Association of Serum Magnesium and Blood Pressure in Patients with Hypertensive Crises: A Retrospective Cohort Study

IfeanyiChukwu O. Onor (✉ ionor@xula.edu)

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Lashira M. Hill

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Modupe M. Famodimu

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Mallory R. Coleman

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Carolkim H. Huynh

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Robbie A. Beyl

Pennington Biomedical Research Center

Casey J. Payne

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Emily K. Johnston

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

John I. Okogbaa

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Christopher J. Gillard

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Daniel F. Sarpong

Center for Minority Health and Health Disparities Research and Education, College of Pharmacy, Xavier University of Louisiana

Amne Borghol

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Samuel C. Okpechi

Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center

Ifeyinwa Norbert

CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana

Shane E. Sanne

Department of Medicine, Louisiana State University Health Sciences Center School of Medicine

Shane G. Guillory

Department of Medicine, Louisiana State University Health Sciences Center School of Medicine

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6   IfeanyiChukwu O. Onor, Pharm.D., BCPS, FNKF ^{1,2, 3}

7   Lashira M. Hill, Pharm.D.¹

8   Modupe M. Famodimu, Pharm.D., BCPS ¹

9   Mallory R. Coleman, Pharm.D. ¹

10   Carolkim H. Huynh, Pharm.D. ¹

11   Robbie A. Beyl, Ph.D. ⁴

12   Casey J. Payne, Pharm.D. ¹

13   Emily K. Johnston, Pharm.D., BCCCP ¹

14   John I. Okogbaa, Pharm.D., BCPS ^{1,2}

15   Christopher J. Gillard, Pharm.D., BCPS ^{1,2,3}

16   Daniel F. Sarpong, Ph.D. ^{1,5}

17   Amne Borghol, Pharm.D., BCPS ^{1,2,3}

18   Samuel C. Okpechi, B.S. ⁶

19   Ifeyinwa Norbert, M.D. ¹

20   Shane E. Sanne, D.O. ²

21   Shane G. Guillory, M.D. ²

22   CardioRenal Research Group (CRRG)

23

24

¹ CardioRenal Research Group (CRRG), College of Pharmacy, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, LA 70125

² Department of Medicine, Louisiana State University Health Sciences Center School of Medicine, 1542 Tulane Avenue, New Orleans, LA 70112

³ Department of Pharmacy, University Medical Center New Orleans, 2000 Canal Street, New Orleans, LA 70112

⁴ Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808

⁵ Center for Minority Health and Health Disparities Research and Education, College of Pharmacy, Xavier University of Louisiana, 1 Drexel Drive, New Orleans, LA 70125, USA

⁶ Department of Biochemistry and Molecular Biology, Louisiana State University Health Sciences Center, 1901 Perdido Street, New Orleans, LA 70112

Corresponding Author: IfeanyiChukwu O. Onor, Pharm.D., BCPS, FNKF

Abstract

Background: The role of magnesium in blood pressure has been studied among hypertensive patients, however, no study has explored the role of magnesium in hypertensive crises. The primary objective of this study is to evaluate the relationship between serum magnesium and blood pressure in patients with hypertensive crises.

Methods: This study is a single-center, retrospective, chart review, cohort study of patients with hypertensive crises. Patients were included in the study cohort if they were eighteen years of age or older with an international classification disease ninth revision (ICD-9) code of 401.9 (hypertensive crises: emergency or urgency) and a documented magnesium level on their electronic medical record. The primary outcome of the study was to assess the correlation between serum magnesium on blood pressure (systolic blood pressure and diastolic blood pressure) in patients with hypertensive crises. The secondary outcomes were to assess the association between serum calcium, corrected calcium, and serum potassium on blood pressure in patients with hypertensive crises and to determine the effects of covariates in modulating the relationship between serum magnesium and blood pressure.

Results: Two hundred and ninety-three patients were included in the study. The primary outcome result showed that serum magnesium was positively correlated with systolic blood pressure ($r=0.143$, $p=0.014$), but not diastolic blood pressure. Serum calcium was also found to be positively correlated with systolic blood pressure, but not diastolic blood pressure. After adjusting for covariates in the solution for fixed effects analysis, serum magnesium, serum calcium, corrected calcium, and use of home proton pump inhibitors were correlated with systolic blood pressure at crises; while age, serum calcium, and corrected calcium were significantly correlated with diastolic blood pressure at crises.

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74 **Conclusion:** This study found a significant positive association between magnesium and systolic blood
75 pressure, but not diastolic blood pressure among patients with hypertensive crises. This positive
76 association of serum magnesium with systolic blood pressure was maintained after adjusting for
77 covariates. This study findings suggests a potential role of magnesium in blood pressure among patients
78 with hypertensive crises. Future studies should evaluate the role of serum magnesium modifying
79 therapies in controlling blood pressure in patients with hypertensive crises.

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82 **Keywords:** Magnesium, Blood Pressure, Hypertensive Crises

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Introduction

Magnesium is the second most abundant intracellular cation after potassium and the fourth most abundant cation in the body (1–3). In adult humans, total body magnesium store is approximately 24 grams with 99% existing intracellularly [bone (53%), muscle (27%), and soft tissue (19%)] and 1% existing in the extracellular space (serum and erythrocytes) (1,2). Normal total serum concentration is in the range of 1.7–2.6 mg/dL (0.7–1.1 mmol/L) (1). This serum magnesium range represents approximately 0.3% of total body magnesium and may not accurately reflect the total magnesium status (2,4). Ten percent of serum magnesium is complexed to serum anions, thirty percent of serum magnesium is albumin-bound, and sixty percent of serum magnesium exists in the ionized, free physiologically active form (1). Serum magnesium homeostasis is regulated by the interplay between intestinal transport, bone transport, and renal exchange (1). Magnesium is involved in a plethora of physiologic processes in the body namely: intracellular signaling, serving as a cofactor for DNA & protein synthesis, oxidative phosphorylation, cardiac excitability, vasomotor tone, blood pressure regulation, neuromuscular transmission, and bone formation (1–3).

Hypertension is a condition characterized by elevation in the systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) (5,6). Clinical practice guidelines define hypertension using different cutpoints as either SBP $\geq$ 130 mmHg and/or DBP $\geq$ 80 mmHg(7) or SBP $\geq$ 140 mmHg and/or DBP $\geq$ 90 mmHg (8,9). The global prevalence of hypertension in adults is between 30% - 45%; with a global age-adjusted prevalence of 24% and 20% in men and women, respectively (9). The prevalence of hypertension among US adults depends on the clinical practice guideline cutpoints to categorize blood pressure; with an overall prevalence of hypertension among US adults between 32% - 46% and age-sex adjusted prevalence range of 31% - 48% for men and 32% - 43% in women (7,8). Hypertension remains a leading risk factor for cardiovascular diseases (hemorrhagic stroke, ischemic stroke, myocardial

infarction, angina, heart failure, peripheral artery disease, and aortic aneurysm), end-stage renal disease, death, and disability (5–10). Hypertensive crises is defined as SBP greater than 180 mmHg and/or DBP greater than 120 mmHg (7,8). Hypertensive crises can be further classified into: hypertensive urgency (when there is no evidence of target organ damage) and hypertensive emergency (when there is evidence of target organ damage) (7,8). Although hypertensive urgency reflects a marked elevation in blood pressure, it can be managed by increasing or optimizing the dose of oral antihypertensive agents. Hypertensive emergency, however, is characterized with target organ damage and is associated with a 1-year mortality rate of > 79%; thus necessitating swift blood pressure reduction with intravenous antihypertensive agents to prevent sustained deterioration of target organ damage (7,8). The principal focus of our study is to examine the role of magnesium on SBP and DBP in hypertensive crises anchored by background evidence from studies evaluating the role of magnesium in hypertension.

Multiple clinical trials have shown, albeit inconsistently, that magnesium deficiency (serum and/or tissue) occurs to some degree in hypertensive subjects; with low magnesium levels linked to a significant undesirable effect on blood pressure (11–16). Although magnesium has been postulated to modulate blood pressure regulation, the precise mechanism of altered magnesium metabolism in hypertensive individuals remain unclear (11). The prevalent postulated mechanism of the effect of magnesium on blood pressure is that magnesium acts as a natural calcium antagonist on most types of calcium channels in vascular smooth muscles, thus reducing arterial blood pressure through lowering of peripheral and cerebral vascular resistance (11). More specifically, the activity of magnesium as a calcium antagonist produces endothelial dependent vasodilation and reduction of blood pressure through increases of extracellular magnesium and reduction of calcium influx (4,11,17,18). Magnesium has also been shown to produce vasodilation by increasing prostaglandin E – a vasodilator and platelet

inhibitor (17,18). Magnesium is also an essential cofactor for delta-6-desaturase enzyme which converts linoleic acid to gamma linolenic acid, a precursor to prostaglandin E (17,18). Additionally, a strong interaction has been found between magnesium and other electrolytes (potassium, calcium, and sodium) in blood pressure reduction; with reduction of intracellular sodium and calcium, and increases in intracellular magnesium and potassium shown to improve blood pressure (17,18).

Several observational clinical studies and a meta-analysis have evaluated the relationship between serum magnesium and blood pressure in patients with and without hypertension (12,14,25,15,16,19–24); however, no published study to our knowledge has evaluated serum magnesium and blood pressure relationship among patients with hypertensive crises. The available published studies performed tests of association (correlation, odds ratio, risk ratios, and hazard ratios) between magnesium and either blood pressure or hypertension (12,14,25,15,16,19–24). Among the ten studies that performed a test of association between serum magnesium and either blood pressure or hypertension, six studies found a significant negative association (14–16,20,21,24), three studies found no significant relationship (12,19,23), and one study found a significant positive correlation between serum magnesium and blood pressure in women only (25). The meta-analysis by Han et al. found no significant association between serum magnesium and blood pressure, although there was a trend towards negative association between serum magnesium and blood pressure (Risk Ratio (RR) = 0.91, 95% CI: 0.80 – 1.02) (22). Collectively, these studies have revealed conflicting evidence on the relationship between serum magnesium levels and either blood pressure or hypertension; with some studies showing negative association (14–16,20,21,24), and others showing either no association (12,19,22,23,25) or a positive association (25). Similarly, the effect of magnesium supplementation on blood pressure has been studied extensively. Nine out of the ten studies (clinical trials, Cochrane Review and meta-analyses) reviewed showed mostly positive association/effect of magnesium supplementation

in lowering SBP, DBP, or both (22,26–33); and only one study found no significant effect of magnesium supplementation on blood pressure (34). This prevailing positive effect of magnesium supplementation in lowering blood pressure proved compelling and served as the foundational rationale for our study evaluating whether serum magnesium is a factor that contributes to the dysregulated high blood pressure seen in patients with hypertensive crises. We hypothesized that low serum magnesium will be significantly associated with blood pressure (SBP and DBP) in patients with hypertensive crises.

The primary objective of this study is to evaluate the correlation between serum magnesium and blood pressure (SBP and DBP) in hypertensive crises. Secondary objectives were to evaluate the association between serum calcium, corrected calcium, and serum potassium on blood pressure in patients with hypertensive crises, and to determine the effects of covariates [age, sex, race, body mass index (BMI), history of diabetes mellitus, use of proton pump inhibitors at home, use of blood pressure medications at home or hospital, use of oral magnesium at home, use of intravenous magnesium at hospital, serum calcium at crises, corrected calcium at crises, and serum potassium at crises] in modulating the relationship between serum magnesium and blood pressure.

Study Design and Methods:

This study is a single-center, retrospective, chart review, cohort study conducted at the Interim Louisiana State University Hospital (ILH) – New Orleans, Louisiana. The study cohort data was reviewed from patients who were admitted to ILH with hypertensive crises during a 2-year period from July 2012 to July 2014. This study was approved by the Xavier University of Louisiana Institutional Review Board (IRB) and ILH Research Review Committee (RRC).

Patients who were eighteen years of age or older with an international classification disease ninth revision (ICD-9) code of 401.9 (hypertensive crises: emergency or urgency) and a documented magnesium level on their electronic medical record (during the hypertensive crises hospital admission) were included in the study cohort. Hypertensive crises was defined as systolic blood pressure (SBP) greater than 180 mmHg and/or diastolic blood pressure (DBP) greater than 120 mmHg. Patients identified as having hypertensive crises based on ICD-9 codes were confirmed to have either systolic blood pressure (SBP) greater than 180 mmHg and/or diastolic blood pressure (DBP) greater than 120 mmHg. Hypertensive crises was further categorized as either hypertensive urgency (absence of acute or on-going target organ damage) or hypertensive emergency (presence of acute or on-going target-organ damage). Target organ damage by system included neurologic (hypertensive encephalopathy, intracranial hemorrhage, acute ischemic stroke), cardiac (acute myocardial infarction, acute left ventricular failure, unstable angina, dissecting aortic aneurysm), and renal (acute kidney injury). All diagnoses of target organ damage were confirmed with both the physician diagnosis documented on the patients' problem list and clinical findings (laboratory results, imaging, signs, and symptoms) made on the patients. Hypertensive encephalopathy diagnosis was verified based on physical exam findings of headache and altered level of consciousness. Diagnosis of intracranial hemorrhage and acute ischemic stroke was confirmed using a computed tomography (CT) scan or magnetic resonance imaging of the

head with or without contrast, and was performed on patients with neurologic symptoms, which includes change in mental status or focal neurologic signs indicative of cerebrovascular accident or hemorrhage. Unstable angina diagnosis was made clinically and confirmed with documented new or sudden chest pain, while myocardial infarction diagnosis was confirmed with elevated serum troponin levels and electrocardiogram (EKG) findings. Acute left ventricular failure was diagnosed with echocardiographic findings of a decreased ejection fraction less than 40% as well as physical exam findings of elevated jugular venous pressure (distension), crackles, or edema. Diagnosis of dissecting aortic aneurysm was confirmed from imaging studies revealing wide mediastinum on chest x-ray and/or chest CT scan with or without contrast. Acute kidney injury was defined as a serum creatinine (SCr) greater than 2 mg/dL, which is new onset in absence of prior renal disease and/or increase in SCr of 0.5 mg/dL or greater.

Patients were excluded if they had conditions interfering with serum magnesium levels such as: chronic kidney disease (CKD) stages 4 and 5, end-stage renal disease (ESRD), hepatic cirrhosis, pheochromocytoma, chronic diarrhea, and hyperaldosteronism. Additionally, patients who received inotropes or vasopressors (including epinephrine, norepinephrine, dopamine, phenylephrine, vasopressin, dobutamine, or milrinone) during the hospital encounter were excluded from the study.

All patient data was obtained from ILH's electronic medical record. The following demographic data was collected: age, sex, race, body mass index (BMI), and history of diabetes mellitus. Outcome variables collected included serum magnesium (mg/dL), serum calcium (mg/dL), serum potassium (mEq/L), SBP (mmHg), and DBP (mmHg). All outcome variables were collected at a time closest to the first documented hypertensive crises' blood pressure during the hospital encounter and is denoted as "at crises". Additionally, maximum and minimum values of SBP and DBP were recorded within 24-hours of

the first recorded hypertensive crises' blood pressure. Corrected calcium (mg/dL) was calculated using the formula: $\text{corrected calcium} = \text{patient's measured serum calcium in mg/dL} + (0.8 * (4 \text{ gm/dL} - \text{patient's measured albumin in gm/dL}))$. The corrected calcium was only calculated for patients whose serum albumin was less than 4 gm/dL. Additional predictor variables collected include: home and hospital use of blood pressure medications [inclusive of all blood pressure medication classes (for example: calcium channel blockers) grouped in the electronic health record], at home use of proton pump inhibitors, home use of oral magnesium, hospital use of intravenous magnesium, and albumin levels (gm/dL).

Outcomes

The primary outcome of the study was to assess the correlation between serum magnesium on blood pressure (SBP and DBP) in patients with hypertensive crises. The secondary outcomes of this study were to evaluate the association between serum calcium, corrected calcium, and serum potassium on blood pressure in patients with hypertensive crises, and to determine the effects of covariates (age, sex, race, BMI, history of diabetes mellitus, use of proton pump inhibitors at home, use of blood pressure medications at home or hospital, use of oral magnesium at home, use of intravenous magnesium at hospital, serum calcium at crises, corrected calcium at crises, and serum potassium at crises) in modulating the relationship between serum magnesium and blood pressure. An additional exploratory outcome was to perform correlation analyses of serum magnesium, serum calcium, corrected calcium, and serum potassium on the two independent variables: SBP and DBP measured at different time points.

Statistical Analyses

We performed a power analysis based on findings of our primary outcome variables (serum magnesium, SBP, and DBP) from prior studies.(16,26,28) Based on these studies, we estimate that the R^2 (coefficient of determination) for the linear regression between serum magnesium and either SBP or DBP will range between of 0.06 – 0.56. Our power analysis revealed that the target sample size for this study will range between 140 – 180 subjects, to give us a power of 0.80 at a significance level of 5%.

Descriptive statistical analysis was performed on demographic characteristics. Measures of central tendency were obtained for continuous measures and frequency distribution for categorical measures. Simple linear regression was performed to assess the correlation (r) and coefficient of determination (R^2) between serum magnesium, serum calcium, corrected calcium, and serum potassium on blood pressure (SBP and DBP) in patients with hypertensive crises. A linear model analysis was performed to assess effects of serum magnesium (and other electrolytes) on blood pressure (SBP and DBP) at the time of hypertensive crises while adjusting for covariates. Statistical analyses were performed using SAS® version 9.4. An alpha value of less than 0.05 was considered statistically significant.

Results:

Figure 1. Flow chart of inclusion to study cohort.

305 **Table 1. Baseline Characteristics (N = 293)**

Demographic variables	
Age [Mean $\pm$ SD years; (range)]	56.70 $\pm$ 12.86 (19 – 97)
Sex	Male: 146 (49.83%)
	Female: 147 (50.17%)
Race	White: 62 (21.16%)
	Black/African-American: 213 (72.7%)
	Asian: 3 (1.02%)
	Other: 15 (5.12%)
Hypertensive Crises Diagnosis	Hypertensive Urgency: 220 (75.09%)
	Hypertensive Emergency: 73 (24.91%)
History of Diabetes mellitus	Diabetic: 102 (34.81%)
	Non-diabetic: 191 (65.19%)
Body Mass Index (BMI) [Mean $\pm$ SD kg/m ² ; (range)] (N=290)	30.59 $\pm$ 9.33 (16.70 – 69.10)
Use of Home Proton Pump Inhibitors (N=259)	53 (20.46%)
Use of Home Blood Pressure Medications (N=264)	227 (85.98%)
Use of Hospital Blood Pressure Medications	283 (96.59%)
Use of Home Magnesium (Oral) (N=292)	31 (10.62%)
Use of Hospital Magnesium (Intravenous) (N=292)	95 (32.53)
Serum Magnesium at Crises (Mean $\pm$ SD mg/dL; (range))	1.93 $\pm$ 0.36 (0.80 – 3.90)
Serum Calcium at Crises (Mean $\pm$ SD mg/dL; (range))	8.92 $\pm$ 0.92 (0.80 – 13.10)
Corrected Calcium at Crises (Mean $\pm$ SD mg/dL; (range)) (N=207)	9.33 $\pm$ 0.90 (1.12 – 13.34)

Serum Potassium at Crises (Mean $\pm$ SD mg/dL; (range))	3.92 $\pm$ 0.64 (1.40 – 6.30)
Systolic Blood Pressure [Mean $\pm$ SD mmHg; (range)]	194.2 $\pm$ 21.31 (136 – 265)
Diastolic Blood Pressure [Mean $\pm$ SD mmHg; (range)]	113.7 $\pm$ 21.38 (53 – 180)

Table 2. Association of serum magnesium (other electrolytes) and SBP at Crises or DBP at Crises

Relationship between magnesium and SBP at Crises or DBP at Crises (N=293)			
	SBP at Crises		
Variables	r	R ²	P-value
Serum Magnesium	0.143	0.020	0.014
Serum Calcium	0.187	0.035	0.001
Corrected Calcium (N=207)	0.049	0.002	0.482
Serum Potassium	-0.076	0.006	0.195
	DBP at Crises		
Variables	r	R ²	P-value
Serum Magnesium	0.033	0.001	0.570
Serum Calcium	0.090	0.008	0.124
Corrected Calcium (N=207)	-0.011	0.000	0.873
Serum Potassium	-0.113	0.013	0.053

Table 3. Association of serum magnesium and SBP at Crises or DBP at Crises using linear models
(adjusted for covariates)

Relationship between serum magnesium and SBP at Crises or DBP at Crises (N=293)		
	SBP at Crises	
Variables	$\beta \pm SE$	P-value
Serum Magnesium	11.25 $\pm$ 4.67	0.017
	DBP at Crises	
Variables	$\beta \pm SE$	P-value
Serum Magnesium	2.56 $\pm$ 4.93	0.6031
Adjusted for covariates – Age, sex, race, history of diabetes, BMI, use of proton pump inhibitors at home, use of blood pressure medications at home or hospital, use of oral magnesium at home, use of intravenous magnesium at hospital, serum calcium at crises, corrected calcium at crises, and serum potassium at crises.		

Table 4. Best Predictor Variables on SBP at Crises using linear models (adjusted for covariates)

	SBP at Crises	
Predictor Variables	$\beta \pm SE$	P-value
Serum Magnesium	11.25 ± 4.67	0.017
Serum Calcium	9.50 ± 3.37	0.006
Corrected Calcium	-7.82 ± 3.54	0.029
Use of Home Proton Pump Inhibitors	9.13 ± 3.85	0.019
Covariates in the Mixed Model – Age, sex, race, history of diabetes, BMI, use of proton pump inhibitors at home, use of blood pressure medications at home or hospital, use of oral magnesium at home, use of intravenous magnesium at hospital, serum magnesium at crises, serum calcium at crises, corrected calcium at crises, and serum potassium at crises.		
Alpha of < 0.05 defined as significant for best predictor variables.		

339 **Table 5.** Best Predictor Variables on DBP at Crises using linear models (adjusted for covariates)

	DBP at Crises	
Predictor Variables	$\beta \pm SE$	P-value
Serum Calcium	16.21 $\pm$ 3.56	<0.0001
Corrected Calcium	-14.12 $\pm$ 3.74	0.0002
Age	-0.53 $\pm$ 0.12	<0.0001
Covariates in the Mixed Model – Age, sex, race, history of diabetes, BMI, use of proton pump inhibitors at home, use of blood pressure medications at home or hospital, use of oral magnesium at home, use of intravenous magnesium at hospital, serum magnesium at crises, serum calcium at crises, corrected calcium at crises, and serum potassium at crises.		
Alpha of < 0.05 defined as significant for best predictor variables.		

Table 6. Correlation of Serum Magnesium at Crises on SBP and DBP at different time points

	Serum Magnesium at Crises (N=293)		
Variables	r	R ²	P-value
SBP at Crises	0.143	0.020	0.014
SBP Maximum (24-hr)	0.104	0.011	0.074
SBP Minimum (24-hr)	-0.034	0.001	0.563
DBP at Crises	0.033	0.001	0.570
DBP Maximum (24-hr)	0.041	0.002	0.480
DBP Minimum (24-hr)	0.021	0.000	0.726

Table 7. Correlation of Serum Calcium at Crises on SBP and DBP at different time points

	Serum Calcium at Crises (N=293)		
Variables	r	R ²	P-value
SBP at Crises	0.187	0.035	0.001
SBP Maximum (24-hr)	0.134	0.018	0.022
SBP Minimum (24-hr)	0.237	0.056	<0.0001
DBP at Crises	0.090	0.008	0.124
DBP Maximum (24-hr)	0.121	0.015	0.038
DBP Minimum (24-hr)	0.183	0.033	0.002

Table 8. Effect of Corrected Calcium at Crises on SBP and DBP at different time points

	Corrected Calcium at Crises (N=207)		
Variables	r	R²	P-value
SBP at Crises	0.049	0.002	0.482
SBP Maximum (24-hr)	-0.028	0.001	0.690
SBP Minimum (24-hr)	0.256	0.066	0.0002
DBP at Crises	-0.011	0.000	0.873
DBP Maximum (24-hr)	-0.000	0.000	0.996
DBP Minimum (24-hr)	0.177	0.031	0.011

Table 9. Effect of Serum Potassium at Crises on SBP and DBP at different time points

	Serum Potassium at Crises		
Variables	r	R²	P-value
SBP at Crises	-0.076	0.006	0.195
SBP Maximum (24-hr)	-0.074	0.005	0.209
SBP Minimum (24-hr)	-0.130	0.017	0.026
DBP at Crises	-0.113	0.013	0.053
DBP Maximum (24-hr)	-0.065	0.004	0.265
DBP Minimum (24-hr)	-0.175	0.031	0.003

Eight-hundred and thirty-seven patients who had a serum magnesium level and an ICD-9 code of 401.9 or a diagnosis of hypertensive crises, hypertensive urgency, and hypertensive emergency were identified from ILH's electronic medical record (Figure 1). 544 patients were excluded after applying the study exclusion criteria and 293 patients were included in the statistical analysis (Figure 1). Baseline demographics are presented in table 1. The majority of patients were African Americans (72.7%) and the mean age of patients in the study was 56.7 years. Hypertensive urgency (75.1%) was greater in prevalence than hypertensive emergency (24.9%) among all hypertensive crises diagnosis. Nearly 35% of patients had diabetes mellitus and the average BMI of the study population was 30.6 kg/m².

The primary outcome result is displayed on table 2 and showed that serum magnesium was positively correlated ($r = 0.143$, $p\text{-value} = 0.014$) with SBP at crises, but not DBP at crises. The coefficient of determination (R^2) reveals that 2% of the variability in SBP at crises can be attributed to serum magnesium. Beside serum magnesium, serum calcium was the only additional electrolyte significantly correlated with SBP at crises. Serum calcium was positively correlated with SBP at crises, with 3.5% of the variability in SBP at crises attributable to serum calcium. When evaluating DBP at crises, no electrolyte was significantly correlated with DBP at crises; however, serum potassium showed a slight trend towards negative correlation with DBP at crises.

Table 3 assessed the relationship with serum magnesium and both SBP and DBP at crises when adjusting for covariates. The results showed that as serum magnesium increases by 1 mg/dL, SBP at crises increases 11.25 mmHg after adjusting for covariates in the model ($p\text{-value} = 0.017$). Although a significant association was found with serum magnesium and SBP at crises after adjusting for covariates, no significant association was found with serum magnesium and DBP at crises after adjusting for covariates in the model.

Variables that significantly predicted SBP at time of hypertensive crises was assessed using a linear model (adjusted for covariates) and the results are displayed on table 4. When adjusting for covariates, serum magnesium, serum calcium, corrected calcium, and the use of proton pump inhibitors independently emerged as the best variables that predicted SBP at crises, with all showing a positive relationship with SBP at crises except for corrected calcium level showing a negative relationship with SBP at crises. Similarly, table 5 displays the variables that best predicted DBP at time of hypertensive crises using a linear model (adjusted for covariates). In the model, after adjusting for covariates, serum calcium, corrected calcium, and age independently emerged as best variables that significantly predicted DBP at crises. Serum calcium positively predicted DBP at crises in the model, while corrected calcium and age negatively predicted DBP at crises in the model.

Tables 6 through 9 display a result of the correlation matrix analyses of serum magnesium, serum calcium, corrected calcium, and serum potassium on the two independent variables: SBP and DBP measured at different time points. Table 6 showed that serum magnesium was significantly correlated only with SBP at time of crises and the maximum SBP measured within 24-hours of the first hypertensive crises diagnosis. Results displayed on table 7 showed that serum calcium was significantly correlated with SBP and DBP measured at different time points, with the exception of DBP measured at time of crises not showing significant correlation with serum calcium. Corrected calcium results displayed on table 8 revealed that corrected calcium was only significantly correlated with minimum SBP and minimum DBP measured within 24-hours of the first hypertensive crises diagnosis. Lastly, serum potassium was only significantly correlated (negative correlation) with minimum SBP and minimum DBP measured within 24-hours of the first hypertensive crises diagnosis.

Discussion

This study contributes much new knowledge on the role of magnesium in patients with hypertensive crises – a population where the role of magnesium has been sparsely evaluated. The primary outcome of our study evaluated the relationship between magnesium and blood pressure (SBP and DBP) in patients with hypertensive crises.

Using correlation analysis (table 2) and linear regression analysis (table 3), our study found a significant positive correlation between serum magnesium and SBP at crises, but no significant relationship was found between serum magnesium and DBP at crises. This finding of positive correlation between serum magnesium and SBP in our study conflicts with majority of studies that assessed serum magnesium and SBP which have predominantly shown significant negative correlation (12,14–16,21,24,25). Among the seven studies that evaluated the linear relationship (correlation coefficient) between magnesium and either SBP or DBP (12,14–16,21,24,25), majority of these studies (N = 5 out of 7, 71.4%) showed negative relationship between serum magnesium and SBP (14–16,21,24). One of the studies showed no significant relationship between serum magnesium and SBP (12), while one study by Rinner et al. approximated our study finding and revealed a positive relationship between serum magnesium and SBP in women, but not in men (25). With respect to the relationship between serum magnesium and DBP, majority of the studies (N = 4 out of 7, 57%) have shown non-significant relationship which is consistent with our study findings (12,14,24,25). However, three studies found negative correlation between serum magnesium and DBP which contradicts our study results (15,16,21). Our study finding therefore is consistent with most of the available literature showing no strong relationship between serum magnesium and DBP; however our study finding conflicts with the predominant negative linear relationship observed between serum magnesium and SBP in studies. Altogether, our study's detection of a significant positive association between serum magnesium and SBP in patients with hypertensive crises suggests that serum magnesium may play an important role in the dysregulated blood pressure

seen in patients with hypertensive crises. It is plausible to consider that our study may have had disparate results from the literature due to potential sources of error from selection bias and confounding variables.

Among the additional electrolytes (calcium, corrected calcium, and potassium) that we assessed for a relationship with blood pressure, we found that serum calcium showed significant positive correlation to SBP at crises, but not DBP at crises. After adjusting for covariates (tables 4 and 5), we found positive relationship between serum calcium and both SBP and DBP at crises. Similar to our study finding, the positive association of serum calcium to both SBP and DBP has been reported in several studies that evaluated the linear relationship between serum calcium and blood pressure (16,35–39). It is important to reinforce that our study found a relationship between serum calcium and both SBP and DBP at crises after adjusting for covariates; however the correlation analysis without adjustment for covariates showed significant positive correlation between serum calcium for SBP at crises, but not DBP at crises. Corrected calcium was not significantly correlated to either SBP or DBP at crises. In the exploratory results, we found that corrected calcium was positively associated with both minimum SBP and DBP within 24-hour of hypertensive crises. The data with corrected calcium should be interpreted cautiously given that we did not include 86 missing data among patients who did not have serum albumin less than 4 gm/dL. Potassium was also not significantly correlated to either SBP or DBP at crises, although there was a trend towards a negative correlation between potassium and DBP at crises. This finding is inconsistent with prior studies which have predominantly shown a negative correlation between serum potassium and both SBP and DBP (25,40–42). In the exploratory results (tables 6 – 9), we found that serum potassium was negatively associated with both minimum SBP and DBP within 24-hour of hypertensive crises. Calcium and potassium were measured because of strong linkages of these electrolytes with blood pressure, especially in concert with magnesium (7,13,15–18,25).

The strengths of our study include our use of statistical tests that explored association between variables, the pilot nature of our study, and the attainment of our study's desired sample size. We performed regression analysis to examine the association between magnesium (and other electrolytes) and blood pressure in hypertensive crises. Findings from the regression analysis provide us useful information on the relationship between electrolytes and variables. This study is also a pilot/exploratory study and is thus a hypothesis generating study and can provide population estimates to help determine the appropriate sample size to study the effect of magnesium on hypertensive crises in future studies. Lastly, our study reached and exceeded our desired sample size for the study which decreased the probability of type II errors and improved the probability to detect significant differences that may exist in the true population of patients from which our sample population was obtained.

Our study has several limitations which impact the internal and external validity of our study. First, this study is a single-center study and as such limits the generalizability of our study to patients across institutions. The findings from this single-center study should be extrapolated cautiously to individual patients and patient populations with hypertensive crises. This study was a retrospective study which introduces variability on the time when variables were available; since variables available from the electronic medical record were not collected uniformly at specific times as would be the case in a prospective study. Our study was also a non-interventional/non-experimental study which impacts the internal validity and excludes our study from the ability to assess causation. Our study was not a randomized study and confounding variables may have effect on our study results. Lastly, our study may be susceptible to selection bias as a source of error due to the study inclusion/exclusion criteria and the unique demographic distribution of the study patients at our hospital compared to our study's broad target population of patients with hypertensive crises. Another important study limitation is that

magnesium is predominantly an intracellular cation, thus, the serum magnesium obtained from the electronic hospital record may not be a good reflection of patients' magnesium stores.(1,2)

Conclusion

This study found a significant positive association between magnesium and systolic blood pressure, but not diastolic blood pressure among patients with hypertensive crises. This positive association of serum magnesium with systolic blood pressure was maintained after adjusting for covariates. This study findings suggests a potential role of magnesium in blood pressure among patients with hypertensive crises. Large sample experimental studies are needed to evaluate the role of serum magnesium modifying therapies in controlling blood pressure in patients with hypertensive crises. Future studies should also evaluate the role of serum calcium modifying therapies in blood pressure control in patients with hypertensive crises.

List of Abbreviations:

SBP, Systolic blood pressure
DBP, Diastolic blood pressure
ILH, Interim Louisiana State University Hospital
IRB, Institutional Review Board (IRB)
RRC, Research Review Committee
ICD-9, International classification disease ninth revision
CT, Computed Tomography
EKG, Electrocardiogram
SCr, Serum creatinine
CKD, Chronic kidney disease

511 ESRD, End-stage renal disease

512 BMI, Body Mass Index

513 r, Correlation

514 R^2 , Coefficient of determination

515

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531

532 **Authors' contributions**

533 Research idea and study design: IOO, JIO, CJG, DFS; data acquisition: LMH, MMF, MRC, CHH, CJP, EKJ;

534 data analysis/interpretation: IOO, LMH, MMF, MRC, CHH, CJP, EKJ RAB, DFS, JIO, CJG, AB, SCO, IN, SES,

SGG; statistical analysis: RAB, IOO, DFS; supervision or mentorship: IOO, JIO, CJG, DFS, AB, SES, SGG.

Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. The author(s) read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Xavier University of Louisiana Institutional Review Board (IRB) and ILH Research Review Committee (RRC). All methods were carried out in accordance with relevant guidelines and regulations. This study was a retrospective, chart-review, non-interventional study and was granted a waiver of informed consent by the Xavier University of Louisiana Institutional Review Board (IRB) and ILH Research Review Committee (RRC).

Consent for publication

Not applicable.

Competing interests

The authors have no financial disclosures

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675

Figures

Figure 1

Flow chart of inclusion to study cohort.