Vol 5 No. 2 Oktober 2025
Solo Journal of Anesthesi, Pain and Critical Care

E-ISSN : 2797-0035
P- ISSN : 2776-1770

CASE REPORT

Evaluating the Role of Magnesium Sulphate as an Adjunct Therapy in Non-Obstetric Refractory Status Epilepticus

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Article Info :
Submitted :
26-05-2025
Accepted :
21-10-2025
Published :
31-10-2025
https://doi.org/10.20961/sojaV5i2.102964

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ABSTRACT

Background : Refractory Status Epilepticus (RSE) is a condition of persistent status epilepticus seizures despite appropriate anticonvulsant therapy. RSE can be fatal if not treated promptly and properly. Standard treatments for SE and RSE include benzodiazepines as first line, non-benzodiazepine agents as second line, and general anesthetic agents as third line. Magnesium Sulfate (MgSO4) is known as an anticonvulsant agent that is more often used in obstetric cases, but its use in non-obstetric RSE is limited. The purpose of this case report is to report a case of RSE that improved after administration of Mgs4

Case Illustration : A 56-year-old male patient with a history of epilepsy and left ischemic stroke, was referred with decreased consciousness after falling. The patient experienced recurrent seizures, and after treatment with diazepam and phenytoin, recurrent seizures were still found despite additional doses. After being transferred to the ICU, the patient was given therapy with midazolam, propofol, and phenobarbital, but the seizures continued to recur. After 30 hours in the ICU, MgSO4 was given intravenously two grams followed by maintenance doses. The seizures stopped and the patient remained seizure-free during the 138-hour ICU stay, with improved neurological and hemodynamic conditions.

Conclusion : MgSO4 has been shown to be effective as an anticonvulsant agent in RSE in the ICU. Its use helps stop persistent seizures and supports the patient's clinical stability. This report shows the potential of MgSO4 as a useful adjunct therapy in the management of RSE in critically ill patients.

Keywords: Anticonvulsant Therapy; Magnesium Sulfate; Persistent Seizure; Refractory Status Epilepticus.

INTRODUCTION

Refractory Status Epilepticus (RSE) is a term that describes persistent status epilepticus seizures despite the administration of appropriate anticonvulsant therapy [1]. Status Epilepticus (SE) is a neurological emergency that can be fatal if not managed properly (2). SE refers to seizures lasting 30 minutes or more, during which the patient is unable to regain normal mental status between episodes. SE can manifest as either focal or generalized seizures (3). The underlying mechanism of both SE and RSE involves an imbalance between excitatory (glutamate, aspartate, acetylcholine) and inhibitory (gamma-aminobutyric acid) components in the central nervous system, resulting in excessive excitation without adequate inhibitory compensation [4].

Currently, anticonvulsant therapy for SE and RSE includes benzodiazepine agents as the first-line treatment (midazolam, diazepam, lorazepam), non- benzodiazepine agents as the second-line treatment (phenytoin, valproate, levetiracetam, phenobarbital), and general anesthetic agents as the third-line treatment (propofol, titrated-dose midazolam, ketamine, barbiturates)[5]. These regimens vary in effectiveness, and as more advanced regimens are administered, the risk of complications such as hypotension, bradycardia, and respiratory depression increases [6–8].

Magnesium sulfate ($MgSO_4$) is one of the drugs that can function as an antiepileptic agent [9]. Clinically, $MgSO_4$ is frequently used in obstetric cases, while its use in non-obstetric cases remains limited [10]. The mechanism of $MgSO_4$ is related to the inhibition of NMDA receptor activity, which plays a role in epileptogenesis, although the specific mechanism of this drug is not yet fully understood [11]. Previous case reports suggest that $MgSO_4$ is effective in treating and preventing seizures in non-obstetric SE and RSE cases [12].

The purpose of this case report is to document and evaluate the management of a non-obstetric refractory status epilepticus (RSE) case that showed clinical improvement following the administration of $MgSO_4$.

CASE ILLUSTRATION

A 56-year-old male weighing 70 kg was referred to our hospital with decreased consciousness following a fall at home one day before hospital admission. The family reported that after

the fall, the patient experienced recurrent seizures, had difficulty communicating, and developed limb weakness. Upon arrival at our hospital's Emergency Department, the patient had two episodes of tonic-clonic seizures. The patient had a history of epilepsy for the past 20 years and was on phenytoin treatment. In addition to epilepsy, the patient also had a history of organic mental disorder.

Vital signs assessment showed that the patient appeared critically ill with apathetic consciousness, blood pressure of 181/94 mmHg, heart rate of 128 beats per minute, respiratory rate of 22 breaths per minute, peripheral oxygen saturation of 96% on room air, and body temperature of 36.4°C. Neurological status was difficult to assess due to the patient's postictal decreased consciousness. Examination of other organ systems was within normal limits. A non-contrast head CT scan revealed a chronic thromboembolic infarct in the left frontal region corresponding to the left anterior cerebral artery territory, porencephaly, and moderate brain atrophy (Figure 1.). A chest X-ray suggested cardiomegaly and laboratory tests showed hemoglobin of 14.3 g/dL, hematocrit of 43%, leukocytes of 12.3 x 10^3 /uL, platelets of 203 x 10^3/uL, blood glucose of 85 mg/dL, segmented WBC 80%, lymphocytes 13%, monocytes 1%, eosinophils 2%, basophils 9%, SGOT 52 U/L, SGPT 38 U/L, BUN 35 mg/dL, creatinine 1.2 mg/dL. Arterial blood gas analysis showed pH 7.412, pCO_2 40.8, pO_2 164, BE 1.1, Total CO_2 27.2, HCO_3 26, SaO_2 99.5%. Urinalysis results showed leukocytes 6–8, erythrocytes 50–55, pH 6.0, ketones ++, urobilinogen 34, nitrites –, and blood +++. ECG showed sinus tachycardia at 128 beats per minute, normal axis without signs of ischemia or hypertrophy.

The patient was assessed with convulsive seizures with a history of epilepsy, left frontal ischemic stroke, and urinary tract infection. The patient received 5 mg of diazepam injection twice in the Emergency Department to manage seizures and was given a bolus dose of 300 mg phenytoin followed by maintenance of 100 mg every 8 hours. The patient also received supportive therapy with ceftriaxone, citicoline, neurobion, omeprazole, piracetam, methylprednisolone, candesartan, and aspirin. The patient was planned for further care in the High Care Unit (HCU) for observation of consciousness and vital signs under the joint management of

neurology and internal medicine department. The course of all follow-up treatment in various care unit are documented (Figure 2).

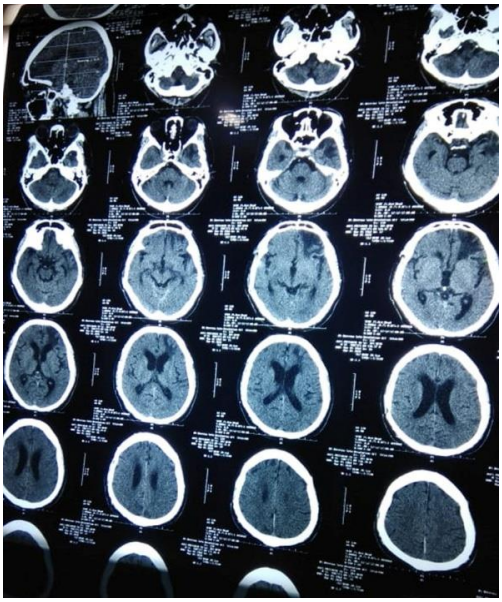

Figure 1. Initial Non-contrast Head Computed Tomography Scan

After 7 hours in the HCU, the patient had two additional episodes of tonic-clonic seizures, each lasting 10 to 20 seconds. Post-seizure, the patient's consciousness was recorded as E3V4M3, blood pressure. 113/68 mmHg, heart rate 124 beats per minute, respiratory rate twenty-two breaths per minute, peripheral oxygen saturation. Ninety-seven percent, and body temperature 35.7°C. The patient received an additional 30 mg intravenous phenytoin bolus, after which the seizures ceased. After 11 hours in the HCU, the patient had another tonic-clonic seizure lasting 30 seconds. Consciousness was difficult to evaluate, with blood pressure at 103/76 mmHg, heart rate at 97 beats per minute, respiratory rate at 20 breaths per minute, peripheral oxygen saturation at 97% with 10 LPM Non- Rebreathable mask, and body temperature at 37.4°C. Another 30 mg intravenous phenytoin bolus was administered, and the seizures stopped.

After 24 hours in the HCU, the patient had two additional tonic-clonic seizures lasting 30 to 60 seconds each. Oxygen saturation and respiratory function declined, with a respiratory rate of ten breaths per minute and peripheral oxygen saturation at 80% with 10 LPM Non-Rebreathable mask. Post-seizure, consciousness declined further and was difficult to evaluate. Blood pressure was. 103/58 mmHg, and heart rate was 124 beats per minute. The patient was given a 10 mg diazepam injection, intubated, and connected to a ventilator in PSIMV mode. Post-intubation, the patient was transferred to the Intensive Care Unit (ICU) under the care of the anesthesiology and intensive therapy department. The patient received intravenous boluses of midazolam (5 mg), propofol (50 mg), and phenobarbital (100 mg), followed by

maintenance doses of midazolam (1–5 mg/hour), propofol (50 mg IV bolus), and phenobarbital (50 mg every 12 hours). Supportive therapy included intravenous fluids with Ringer's lactate and levofloxacin.

Fifteen minutes after ICU admission, the patient had another tonic-clonic seizure lasting 20 to 30 seconds. Vital signs showed blood pressure of 115/73 mmHg, heart rate of 110 beats per minute, respiratory rate of 12 breaths per minute, peripheral oxygen saturation of 99% with a ventilator, and body temperature of 37°C. The patient received an additional 50 mg slow IV bolus of propofol and was maintained on a 25 mg/hour infusion, with midazolam titrated to 5 mg/hour while monitoring hemodynamic status with a target MAP of 65 mmHg.

After 10 hours in the ICU, the patient did not have further seizures but experienced hypotension with blood pressure dropping to 89/54 mmHg. Heart rate was 120 beats per minute, respiratory rate twelve breaths per minute, and peripheral oxygen saturation 99% with a ventilator. The patient was supported with norepinephrine titrated at 0.05 mcg/kg/min, while the propofol infusion was reduced to 15 mg/hour. Midazolam was maintained at 5 mg/hour, and other therapies continued with hemodynamic monitoring. After 20 hours in the ICU, the patient had two more seizures lasting thirty to 60 seconds each. Hemodynamic and respiratory functions were stable. Midazolam and propofol were increased to 6 mg/hour and 30 mg/hour, respectively. The patient also received. additional oral anticonvulsants of 100 mg phenobarbital every 12 hours and valproic acid syrup administered via NGT.

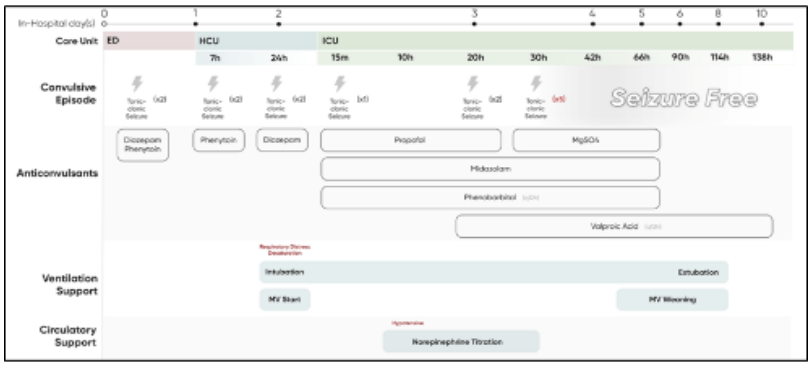

Figure 2. Daily Monitoring of Anticonvulsants and Patient's Clinical Improvement During course of Treatment. ED: Emergency Department; HCU: High-Care Unit; ICU: Intensive Care Unit; MV: Mechanical

After 30 hours in the ICU, the patient had five more seizures. Additional anticonvulsant therapy included intravenous magnesium sulfate ($MgSO_4$) Two grams over 30 minutes, followed by 1 mg/hour for 12 hours, then 0.5 mg/hour for another 12 hours, for a total of 24 hours. The propofol infusion was discontinued. After 42 hours in the ICU, the patient remained seizure-free for the past 12 hours following $MgSO_4$ administration. Hemodynamic and respiratory functions were stable. The patient's consciousness began to improve (E3VettM5). Therapy continued, with $MgSO_4$ maintained at 0.5 mg/hour for another 12 hours, to be discontinued if the patient remained seizure-free. Midazolam was gradually tapered to 1–3 mg/hour, while phenobarbital (100 mg/12 hours) and phenytoin (100 mg/8 hours) were continued. Oral valproic acid syrup (500 mg/12 hours) was administered via Nasogastric Tube (NGT).

After 66 hours in the ICU, the patient remained seizure-free for 36 hours. Hemodynamic and respiratory functions were stable, and therapy continued. $MgSO_4$, phenobarbital, and midazolam were discontinued, while phenytoin and valproic acid syrup were maintained. After 90 hours in the ICU, the patient remained seizure-free for 60 hours. Hemodynamics and respiration were stable, and consciousness improved (E4VettM6). Spontaneous breathing improved, and ventilator weaning was initiated with a target SaO_2 above 96% and $FiO_2 \geq 40\%$. Chest physiotherapy and periodic suctioning were planned.

After 114 hours in the ICU, the patient remained seizure-free for 84 hours and was successfully extubated. Hemodynamics and respiration were stable, and the patient's consciousness was E4V5M6. Neurological examination revealed right- sided motor deficits. Therapy continued. After 138 hours in the ICU, the patient remained seizure-free. Hemodynamics, respiration, and consciousness were stable, and the patient was planned for transfer to neurology and internal medicine departments.

Electroencephalographic (EEG) monitoring was not performed in this case due to the unavailability of diagnostic equipment at the facility and the patient's unstable clinical condition, which precluded safe transport or performance of the procedure. Seizure activity was monitored through direct clinical observation and continuous

bedside assessment in the intensive care unit. The absence of EEG monitoring represents a limitation of this case report, as objective electrographic confirmation of seizure activity and seizure cessation could not be documented, and subclinical seizures may have gone undetected despite clinical observation.

DISCUSSION

Refractory Status Epilepticus (RSE) is a condition characterized by the persistence of seizures due to status epilepticus (SE), despite the administration of antiepileptic therapy such as benzodiazepines and one antiepileptic drug [1,2]. The fatality rate of RSE is estimated to reach 16% to 39% of cases and is three times higher compared to non-refractory SE cases [13].

The main principle in SE therapy is the rapid control of seizures and the prevention of complications. The administration of benzodiazepines can be considered as a first-line regimen to quickly achieve seizure control [5]. If seizure resolution and freedom are not achieved, antiepileptic drugs (AEDs) can be administered to further control seizures. In refractory cases, the use of general anesthetic agents may also be considered [1]. General anesthetics such as propofol can be administered in combination with benzodiazepines (e.g., midazolam) [2]. Currently, literature exists discussing the combination of general anesthetic agents with other antiepileptic therapies and benzodiazepines, with favorable outcomes in managing RSE [,2]. The high mortality rate of RSE highlights the need for aggressive therapy to rapidly control seizures. The implementation of an aggressive strategy in RSE management remains grounded in the three previously mentioned regimens: benzodiazepines, antiepileptics, and general anesthesia. Each regimen is administered both as bolus and maintenance therapy [2,6]. The effects of these regimens include hemodynamic instability and respiratory depression . The incidence of hypotension following general anesthesia regiments administration for uncontrolled seizure is common (especially continuous dose of propofol at maximum titration rate of 1 mg/kg/min), hence the use of norepinephrine as vasopressor became important (6), as done in this case of RSE. Because the maximum dose of propofol could not be utilized, propofol was discontinued and replaced with continuous titrated administration of Magnesium Sulphate ($MgSO_4$) [14].

The use of magnesium as a seizure control therapy, whether in case-specific or general contexts in intensive care settings, has not been widely reported. Although magnesium has been used in RSE therapy, the results have been inconclusive [2]. This has also been noted in other studies, and this phenomenon is associated with inadequate dosing and measurement of serum magnesium concentration. Theoretically, magnesium administration can reduce epileptic activity in the central nervous system; however, previous studies have failed to show a consistent dose-response correlation [5,15]. In cases of RSE, a loading dose of 50 mg/kg $MgSO_4$ can be administered, with a maximum dose of four grams, followed by a maintenance dose of 20 to 40 mg/kg/hour intravenously [7]. The cessation of seizures following magnesium administration in certain specific cases may also be due to other mechanisms not yet fully understood and may be unrelated to any dose-response effect. Other studies also noted similar findings, where the effect of magnesium dosage and serum concentration on clinical improvement after stroke has not yet been significantly proven in written literature [8]. Magnesium plays a role in many physiological aspects of the body, including ion transport, energy metabolism, and intercellular membrane stabilization [9]. In the nervous system, magnesium exerts a depressant effect on synapses. Magnesium competes with calcium ions in stimulating the coupling secretion for transmitter release. Magnesium also acts as an antagonist to N-methyl D-aspartate (NMDA) receptors and inhibits the presynaptic secretion of acetylcholine [2,9]. These mechanisms account for the anticonvulsant effects of magnesium.

The use of $MgSO_4$ as an anticonvulsant therapy has been used since back in 1906 in patients with eclampsia [10]. To this day, $MgSO_4$ administration has been reported in various pathologies: acute asthma, acute ischemic stroke, traumatic brain injury, and electrolyte imbalance disorders (such as hypomagnesemia) [10]. The prevalence of hypomagnesemia (serum magnesium <1.6 mg/dL) in critically ill patients is estimated to range from 14% to 70%, and the occurrence of hypomagnesemia refers to low magnesium levels detected in either red blood cells or serum [11]. In acute stroke cases, $MgSO_4$ administration has shown to provide functional clinical improvement at 90 days if administered

within the first 24 hours of stroke onset [12]. In animal studies, this improvement is attributed to a significant reduction in infarct size after $MgSO_4$ administration[12]. $MgSO_4$ administration can induce vasodilation in cerebral vasculature, reduce ischemia, and increase prostacyclin concentration (which prevents endothelial injury) [10]. A review conducted in 2015 showed that in RSE, $MgSO_4$ administration had a response rate of approximately 50% [4]. Nevertheless, the same study also noted that there is no standardized dosing protocol across the literature included in the review. The review emphasized a key point: with a response rate of only 50%, $MgSO_4$ serves as a temporary and not a definitive therapy [4]. The purpose of $MgSO_4$ in RSE cases are to aid in the titration of other antiepileptic drugs in the effort to resolve seizures [4,9]. In this case, serum magnesium levels were not obtained due to in-hospital limitations of such diagnostic testing procedure.

CONSLUSION

Administration of MgSO4 has demonstrated effectiveness as an antiepileptic agent in patients with refractory status epilepticus (RSE) treated in the ICU. Its role in inhibiting NMDA receptor activity contributes to seizure control, particularly in cases where standard anticonvulsant and anesthetic regimens have limited efficacy or cause significant hemodynamic instability. In this case, the administration of MgSO4 resulted in sustained seizure cessation, improved neurological status, and stable hemodynamics, supporting its potential as a valuable adjunct therapy for RSE. While further studies are needed to establish standardized protocols, this case highlights the therapeutic benefit of MgSO4 in managing RSE in critically ill patients.

INFORMED CONSENT AND ETHICS

Informed consent for publication of this case report could not be obtained from the patient or family members at the time of manuscript preparation. Therefore, all patient identifying information, including name, medical record number, specific dates of admission and treatment, and any other details that could potentially reveal the patient's identity, have been completely withheld from this report to ensure strict adherence to patient confidentiality and privacy regulations.

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