


# Effect of magnesium sulfate treatment on mediators of endothelial dysfunction and electrolytes in mild and severe preeclampsia: A case-control study

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## Abstract

**Background and Aims:** Magnesium sulfate (MgSO<sub>4</sub>) treatment is widely used for the prevention of eclamptic seizures. However, its effect on mediators of endothelial dysfunction (ED) and electrolytes remains unclear. We evaluated the effects of MgSO<sub>4</sub> treatment on mediators of ED and electrolytes.

**Methods:** We recruited 100 women comprising 50 severe, 50 mild preeclampsia (PE) as cases and 50 normotensive pregnant women as controls from the Sampa Government Hospital, Ghana. We estimated for adrenomedullin (AM), calcitonin gene-related peptide (CGRP), soluble forms of intercellular adhesion molecule-1 (sICAM-1), Na<sup>+</sup>, K<sup>+</sup>, and Mg<sup>2+</sup> before MgSO<sub>4</sub> treatment, 24 h after MgSO<sub>4</sub> treatment, and 48 h after delivery.  $p < 0.05$  were considered significant for statistical analyses.

**Results:** Levels of AM, sICAM-1, and Na<sup>+</sup> decreased significantly at 24 h after MgSO<sub>4</sub> treatment and 48 h after delivery among PE women compared to the AM levels before treatment ( $p < 0.0001$ ). The levels of CGRP and Mg<sup>2+</sup> increased significantly after 24 h of MgSO<sub>4</sub> treatment and 48 h after delivery among PE compared to the AM levels before treatment ( $p < 0.0001$ ). The changes in AM, sICAM-1, CGRP, and Mg<sup>2+</sup> at 24 h after treatment and 48 h after delivery were significantly higher in severe compared to mild PE ( $p < 0.0001$ ). AM levels reduced significantly by 14.7% in mild and 42.7% in severe PE after MgSO<sub>4</sub> treatment ( $p < 0.05$ ). sICAM-1 levels reduced significantly by 20.9% in mild and 25% in severe PE after MgSO<sub>4</sub> treatment. After MgSO<sub>4</sub> treatment, there was significant increase of 42.1% and >100% in CGRP levels in mild and severe PE, respectively ( $p < 0.05$ ). After MgSO<sub>4</sub> treatment, Mg<sup>2+</sup> levels increased significantly by 67.0% and 63.8% in mild and severe PE, respectively ( $p < 0.05$ ).

**Conclusion:** MgSO<sub>4</sub> treatment reduces AM, sICAM-1, and sodium levels but improves magnesium and CGRP in severe than mild PE thus have more beneficial role in severe PE.

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**KEYWORDS**

adrenomedullin, calcitonin gene-related peptide, electrolytes, endothelial dysfunction, magnesium sulfate, Mg, preeclampsia, soluble forms of intercellular adhesion molecule-1

## 1 | INTRODUCTION

Preeclampsia (PE) remains a leading cause of maternal–perinatal morbidity and mortality globally. PE is mostly characterized by the onset of hypertension with substantial proteinuria or multiorgan dysfunction after 20th week of pregnancy.<sup>1</sup> Almost 6% of all pregnancies globally are affected by PE with a high mortality rate.<sup>2,3</sup> Every year more than 70,000 pregnant women die of PE worldwide.<sup>4</sup> Moreover, PE accounts for over 500,000 neonatal deaths worldwide every year.<sup>4</sup> In most developing countries, the prevalence of PE ranges between 4% and 18%,<sup>5</sup> with majority of the maternal mortalities occurring in Africa.<sup>6</sup> In Ghana, the prevalence of PE ranges from 6.55% to 7.03%.<sup>7</sup>

Although the etiology of PE is still unknown, its pathophysiology is known to be related to impaired remodeling of the maternal spiral arteries with subsequent hypoxia, oxidative stress, endothelial dysfunction (ED), and loss of electrolytes. In normal gestation, cytotrophoblast cells from the zygote invade the spiral arteries of the maternal endometrium to transform them from an epithelial phenotype to an endothelial phenotype making them wider in lumen diameter with low resistance. This enhances their ability to transport nutrients and oxygen to the fetus. However, in PE trophoblastic invasion is impaired; the spiral arteries are rendered highly resistant and low capacitance vessels making them less effective in transporting nutrients and oxygen to the fetus, leading to placenta hypoperfusion. This further creates an oxidative stress hypoxic environment. The hypo-perfused placenta triggers an inflammatory response which leads to endothelial damage and dysfunction.<sup>8</sup> ED causes a loss of maintenance of electrolyte balance resulting in high intravascular volume and blood pressure (BP).<sup>9</sup> Several treatment options have been used in management of PE including magnesium sulfate (MgSO<sub>4</sub>) therapy.

MgSO<sub>4</sub> therapy has been used throughout the 20th century for prevention of eclamptic seizures and it continues to be used extensively.<sup>10</sup> Magnesium is a unique calcium antagonist as it can act on most types of calcium channels in vascular smooth muscle<sup>11</sup> and as such would be expected to decrease intracellular calcium. Empirical evidence supports the effectiveness of MgSO<sub>4</sub> in preventing and treating eclamptic seizures.<sup>10,12</sup> Although the effectiveness of MgSO<sub>4</sub> in treating and preventing eclampsia has been established,<sup>10,12</sup> questions still exist as to its side effects and safety. It remains unclear the effect of MgSO<sub>4</sub> therapy on the levels of ED mediators (adrenomedullin [AM], calcitonin gene-related peptide [CGRP], and soluble forms of intercellular adhesion molecule-1 [sICAM-1]), and electrolytes [Na, K, and Mg]). There are concerns regarding the possibility of hypermagnesemia toxicity in eclampsia treatment, among other complications.<sup>13</sup>

Moreover, study shows complications of pregnancy arise as a result of several pathophysiologic conditions including ED and electrolyte imbalance.<sup>14</sup> Mediators of ED and electrolytes are known to play crucial roles in the development of PE; however, the levels and physiological changes that trigger symptoms have not been elucidated. This study therefore aimed at evaluating the effect of MgSO<sub>4</sub> treatment on mediators of ED and electrolytes in mild and severe PE.

## 2 | METHODS

### 2.1 | Study design and setting

This was a hospital-based case-control study conducted on pregnant women visiting the maternity unit of the Sampa Government Hospital in the Jaman North District of the Bono Region, Ghana. The cases were pregnant women with PE and the controls were normotensive pregnant women who came for antenatal services and delivered at the maternity unit of the hospital. Jaman North has a population of about 93068 (2010 Population Census). Sampa Government Hospital is the largest hospital in the Jaman North District with a 100-bed capacity. The hospital serves the Sampa town and its surrounding villages. It receives referrals from health centers in subdistricts and villages in neighboring districts.

### 2.2 | Study participants

In this study, a total of 150 pregnant women, consisting of 100 with PE (50 severe PE and 50 mild PE) and 50 normotensives were recruited. This study included pregnant women within the ages of 18–45 years, with gestational ages >20 weeks. The diagnosis of PE was done by a qualified obstetrician/gynecologist using the National High Blood Pressure Education Program Working Group diagnostic criteria.<sup>15</sup> Briefly, PE was diagnosed based on the new onset of hypertension and proteinuria ( $\geq 1+$  reading on dipstick) occurring after the 20th week of gestation in a previously normotensive and nonproteinuric woman. Pregnant women with BP  $\geq 160/110$  mmHg and proteinuria ( $\geq 3+$  reading on dipstick) were classified as having severe PE while pregnant women with systolic blood pressure of 140–159 mmHg, diastolic blood pressure of 90–109 mmHg, and proteinuria ( $\geq 1+$  reading on dipstick) were classified as having mild PE. The control group consisted of age-matched healthy normotensive pregnant women.

## 2.3 | Eligibility criteria

Pregnant women with a confirmed diagnosis of PE and prepared for caesarian section and healthy normotensive pregnant women were included. We excluded pregnant women who did not consent to participate, those with chronic medical conditions such as renal diseases, diabetes, and hypertension or cardiovascular diseases, those with obstetric complications and pregnant women taking food supplements that contain magnesium, sodium, or potassium were excluded from the study.

## 2.4 | Questionnaire administration

A well-structured, closed-ended questionnaire was administered to obtain primary data from study participants at the maternity unit of the Sampa Government Hospital. Study variables for participants' medical history were obtained from patients' folders and hospital database. The first section of the questionnaire comprised of the sociodemographic, clinical, and obstetric parameters. Other sections of the questionnaire were designed according to the research objectives.

## 2.5 | Anthropometric measurements

Weight was measured while subjects wore light clothing using an adult weighing scale (Zhongshan Camry Electronic Co. Ltd.) and their height measured using a height meter (Seca mod. 220). Body mass index (BMI) of each subject was calculated by dividing weight (Kg) by height squared ( $m^2$ ). BP was measured using a mercury sphygmomanometer (Accoson Mercurial Sphygmomanometer) and a stethoscope (3M™ Littmann® Stethoscopes). The left upper arm was used in the measurements after subjects had rested for a period of about 5 min following the recommendation of American Heart Association. BP measurements were done three times at 10–15 min interval and the average value calculated and recorded in two decimal places.

## 2.6 | Sample collection and biochemical analyses

After questionnaire administration, about 3 mL venous blood and early morning urine samples in leak-proof wide-mouth transparent clean dry plastic container were collected from all the study participants. All of the PE women were treated with the standard dose of  $MgSO_4$  therapy (loading of 4 g and maintenance dose of 5 g 4 hourly for 6 doses over 24 h). After 24 h of  $MgSO_4$  treatment, about 3 mL venous blood was again collected from each of the PE women. Finally, about 3 mL venous blood was collected from each of the PE women and the controls 48 h after delivery. The blood samples were collected early morning after 8–12 h overnight fast. The samples were centrifuged (Hettich Universal 320) at 1000 rpm for 15 min within 30 min after collection. The plasma was also aliquoted for the biochemical analyses. Samples that were not analyzed immediately were stored frozen at  $-20^\circ C$  for

about 24–72 h in a Freezer (West point Tropical Model WIR-204. GX). Biochemical analyses of all samples were done without prior knowledge of the participants clinical status by assigning unique codes to each participant. Electrolytes (sodium, potassium, and magnesium) were measured using Selectra Junior automated chemistry analyzer (Vital Scientific, Junior series 89061) with reagents from Elitech clinical systems, France. ED Mediators (AM, CGRP, and sICAM-1) were measured using Enzyme-Linked Immunosorbent assay kits obtained from Elabscience biotechnology, China following the manufacturer's protocol. The optical density was read at 450 nm using Mindray MR-96A microplate reader.

## 2.7 | Statistical analysis

Statistical analysis was performed using SPSS version 26.0 and R Language for statistical computing version 4.0.2.<sup>16</sup> Data were screened for normality using the Kolmogov-Smirnov test. Continuous data were presented as means with standard deviations. The Kruskal-Wallis test was followed by Dunn's posthoc multiple comparison test was used to compute the difference in parameters between the normotensive pregnant women, those with mild and severe PE. The mixed-model ANOVA was used to compare the difference in electrolytes and makers of ED between the three time points (within-subject effects) and also between mild and severe PE at each time point (between-subject effects). The mean difference and percentage effect of  $MgSO_4$  treatment on mediators of ED and electrolytes were calculated.  $p$  Values  $<0.05$  were considered statistically significant for all statistical analyses.

## 3 | RESULTS

### 3.1 | Sociodemographic, clinical, and obstetric characteristics of study participants

A total of 150 pregnant women, consisting of 100 with PE (50 severe PE and 50 mild PE) and 50 normotensives were included in the analysis. There was no significant difference in age between women with mild PE ( $31.0 \pm 8.7$ ), severe PE ( $31.0 \pm 8.9$ ), and the normotensives ( $28.8 \pm 6.1$ ) ( $p = 0.2380$ ). The obstetric parameters show that mean gestational age at sampling and mean gestational age at delivery and birth weight (kg) were significantly ( $p < 0.05$ ) higher in normotensive pregnant women ( $32.7 \pm 2.4$ ,  $39.0 \pm 0.9$ , and  $3.26 \pm 0.15$ ) compared to mild PE ( $30.7 \pm 3.6$ ,  $37.0 \pm 2.6$ , and  $2.38 \pm 0.17$ ) and severe PE ( $30.3 \pm 3.3$ ,  $35.6 \pm 3.8$ , and  $2.23 \pm 0.15$ ), respectively. The mean BMI ( $Kg/m^2$ ) was significantly ( $p = 0.010$ ) higher in participants with severe PE ( $27.9 \pm 1.1$ ) and mild PE ( $27.4 \pm 1.2$ ) than participants without PE ( $26.0 \pm 1.2$ ). The hemodynamic indices, systolic BP (mmHg) and diastolic BP (mmHg) were significantly ( $p < 0.0001$ ) higher in participants with mild PE ( $152.0 \pm 4.4$  and  $99.1 \pm 3.5$ ) and severe PE ( $164.7 \pm 3.9$  and  $113.5 \pm 3.5$ ) as compared to the normotensive pregnant women

(106.0 ± 8.6 and 66.0 ± 8.8). Table 1 displays the socio-demographic, clinical, obstetric characteristics among the three study groups.

### 3.2 | Levels of mediators of ED and electrolytes between normotensives, mild PE, and severe PE before MgSO<sub>4</sub> treatment

The serum levels of severe AM (107.4 ± 8.9 pg/mL vs. 75.2 ± 5.0 pg/mL vs. 43.1 ± 3.8 pg/mL,  $p < 0.0001$ ) sICAM (524.5 ± 21.7 pg/mL vs. 470.8 ± 52.4 pg/mL vs. 338.6 ± 24.5 pg/mL), and Na<sup>+</sup> (150.4 ± 2.1 mmol/L vs. 141.4 ± 18.2 mmol/L vs. 138.3 ± 2.3 mmol/L,  $p < 0.0001$ ) were significantly higher in severe PE followed by those with mild PE and normotensives. However, the serum levels of CGRP (58.1 ± 5.6 pg/mL vs. 31.5 ± 4.5 pg/mL vs. 21.5 ± 2.03 pg/mL,  $p < 0.0001$ ) were significantly lower in severe PE women followed by those with mild PE and normotensives. The serum K<sup>+</sup> was significantly lower in both mild and severe PE compared to the normotensive pregnant women ( $p < 0.0001$ ). Serum K<sup>+</sup> however, did not differ significantly between mild and severe PE ( $p > 0.05$ ). Moreover, serum magnesium was significantly lower in mild PE compared to both the severe PE and the normotensives. However, Mg<sup>2+</sup> did not differ significantly between the severe PE and the normotensives (Figure 1).

### 3.3 | Comparing the levels of mediators of ED and electrolytes before MgSO<sub>4</sub> supplementation, 24 h after treatment, and 48 h after delivery

Table 2 shows that the mean AM levels decreased significantly 24 h after MgSO<sub>4</sub> treatment (62.77 ± 4.81 pg/mL) and 48 h after delivery

(60.29 ± 5.14 pg/mL) among PE women compared to the AM levels before treatment (91.27 ± 17.72 pg/mL) ( $p < 0.0001$ ). It was observed that there was a significant difference in AM reductions at 24 h after treatment and 48 h after delivery between mild and severe PE ( $p < 0.05$ ). Similarly, the serum levels of sICAM decreased significantly 24 h after MgSO<sub>4</sub> treatment (382.22 ± 24.02 ng/mL) and 48 h after delivery (379.27 ± 24.37 ng/mL) among PE women compared to the sICAM levels before treatment (497.68 ± 33.62 ng/mL) ( $p < 0.0001$ ). It was again observed that there was a significant difference in sICAM reductions at 24 h after treatment and 48 h after delivery between mild and severe PE ( $p < 0.0001$ ). Contrary to AM and sICAM, serum levels CGRP increased significantly 24 h after MgSO<sub>4</sub> treatment (47.15 ± 6.63 ng/mL) and 48 h after delivery (49.51 ± 5.36 ng/mL) compared to CGRP levels before treatment (26.54 ± 6.11 ng/mL) ( $p < 0.0001$ ). The increase in CGRP was significantly higher in severe PE compared to mild PE at 24 h after treatment and 48 h after delivery ( $p < 0.0001$ ).

With respect to electrolytes, Na<sup>+</sup> levels decreased significantly at 48 h after delivery (145.16 ± 4.43 mmol/L) compared to the Na<sup>+</sup> levels before treatment (145.70 ± 5.11 mmol/L) ( $p < 0.0001$ ). However, Na<sup>+</sup> levels at 24 h after treatment did not differ significantly compared to Na<sup>+</sup> levels before treatment ( $p > 0.05$ ). Compared to those that had severe PE where Na<sup>+</sup> levels decreased significantly at 48 h after delivery (148.92 ± 2.24 mmol/L) compared to Na<sup>+</sup> levels before treatment ( $p < 0.0001$ ), there was no significant difference in Na<sup>+</sup> between the three time points among those with mild PE ( $p = 0.1983$ ). Serum Mg<sup>2+</sup> levels increased significantly at 24 h after treatment (2.20 ± 0.51 mmol/L) and 48 h after delivery (2.04 ± 0.28 mmol/L) compared to the Mg<sup>2+</sup> levels before treatment (1.33 ± 0.55 mmol/L) ( $p < 0.0001$ ). The increase in Mg<sup>2+</sup> was significantly

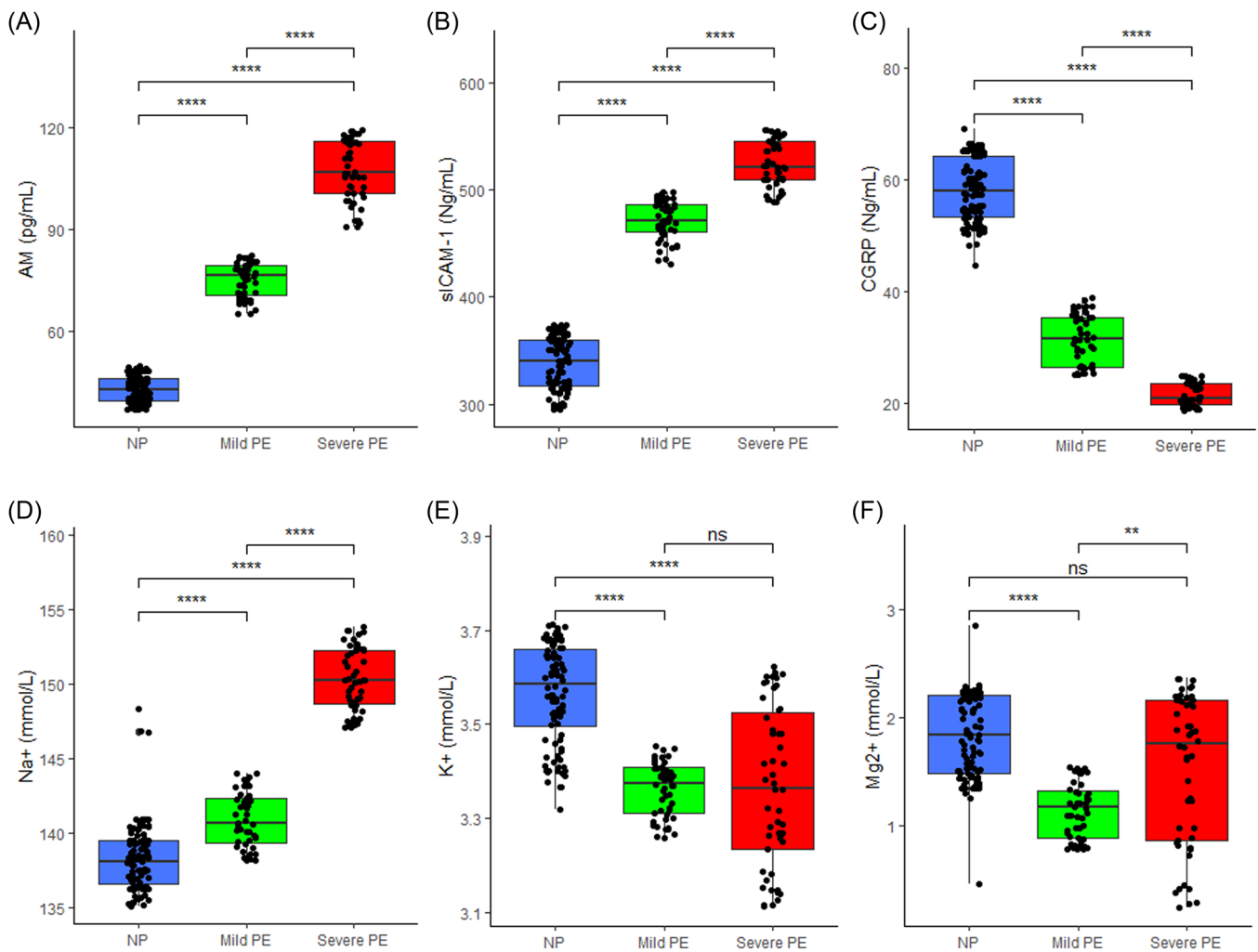
Characteristics	NP N = 50	Mild PE N = 50	Severe PE N = 50	<i>p</i> Values
Maternal age (years)	30.8 ± 7.1	31.0 ± 8.7	31.0 ± 8.9	0.2380
BMI (kg/m <sup>2</sup> )	26.0 ± 1.2	27.4 ± 1.2‡	27.9 ± 1.1¥	0.0110
Gestational age sampling (weeks)	32.7 ± 2.4	30.7 ± 3.6‡	30.3 ± 3.3¥	0.0100
Gestational age delivery (weeks)	39.0 ± 0.9	37.0 ± 2.6‡	35.6 ± 3.8¥	0.0001
Birth weight (kg)	3.26 ± 0.15	2.38 ± 0.17‡	2.23 ± 0.15¥	<0.0001
Systolic BP (mmHg)	106.0 ± 8.6	152.0 ± 4.4‡	164.7 ± 3.9¥	<0.0001
Diastolic BP (mmHg)	66.0 ± 8.8	99.1 ± 3.5‡	113.5 ± 3.5¥	<0.0001
Number of live births	1.6 ± 1.4	1.4 ± 1.3‡	0.9 ± 1.2¥	<0.0001
Number of pregnancies	2.7 ± 1.3	2.1 ± 1.2‡	2.5 ± 1.2	0.03010
Pregnancy interval (years)	1.9 ± 0.01	2.5 ± 0.03‡	4.1 ± 0.08¥	<0.0001
Meals per day	3.0 ± 0.0	2.6 ± 0.5‡	2.9 ± 0.4	0.0418

Note: Values are presented as Mean ± SD.

Abbreviations: BMI, body mass index; BP, blood pressure; NP, normotensive pregnancy; PE, preeclampsia.

‡ or ¥ denoted statistically significant difference compared to normal pregnancy.

**TABLE 1** Sociodemographic, clinical, and obstetrics characteristics of study participants.



**FIGURE 1** Comparison of mediators of endothelial dysfunction and electrolytes between study groups before magnesium sulfate treatment.

higher in severe PE compared to mild PE at 24 h after treatment and 48 h after delivery ( $p < 0.0001$ ).

Serum  $K^+$  levels did not differ significantly at 24 h after treatment and 48 h after delivery among the entire PE women (0.1010), those with mild PE ( $p = 0.2470$ ) and women with severe PE ( $p = 0.1460$ ).

### 3.4 | Effects of $MgSO_4$ treatment on mediators of ED and electrolytes in women with mild and severe PE

Table 3 displays the mean difference and percentage effect of  $MgSO_4$  treatment on mediators of ED and electrolytes among women with mild and severe PE. Serum AM levels reduced significantly by 14.7% in mild PE and 42.7% in severe PE after  $MgSO_4$  treatment ( $p < 0.05$ ). After delivery, AM levels reduced significantly by 4.4% in mild PE ( $p < 0.05$ ). However, in severe PE, there was a 3.4% reduction which was not significant ( $p > 0.05$ ). sICAM-1 levels reduced significantly by 20.9% in mild PE and 25% in severe PE after  $MgSO_4$  treatment. After delivery, sICAM-1 levels reduced by only 0.8% in both mild and

severe PE participants. These reductions were not significant ( $p > 0.05$ ). After  $MgSO_4$  treatment, there were significant increase of 42.1% and >100% in CGRP levels in mild and severe PE, respectively ( $p < 0.05$ ). After delivery, CGRP increased by 3.4% in mild PE. This was not significant ( $p > 0.05$ ). It increased by 6.5% in severe PE ( $p < 0.05$ ). This was, however, significant ( $p < 0.05$ ).

$Na^+$  levels increased by 2.1% after  $MgSO_4$  treatment in mild PE and reduced by 0.02% in severe PE. These were not significant ( $p > 0.05$ ).  $Na^+$  levels reduced by 0.02% after delivery in mild PE ( $p > 0.05$ ). This was not significant. It reduced by 0.93% in severe PE. This was, however, significant ( $p < 0.05$ ).  $K^+$  levels increased by 0.30% in mild PE and increased by 0.09% in severe PE after  $MgSO_4$  treatment. These differences were not significant ( $p > 0.05$ ). After delivery,  $K^+$  levels increased by 0.18% in mild PE and also increased by 0.09% in severe PE. These were not significant ( $p > 0.05$ ). After  $MgSO_4$  treatment,  $Mg^{2+}$  levels increased significantly by 67.0% and 63.80% in mild and severe PE, respectively ( $p < 0.05$ ). After delivery,  $Mg^{2+}$  levels increased by 0.62% in mild PE. This was not significant ( $p > 0.05$ ). In severe PE, however, there was a significant increase of  $Mg^{2+}$  12.0% ( $p < 0.05$ ).

Variable	Before treatment	24 h after treatment	48 h post delivery	p Value
AM (pg/mL)	91.27 ± 17.72	62.77 ± 4.81	60.29 ± 5.14	< 0.0001 <sup>a,b,c</sup>
Mild	75.16 ± 5.04	64.03 ± 4.72	61.19 ± 5.53	< 0.0001 <sup>a,b,c</sup>
Severe	107.39 ± 8.92	61.51 ± 4.61	59.39 ± 4.61	< 0.0001 <sup>a,b,c</sup>
p Value	< 0.0001	<b>0.0080</b>	0.0790	
sICAM (ng/mL)	497.68 ± 33.62	382.22 ± 24.02	379.27 ± 24.37	< 0.0001 <sup>a,b,c</sup>
Mild	470.83 ± 18.48	372.25 ± 14.10	369.41 ± 14.44	< 0.0001 <sup>a,b,c</sup>
Severe	524.52 ± 21.70	392.19 ± 27.65	389.13 ± 28.16	< 0.0001 <sup>a,b,c</sup>
p Value	< 0.0001	< 0.0001	< 0.0001	
CGRP (ng/mL)	26.54 ± 6.11	47.15 ± 6.63	49.51 ± 5.36	< 0.0001 <sup>a,b,c</sup>
Mild	31.54 ± 4.51	44.83 ± 5.03	46.36 ± 5.03	< 0.0001 <sup>a,b</sup>
Severe	21.54 ± 2.04	49.46 ± 7.25	52.66 ± 3.54	< 0.0001 <sup>a,b,c</sup>
p Value	< 0.0001	< 0.0001	< 0.0001	
Na <sup>+</sup> (mmol/L)	145.70 ± 5.11	145.87 ± 5.01	145.16 ± 4.43	< 0.0001 <sup>b,c</sup>
Mild	140.95 ± 1.84	141.33 ± 2.24	141.32 ± 2.29	0.1983
Severe	150.36 ± 2.06	150.33 ± 2.14	148.92 ± 2.24	< 0.0001 <sup>b,c</sup>
p Value	< 0.0001	< 0.0001	< 0.0001	
K <sup>+</sup> (mmol/L)	3.36 ± 0.12	3.35 ± 0.13	3.35 ± 0.12	0.1010
Mild	3.36 ± 0.56	3.34 ± 0.07	3.35 ± 0.07	0.2470
Severe	3.37 ± 0.16	3.36 ± 0.16	3.34 ± 0.16	0.1460
p Value	0.8130	0.5680	0.8040	
Mg <sup>2+</sup> (mmol/L)	1.33 ± 0.55	2.20 ± 0.51	2.04 ± 0.28	< 0.0001 <sup>a,b,c</sup>
Mild	1.14 ± 0.25	1.91 ± 0.38	1.89 ± 0.38	< 0.0001 <sup>a,b</sup>
Severe	1.52 ± 0.69	2.50 ± 0.44	2.20 ± 0.28	< 0.0001 <sup>a,b,c</sup>
p Value	< 0.0001	< 0.0001	< 0.0001	

Note: p Values for within-subject effects (treatment time) and between-subject effects (mild vs. severe) were computed by the mixed-model ANOVA. Bold values show statistical significance.

Abbreviations: AM, adrenomedullin; CGRP, calcitonin gene-related peptide; K, potassium; Mg, magnesium; Na, sodium; sICAM-1, soluble forms of intercellular adhesion molecule 1.

<sup>a</sup>Significant difference between before treatment and 24 h after treatment.

<sup>b</sup>Significant difference between before treatment and 48 h after delivery.

<sup>c</sup>Significant difference between 24 h after treatment and 48 h after delivery.

**TABLE 2** Levels of mediators of endothelial dysfunction and electrolytes before treatment, 24 h after MgSO<sub>4</sub> treatment, and 48 h after delivery among women with mild and severe preeclampsia.

## 4 | DISCUSSION

PE is a life-threatening complication of pregnancy and usually leads to poor pregnancy outcomes such as maternal and fetal morbidity and mortality. The pathophysiology is related to impaired remodeling of the maternal spiral arteries with subsequent hypoxia, oxidative stress, ED, and loss of electrolytes. MgSO<sub>4</sub> is widely used for the prevention of eclamptic seizures.<sup>10</sup> It remains unclear the effect of MgSO<sub>4</sub> therapy on the levels of ED mediators (AM, CGRP, and sICAM-1) and electrolytes (Na, K, and Mg). In this study, we measured the levels mediators of ED (AM, CGRP, sICAM -1) and electrolytes (Na, K, and Mg) in pregnant women with mild and severe PE and normotensive pregnant women at baseline. The levels of ED

mediators and electrolytes in preeclamptic women were measured 24 h after MgSO<sub>4</sub> treatment and 48 h after delivery. We found that MgSO<sub>4</sub> treatment was associated with reduction in AM, sICAM-1, and sodium levels but increases magnesium and CGRP levels in women with PE. However, MgSO<sub>4</sub> treatment modifies mediators of ED and electrolytes more in severe PE than in mild PE.

In this study, AM levels were significantly higher in severe PE followed by those with mild PE and normotensives (Figure 1). Some studies have reported lower AM levels in women with PE<sup>17</sup> while others have stated that there is no significant difference in AM levels between preeclamptic and normotensive pregnant women.<sup>18</sup> Nonetheless, Di Iorio et al.,<sup>19</sup> in a case-control study carried out in Italy corroborates this present finding that there is increased production

**TABLE 3** Mean difference in the percentage effect of MgSO<sub>4</sub> treatment on mediators of endothelial dysfunction and electrolytes among women with mild and severe preeclampsia.

Characteristics	Mild PE			Severe PE		
	Mean diff. (95% CI)	p Value	% mean effect	Mean diff. (95% CI)	p Value	% mean effect
<b>AM</b>						
BT vs. 24 h AT	11.12(8.70–13.54)	< 0.0001	14.70	45.88(42.86–48.90)	< 0.0001	42.70
BT vs. 48 h AD	13.96(11.54–16.38)	< 0.0001	18.60	48(44.98–51.02)	< 0.0001	44.70
24 h AT vs. 48 h AD	2.84(0.41–5.25)	<b>0.0171</b>	4.43	2.121(–0.90 to 5.143)	0.2235	3.40
<b>sICAM- 1</b>						
BT vs. 24 h AT	98.58(91.10–106.1)	< 0.0001	20.90	132.3(120.0–144.6)	< 0.0001	25.20
BT vs. 48 h AD	101.4(93.93–108.9)	< 0.0001	21.50	135.4(123.1–147.7)	< 0.0001	25.80
24 h AT vs. 48 h AD	2.83(–4.649 to 10.32)	0.6430	0.80	3.06(–9.25 to 15.38)	0.8262	0.80
<b>CGRP</b>						
BT vs. 24 h AT	–13.29(–15.60 to –10.98)	< 0.0001	42.10	–27.92(–30.20 to –25.64)	< 0.0001	>100.0
BT vs. 48 h AD	–14.81(–17.12 to –12.51)	< 0.0001	46.90	–31.12(–33.40 to –28.85)	< 0.0001	>100.0
24 h AT vs. 48 h AD	–1.52(–3.82 to 0.78)	0.2640	3.40	–3.20(–5.48 to –0.92)	<b>0.0031</b>	6.47
<b>ELECTROLYTES</b>						
<b>Na<sup>+</sup></b>						
BT vs. 24 h AT	–2.94(–7.99 to 2.09)	0.3520	2.10	0.03(–0.98 to 1.05)	0.9970	0.02
BT vs. 48 h AD	–2.91(–7.96 to 2.13)	0.3595	2.10	1.44(0.42–2.46)	<b>0.0031</b>	0.95
24 h AT vs. 48 h AD	0.03(5.01–5.07)	0.9999	0.02	1.40(0.38–2.42)	<b>0.0039</b>	0.93
<b>K<sup>+</sup></b>						
BT vs. 24 h AT	0.01(–0.03 to 0.05)	0.6498	0.30	0.003(–0.08 to 0.082)	0.9944	0.09
BT vs. 48 h AD	0.006(–0.03 to 0.05)	0.8912	0.18	0.018(–0.06 to 0.09)	0.8412	0.53
24 h AT vs. 48 h AD	–0.006(–0.04 to 0.03)	0.9037	0.18	0.015(–0.06 to 0.09)	0.8904	0.45
<b>Mg<sup>2+</sup></b>						
BT vs. 24 h AT	–0.769(–0.93 to –0.60)	< 0.0001	67.00	–0.974(–1.21 to –0.74)	< 0.0001	63.80
BT vs. 48 h AD	–0.757(–0.92 to –0.59)	< 0.0001	66.30	–0.673(–0.91 to –0.43)	< 0.0001	44.10
24 h AT vs. 48 h AD	0.012(–0.15 to 0.18)	0.9839	0.62	0.301(0.06–0.54)	<b>0.0090</b>	12.00

Note: Bold values show statistical significance.

Abbreviations: AD, after delivery; AT, after treatment; BT, before treatment; CI, confidence interval; PE, preeclampsia; AM, adrenomedullin; CGRP, calcitonin gene-related peptide; sICAM-1, soluble forms of intercellular adhesion molecule 1; Na, sodium; K, potassium; Mg, magnesium, Mean Diff, mean difference.

of AM in PE. It has been speculated that in PE the fetus produces higher amount of AM as a compensatory mechanism to maintain the integrity of placental vasculature because it acts as a vasodilator.<sup>20–22</sup> In mild PE, AM levels reduced significantly after treatment. There was a further significant reduction 48 h postpartum ( $p < 0.05$ ). In severe PE the trend of reduction was almost the same except that there was no significant reduction 48 h postpartum ( $p > 0.05$ ) (Table 3). MgSO<sub>4</sub> is a potent vasodilator and known to act on the brain.<sup>10</sup> The reduction in the levels of AM after treatment and after delivery was probably due to the restoration of magnesium levels after treatment and also due to the absence of the fetus which has been speculated to produce large quantities of AM in PE to maintain the structure of the blood vessels in the placenta.<sup>19</sup>

In this study, sICAM-1 levels varied significantly among the three groups in the order of severe PE > mild PE > normotensives ( $p < 0.0001$ ) (Figure 1). sICAM-1 is an angiogenic factor needed for the formation of new vessels from preexisting ones.<sup>23,24</sup> Higher levels in PE may indicate a compensatory mechanism to form new vasculature after endothelial damage because in normal blood vessels, sICAM-1 has little or no expression.<sup>25</sup> In both mild and severe PE, levels reduced significantly 24 h after treatment ( $p < 0.05$ ) with an insignificant reduction postpartum ( $p > 0.05$ ) (Table 3). The reduction in the levels of sICAM after MgSO<sub>4</sub> treatment among women with PE could be partly be due to the fact that MgSO<sub>4</sub> can partly prevent platelet cross-linking and aggregation, inhibit the expressions of adhesion factors, inflammatory factors, and

chemokines, thereby reducing the level of sICAM-1.<sup>12,26,27</sup> This has been proposed to improve the quality of life of patients with cardiovascular complication,<sup>28,29</sup> confirming that MgSO<sub>4</sub> treatment have beneficial effects in maintaining vascular integrity in PE.

Another finding in this study is that CGRP levels were significantly different among the three groups. They were in the order of No PE > mild PE > severe PE ( $p < 0.0001$ ) (Figure 1). In both mild and severe PE, there was a significant increase after MgSO<sub>4</sub> treatment and a further increase 48 h postpartum ( $p < 0.05$ ) (Tables 2 and 3). This is consistent with the findings of another study which also reported increased levels after treatment but they did not measure CGRP after delivery.<sup>30</sup> It is believed that nitric oxide an endothelium-derived vasodilator acts by playing a major role in the synthesis of CGRP.<sup>31</sup> Low levels of CGRP in PE suggest that there could be a corresponding low level of nitric oxide, resulting in high BP observed in PE. Moreover, we have earlier reported low nitric oxide levels in PE.<sup>32</sup>

Another important finding in this study is that the Mg<sup>2+</sup> levels were significantly lower in PE. They varied in the order of No PE > mild PE > severe PE ( $p < 0.0001$ ) before treatment (Figure 1). In mild PE, levels increased significantly after treatment ( $p < 0.05$ ). In severe PE, Mg levels increased significantly after treatment but reduced significantly after delivery ( $p < 0.05$ ) (Table 3). In a similar study, Ephraim et al.,<sup>33</sup> reported lower levels of Mg<sup>2+</sup> in pregnant women with PE as compared to healthy pregnant women in Cape Coast, Ghana. Also, Das et al.,<sup>34</sup> found similar decreased levels of Mg<sup>2+</sup> among Indian women with PE compared to normotensives. Hypomagnesemia in PE is mainly caused by hemodilution, altered renal clearance and consumption by the growing fetus.<sup>35</sup> Although Mg<sup>2+</sup> was reduced after delivery, it was still higher than the level before treatment. After treatment probably, the magnesium deficiency was corrected due to the high concentration of Mg in MgSO<sub>4</sub>, showing that MgSO<sub>4</sub> treatment can correct Mg<sup>2+</sup> levels in PE.

Interestingly in this study, there was a significant hypernatremia in severe PE (Figure 1). Some studies have reported raised serum sodium levels in women with PE.<sup>36,37</sup> How sodium raises BP has been explained by two main mechanisms. The first one is that excess sodium intake causes expansion of intravascular and extravascular fluid leading to increased venous return and cardiac output and therefore increased blood flow to tissues. When this persists an auto-regulatory mechanism causing increased peripheral resistance is triggered.<sup>38</sup> The other mechanism is that “peripheral arterial vasodilatation hypothesis” of water and sodium retention in pregnancy explains that increased endothelial damage, sodium retention, and increased sensitivity to angiotensin leads to hypertension, edema, and proteinuria.<sup>39</sup> Hypernatremia observed in severe PE decreased 48 h after treatment. This most likely due to reduced aldosterone level after delivery causing decreased renal reabsorption of sodium. PIH is associated with hyperaldosteronism.<sup>14</sup>

Moreover, there was significantly lower levels of potassium in mild PE and severe PE compared with normotensive study participants before treatment ( $p < 0.0001$ ) (Figure 1). In a similar study, Yussif et al.,<sup>40</sup> reported lower levels of K<sup>+</sup> among PE women

compared to healthy controls in Iraq.<sup>40</sup> It has been shown in a clinical study that diet low in potassium (10–16 mmol/day) coupled with patient usual sodium intake of 120–200 mmol/day cause sodium retention and elevation of BP. In this present study, K<sup>+</sup> levels did not change after treatment with MgSO<sub>4</sub> and after delivery (Table 3), suggesting that MgSO<sub>4</sub> treatment has little or no direct effect on potassium levels.

Furthermore, in this study, the preeclamptic women had significantly higher BMI as compared to the normotensive controls. Several studies have reported the higher risk associated with excessive weight gain during pregnancy, prepregnancy obesity and the development of PE.<sup>41–44</sup> Excess fat may accelerate oxidative stress, promote damage to endothelial cells which may result in PE. Although, all the study participants were aged 20 weeks and above, gestational age at sampling differed between the three groups and this may be attributed to the fact most women especially in our part of the continent do not report for antenatal care services early and do not attend at least four visits,<sup>45</sup> and very often will only visit the hospital when they experience some unfavorable symptoms. Moreover, the preeclamptic women especially the those in the severe PE group delivered significantly earlier. PE is a significant cause of preterm deliveries, when the life of the mother or fetus is threatened, the babies are delivered to preserve the life of both or one of them. This may have accounted for the disparities in the gestational age of the women at delivery.

One limitation of our study its single-center nature, however, our findings add the scientific body of knowledge and would be a strong basis for multicenter studies using a larger sample size to explore the cause-effect relationship between MgSO<sub>4</sub> therapy, maternal, and fetal outcomes.

## 5 | CONCLUSION

MgSO<sub>4</sub> treatment reduces AM, sICAM-1, and sodium levels but improves magnesium and CGRP levels among women with PE. MgSO<sub>4</sub> treatment modifies mediators of ED and electrolytes in severe PE than mild PE and may have more beneficial role in severe PE. MgSO<sub>4</sub> treatment has little or no effect on potassium levels among women with PE. Investigating the Mg levels in PE women before MgSO<sub>4</sub> therapy is imperative.

### AUTHOR CONTRIBUTIONS

**Linda Ahenkorah Fondjo:** Conceptualization; formal analysis; investigation; methodology; resources; supervision; validation; writing—original draft; writing—review and editing. **Davis Sarpong:** Conceptualization; formal analysis; investigation; methodology; resources; writing—review and editing. **William K. B. A. Owiredu:** Investigation; methodology; supervision; writing—review and editing. **Stephen Opoku:** Formal analysis; investigation; methodology; writing—original draft; Writing—review and editing. **Kwame Adu-Bonsaffoh:** Resources; validation; writing—review and editing. **Emmanuel Teviu:** Investigation; methodology; writing—review and editing.



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## CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

All data used and/or analyzed during this current study are included within this article.

## ETHICS STATEMENT

The study was approved by Committee on Human Research Publication and Ethics, KNUST (reference number CHRPE/AP/001/16) as well as the management board of Sampa Government Hospital. Written informed consent was also obtained from the participants after the aim of the study had been explained to them. The study was conducted following the guidelines of the Helsinki Declaration.

## TRANSPARENCY STATEMENT

The lead author Linda Ahenkorah Fondjo affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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