

Received: 2018.05.07
Accepted: 2018.07.06
Published: 2018.09.25

e-ISSN 1941-5923
© Am J Case Rep, 2018; 19: 1129-1134
DOI: 10.12659/AJCR.911004

Recurrent Seizures in 2 Patients with Magnesium Sulfate-Treated Eclampsia at a Secondary Hospital

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Case series

Patient: Female, 20 • Female, 19
Final Diagnosis: Recurrent seizure eclampsia
Symptoms: Hypertension • seizure
Medication: —
Clinical Procedure: Magnesium sulfate therapy
Specialty: Obstetrics and Gynecology

Objective: Unusual clinical course

Background: Recurrent seizure in patients with magnesium sulfate-treated eclampsia is very rare and requires meticulous management due to poor prognosis. The development of eclamptic convulsions is considered a preventable obstetric situation. Magnesium sulfate has been the drug of choice in such cases. However, some cases are persistent and need more aggressive treatment.





Case Report: First case: A 20-year-old, nulliparous woman was referred from a private midwifery practice with history of convulsion, 40 weeks of gestational age (GA), and in the active phase of labor. She had been treated with magnesium sulfate and nifedipine beforehand. Her fetus was tachycardic, so an emergency caesarean section was done and placental abruption was found. The day after the surgery, the patient had recurrent seizures despite receiving a maintenance dose of magnesium sulfate. The patient then received thiopental sodium and remained stable.

Second case: A 19-year-old, nulliparous woman came to the hospital with 40 weeks of GA, prolonged premature rupture of the membrane (PROM), preeclampsia, and cephalopelvic disproportion (CPD). An emergency caesarean section was performed. Eighteen hours after surgery, the patient had convulsions despite receiving magnesium sulfate maintenance therapy. We repeated the loading dose of 2 g magnesium sulfate, but the seizures persisted. Hence, midazolam was given and the seizures remained controlled. Both babies were delivered without any significant complications.

Conclusions: We report 2 cases of G1P0-0 women with 40 weeks GA who had magnesium sulfate-resistant eclampsia and needed additional anticonvulsant drugs. These cases show the importance of comprehensive management and the need for alternative drugs in eclampsia.

MeSH Keywords: Eclampsia • Magnesium Sulfate • Pre-Eclampsia • Seizures

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Background

Hypertension in pregnancy is still a major cause of high maternal-perinatal mortality and morbidity, as it affects about 10% of pregnancies worldwide [1]. Preeclampsia, as part of this spectrum, affects 3% of pregnant women [2], while eclampsia, as one of the most serious complications, occurs in approximately 1–2% of women with severe preeclampsia, and in 2.7–3.3 per 10 000 pregnant women [3]. A prospective cohort study in Uganda states that the case-fatality rate for severe preeclampsia and eclampsia are 2.3% and 17.8%, respectively [4].

According to the International Society for the Study of Hypertension in Pregnancy (ISSHP), diagnosis of preeclampsia is based on the finding of new-onset hypertension (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic) after 20 weeks of gestation, complemented with proteinuria of >300 mg/day or $+2$ on dipstick testing [3,5]. To prevent eclampsia, screening complemented with aspirin and calcium supplementation has been recommended [6]. Although early diagnosis and treatment of preeclampsia have been strongly emphasized, the progression to eclampsia still happens, which causes significant maternal and neonatal complications [7].

The onset of the convulsions can vary depending on whether the woman is in the antepartum (38–53%), intrapartum (18–36%), or postpartum (11–44%) period. Therefore, magnesium sulfate, due to its better tolerability and more effectiveness, has been used as the drug of choice to prevent the incidence and the recurrence of eclamptic seizure for more than 70 years [8,9]. Despite comprehensive management to prevent eclampsia, some patients still suffer recurrent seizure despite magnesium sulfate administration. In this report, we present 2 cases and discuss their management.

Case Report

Case 1

A 20-year-old nulliparous woman was referred from a midwife's private practice to the emergency room (ER) of Ibnu Sina General Hospital, Gresik, Indonesia at 40 weeks of GA, in active labor phase (5 cm of cervical dilatation), and history of seizure 3 h before coming to the ER. The patient had received 5 g of intramuscular magnesium sulfate 40% and 5 mg of sublingual nifedipine from the midwife before being referred. The patient did not experience any headache, nausea, or blurry vision before the seizure or in the ER.

The patient appeared *compos mentis* but was exhausted. Vital signs show that blood pressure was 147/95 mmHg, heart rate was 128/min, respiratory rate was 21/min, and axillar

temperature was 36.8°C. Fetal heart rate was 168/min. The patient was overweight with BMI of 25.63. Laboratory finding showed normal hemoglobin level, normal platelet count, $+1$ proteinuria in urinalysis, and normal serum aspartate aminotransaminase (AST) and serum alanine aminotransaminase (ALT) levels (28.7 IU/L and 16.4 IU/L, respectively). Blood urea nitrogen level was 8.2 and serum creatinine was 0.90. Blood coagulation profile was normal.

The final diagnosis was G1P0-0 40 weeks of GA, eclampsia, active phase of labor, and fetal tachycardia. One hour after admission, the patient had recurrent seizures in the ER, so 2 g of 40% magnesium sulfate was administered, followed by 10 mg of nifedipine and oxygen supplementation through a non-rebreathing mask.

An emergency caesarean section with Pfannenstiel incision was performed 1 h later. After reaching the uterus, we found placental abruption with Couvelaire uterus. Contraction of the uterus was sufficient and blood loss was minimal. The baby was delivered safely, weighing 3550 g with Apgar score of 6 and 8. Bleeding was minimal and the patient was still stable hemodynamically with blood pressure of 137/78. She was then given 2 g of magnesium sulfate and continued with a maintenance dose of 1 g through a syringe pump to prevent the recurrence of seizure.

One hour after surgery, the patient suffered the third eclamptic attack. A repeated loading dose of 2 g magnesium sulfate was then administered, but the seizure persisted. No signs of magnesium toxicity, such as loss of patellar reflex, respiratory paralysis, and cardiac conduction abnormalities, were detected. Hence, the patient was moved to the Intensive Care Unit (ICU) and received thiopental sodium as anti-epileptic drug (AED) and sedative. Thiopental sodium was continued for 2 days and the patient did not suffer any seizures afterwards. There were no signs of impending eclampsia such as blurry vision, headache, or abdominal discomfort. Without any antihypertensive drugs, the patient remained consistently normotensive, ranging from 114/80 to 132/84 in the ICU. After 3 days of treatment in the ICU, the patient's condition improved without any recurrent seizures, so she was moved to the ward under the monitoring of multiple specialties and magnesium sulfate was discontinued.

The patient was discharged from the hospital on postpartum day 5. There were no signs or symptoms of eclampsia found until 40 days postpartum. The baby was monitored in the Neonatal Intensive Care Unit (NICU) for 3 days and was discharged without any subsequent problems.

Case 2

A 19-year-old nulliparous woman came to the Emergency Department of our hospital after being referred from a private midwifery practice, with gestational age of 40 weeks, premature rupture of the membrane (PROM) for more than 24 h, and inadequate contractions. She had irregular history of prenatal care by a midwife and no blood pressure abnormalities were detected during her midwife visits. There was no history of tobacco smoking, alcohol, or substance abuse. Vital signs were blood pressure 133/92 mmHg, heart rate 86/min, respiratory rate 20/min, and axillary temperature 37°C. Physical examination showed uterine height 31 cm, fetal heart rate 134 times/min, and 2-cm cervical dilation.

The patient was overweight with BMI of 28.76. Laboratory finding showed normal values except severe proteinuria of +3. The final diagnosis was G1P0-0 40 weeks of GA, prolonged PROM, cephalopelvic disproportion (CPD), severe preeclampsia, and prolonged labor.

An emergency caesarean delivery was performed with Pfannenstiel incision. No complication was found during the surgery and the baby was delivered safely with birthweight of 3200 g and Apgar score of 7–8. After the surgery, the patient received a combination of amlodipine and bisoprolol to control blood pressure, and 2 g of loading dose followed by 1 g per hour of magnesium sulfate as maintenance.

The next day, 18 h after surgery, the patient showed increasing blood pressure, reaching 151/100, despite the antihypertensive therapy, followed by decrease of appetite, with no sign of blurry vision, pulmonary edema, or other impending eclampsia signs. Despite all the therapies, the patient had a tonic-clonic seizure (eclampsia). We administered a loading dose of 2 g of magnesium sulfate, continued at 1 g per hour by syringe pump. The seizures stopped after the therapy but reoccurred 1 h afterwards. Therefore, we administered another 2 g of magnesium sulfate and admitted the patient to the ICU. No signs of magnesium toxicity were found between the administrations. The seizure stopped after we administered 1 mg/h midazolam through a syringe pump.

The midazolam was stopped on day 3 because the patient showed no signs of imminent or recurrent seizure, and blood pressure was below 140/90. She experienced slight nausea and was given ondansetron and ranitidine to reduce the symptoms. On day 4, she was moved to the ward in stable condition.

During the observation in the ward, her blood pressure was controlled at around 120–130 for SBP and 90 for DBP for 3 days. She remained stable without any worsening signs or symptoms. Hence, she was discharged on day 6. The baby was

monitored in the NICU for 2 days and was discharged safely. At the outpatient clinic, the patient showed no signs of recurrent seizure until day 40 postpartum and her blood pressure was well controlled at around 120/90 without any antihypertensive therapy.

Discussion

Both patients had eclampsia in their first pregnancy, at full term, and at a young age (20 and 19 years old, respectively). Both are in line with a previous study indicating that risk of preeclampsia is higher in the first pregnancy (4.1%) compared to later pregnancies (1.7%) [10]. Furthermore, women younger than 20 years of age were reported to be at 3.87 times higher risk of developing preeclampsia compared to those 20 years of age and older [11].

In the first patient, blood pressure was 147/95 and proteinuria was +1 in dipstick examination. Although the blood pressure did not reach the minimal limit of severe preeclampsia (160/110 mmHg), the patient did suffer a seizure (eclampsia). No signs of impending eclampsia were detected before the recurrent seizure happened. This was in conjunction with atypical preeclampsia as it was described in previous studies, which consists of gestational hypertension or proteinuria, plus 1 or more of the following conditions: symptoms of preeclampsia, hemolysis, thrombocytopenia $<100\,000/\text{mm}^3$, and elevated AST or ALT twice the upper limit of the reference value [12–14]. A case report from India noted that a refractile seizure occurred in a fully-conscious, primigravida mother with similar blood pressure (160/100 mmHg) and mild proteinuria. In that case, the patient improved with propofol infusion [15].

The onset of preeclampsia is related to the severity of the disease, clinical management, outcome, and short- and long-term prognosis. The cut-off for the termination of pregnancy in severe preeclampsia is usually 34 weeks of GA [5]. In our 2 cases, both patients came to our hospital when they had reached 40 weeks, with late-onset preeclampsia (LOPE). Lisonkova et al. reported that a higher rate of LOPE is found in nulliparous women younger than 20 years of age. In addition, early-onset preeclampsia (EOPE), which occurs at less than 34 weeks of GA, is associated with higher rates of complications than is LOPE [16]. However, in these cases, there were many complications seen in the patients.

Poor ANC may be contributed to by lack of knowledge on the part of the mothers about the early signs of the disease, thus leading to late arrival at the hospital. This is caused by many factors, such as low socio-economic status and low education level, and lack of compliance in antenatal care visits. This contributes to the delayed recognition of preeclampsia signs,

Table 1. Anti-epileptic drugs for eclamptic seizure [9,15,18–22].

No	Drugs	Mechanism of action	Dosage	Adverse effects
1	Magnesium sulfate	<ul style="list-style-type: none"> – Calcium antagonist – Potent vasodilator of cerebral vasculature and increase cerebral blood flow – <i>N-methyl-D-aspartate</i> (NMDA) receptor inhibitor 	<ul style="list-style-type: none"> – IV regimen: <ul style="list-style-type: none"> • Loading dose of 4 g • Maintenance dose 1–2 g IV/hour by syringe pump for 24h • A further 2–4 g IV over min is given if convulsions recurred – IM regimen: <ul style="list-style-type: none"> • Loading dose of 4 g IV injection over 5 min • 10 g IM injection • 5 g IM/4 h in alternating buttock 	<ul style="list-style-type: none"> – Loss of patella and deep tendon reflex – Blurred vision – Nausea – Nystagmus – Respiratory paralysis – Altered cardiac conduction – Cardiac arrest
2	Benzodiazepine (Diazepam, Midazolam)	<ul style="list-style-type: none"> – Powerful anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties – Used in Intensive care setting 	<p>Diazepam</p> <ul style="list-style-type: none"> • Loading dose: 10 mg IV over 2 min • Repeated if convulsion recurred • Maintenance dose: <ul style="list-style-type: none"> – 40 mg in 500 mL normal saline for 24h – Rate of infusion is titrated – 20 mg in 500 mL for the next 24h and slowly reduced <p>Midazolam</p> <ul style="list-style-type: none"> • Loading dose 0.2 mg/kg IV • Maintenance dose 0.1 mg/kg/h IV 	<ul style="list-style-type: none"> – Respiratory depression – Venous thrombophlebitis – Cardiac arrest – Drowsiness – Confusion – Amnesia
3	Phenytoin	<ul style="list-style-type: none"> – Stabilizing effect on neuronal membranes – Recommended for prevention of convulsions in conjunction with 10 mg of diazepam for seizure attack 	<ul style="list-style-type: none"> – Loading dose of 15 mg/kg IV: <ul style="list-style-type: none"> • 10 mg/kg initially in 30 minutes • 5 mg/kg 2 hours later over 10 minutes – Maintenance dose of 300 mg IV over 10 minutes until 24 hours post seizure – Given in 70–100 ml of normal saline at rate of 25 mg/min 	<ul style="list-style-type: none"> – Dysrhythmia – Hypotension
4	Barbiturate (Sodium Thiopental)	<ul style="list-style-type: none"> – GABA_A agonist with possible actions on calcium channels – NMDA receptor antagonist 	<ul style="list-style-type: none"> • Loading dose: 75–125 mg IV bolus • Maintenance dose: 1–5 mg/kg/h IV 	<ul style="list-style-type: none"> – Accumulation in the body cause prolong action – Hypotension – Fetal depression
5	α2 agonist (Dexmedetomidine)	<ul style="list-style-type: none"> – Centrally-acting α2 agonist – Sedative through locus coeruleus in CNS – Analgesic by activation of α2 receptors by accentuating action of opioids – Used in ICU setting 	<ul style="list-style-type: none"> • Loading dose: 1 mcg/kg per 20 min • Maintenance dose 0.7 mcg/kg/h • 400 mcg dexmedetomidine is put in 100 ml normal saline 	<ul style="list-style-type: none"> – Mild cognitive impairment – Reduce heart rate
6	Propofol	<ul style="list-style-type: none"> – Non-barbiturate anesthetic agent with anticonvulsant properties through potentiation GABA-mediated pre and post synaptic inhibition – NMDA receptor antagonist 	<ul style="list-style-type: none"> • Loading dose: 3–5 mg/kg IV • Maintenance dose 1–15 mg/kg/h IV 	<ul style="list-style-type: none"> – Ventricular tachycardia – Lactic acidosis – Confusion – Agitation

IM – intramuscular; IV – intravenous.

which results in the development of severe complications, including eclampsia [4].

Eclampsia is thought to be a form of posterior reversible encephalopathy syndrome (PRES), in which acute elevation of blood pressure results in the forced dilatation of cerebral arteries, increased BBB permeability, and edema formation [17]. It can be a life-threatening part of major maternal complications of preeclampsia, which include placental abruption, HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, disseminated intravascular coagulopathy, neurologic deficits, aspiration pneumonia, pulmonary edema, cardiopulmonary arrest, acute renal failure, and death [12]. The first case had a placental abruption, which can lead to postpartum hemorrhage, but it was still manageable and fetal complications were minimal.

Magnesium sulfate has been proven effective in preventing and treating eclampsia due to its action as a calcium antagonist, both intracellularly and extracellularly, as well as acting directly on cerebral endothelial cells [17]. However, in these 2 cases, both patients were unresponsive to magnesium sulfate, since treatment with a repeated loading dose of 2 g and maintenance dose of 1 g per hour was not sufficient to prevent reoccurrence of seizures. This administration reached the target therapeutic concentration for preventing seizure, which is 2 to 4 g [9]. Other reports suggest these cases are typical of non-preventable eclampsia, since their convulsions could not be predicted or prevented under hospital care [13]. Toxicity is assessed through clinical manifestations due to limited resources in secondary hospitals. Moreover, toxicity is rare when the drug is carefully administered and monitored due to its established overall tolerability and efficacy in term-gestation eclampsia [9].

Besides magnesium sulfate, there are several options for AED, as detailed in Table 1 [9,15,18–22]. Thiopental sodium, which is an ultra-short-acting barbiturate, and midazolam, a benzodiazepine, have been used as alternative AED, especially for refractory status epilepticus and in the ICU setting [18]. Our first patient received thiopental sodium, which acts on the GABA

receptor, from the anesthesiologist in the ICU. Thiopental is considered safe in pregnancy, even though it crosses the placenta, since the low dose commonly administered (<4 mg/kg) rarely exceeds the threshold for fetal depression [22].

The second patient received midazolam, a benzodiazepine that also acts on the same receptor, after the failure of magnesium sulfate. Midazolam has been used as an alternative AED for eclampsia and as a first-line drug in status epilepticus [23,24]. The safety of benzodiazepine in pregnancy is still controversial, as its administration may be harmful in the first trimester of pregnancy, but the reliability of this evidence is low [22,25]. Both of our patients improved and did not have seizures after the administration of these drugs. This outcome indicates that second-line drugs are sometimes needed in the management of eclampsia in case of magnesium sulfate resistance, despite fetal adverse effects.

Conclusions

These cases emphasize that there are women who have non-typical eclampsia with inadequate response to magnesium sulfate. The seizures occurred at full term without any preceding PE or impending eclampsia signs. Although the management of preeclamptic women must be highly comprehensive to prevent seizures, there are few available prophylactic drugs for eclamptic women after the administration of magnesium sulfate fails. Hence, these cases highlight the need for effective drugs other than magnesium sulfate to prevent recurrent seizures.

Department and Institution where work was done

Department of Obstetrics and Gynecology, Ibnu Sina Hospital, Gresik, Indonesia.

Conflict of interest

None.

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