for spot urine and serum P.

This study excluded infants with a birth weight below 2000 g, a gestational age below 36 weeks, a congenital metabolic disease, a family history of energy deficiency or other diseases, early encephalopathy, widespread parenchymal cranial hemorrhage or life-threatening coagulopathy, chorioamnionitis, trisomy 13, trisomy 18, or multiple organ anomalies.

Ethical approval was obtained from the local ethics committee.

Informed consent was obtained from a parent and/or legal guardian.

Statistical Analysis

The data obtained from the study were input and analyzed using the SPSS 22.0 statistics program. Descriptive values of the data obtained in the evaluation and analysis were recorded as frequency (number and percent), mean, and standard deviation (SD), depending on the type of data. The Shapiro–Wilk test was used to determine whether the data had a normal distribution. Normally distributed data were compared using the t test. The Mann–Whitney U test was used for intergroup comparisons of data that were not normally distributed. The chi-square test was used in the analysis of categorical variables. Statistical significance was set at $p < 0.05$.

Results

The demographics of the patient and control groups were similar (Table 1). As expected, APGAR scores were low in the HIE group ($p < 0.05$). The HIE group and the control group had similar delivery types. In the HIE group, 10 patients (26.3%) had convulsions, 4 (10.5%) patients died during follow-up. Serum Ca levels over the course of 3 days were found to be lower in the HIE group than in the control group, the difference being statistically significant (Table 2, Fig. 1, $p < 0.05$). A total of 14 (36.8%) patients in the HIE group received intravenous Ca support. In all of these patients, the adjusted ionized Ca values was found to be below 4 mg dL. The median for 4 patients in the first 24 hours was 29.5 (18–36) mg/kg, the mean for 7 patients within 24–48 hours was 35.42 ± 6.99 mg/kg, and the median value for 10 patients within 48–72 hours was 36 (18–52) mg/kg and elementary Ca support was given. In the evaluation of Ca excretion with urine, it was observed that Ca excretion at the 24th hour was higher in the HIE group ($p < 0.05$), but the excretion values measured at other hours were similar to the control and HIE groups (Table 2, Fig. 1, $p > 0.05$).

Table 1
Demographic characteristics of HIE and control groups

	HIE group (n = 38)	Control Group (n = 21)	p values
Birth Weight (gr)	3241,32 ± 485,88	3231,43 ± 375,75	0,93
Height (cm)	51(45–54)	50 (46–52)	0,053
Head Circumference (cm)	35,5 (33–38)	35 (33–37)	0,10
Pregnancy Week by Last Menstrual Date	39 (36–42)	39 (36–41)	0,94
Pregnancy Week According to USG	39 (34–41)	39 (36–40)	0,50
APGAR Score (1st minute)	3 (0–5)	8 (7–9)	**0,001**
APGAR Score (5th minute)	5 (1–6)	9 (9–10)	**0,001**
pH (First blood gas)	6.96 ± 0.13	-	-
BE (First blood gas)	-18.44 ± 4.05	-	-
Cesarean	24 (%63.2)	13 (%61.9)	-
Normal Spontaneous Vaginal Delivery	14 (%36.8)	8 (%38.1)	
Maternal-Fetal Pathology	5 (%13.2)	-	-
• Placental Abruption	1 (%2.6)		
• Gestational Diabetes	1 (%2.6)		
• Preeclampsia	31 (%81.6)		
• No Pathology			
Convulsion	10 (%26.3)	-	-
Exitus	4 (%10.5)	-	-

BE: Base Excess, HİE: Hypoxic ischemic encephalopathy

Table 2
Serum electrolytes and urinary excretion of these electrolytes at the 24th, 48th and 72nd hours of the groups

	24th hour			48th hour			72nd hour		
	HIE Group (n = 38)	Control Group (n = 21)	P values	HIE Group (n = 38)	Control Group (n = 21)	P values	HIE Group (n = 38)	Control Group (n = 21)	P values
Serum Ca (mg/dl)	8.57 ± 0.65	9.41 ± 0.59	**0.001**	8.30 ± 0.83	9.23 ± 0.28	**0.001**	8.42 ± 0.92	9.68 ± 0.58	**0.001**
Serum P (mg/dl)	5.76(2.61–8.87)	5.52(3.95–8.42)	0.40	6.48 ± 1.58	5.1 ± 0.51	**0.001**	6.56 ± 1.54	5.12 ± 0.76	**0.001**
Serum Mg (mg/dl)	1.73(0.93–2.16)	1.79(1.63–2.10)	0.18	1.76(1.36–4.45)	1.77(1.61–1.94)	0.81	1.84(1.45–2.83)	1.86(1.65–2.01)	0.60
Urine FeCa	0.95(0.12–26.66)	0.58(0.04–1.09)	**0.001**	0.59(0.06–28.41)	0.61 (0.11–1.01)	0.64	0.74(0.03–18.40)	0.61 (0.08–1.03)	0.22
Urine FeP	2.15(0.26–20.09)	3.14(0.11–8.41)	0.70	9.61(0.28–37.24)	3.06(0.92–11.59)	**0.02**	13.70(0.24–46.62)	2.54(0.49–7.21)	**0.001**
Urine FeMg	0.67(0.05–5.54)	0.41(0-1.23)	**0.03**	0.76(0.01–10.06)	0.42(0.09–0.96)	0.06	0.73 (0.08–17.12)	0.49 (0.04–1.12)	0.08

HIE: Hypoxic ischemic encephalopathy, Ca: Calcium, P: Phosphorus, Mg: Magnesium, Fe: Fraction

When the serum P levels were examined, it was observed that while there was no difference between the P levels at the 24th hour between the HIE and the control group ($p > 0.05$), the serum P levels measured at the 48th and 72nd hours were higher in the HIE group (Table 2, Fig. 2, $p < 0.05$). However, parallel to the increase in serum P levels, urinary FeP excretion was found to be higher in the HIE group at the 48th and 72nd hours (Table 2, Fig. 2, $p < 0.05$).

There was no statistically significant difference in serum Mg levels between the HIE group and the control group (Table 2, Fig. 3, $p > 0.05$). However, hypomagnesemia (< 1.6 mg/dL Mg) was observed in 5 patients (13%) in the HIE group and these patients received intravenous Mg supplementation. FeMg excretion at 24, 48, and 72 hours was found to be higher in the HIE group compared to the control group, but only the value measured at 24 hours was statistically significant (Table 2, Fig. 3).

Discussion

The aim of this study is to evaluate the effect of renal tubular involvement on serum electrolytes in infants with HIE. We have shown that serum Ca, P, and Mg values can be affected by urine excretion. There may be many other factors (e.g., renal effect of hypoxia, effects of hypothermia, hormonal effects) that can cause this phenomenon. However, we have shown that increased urinary excretion of these substances is a causative factor.

Previous studies have shown that hypocalcemia is a common problem in newborns with HIE [9]. However, previous studies of TH use in newborns with HIE did not report any difference in the incidence of hypocalcemia between chilled babies and controls. In other words, it has been shown that TH does not increase the risk of hypocalcemia [10,11]. Saha et al. [12] found the rate of hypocalcemia in babies with PA to be 23.33%. In Yamamoto et al.'s study [13] evaluating 16 patients who underwent brain hypothermia, they found that serum ionized Ca (iCa) levels measured in the first 6 hours were below 0.8 mmol/L in 4 patients (25%). They found that early hypocalcemia was associated with poor neurological prognosis, with a cutoff value of < 1.05 mmol/L iCa for poor neuroprognosis. In another study in which 89 patients who underwent TH due to HIE were evaluated, 11 (12%) of the patients developed hypocalcemia [14]. Odo et al. [15] evaluated serum iCa in newborns with PA and showed that the

iCa value in the PA group was lower than the healthy control group. Similar to results in the prior literature, hypocalcemia was observed in 14 (36.8%) of the patients in the HIE group in our study. Calcium support was given to 4 patients in the first 24 hours, 7 patients within 24–48 hours, and 10 patients within 48–72 hours. Hypocalcemia was not observed in any of the babies in the control group. Serum Ca values measured at 24, 48, and 72 hours were found to be statistically significantly lower in the HIE group than in the control group.

Urine Ca excretion at 24 and 72 hours was higher in the HIE group than the control group, which was statistically significant at the 24th hour. There have been no prior studies in the literature on urinary FeCa values in patients receiving TH treatment for HIE.

Normal newborns have increased serum P levels in the first 3 days of life due to decreased renal glomerular filtration, insufficient parathyroid hormone (PTH) secretion, and less tubular effects of PTH. Serum P levels decrease over time and these effects disappear at other stages of life [16]. In PA, serum P levels increase due to the release of intracellular P into the extracellular environment and decreased glomerular filtration [17]. Similar to results in the literature, serum P levels measured at 48 and 72 hours were found to be significantly higher in babies with HIE compared to the control group. However, serum P levels measured at the 24th hour were similar to the control group. Polderman et al. studied applied hypothermia treatment in adult patients who had severe head trauma and found that serum P levels of these patients decreased and urinary P levels increased. They concluded that increased urinary excretion of phosphorus decreased serum phosphorus levels [18], similarly to this study, in which we found increased urinary P levels at 48 and 72 hours in babies who underwent TH.

It has been reported in previous studies that patients with PA may develop hypomagnesemia. Saha et al. [12] found the rate of hypomagnesemia in babies with PA to be 10%. Tocco et al. showed that 80% of infants with whole body cooling had magnesium levels below 1.6 mg/dL [19]. Similar to this study, the rate of hypomagnesemia (< 1.6 mg/dL) was found to be 13% in our HIE group. Hypomagnesemia (< 1.6 mg/dL) was not observed in the control group. Urine FeMg excretion at 24, 48, and 72 hours was higher in the HIE group. However, only the 24-hour urinary magnesium excretion was statistically significantly higher.

Conclusions

We have shown that the serum Ca, P, and Mg levels of newborns who receive TH treatment for HIE are affected by urinary excretion of these substances. However, studies with more patients are needed to confirm this result.

Abbreviations

PA: perinatal asphyxia; HIE: hypoxic-ischemic encephalopathy; TH: Therapeutic hypothermia; PTH: parathyroid hormone

Declarations

Acknowledgements

Research team members and all the mothers who consented to the study.

Authors' contributions

OB, Bİ, FB, ÇK and AÖ conceptualized the study. OB and Bİ conducted the first draft of the analysis. OB and AÖ reviewed the statistical analysis. OB and Bİ made the first draft. OB, Bİ, BÇ and AÖ reviewed and revised the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from the local ethics committee (Erciyes Medical Faculty). Written consent was obtained from the participants enrolled in the study.

Consent for publication

Not applicable.

Competing interests

None.

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Figures

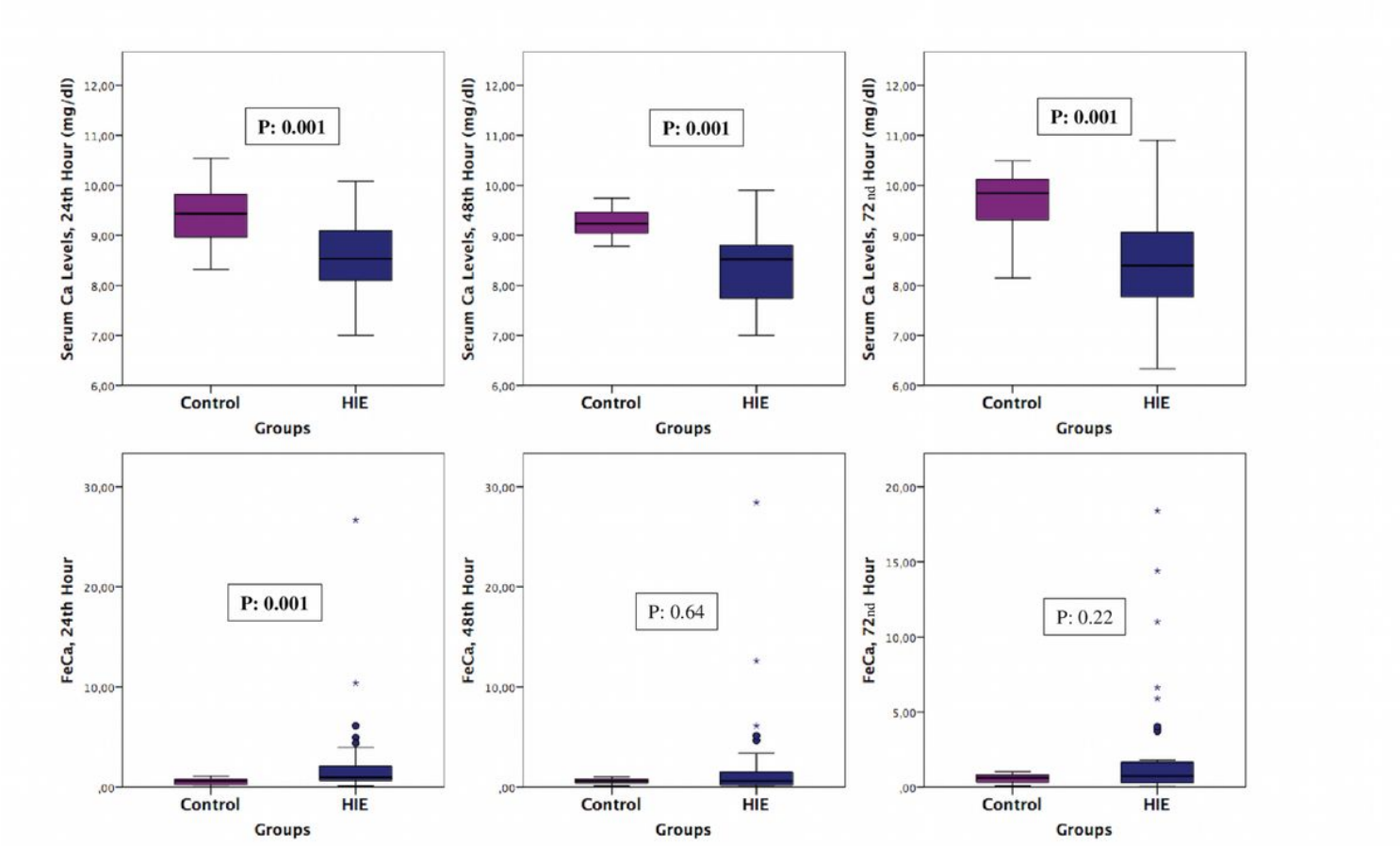

Figure 1: Calcium Levels in Serum and Fractional Excretion of Calcium
HIE: Hypoxic Ischemic Encephalopathy, Ca: Calcium, FeCa: Fractional Excretion of Calcium, P<0.05: Statistically significant

Figure 1

(caption included in figure)

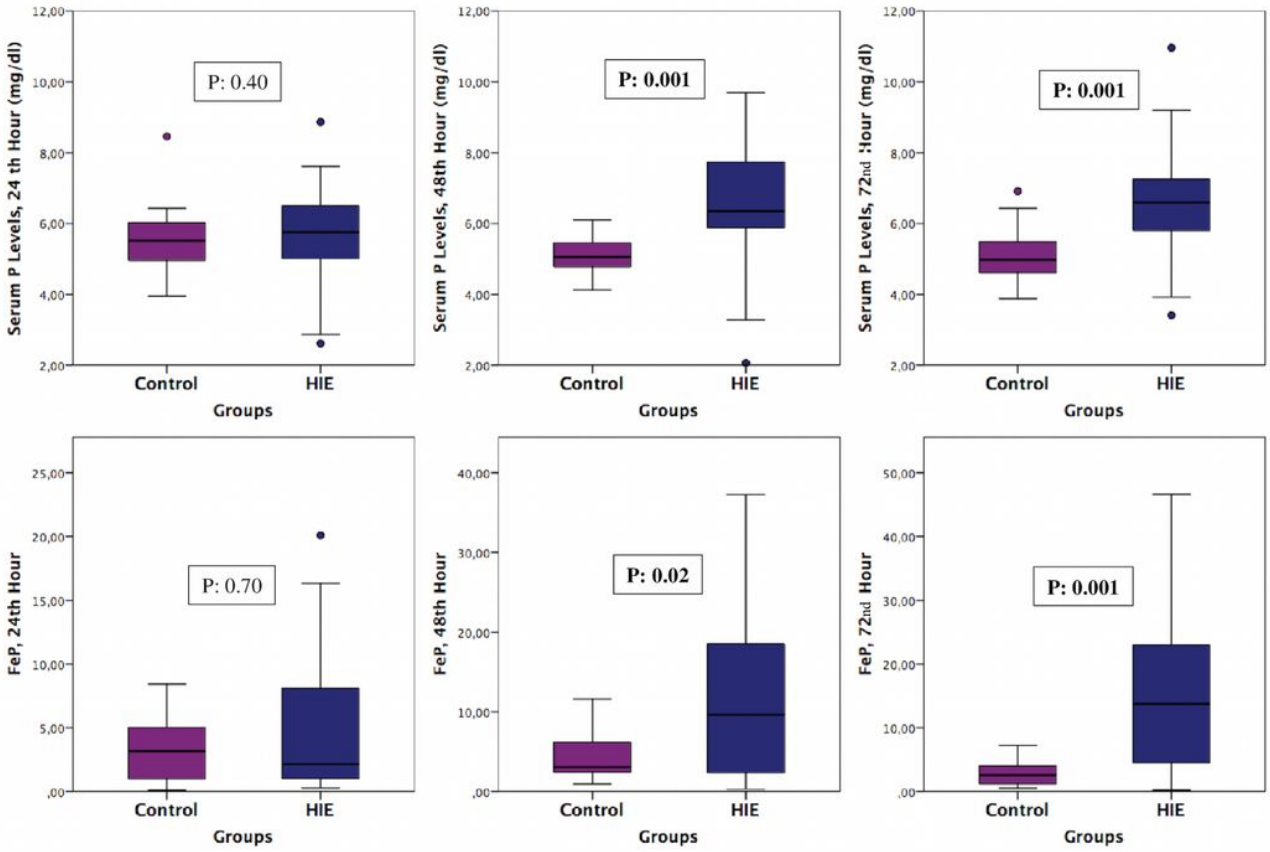

Figure 2: Phosphorus Levels in Serum and Fractional Excretion of Phosphorus
HIE: Hypoxic Ischemic Encephalopathy, P: Phosphorus, FeP: Fractional Excretion of Phosphorus, P<0.05: Statistically significant

Figure 2

(caption included in figure)

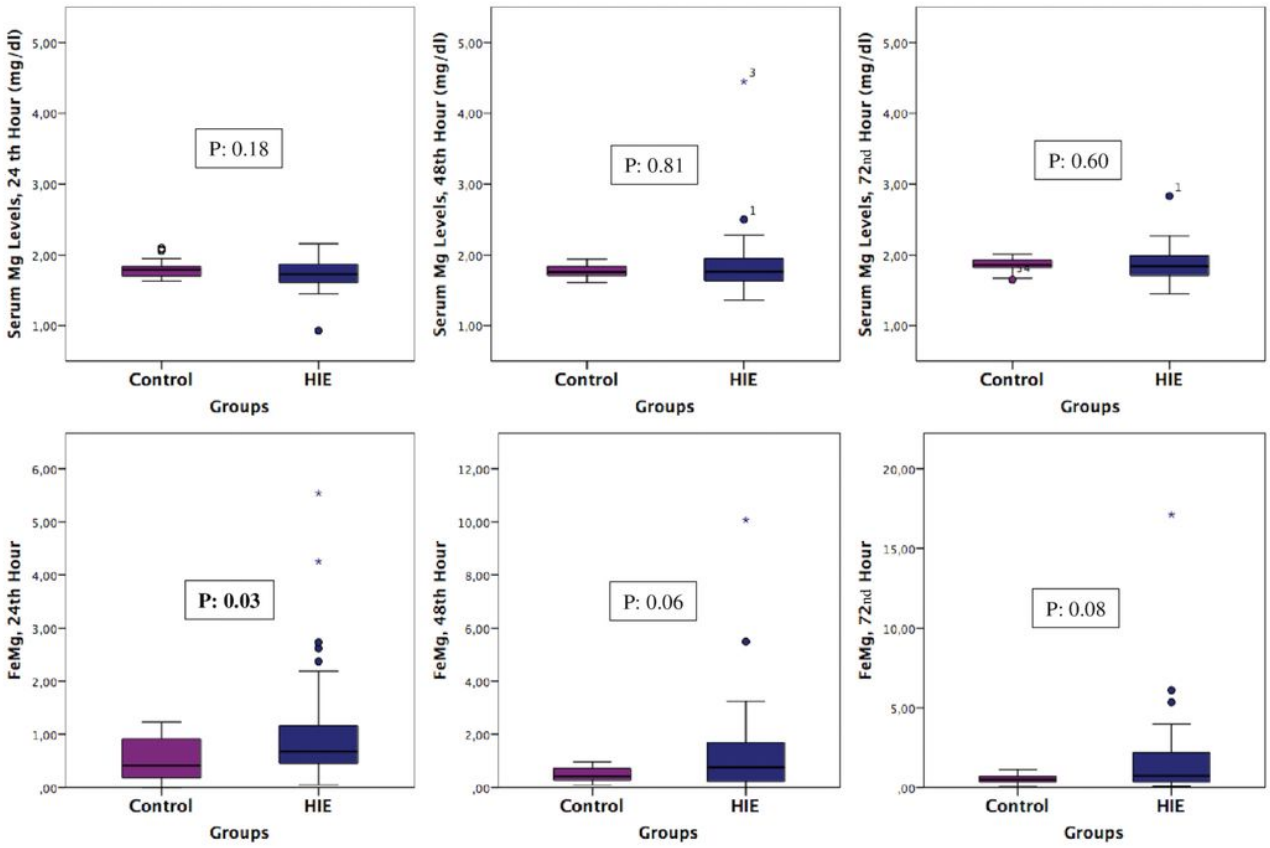

Figure 3: Magnesium Levels in Serum and Fractional Excretion of Magnesium
HIE: Hypoxic Ischemic Encephalopathy, Mg: Magnesium, FeMg: Fractional Excretion of Magnesium, P<0.05: Statistically significant

Figure 3

(caption included in figure)

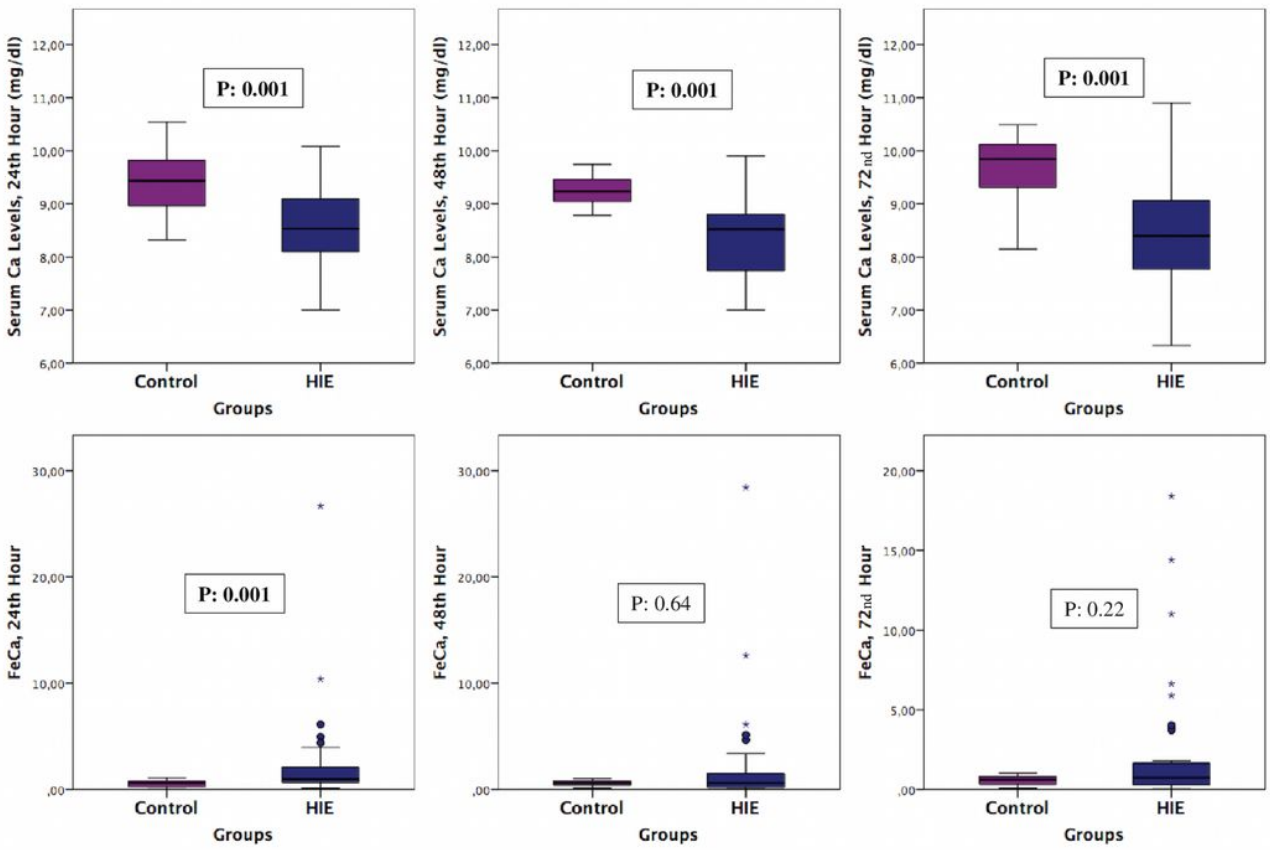

Figure 1: Calcium Levels in Serum and Fractional Excretion of Calcium
HIE: Hypoxic Ischemic Encephalopathy, Ca: Calcium, FeCa: Fractional Excretion of Calcium, P<0.05: Statistically significant

Figure 4

(caption included in figure)