Delivery of Magnesium Sulfate

Technology Opportunity Assessment

Prepared for the Merck for Mothers Program
Delivery of magnesium sulfate

Summary

Preeclampsia and eclampsia (PE/E) are life-threatening disorders that can occur during pregnancy, childbirth, and the postpartum period. Anticonvulsive therapy with magnesium sulfate (MgSO4) can prevent eclampsia in women with severe PE and prevent recurrent seizures in women with eclampsia, but the drug is still underutilized, incorrectly administered, or unavailable in many low-resource settings. Technologies that address barriers to safe, correct use are in various stages of development and use; some will require additional research before they can be recommended. Two promising options are (1) a simplified delivery technology that could be prefilled with MgSO4 and (2) a simplified regimen of MgSO4 for treatment of eclampsia.

Statement of need

Preeclampsia (PE) is a life-threatening disorder that only occurs during pregnancy, childbirth, and the postpartum period. It is characterized by high blood pressure (hypertension) and protein in the urine of the mother (proteinuria). Convulsions (fits) with signs of PE indicate eclampsia, although occasionally convulsions occur in the absence of hypertension and/or proteinuria. Preeclampsia and eclampsia (PE/E) are among the leading causes of maternal death and disability worldwide. The World Health Organization (WHO) estimates that PE/E account for at least 16% of maternal deaths in settings with low resources that lack the skilled providers and facilities required for prevention, identification, and management of the condition.1 In most countries, PE/E ranks second only to hemorrhage as a specific, direct cause of maternal death. The risk of PE/E varies greatly depending on where a woman lives; the risk that a woman in a low-resource country will die of PE/E is approximately 300 times greater than that for a woman in a high-resource country.2

Eclampsia is commonly defined as new onset of grand mal seizure activity and/or unexplained coma during pregnancy or postpartum in a woman with signs or symptoms of preeclampsia. Although eclampsia is considered a complication of severe PE, it may occur in the absence of hypertension and/or proteinuria.3 Most cases of eclampsia present in the third trimester of pregnancy, during birth (intrapartum), or within the first 48 hours following childbirth, but eclampsia may occur up to three weeks after birth. WHO estimates that eclampsia develops in 2.3% of preeclamptic women in low-resource countries, compared with 0.8% of preeclampsia cases in high-resource countries.2

Preeclampsia and eclampsia are associated with derangements of multiple organ systems including hematologic, hepatic, renal, cardiovascular, and central nervous systems. The main causes of maternal death are intracerebral hemorrhage, pulmonary complications, kidney failure, liver failure, and multi-organ system failure. Perinatal outcomes when a mother has preeclampsia usually depend on one or more
of the following factors: gestational age of the mother at the onset of PE and at the time of childbirth, severity of the disease process, presence of multiple gestation, and presence of co-morbidities. There is an increased risk of perinatal death; this is mainly related to prematurity, intrauterine growth restriction, abruptio placentae, and perinatal asphyxia. When a woman has severe PE or eclampsia, positive maternal and perinatal outcomes depend on the woman having timely access to a treatment package including inpatient monitoring, optimal timing of childbirth, skilled attendance at birth, antihypertensive therapy, and anticonvulsive therapy.

Much of maternal death and disability is associated with eclampsia, and the woman and her baby may die after only one or two eclamptic seizures. Higher mortality rates are associated with women who have multiple convulsions (fits) outside of a hospital. Anticonvulsive therapy can prevent eclampsia in women with severe PE and prevent recurrent seizures in women with eclampsia.

Over the years, different anticonvulsants have been used, including magnesium sulfate (MgSO₄), phenytoin, diazepam, and “lytic cocktail” (usually chlorpromazine, promethazine, and pethidine). Two randomized control trials, the Collaborative Eclampsia Trial for women with eclampsia and the MAGnesium sulfate for Prevention of Eclampsia (MAGPIE) Trial for women with PE, provided the scientific evidence needed to promote MgSO₄ as the anticonvulsive of choice for the treatment of severe PE/E. In 2011, WHO developed evidence-based recommendations for the prevention and treatment of PE/E and recommended MgSO₄ as the anticonvulsant of choice in cases of severe PE/E. A review of National Essential Medicines Lists (EMLs) available on the WHO website and a survey conducted by the United States Agency for International Development’s Maternal and Child Health Integrated Program (MCHIP) in 2012 revealed that 88% (99/113) of countries surveyed included MgSO₄ in their EML.

Despite WHO endorsement and the presence of MgSO₄ on most EMLs, MgSO4 is still underused, incorrectly administered, or unavailable in many low-resource settings. This is due to a combination of provider and supply factors and directly related to the complexity of the treatment regimen:

• The current WHO regimen for MgSO₄ is extremely complex and requires intravenous (IV) and intramuscular (IM) administration, different dilutions for IV and IM doses, and different doses for IV, IM, loading, and maintenance doses. The current WHO regimen for MgSO₄ requires a 20% dilution for the IV loading dose, which requires health providers to calculate the quantity of sterile water to add to the MgSO₄ solution. Most health providers do not encounter eclampsia very often; when they do, trying to remember the complex regimen is daunting.
• Several presentations of MgSO₄ are on the market (1%, 2%, 15%, 50%, etc.) which make the calculation of dosing and dilution even more complex and confusing.
• Health care providers administering maintenance doses must carefully monitor the woman and her fetus, which may be difficult when there are shortages of qualified health care professionals.

The recommended level of health care for management of severe PE/E is in a facility with comprehensive obstetric and neonatal care capacity. Each level of care would, therefore, have specific treatment guidelines. For example, guidelines for initial management would be provided at all levels of care, and ongoing management would be provided at a facility with the capacity to provide comprehensive obstetric and neonatal care services.
• Although maintenance doses are associated with a small risk of magnesium toxicity, some providers do not administer maintenance therapy because they are afraid that toxicity could result in respiratory arrest.

• Most regimen for MgSO4 require administration of large, painful intramuscular (IM) injections (11 mL) every 4 hours for maintenance doses. Some providers do not administer maintenance therapy because they are reluctant to give these painful injections; patients may decline the maintenance dose for the same reason.

• If respiratory distress due to magnesium toxicity occurs, it is necessary to administer calcium gluconate, the antidote for MgSO4, but there are frequent stockouts and wastage of calcium gluconate due to product expiration.

• IM administration of MgSO4 requires 10 mL of MgSO4 plus 1 mL of 2% lignocaine. This requires a syringe size that may not be routinely available in health care facilities.

The underutilization of MgSO4 has led to a global call for workable, sustainable ways to increase access to and use of MgSO4.

Several ongoing studies are addressing barriers to use of the current WHO MgSO4 regimen.† Other researchers have studied alternate regimens for MgSO4 that reduce the dosage or change the endpoint for treatment in the postpartum period. However, the trials were too small to produce reliable conclusions.‡ Some providers observed that many patients who did not receive maintenance therapy due to suspicion or fear of toxicity or stockouts of MgSO4 did not convulse any further. This led to several small studies demonstrating the effectiveness of using a loading-dose-only regimen of MgSO4 for eclampsia.10,11,12,13,14 Unfortunately, the small size of these studies has made it difficult to draw any statistically reliable conclusions about the differential effects on the two reported primary outcomes: recurrence of convulsion and maternal death.

The following innovations may support access to and safe administration of MgSO4:

• A delivery system that makes it easier to safely administer MgSO4.

• Simplified treatment protocols.

• Prefilled injections that include lignocaine for IM injections.

• Job aids to help health care workers measure the correct dose of MgSO4, measure the amount of solution to add to get the correct dilution, and select the best way to administer the treatment.‡

† The Community level Interventions for Pre-eclampsia (CLIP) is conducting a cluster randomized controlled trial to test the hypothesis that a community-level intervention that shifts evidence-based approaches to primary health care (community and primary health center) will reduce the incidence of preeclampsia-related maternal morbidity and mortality. (http://pre-empt.cfire.ca/OBJECTIVES/CLIPTrial.aspx)

‡ Safe administration of maintenance doses and ongoing management of a woman with severe PE or eclampsia requires the following accompanying equipment and supplies: (1) a simple monitoring sheet to record pulse, blood pressure, respirations, urine output, proteinuria, reflexes, fetal heart rate, and administration of the drug; (2) a reliable device for measuring blood pressure, stethoscope, and fetal stethoscope; (3) a reflex hammer; (4) a urinary collection system; (5) dipsticks to measure proteinuria; (6) a timing device with a second hand; and (7) infection prevention and injection safety supplies.
In this short analysis we discuss the benefits and shortcomings of MgSO₄ delivery technologies currently available and outlines a rectal suppository delivery system under study. We also recommend investment in a study on simplified dosing and a simplified delivery system for MgSO₄.

**Technology solutions landscape**

A key element of managing severe PE/E is administration of MgSO₄ to prevent or control convulsions. MgSO₄ may be administered by continuous IV infusion or, alternately, by giving an IV bolus and IM doses for the loading dose followed by IM injections every 4 hours.¹⁵ Both IV and IM administration are appropriate. IM administration of the undiluted 50% solution results in therapeutic plasma levels in 60 minutes, whereas IV doses will provide a therapeutic level almost immediately.

In low-resource settings, the IM maintenance regimen is usually promoted for the following reasons: (1) ease of IM injections relative to IV injections and (2) relative safety of IM over IV doses in settings that do not have pumps to control the IV infusion.

**Syringe for IM or manual IV injection**

Both the IV and IM maintenance regimen require administration of a bolus IV loading dose of 4 g of a 20% solution of MgSO₄. Delivering the IV bolus dose of MgSO₄ manually via syringe requires the health provider to slowly administer the bolus over 5 to 20 minutes, which may be challenging for the provider and difficult in busy wards. If the initial IV bolus is administered faster than the recommended 5 to 20 minutes, this could potentially lead to increased pain, headaches, nausea, vomiting, and flushing.

The IM regimen is widely used, particularly in low-resource settings where resources to support IV administration are not available. Because syringes are readily available and cost less than US$1, IM is also the most affordable method. However, the IM regimen is not without its shortcomings: (1) it requires an initial loading dose with both IV and IM injections, (2) it requires somewhat complicated preparation of 50% and 20% solutions from available MgSO₄ preparations, and (3) it requires health providers to add lignocaine to the MgSO₄ solution to reduce pain from the IM injection. In addition, repeated IM maintenance injections are often extremely painful and can lead to risk for and development of abscess. Complaints of pain and side effects during IM injections may negatively influence a health care provider’s and patient’s decision to initiate or continue treatment. In extreme cases, magnesium toxicity may occur, which can cause respiratory paralysis, central nervous depression, and cardiac arrest.¹⁶ If toxicity does occur with the IM regimen, the IM dose cannot be “stopped.” Therefore, the fear that toxicity may occur may lead providers to under treat with MgSO₄. These limitations in administration may result in delayed or inadequate treatment of women with severe PE/E.¹⁷

**Springfusor® IV pump**

Go Medical Industries developed a syringe infusion pump called the Springfusor designed to simplify continuous IV infusions. It consists of a spring-driven cartridge that drives a syringe. The output (flow), is
controlled by Flow Control Tubing® (FCT), which was also developed by Go Medical Industries. The FCT is available in a variety of flow rates which allows the user to pair the appropriate FCT with the Springfusor to achieve the desired output for specific IV delivery needs. The system of Springfusor and FCT costs around $20 and does not require electricity or batteries. The Springfusor can be reused indefinitely on different patients; the FCT, however, must be replaced after each use. The Springfusor has US Food and Drug Administration approval.

The technology has also been used to deliver MgSO₄ in the treatment of severe PE/E in a recent trial in India.¹⁸ The trial was conducted at sites where the use of MgSO₄ by health care workers was low despite the fact that they understood its efficacy. Researchers hypothesized that the pain associated with IM injection of MgSO₄ was a barrier and that the Springfusor could offer a safe and simple IV alternative. The trial compared the current standard of care—a manually administered IV loading dose followed by maintenance therapy using an IM route of administration via syringe—with loading dose and maintenance therapy using an IV infusion administered by the Springfusor. No differences in maternal morbidity and mortality or neonatal mortality were observed between groups. Women participating in the standard of care delivery group (to whom health care providers manually administered the loading dose) experienced significantly more flushing, nausea, headache, and drowsiness compared with the women receiving the IV loading dose with the Springfusor.

Women treated using the Springfusor found the pain at the IV insertion site during the loading bolus to be acceptable or very acceptable (97%) compared with approximately half of the women in the standard of care group (50%) who received maintenance therapy using an IM route of administration via syringe. Women in the Springfusor group were also more likely to find the side effects acceptable or highly acceptable (Springfusor: 93%; standard of care: 39%). One challenge with the Springfusor was that some of the health care providers were not comfortable with or proficient at starting IVs.¹⁸

Medipacs, Inc. IV pump

Medipacs, Inc. is developing a nonmechanical IV infusion pump to deliver MgSO₄ which uses a proprietary, expandable polymer. The Medipacs pump is a wearable, disposable, and programmable device designed to provide accurate dosing and convenience at a low cost, around $20 per device.⁵ Little is known about the Medipacs technology to date because it is still in development. One perceived benefit of the Medipacs device is that it would not require health care providers to perform any dosing calculations because it would be prefilled, preprogrammed, and calibrated at the factory.

Programmable electronic IV infusion pumps

A variety of programmable electronic IV infusion pumps (for example, the Sigma 8000 IV infusion pump), are currently on the market. These are capable of delivering MgSO₄ for treatment of severe PE/E. However, they are expensive—generally around $2,500 per device—and require electricity from a main

---

¹⁸ Est; cost is still to be determined.
power source or a battery to operate. These barriers make electronic infusion pumps less appropriate for widespread MgSO₄ delivery in low-resource settings.

**Gravity-fed intravenous bag and IV stand**

A $20 gravity-fed IV bag and stand is an affordable and readily available way to deliver continuous IV infusion of MgSO₄ for treatment of severe PE/E. A health care provider prepares the IV bag by mixing the correct MgSO₄ dose regimen for the IV maintenance dose—the initial loading dose is given by IV bolus over a period of 5 to 20 minutes. Although it is a relatively simple delivery system, it requires careful calculation of drops per minute based on the drip set used (10, 15, 20, or 60 drops per mL) and the strength of the MgSO₄ solution. It also requires a provider to manually count the drops per minute to regulate the drip rate and achieve the therapeutic dose. In addition, the speed of infusion can change based on the patient’s position. Given the difficulties with manually regulating the drip rate, there is a potential for either under- or overdosing the patient.

**MgSO₄ administered as a suppository**

Dr. Thomas Easterling, MD, Perinatology and Obstetrics at the University of Washington Medical Center, has proposed the idea of administering MgSO₄ as a rectal suppository (personal communication, November 2011). It is not yet known whether MgSO₄ could be delivered by rectal suppository. Feasibility among women who are laboring and giving birth may be an issue because women may experience diarrhea and will most likely expulse the suppository during pushing efforts. If this method is possible, however, it has the potential to simplify dosing, provide a less painful method for delivering MgSO₄ compared to existing delivery methods, and allow use at lower levels of the continuum of care by reducing the need for highly trained health care providers.

Additionally, this method would create an entirely new market opportunity for pharmaceutical companies, facilitating opportunities to profit from MgSO₄ manufacturing and distribution. This has the benefit of increasing pharmaceutical companies’ interest in manufacturing and distributing MgSO₄, a drug that is currently seen as having limited profitability for pharmaceutical companies because it is so inexpensive. Although this delivery method is only in a conceptual stage, it should not be overlooked as a way to treat severe PE/E. An analysis to determine whether MgSO₄ may be successfully administered via rectal suppository for treatment of severe PE/E is probably worth further investigation based on the advantages it could have over existing delivery methods. Because exploration of this technology is still in its earliest stages, costs have not yet been determined.

**Simplified dosing**

One way to help health care providers to confidently, safely and accurately MgSO₄, is by simplifying the complex regimen currently recommended for eclampsia treatment. Small studies in Bangladesh, India, Nepal, and Nigeria have demonstrated the effectiveness of using a loading-dose-only regimen of MgSO₄ to treat eclampsia.¹⁰⁻¹⁴ A collaborative hospital-based, multicenter, multi-country, individually randomized controlled trial is needed to gather evidence that further supports this data.
There are several advantages to a loading-dose-only regimen for the treatment of eclampsia. First, it minimizes the complexity of dosing by reducing the different doses and routes used for loading vs. maintenance doses. Second, it minimizes the risk of toxicity because most cases of magnesium toxicity are related to administration of maintenance doses. This is a particular benefit for facilities that lack the staff, equipment, and medications (i.e., calcium gluconate as an antidote) to safely monitor and treat magnesium toxicity. Third, the volume of MgSO4 needed for the loading-dose-only regimen would be about a third of the standard regimen. Theoretically, this would translate into fewer stockouts of and higher coverage rates for MgSO4 for treatment of eclampsia.

Technology innovations, bolstered by new evidence for simplified dosing regimen, can address multiple challenges to making MgSO4 more accessible and utilized.

**Gap analysis**

There are still many gaps in our knowledge about enabling factors and barriers to providers’ correct use of MgSO4 for the treatment of severe PE/E. It would be useful to assess when and how health providers use the treatment and to gain a more thorough understanding of their overall attitudes and ideas about managing severe PE/E. This more specific understanding of enabling factors and barriers could inform targeted technologies and health system solutions.

A 2010 Cochrane review of alternative regimens of MgSO4 identified several important questions about how best to use MgSO4 for women with severe PE/E.10 These include:

- What is the minimum effective dose (loading and maintenance)?
- What are the advantages and disadvantages of IM and IV administration?
- Can the initial dose be safely given at community or primary health care levels before a patient is transferred to the hospital?
- Is the loading dose alone sufficient to treat severe PE/E?
- When is it best to stop treatment?

Addressing these questions would require large randomized trials of women with severe PE/E that compare alternative regimens and assess comparative effects on mortality, serious morbidity, adverse effects, and use of hospital resources for both the women and their babies.

Experts at a 2003 workshop in Bellagio, Italy, recommended the development of PE/E treatment “kits”19 to support the safe use and administration of MgSO4. These would contain:

- Calcium gluconate (given as an antidote to MgSO4 toxicity).
- Job aids to demonstrate dilution and decide on the dose to administer.
- A simple monitoring sheet to record a woman’s pulse, blood pressure, respirations, urine output, proteinuria, and reflexes; the fetal heart rate; and administration of the drug.
- A reliable blood pressure measuring device, stethoscope, and fetal stethoscope.
• A reflex hammer.
• A urinary collection system.
• Dipsticks to measure proteinuria.
• A timing device with a second hand.
• Infection prevention and injection safety supplies.

There is a need for research that identifies the most efficient and cost-effective ways of making sure all these items are readily available when a woman is receiving MgSO₄.

Preparing the correct solution of MgSO₄ is an important part of ensuring safety of its administration. In 2011, PATH conducted a survey on MgSO₄ with participants at the Maternal and Child Health Integrated Program Africa Regional Meeting on Interventions for Impact in Essential Obstetric and Newborn Care. Survey respondents stated that challenges to using MgSO₄ included difficulty with dose dilution and calculating an accurate dose.

This suggests that even when new, simpler delivery systems make it easier for health workers to administer MgSO₄, these systems will still need to be accompanied by job aids and tools that can assist providers with dilution and dosing.

Finally, although MgSO₄ itself is a relatively low-cost drug, it may be costly to develop delivery technologies that will allow health care providers to use it safely and correctly. It will, therefore, be useful to study the cost-effectiveness of new delivery systems and accessories and to consider whether ministries of health will be willing to pay additional fees for them.

**Investment opportunity**

As described, MgSO₄ has been identified as the most effective, safe, and low-cost treatment available for PE/E. However, MgSO₄ continues to be underused in low resource settings where PE/E is one of the leading causes of maternal death. This has been attributed to limited availability of MgSO₄ and difficulty administering it correctly. The activities described below may increase awareness and use of MgSO₄. Further, these efforts will support the development of a novel, single-dose pre-filled MgSO₄ delivery technology.

• Facilitate awareness of PE/E and use of MgSO₄ at national and international levels.
  – Conduct or gather multi-country situational analyses to review current data, policies, and practices related to PE/E; evaluate logistics systems for equipment, medications, and supplies for prevention, detection, and management of PE/E; and monitor and evaluate systems currently in place.

**The MgSO₄ survey conducted by PATH at the Maternal and Child Health Integrated Program Africa Regional Meeting on Interventions for Impact in Essential Obstetric and Newborn Care held in Addis Ababa, Ethiopia, in February 2011.**
- Conduct or review multi-country research on the use of MgSO₄, including identifying barriers and enabling factors to widespread use.

- Use findings to support advocacy efforts at the national and international level about the importance of PE/E and use of MgSO₄ and existing gaps that prevent access.

- Conduct randomized trials to establish the simplest, most effective dose of MgSO₄ (if possible, in collaboration with WHO).
  - Determine the easiest way to effectively administer the minimum effective dosing regimen for both IV and IM. Compare selected indicators and maternal and perinatal outcomes for administration of MgSO₄ via IV or IM.
  - Determine the minimum effective dosing regimen for both IV and IM regimens, including the possibility of developing dosing regimens based on the woman’s weight.
  - Establish whether a simplified dose regimen based on a single IM or IV dose is effective. To mitigate the risk that it would not be effective, other simplified (but increasingly more complex) dose regimens should be tested at the same time.

- Conduct randomized trials focusing on the development of a prefilled MgSO₄ delivery technology (if possible, in collaboration with WHO) with the goal of developing a product that will make it easier for health care workers at any level of a health care system to reliably and safely deliver the therapeutic dose.
  - Conduct clinical trials to compare administration of MgSO₄ via traditional routes versus the prefilled MgSO₄ delivery technology to determine the easiest way to effectively administer the minimum effective dosing regimen for both IV and IM doses. Compare selected indicators and maternal and perinatal outcomes.
  - Conduct operations research with prefilled MgSO₄ delivery technology and a simplified regimen in representative countries and settings in sub-Saharan Africa and South Asia to document implementation, disruptions, sustainability, lessons learned, and financial and service costs.
  - Collect feedback from women, family members, providers and managers on perceptions of acceptability, quality of care, and impact of the intervention on maternal morbidity and mortality. These may also guide choices around whether and how to scale up the interventions.
  - Compare before and after data to measure impact, disruption to the health system, and cost-effectiveness. Use data to conduct a trade-off analysis and decide on feasibility.

- Accelerate development of an easy-to-use prefilled MgSO₄ delivery technology and initiate efforts to increase availability and improve procurement strategies.
  - Research efforts to repackage and prepackage MgSO₄.
  - Determine whether alternative packaging or prepackaging would facilitate easier administration and increased availability.
  - Establish a manufacturer for prefilled MgSO₄ and gain appropriate global and regional-level regulatory approvals and registration.
  - Determine what other factors (cost, training, policies, etc.) influence availability.
  - Present findings to WHO to update international protocols for management of severe PE/E and for inclusion in the WHO list of essential equipment and supplies.
• Stimulate demand for MgSO₄ use (in general) in select target countries through advocacy, training, and, where necessary, pilot studies. Disseminate results of operations research on implementation of the new MgSO₄ protocols with the new delivery system.
  – Facilitate advocacy efforts at national and international levels for the new MgSO₄ delivery system.
  – Investigate supply systems and patterns of demand.
  – Leverage a large initial investment in procuring MgSO₄ and a large initial investment to strengthen the MgSO₄ supply chain. This will provide immediate sales for current MgSO₄ providers and necessitate maintaining supply channels for delivery of MgSO₄ in the target countries. The increased availability of MgSO₄ will act as a catalyst for its use, facilitate educating and training of providers, and necessitate future demand.
  – Strengthen and update national policies, guidelines, and clinical protocols for management of PE/E at all levels of the care continuum.
  – Provide essential equipment, supplies, and medications.
  – Develop and disseminate simple job aids for health care workers.
  – Develop and disseminate a simple dosing wheel.
  – Train health care workers on the use of MgSO₄ (preparation, dose, frequency); use of delivery system; monitoring women with severe PE/E; and use of calcium gluconate when necessary.
  – Establish a quality assurance system to monitor care and select indicators for PE/E.
  – Conduct community mobilization to sensitize communities about the importance of seeking care early during pregnancy and when danger signs of severe PE/E are present.
References


