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Magnesium intoxication in women with preeclampsia with severe features treated with magnesium sulfate

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ABSTRACT

Objective: To evaluate the maternal-neonatal outcome in magnesium (Mg)-intoxicated women with preeclampsia with severe features (PESF) treated with magnesium sulfate ($MgSO_4$).

Methods: A total of 19 Mg intoxicated PESF women (cases) were compared with 166 PESF women without signs of intoxication (controls).

Results: Mg serum levels of cases was higher compared to control group (12.36 ± 3.54 mg/dl versus 2.69 ± 0.83 mg/dl). 3 women died and 3 had major maternal morbidity in cases group compared with zero in the control group (P = 0.009). Mg intoxication was also significantly associated with perinatal deaths and low Apgar scores at 1 and 5 minutes.

Conclusion: Mg intoxication is associated with a increased risk of maternal and perinatal mortality and morbidity.

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Magnesium intoxication; hypermagnesemia; magnesium sulfate; preeclampsia with severe features

Introduction

Preeclampsia (PE) is a life-threatening syndrome in pregnancy characterized by the new onset of hypertension after 20 weeks of gestational age and accompanied by proteinuria or other signs of organ involvement (1). PE is one of the main problems in pregnancy, causing maternal mortality and morbidity in low and middle-income countries (Duley et al., 1992). About 50,000–63,000 women die each year of PE/eclampsia. Indonesia, the fourth most populous country in the world with a population of 267 million, is a middle-income country with PE incidence of 5-7%. The maternal (2.2%) and perinatal mortality rate (12%) of PE are still high (2). A large segment of the Indonesian population still faces poverty, has lack of access to health care, and often receives inadequate treatment in primary health-care centers. The wrong financial incentives under the current Indonesian universal health coverage system are partially to blame for too late referrals (3).

Magnesium sulfate ($MgSO_4$) is recommended unanimously by all major guidelines as a first-choice agent to prevent eclamptic seizures and is used worldwide (4). The Magpie trial, the large international multicenter randomized controlled trial (RCT), reported that the use of $MgSO_4$ reduces the risk of eclampsia about 58% in women with PE compared with PE women receiving placebo (5). $MgSO_4$ as an anticonvulsant agent works through multiple mechanisms: inhibits seizure excitability in the cerebral cortex, inhibits the N-methyl-D-aspartate receptor in the hippocampus, and calcium metabolism in the neuromuscular junction. $MgSO_4$ also works as a potent vasodilator, especially in the cerebral vasculature, potentially reducing brain ischemia-hypoxia in preeclamptic women (6). Although $MgSO_4$ has been proven to be effective in preventing eclampsia, its use still contains a small but definitive risk of magnesium intoxication or hypermagnesemia (7–9).

Mg intoxication is clinically evident when serum Mg levels exceed 12 mg/dL (hypermagnesemia), which almost exclusively occurs in PE women with marked renal involvement or in women receiving higher $MgSO_4$ infusion rates (10). The main symptoms of Mg intoxication are the result of its general CNS depressant effects, peripheral depression affecting muscle contractility, and central neuromuscular transmission blockade. Clinical manifestation of Mg

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intoxication seldom occurs until magnesium levels reach a total dosage beyond 12 mg/dL in maternal blood. Clinical manifestations of Mg intoxication include general weakness, double vision, low blood pressure, loss of conscious and respiratory distress. The lethal manifestation, cardiac arrest, may happen if Mg concentration rises above 30 mg/dL (8,11,12).

Hypertension in pregnancy, especially PESF is in the top three diagnosis of the sickest high-risk obstetrics cases in Dr. Soetomo General Academic Hospital, the main tertiary referral hospital in Surabaya, Indonesia (13,14). Intravenous $MgSO_4$ is administrated routinely in PESF without measurements of Mg levels unless there are clinical indications (suspicion Mg intoxication) due to lack of adequate hospital funding under the Indonesian national insurance system.

In this study, we evaluated the incidence of Mg intoxication in women with PESF receiving $MgSO_4$ and investigated its association with adverse maternal and perinatal outcomes.

Material and methods

This study was conducted in Dr. Soetomo Hospital, the major tertiary referral center in East-Java, Indonesia, from January 2014 – December 2018; all women with PESF receiving Mg with clinical signs and symptoms of Mg intoxication and confirmed hypermagnesemia (cases n = 19) were compared to 166 PESF patients (8 controls per case) also treated with Mg but without signs of Mg intoxication (control group). The historical control group was recruited randomly with 33–34 patients each year to achieve a balanced distribution (2014–2018). Since Mg levels are not routinely checked in our hospital in PESF patients receiving $MgSO_4$, Mg levels in this study were only measured in women with signs or symptoms of Mg intoxication. In the control group, 24 random women out the 166 also had a Mg level measured. Mg level was measured using the Calmagite Colorimetric method (Hardness reagen set).

PE was defined using ISSHP classification: hypertension developing after 20 weeks gestation and the existence of one or more of the following: proteinuria, other maternal organ dysfunction (renal insufficiency, liver involvement, neurological complications, hematological complications), and uteroplacental dysfunction. HELLP syndrome was defined as a combination of hemolysis (lactic dehydrogenase >1000 U/L, schistocytes in blood smear), elevated liver enzymes, and thrombocytopenia (platelet count < 100.000 u/L) in PE women. PESF was defined as PE with any of the following findings: systolic blood pressure > 160 mmHg or diastolic blood pressure > 110 mmHg on two occasions at least 4 hours apart, thrombocytopenia, elevated liver enzymes (AST > 45 μ/L, ALT > 35 μ/L), progressive renal insufficiency (BUN > 20 mg/dL, serum kreatinin > 1.1 mg/dL), pulmonary edema, and cerebral or visual disturbances. Pulmonary edema was defined based on symptoms of shortness of breath/difficulty breathing, physical examination, and confirmed with a chest X-ray (15). Hypertensive crisis was defined as systolic blood pressure more than 180 mmHg and/or diastolic blood pressure more than 120 mmHg (1,4,16,17).

Every patients with PESF in our hospital received $MgSO_4$, using the Zuspan regimen consisting of a loading dose 4 g in 20 ml (20% solution) administered iv over 15–20 minutes, followed by a maintenance dose of 1 g/hour iv infusion using syringe pump from admission until 12 hours or 24 hours after delivery in case of eclampsia (18). In preterm PESF women managed conservatively, $MgSO_4$ is administered the first 24 hours following admission. In these women, $MgSO_4$ is discontinued during their observation period and started again at the time of delivery. On the other hand, the regimen mostly used in primary health-care centers consists of a modified Pritchard scheme; loading dose of 4 gram 20% iv $MgSO_4$ in 10–15 minutes and 10 gram IM (5 gram in each buttock), followed by maintenance dose 5 gram IM $MgSO_4$ in alternate buttock for every 6 hours (19).

Cases of Mg intoxication were identified as women who received $MgSO_4$ treatment and had documented clinical signs of magnesium intoxication in addition to serum magnesium levels >12 mg/dL. Clinical signs and symptoms included muscles weakness, loss of deep tendon reflexes, respiratory paralysis, ECG changes (prolonged PR interval and widened QRS complex), SA or AV node block, loss of consciousness or cardiac arrest.

The primary outcomes of the study were maternal and perinatal outcomes among the 19 cases compared with the 166 controls. The maternal parameters evaluated included maternal age, body mass index (BMI), parity, referral origin, antenatal history, PE type. Maternal outcomes included mode of delivery, gestational age at delivery, laboratory results, maternal complications, and maternal death. PE complications included any of the following: eclampsia, HELLP syndrome, pulmonary edema, hypertensive crisis, acute kidney injury. The definition of maternal death in this study was any death during the treatment in hospital, and not necessarily a direct effect of Mg intoxication. Perinatal outcomes included fetal sex, birth weight, Apgar scores (minutes 1 & 5), SGA (<10th population birth weight centile), and perinatal death.

The results were analyzed using chi-square test, independent t-test, Mann Whitney test, and Fisher exact test where appropriate. Statistical measurement was performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Released 2017.

Results

Incidence of Mg intoxication in women with PESF

The incidence of PESF during the period 2014–2018 was 1743 cases out of a total of 6823 total deliveries (25.54%); Mg intoxication was diagnosed in 19 patients (1.09%). The annual incidence of Mg intoxication over this 5-year period varied between 0.6% and 1.5%.

Maternal characteristics

The overall characteristics between the two groups were quite similar (Table 1) except the origin of the cases. All Mg intoxicated cases were referred from other hospitals or primary health-care centers compared with 80.2% in the control group: 19.8% women in the control group had regular antenatal care in our hospital (booked case). Twelve (63.2%) cases with Mg intoxication were referred from distant rural areas. There was no significant difference in maternal age, BMI, parity, and PE type between both groups.

Maternal outcomes

The clinical manifestations of Mg intoxication were varied: 42.1% of women demonstrated muscle weakness (loss of patellar reflex), 10.5% respiratory depression, and 42.1% loss of consciousness. The maternal outcomes of cases versus controls are presented in Table 2. The mode of delivery between both groups was not different, most patients in both groups were delivered by cesarean section.

The rate of maternal mortality and severe morbidities was higher among cases compared with the controls; 14 out of the 19 cases (73%) had a major complication, including 3 maternal deaths compared with 30.7% major complication rate in the control group (OR 2.85; 95% CI 2.12–3.82). Eclampsia and HELLP syndrome were the main complications found in the case group. Interestingly we found no pulmonary edema among the cases compared with 13 (7.8%) in the control group.

Importantly, the three maternal deaths were not directly caused by the actual Mg intoxication but were related to other complications such as septic shock, thyroid crisis, and intracerebral hemorrhage. Laboratory manifestations reflecting disease severity were significantly worse in the case group (protein urine, LDH, ALT, AST, BUN, SK, and Albumin).

A subgroup analysis was performed in PESF control women who had their serum Mg levels measured (Table 3). The Mg level among the cases was markedly elevated compared with controls (12.36 ± 3.45 versus 2.69 ± 0.83 mg/dL; $p < 0.001$). The minimum and maximum level of both groups were as follows: cases (8.9–25.6 mg/dL) versus controls (1.5–4.3 mg/dL). In addition, we found a significant difference in the total Mg dose, length, and method of Mg administration between the groups. A significantly higher proportion of cases received >24 g of Mg, and had Mg administered for >24 hours, and had Mg administered by intramuscular injection. As high as 21.1% of cases had oliguria.

Perinatal outcomes

Maternal Mg intoxication had a significant association with worse perinatal outcomes: lower 1 and 5 minute

Table 1. Maternal characteristics of PESF patients treated with Mg with (cases) and without Mg intoxication (controls).

	Cases n = 19	Controls n = 166	*p* value	OR (95% CI)
Maternal Age	28.83 + 6.191	31.96 + 6.769	0.415	NA
BMI	30.9875 + 8.694	30.6698 + 7.210	0.973	NA
Parity				
Primipara	4 (21.2%)	51 (31.1%)	0.349	NA
Multipara	15 (78.9%)	115 (68.9%)		
Referral origin				
Country	12 (63.2%)	42 (25.5%)	0.001*	5.02
The City	7 (36.8%)	124 (74.5%)		(1.85–13.59)
Booked Case				
No	19 (100%)	134 (80.2%)	0.005*	9.72
Yes	0	32 (19.8%)		(0.57–165.03)
PE type				
Early onset PE	14 (73.6%)	104 (62.7%)	0.314	NA
Late onset PE	5 (26.4%)	62 (37.3%)		

Table 2. Maternal outcomes of cases versus controls.

	Cases n = 19	Controls n = 166	*p* value	OR (95% CI)
GA at delivery	31.63 ± 3.51	33.81 ± 3.33	0.014*	NA
Mode of delivery				
CS	11 (57.9%)	110 (66.3%)	0.473	NA
Vaginal delivery	8 (42.1%)	56 (33.7%)		
Complication				
Yes	14 (73.7%)	51 (30.7%)	0.0002*	2.85
No	5 (26.3%)	115 (69.3%)		(2.12–3.82)
Complication type	14	51	0.0113*	NA
Eclampsia	6 (42.9%)	9 (17.6%)		
HELLP Syndrome	3 (21.4%)	11 (21.6%)		
Pulmonary edema	0	13 (25.5%)		
IUGR	1 (7.1%)	4 (7.8%)		
IUFD	3 (21.5%)	1 (2%)		
Multiple complication	0	9 (17.6%)		
Emergency Hypertension	0	1 (2%)		
Acute Kidney Injury	1 (7.1%)	3 (5,9%)		
Maternal death				
Yes	3 (15.8%)	0	0.009*	
No	16 (84.2%)	166 (100%)		
BUN	33.75 + 20.56	10.93 + 8.84	0.000*	
Serum Creatinine	2.61 + 1.68	0.65 + 0.07	0.000*	
Serum Albumin	2.64 + 0.38	2.58 + 0.55	0.000*	
ALT	59.58 + 94.79	43.35 + 12.72	0.057*	
AST	96.68 + 203.56	21.25 + 3.8	0.000*	
Protein Urine			0.024*	NA
(-)	0	3 (1.8%)		
+1	1 (5.3%)	20 (12.1%)		
+2	1 (5.3%)	56 (33.9%)		
+3	10 (52.6%)	55 (33.3%)		
≥4	7 (36.8%)	31 (18.8%)		

Table 3. Subgroup analysis of cases vs controls group.

	Cases n = 19	Controls n = 24	*p* value	OR (95% CI)
Mg level (g)	12.36 ± 3.45	2.69 ± 0.83	<0.001*	NA
Urine output (ml/hour)				
<30	4 (21.1%)	0	0.031*	2.6
≥30	15 (78.9%)	24 (100%)		(0.9–7.2)
Methods of $MgSO_4$ administration				
im	10 (52.6%)	5 (20.8%)	0.004*	2.07
iv	9 (47.4%)	19 (79.2%)		(1.56–19.4)
Total Mg Dose (g)				
≥ 24	14 (73.7%)	11 (45.8%)	0.027*	2.01
< 24	5 (26.3%)	13 (54.2%)		(1.51–1.75)
Length of administration (hour)				
≥ 24	14 (73.7%)	11 (45.8%)	0.027*	2.01
< 24	5 (26.3%)	13 (54.2%)		(1.51–1.75)

Apgar scores, lower birth weights, and a higher SGA and perinatal death rate (Table 4). The perinatal death rate in the case group was 36.8% compared with 6.6% in the control group.

Discussion

The results of this study confirm that while the incidence of Mg intoxication in women with PESF treated with $MgSO_4$ is quite low (1,09%), Mg intoxication is associated with significantly increased adverse maternal and perinatal outcomes. The incidence of Mg intoxication in a large systematic review involving 9556 women, was 1.3–1.6% (8). Duley et al., in another large meta-analytic study, also found that Mg intoxication was rare and only occurred in around 1% of women receiving $MgSO_4$ (20). Importantly, Mg intoxication was not seen in patients receiving the "Magpie protocol" (5).

Three maternal deaths occurred among the 19 Mg intoxicated women, but the cause of maternal death was not directly related to the Mg level. The cause of death in these three cases was: septic shock, thyroid crisis, and intracerebral hemorrhage. Serum Mg level in these three cases had normalized a couple of days before they died. Lowe et al. reported no maternal death in their large systematic review, while Duley

Table 4. Perinatal outcomes of cases versus controls.

	Cases n = 19	Controls n = 166	*p* value	OR (95% CI)
Baby sex				
Male	13 (68.4%)	79 (50.3%)	0.131	NA
Female	6 (31.6%)	78 (49.7%)		
Baby Birthweight	1516.67 + 565.015	1872.32 + 662.860	0.005*	NA
Apgar Score				
Minutes 1	2.75 + 2.179	5.57 + 2.250	0.000*	NA
Minutes 5	5.42 + 1.782	7.34 + 1.573	0.000*	NA
SGA				
Yes	6 (31.6%)	14 (8.4%)	0.002*	3.74
No	13 (68.4%)	152 (91.6%)		(2.66–11.38)
Perinatal Death				
Yes	7 (36.8%)	11 (6.6%)	0.000*	5.56
No	12 (63.2%)	155 (93.4%)		(2.29–5.94)

et al. found two trials reported maternal deaths (8,20). The highest serum Mg level found among the cases in the current study was 25.6 mg/dL, this level is not considered to be high enough to directly cause maternal death. With serum levels of 20–34 mg/dL, Mg intoxication will be manifest as hypoventilation, acidosis, loss of tendon reflexes, and general weakness. Severe and life-threatening complications like respiratory depression and cardiac arrest will occur with the serum levels of 48–72 mg/dL (8). The clinical signs and symptoms in these Mg intoxication cases were general muscle weakness (loss of patellar reflex), loss of consciousness, and respiratory distress. The overall incidence of loss of patellar reflexes, loss of consciousness, and respiratory depression among all 1743 patients receiving $MgSO_4$ treatment was, respectively, 0.4% (8 cases), 0.5% (9 cases), and 0.1% (2 cases). The side effects caused by $MgSO_4$ treatment found in this study were significantly lower compared with the large systematic review by Lowe et al. (8). This review is comparable to our study since the research sample was only taken from middle- and low-income countries. The overall incidence of loss of patellar reflexes and respiratory distress in this systematic review was 1.2% and 1.3% (8). Unfortunately, this review did not evaluate the clinical sign of loss of consciousness. Perhaps this sign is not commonly interpreted as one of the major manifestations of Mg intoxication. The possible explanation of the much higher incidence of side effects reported in Lowe et al. (8) review compared with our study may be related to the regimen choices. Only eight studies used the Zuspan regimen (which is the same regimen used in our hospital) (18), while the other studies used the Pritchard (19) or the Dhaka regimens (21) with a relatively higher total dose of $MgSO_4$. Administration of $MgSO_4$ longer than 24 hours and a total dose of more than 24 grams would be potentially hazardous for the maternal outcome, as seen in the current study.

Interestingly, intramuscular administration of $MgSO_4$ was associated with a doubling of the rate of Mg intoxication; 52.6% of patients in the case group received $MgSO_4$ intramuscular versus 21.8% in the control group (p = 0.004). Similar findings have been reported by Kanti et al. (21); these authors reported a higher rate of signs and symptoms indicative of Mg intoxication and local site complications to be associated with intramuscular Mg administration. The Magpie trial also showed that intravenous administration had fewer side effects compared with the intramuscular route (5).

In the current study, the majority of the cases received intramuscular $MgSO_4$, since most of these patients were referred from primary health centers or primary health care or rural areas. This is in line with the regional referral guidelines on the management of PESF. Our regional policy for community-based care (primary health care) is to give a loading dose following the Pritchard regimen as initial management of PESF, before transferring the patients to a tertiary center. This approach has been implemented in many low- and middle-income countries such as Bangladesh, and India (22). The majority of smaller Indonesian medical centers prefer Pritchard IM administration regimen because of ease of administration, non-availability of infusion set/syringe pump, lack of nursing staff, and the fact that intramuscular administration is more cost-effective compared with iv regimen (23). Encouraging the government to provide syringe-pump availability throughout the nation could potentially improve outcomes in Indonesian women with PESF.

In our tertiary referral center, $MgSO_4$ is given via an intravenous route (syringe pump infusion) following the Zuspan regimen (18,22). Maintaining the therapeutic level of Mg while monitoring for sign of Mg

intoxication is important. Simple clinical assessment is adequate in most PESF women treated with $MgSO_4$, and more suitable in low- and middle-income countries (5,12,22), as is also demonstrated by the low overall rate of just over 1% in the current series.

The incidence of eclampsia and HELLP syndrome was significantly higher in the case group, while unexpectedly acute pulmonary edema, a common PE complication in Indonesia (15) was not seen among the 19 Mg intoxication cases. The presence of these complications may represent a significant risk factor of Mg intoxication due to the clinical necessity for a more prolonged $MgSO_4$ administration. Among the cases, more women received $MgSO_4$ for more than 5 days compared with the controls, although the average length of hospital stay between both groups did not differ significantly (cases versus controls: 10.21 ± 8.43 versus 11.29 ± 15.20, $p = 0.783$). The study results appear to indicate that giving $MgSO_4$ for more than 24 hours is not advisable unless Mg levels can be checked at regular intervals.

Another significant risk factor that could be contributing to the occurrence of Mg intoxication is oliguria and renal insufficiency. In this series, Mg-intoxicated patients had a worse renal function, reflected by higher BUN and serum creatinine level. Almost all of the serum magnesium is cleared by renal excretion, so any problems of urine production will significantly increase the risk of magnesium intoxication (6).

All patients in the Mg intoxicated group received calcium gluconate therapy as immediate management in line with our national protocol. This routine intervention is not found in the large systematic review by Lowe et al. The use of calcium gluconate in their review was extremely rare (0.18%). There is no clear explanation of this finding. However, Lowe et al. assumed that the low use of calcium gluconate reflects an infrequent need for its use as an antidote, rather than the unavailability of the drugs in the hospital (8,24).

The case had a higher rate of perinatal death, SGA, and low Apgar scores. Seven perinatal deaths (4 fetal demise) (36.8%) occurred in Mg-intoxicated group compared with 11 deaths (6.6%) in the control group. The higher rate of SGA in the case group reflects disease severity. About one-third of the cases were delivered of neonates who developed respiratory distress syndrome (RDS), significantly different from the 4% in the control group. Low Apgar scores were also more prominent among cases, in line with the strong correlation between maternal and fetal Mg levels resulting in respiratory muscle suppression and general muscle weakness. Previously, the use of antenatal $MgSO_4$ was discouraged by the majority of neonatologists because of a perceived risk of neonatal respiratory depression (25). However, recent studies with a large number of subjects have shown that particular concerns regarding the use of antenatal $MgSO_4$ for adverse neonatal implications were only encountered after long duration of Mg administration (26). We also discourage the prolonged use of antenatal $MgSO_4$ in PESF cases, not only because of the aforementioned neonatal concern but also because of the association with an increased risk of maternal and perinatal complications. The meta-analytic study by Duley et al. did not find any difference in the risk of stillbirth or neonatal death, but there was a small increase in the overall risk of perinatal mortality associated with $MgSO_4$ use (RR 1.04) (27).

Conclusion

Mg intoxication was found in just over 1% of PESF women treated with $MgSO_4$, as was found to be associated with a significant risk to the mother and fetus. While Mg serum levels cannot be measured as a routine in many developing countries, serial monitoring for the simple clinical signs and symptoms indicative of Mg intoxication is effective as a monitoring tool. In these countries, Mg serum level monitoring is indicated in patients requiring longer duration and higher accumulated doses of $MgSO_4$, both carry a high risk of Mg intoxication.

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Disclosure statement

The authors declare no conflict of interest.

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