Barriers to Use of Magnesium Sulfate for Pre-eclampsia and Eclampsia Management in Low- and Middle-Income Countries

A Brief Review of the Literature

Maternal deaths worldwide declined by 47 percent between 1990 and 2010, but for some regions of the world, the 2015 Millennium Development Goals remain a distant target. A staggering 85 percent of maternal deaths in 2010 occurred in just two regions: sub-Saharan Africa and Southern Asia (United Nations 2012a). Women in these two regions were less likely than women in other regions to be seen by a provider at least four times during their pregnancy, and they were less likely to be attended by skilled health personnel during childbirth (United Nations 2012b).

Pre-eclampsia/eclampsia (PE/E)—one of the leading causes of maternal mortality in low- and middle-income countries—claims the lives of an estimated 63,000 women worldwide each year (United Nations 2012a). The risk of dying of PE/E is approximately 300 times higher for women in developing countries than for women in developed countries (United Nations 2012a). As early as 1925, magnesium sulfate (MgSO4) became the standard treatment for PE/E in the United States. Until recently, there was widespread use of other, less effective anticonvulsants in the rest of the world. However, large clinical trials conducted between 1995 and 2002 found MgSO4 to be more effective than diazepam and phenytoin (Maggie Trial Collaborative Group 2002). MgSO4 has since been placed on the World Health Organization (WHO) Essential Medicines List and the United Nations 13 Life-Saving Commodities List.

Despite strong evidence that MgSO4 is the most effective drug available for the treatment of PE/E, it is not widely used in low- and middle-income countries.

Brief Literature Review

To enhance our understanding of the known barriers to the use of MgSO4, and to explore whether or not there are important additional relevant challenges, a brief review of the literature on barriers to the use of MgSO4 was conducted, inclusive of articles published since 2007. The following search terms were used: MgSO4, pre-eclampsia/eclampsia, low-resource countries, developing countries, barriers, and challenges. A comprehensive list of databases, including PubMed, MEDLINE, Academic Search Complete, MAS Ultra – School Edition, and others, were utilized, as were select websites. Articles referred to in the recent literature were included, as was USAID’s Maternal and Child Health Integrated Program (MCHIP) report on national programs for the prevention and management of postpartum hemorrhage (PPH) and PE/E. In addition, the 2011 WHO Model List of Essential Medicines and WHO’s 2011 Recommendations for the Prevention and Treatment of Pre-eclampsia and Eclampsia were reviewed (WHO 2011a and 2011b). WHO and United Nations websites were searched for relevant statistics. Altogether, 28 articles, websites, reports, and PowerPoint presentations were reviewed.

Thirty-seven countries in Africa, Asia, and Latin America participated in the 2012 MCHIP survey of national programs for the prevention and management of PPH and PE/E. The use of MgSO4 as the first-line treatment for severe PE/E has been approved by all of these nations, and the majority now include

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current PE/E management in pre-service and in-service training programs (Smith et al. 2013a). Additional findings from the MCHIP survey will be referred to throughout this literature review.

**Health Sector Infrastructure**

**Policy and Service Delivery Guidelines**

Based on the research and WHO guidelines, recommendations for the use of MgSO4 have been incorporated into policy in many countries, but this has not necessarily translated into practice modifications at the lower levels of care (Ridge, Eero, and Hill 2010; Smith et al. 2013a). The fact that practices have not changed may be a consequence of implementation guidance that remains unclear in many instances (despite available protocols from WHO) and poor dissemination of guidelines. In Zambia, standard treatment guidelines and guidelines for pregnancy, childbirth, and postpartum and newborn care were not consistent in their recommendations for the use of MgSO4 (Ridge, Eero, and Hill 2010). According to Bigdeli et al. (2013), Pakistan has approved MgSO4 as a first-line treatment for eclampsia, but there is no mention of an intramuscular (IM)-only regimen in any of the key policy documents. Drugs such as diazepam, shown to be less effective than MgSO4, are still listed as first-line treatment for severe PE/E. For instance, 25 of the countries surveyed by MCHIP in 2012 still included diazepam as a first-line treatment for severe PE/E (Smith et al. 2013a).

**Production and Availability of MgSO4**

If national policies and guidelines are not translated into well-coordinated implementation strategies, their dissemination remains ineffective (Smith et al. 2013a; Tita et al. 2005; Ridge, Eero, and Hill 2010; Bigdeli et al. 2013). In spite of Pakistan’s participation in studies that demonstrated the MgSO4’s effectiveness, as well as a cadre of supportive obstetricians and high awareness of the drug’s benefits, its use remains low there due to a fragmented system of registration, procurement, and distribution (Bigdeli et al. 2013). Similarly, in Mozambique and Zimbabwe, the procurement system is complex and cumbersome (Sevene et al. 2005). Evidently, since the market for MgSO4 is relatively small (as it is not widely used for other conditions), it is ordered by central medical stores only in response to requests from local physicians or specialists (Sevene et al. 2005).

The barriers to production and availability of MgSO4 include disincentives due to low market price and licensing. A number of the articles reviewed suggest that low pricing and a small market for the medicine (pre-eclampsia and eclampsia are relatively rare*) are significant deterrents to its production by pharmaceutical companies (Bigdeli et al. 2013; Aserud et al. 2005; Ridge, Eero, and Hill 2010; Sevene et al. 2005). Bigdeli et al. (2013) found that just one company was manufacturing the drug in Pakistan. In Zambia, at the time of the Ridge, Eero, and Hill (2010) assessment, MgSO4 was not licensed and there were no records of applications by private manufacturers or distributors to have MgSO4 injection licensed.

Recent data obtained by the MCHIP survey shows that progress has been made in terms of MgSO4 availability. Forty-eight percent of countries surveyed in 2011 (N=31) report regular availability, compared to 76 percent in 2012 (N=37). Results of the surveys are shown in the table below.

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* The global prevalence of hypertension in pregnancy is 5–11 percent, and eclampsia was responsible for 12 percent of maternal deaths in 2005 (Kang and Struben 2008; WHO 2013).
<table>
<thead>
<tr>
<th>Results of MCHIP Survey Countries, 2011 and 2012</th>
<th>2012</th>
<th>2011</th>
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<tbody>
<tr>
<td></td>
<td>All countries (%)</td>
<td>Latin America (n)</td>
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<tr>
<td>MgSO4 regularly available</td>
<td>76% (N=37)</td>
<td>5</td>
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<tr>
<td>Midwives authorized to diagnose PE/E and administer MgSO4</td>
<td>78% (N=30*)</td>
<td>4/5</td>
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<tr>
<td>Stock-outs:</td>
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<td>Rare</td>
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<td>Sometimes</td>
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<td>Frequent</td>
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<td>Current international standards for PE/E management included in:</td>
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<tr>
<td>Pre-service education curricula</td>
<td>86%</td>
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<tr>
<td>In-service training programs</td>
<td>92%</td>
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Smith et al. 2013a
* Number of countries participating in the survey in both years

Availability of Supplies

A limited supply of MgSO4 at the health care facility is certainly a barrier to its use, as are the high costs of related necessary supplies such as proteinuria dipsticks, airway, suction, mask and ambu bag, oxygen, intravenous (IV) equipment, furosemide for pulmonary edema, anesthesia apparatus, and the antidote drug calcium gluconate (Hassan-Bitar and Wick 2007; Barua et al. 2011; Ridge, Eero, and Hill 2010; Aserud et al. 2005; Tita et al. 2005; Firoz et al. 2011; WHO 2007). In their study of 15 health facilities in Pakistan, Bigdeli et al. (2013) found that MgSO4 was available at all teaching hospitals in the study (n=5), but just 20 percent of non-teaching hospitals had it (n=10). All of the hospitals in this study were missing some of the necessary equipment, many were missing related medicines such as calcium gluconate, and most of the pharmacies surveyed had no supplies of MgSO4 at all. In some countries, physicians report that the lack of drug availability is an obstacle, yet pharmacies only procure the drug if there is a demand from practitioners (Bigdeli et al. 2013; Sevène et al. 2005).

Although supplies of MgSO4 have improved, Smith et al. (2013a) found that more countries reported regular availability of MgSO4 at their Ministry of Health stores (86 percent) than at the health facility level (76 percent), reflecting a supply chain and distribution problem.
Health Service Delivery

Education and Training
With or without adequate supplies, providers are often reluctant to use MgSO4 due to the complexity of administration and a fear of adverse effects. Dosage quantities vary widely, with providers sometimes giving less than the recommended dosage and sometimes giving more (Mundle et al. 2010; Barua et al. 2011; Bigdeli et al. 2013). In other cases, women are referred immediately to higher-level facilities, without any emergency management, creating greater risk for the patient (Bigdeli et al. 2013). This occurs due to the belief that the drug must be administered at a tertiary facility, and when there are no protocols for its use or guidelines for referral (Barua et al. 2011; Bigdeli et al. 2013; van Dijk et al. 2013a).

Insufficient awareness, education, and training were mentioned as barriers in almost all of the articles reviewed (Bigdeli et al. 2013; Hassan-Bitar and Wick 2007; Barua et al. 2011; Ridge, Eero, and Hill 2010; van Dijk et al. 2013a; Tita et al. 2005). Regarding awareness and use of evidence-based reproductive health interventions, less than 50 percent of providers in Cameroon knew about MgSO4 (Tita et al. 2005). Although most providers in the Bigdeli et al. (2013) study were aware of MgSO4 as the first-line treatment for eclampsia, researchers reported that many were not aware of its use for severe pre-eclampsia. The majority of staff—both providers and pharmacists—had not had any formal training in the use of MgSO4 and knowledge of proper use of the drug was poor (Bigdeli et al. 2013). Maternal health experts interviewed in Mexico believed that few physicians were familiar with or used the MgSO4 guidelines (van Dijk et al. 2013a). Formal training was also found to be suboptimal in that curricula did not emphasize evidence-based care (Tita et al. 2005).

If health care providers are not in a high-volume facility, they are not called upon to treat severe PE/E with the frequency necessary to maintain their knowledge and skills. For this reason, researchers and respondents expressed a need for access to continuing education via the Internet, supervision and monitoring, seminars, refresher courses, daily physician-led ward rounds, and weekly lectures at hospitals (Tita et al. 2005).

Cumbersome Presentation
An important barrier at the facility level, which has received little attention in the literature, is the presentation and administration of MgSO4. Providers in the Bigdeli et al. (2013) study clearly identified this challenge. According to health staff who participated in focus group discussions and interviews, dosage preparation is one of the biggest barriers to use of MgSO4, because they must recall, calculate, and prepare the dosage themselves (Bigdeli et al. 2013). According to physicians in the Oaxaca study, the time it takes to find and prepare MgSO4 can be too much, especially in the overcrowded, understaffed situations that are common in the region. Instead, a more readily accessible and less time-intensive drug such as diazepam will be chosen (van Dijk et al. 2013b).

When MgSO4 is used, in the absence of clear guidelines and protocols, there are large variations in dosage quantity, most of which diverge from international guidelines (Bigdeli et al. 2013). This complexity is reflected in the following statement from a leading physician at Pathfinder International in India: “There is huge confusion in the field about intravenous and intramuscular (IM) doses. Even medical doctors are unable to calculate the accurate doses for MgSO4.” Incorrect calculations, he says, sometimes lead to complications, and the antidote, calcium gluconate, may not be available. This has created a myth in India that MgSO4 injection is a complex injection and only specialists (OB/GYNs) can give it.” Similarly, researchers in Oaxaca found the use of MgSO4 to be quite erratic and doses not at all standardized in practice (van Dijk et al. 2013b).
Providers in the Bigdeli study agreed that MgSO4 could be used in primary health care only if there is proper training (which should include follow-up and coaching) and availability of packaged and ready-to-use dilutions (Bigdeli et al. 2013).

Management and Staff Shortages
Inadequate and poorly implemented clinical guidelines are common (Aserud et al. 2005; Barua et al. 2011; Hassan-Bitar and Wick 2007). Clear policies and guidelines are often unavailable at health care facilities, one explanation for which may be the lack of national guidelines and lack of institutional accountability for following policies and guidelines (Aserud et al. 2005). Written protocols were not available in many of the facilities in the Bigdeli et al. study and, according to Barua et al., clinicians at hospitals studied in India noted a lack of specific institutional guidelines on dose, timing, and indications (Bigdeli et al. 2013; Barua et al. 2011).

The use of MgSO4 in its current presentation takes time to administer, and patients require frequent monitoring by properly trained staff. For a condition that is relatively infrequent, these requirements can deter implementation of MgSO4 use, particularly when workloads are overwhelming as a result of high patient volumes and staff shortages (van Dijk et al. 2013b; Lumbiganon et al. 2007; Hassan-Bitar and Wick 2007). Personnel shortages in a Palestinian hospital meant that the senior midwife had to share the workload with her staff and therefore could not provide adequate supervision (Hassan-Bitar and Wick 2007). Maintaining quality standards is a challenge when OB/GYNs and residents are responsible for 50 patients and eight surgeries in one shift (van Dijk et al. 2013b). Generally speaking, staff shortages are a major barrier to the provision of health care in low-resource countries. WHO has determined that 58 countries—36 in sub-Saharan Africa alone—face an acute health care worker crisis (Save the Children 2010).

With the necessary approvals, support, and training, midwives and skilled birth attendants can provide the services that are necessary for the reduction of maternal mortality. Among the countries surveyed by MCHIP in 2012, 78 percent authorize midwives to diagnose severe PE/E and administer MgSO4 (Smith et al. 2013a). Among countries that responded to the survey in both 2011 and 2012, the percentage authorizing midwives actually declined, from 84 percent in 2011 to 76 percent in 2012.

Additional Health Service Delivery Barriers
The following barriers were also identified in the literature reviewed:
- Political/social factors (Barua et al. 2011)
- Perceived lack of support from supervisors and low morale (Hassan-Bitar and Wick 2007)
- Delays in triage, transport, and treatment (Firoz et al. 2011)

Discussion

Health Sector
MgSO4 has gained widespread approval globally as a first-line treatment for pre-eclampsia and eclampsia, and it is included in national policy in many countries. However, several significant barriers to its use remain at the health sector level in low- and middle-income nations. Policies and guidelines are inconsistent across different regulatory bodies and levels of the system. There is poor dissemination of guidelines to facilities and weak or nonexistent accountability. Pharmacological companies are not motivated to produce the inexpensive drug for a small market, and central medical stores do not routinely stock MgSO4. Medical school curricula do not place an emphasis on evidence-based practices.
Health Services Delivery
According to Smith et al. (2013b), provider fears about harmful effects of MgSO4 are largely unfounded. Studies reviewed by Smith and colleagues show that the MgSO4 is a safe and effective treatment for PE/E, with relatively rare adverse events. Smith and colleagues also determined that concerns regarding the ability to provide adequate nursing care and laboratory resources are unfounded, as frequent measurements of serum levels are necessary only when there are clinical signs of toxicity (Smith et. al. 2013b).

While research continues to point to the need for better and ongoing education regarding the use of MgSO4, it will be necessary first to address the complexity of dosage and pervasive myths about who is qualified to administer the drug. A brief survey of Jhpiego field staff revealed that the different formulations on the market create confusion several countries, as well as a reason not to use MgSO4 and errors in administration. (These data will be presented at a PE/E symposium before the Women Deliver conference in Kuala Lumpur in May 2013.)

The presentation and administration of MgSO4 must be simplified and accompanied by clear guidelines and job aids distributed to all levels of the health system. This guidance would have a significant positive impact on provider comfort and confidence and, with proper training that includes follow-up and coaching, would increase the use of MgSO4. The majority of pre-eclampsia-related deaths in low- and middle-income countries occur in the community, and, therefore, interventions must be focused at the community level (Firoz et al. 2011). If treatment could begin before transfer to a higher-level facility, the negative effects of delayed triage, transport, and treatment would be mitigated. It is encouraging to note that Tukur et al. (n.d.) found promising results after lower cadre health workers were trained to administer a loading dose of MgSO4 before referral.
Bibliography


### Health Sector

#### Policy and Service Delivery Guidelines

- Guidelines not clear: WHO gives no dosages, no timing, etc.
- Two formulations on WHO’s essential medicines list, while one would suffice
- WHO does not support use by midwives
- Diazepam (also) as first-line treatment on WHO’s essential medicines list
- In some countries no national guidelines for the use of MgSO4
- Sometimes there is a national guideline, but it is poorly disseminated and/or not down to provider level
- Sometimes a guideline was developed and written by the department of OB/GYN of the hospital, but it is not widely used due to inadequacy of personnel
- In some sites, only doctors administer MgSO4 for SPE cases and decide when to deliver
- Some doctors use their own administration schedules and dosages, “based on experience”
- No monitoring of compliance to the guidelines
- Too many different formulations without job aids or instructions
- Sometimes MgSO4 is available, but quality is unknown: no prequal products
- Dosage not standardized

#### Production and Availability of MgSO4

- Magnesium sulfate often not available at sites
- No incentive for companies to invest in supply chain management, because of too little profit
- Transportation more expensive than production
- High tariffs and import fees on medicines
- To check possible side effects, a patella hammer must be in hospital
- Unavailability of calcium gluconate
- Unavailability of resuscitation kit, including ambu bag
- When governments order bulk at fixed times, medicines often expire before the next order
Health Service Delivery

Education and Training

- Not enough trainers
- Internal rotation of trained service providers every six months to one year
- No post-training follow-up
- When a new shipment has a different formulation, new training has to be given
- How to monitor signs and symptoms of pulmonary edema
- How to monitor patellar reflex
- Management of low urine output
- Repeating the dose of magnesium sulfate if further fits occur after 15 minutes
- Due to low caseloads staff tend to forget what they learned
- When high caseloads, service providers too busy for update and training
- Some doctors not confident in giving IV dosages
- Perception that the drug may be only used in high-level facilities with intensive care units
- Hesitancy among nurses and midwives to diagnose and treat eclampsia
- In some countries only midwives, and not nurses, are allowed to administer, and then only IM

Cumbersome Presentation

- Loading and maintenance dosages of magnesium sulfate
- Complicated dosage calculations and dilutions schedules

Culture/Awareness

- Providers are hesitant to treat due to fear for personal safety if poor outcome
- Community leaders do not know the benefits, so do not support use