

Magnesium Sulphate

For the Prevention and Treatment of Eclampsia
and Preeclampsia in Pakistan



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MAGNESIUM SULPHATE FOR THE PREVENTION AND TREATMENT OF PREECLAMPSIA AND ECLAMPSIA IN PAKISTAN

1. EXECUTIVE SUMMARY

Maternal health in Pakistan has been in a deplorable state for the indefinite past. Eclampsia is among the leading causes of maternal mortality, which accounts for around 10% of all maternal deaths. Importantly, eclampsia cannot be effectively treated at home once it occurs. Symptoms of preeclampsia and eclampsia need to be identified during antenatal care and treated by trained medical practitioner. Pathogenesis of eclampsia is not fully known and therefore its prevention strategies are limited. It is done primarily through preventing the development of preeclampsia or secondary by using pharmacologic agents to prevent convulsions in women with established preeclampsia. In the treatment of preeclampsia and eclampsia, the role of anticonvulsants is crucial for managing seizures during pregnancy. As for the choice between different drugs, much of the controversy has subsided under ever-growing and irrefutable evidence on the greater efficacy of magnesium sulphate. In light of the findings of several large-and small-scale randomized controlled trials, conducted in and outside Pakistan and also conducted collaboratively in multiple countries, there is now wide consensus among health practitioners and public health experts that magnesium sulphate is more effective in reducing convulsions and maternal deaths, compared to other anticonvulsants, i.e. Diazepam or Phenytoin. Magnesium sulphate is an anticonvulsant drug recommended by the World Health Organization as the most effective, safe, and low-cost treatment available for the treatment of severe preeclampsia and eclampsia.

Despite compelling evidence, magnesium sulphate use is below desired levels in Pakistan. Primary barriers to the use of magnesium sulphate in Pakistan are lack of national priority and guidelines, lack of education and training of concerned health staff and supply shortages. Further review of existing evidence show that there is not just absence of a coherent policy and guidelines on the use of magnesium sulphate, there are also issues with the supply of the drug. Its procurement and distribution is reflective of the demand made by health facilities where health practitioners lack training and therefore shy away from demanding the drug. Magnesium Sulphate is an extremely cost-effective drug and therefore its suppliers has very little profit margin. Resultantly, the drug remains unattractive for pharmaceutical companies. There is only one pharmaceutical company in Pakistan, which is supplying the drug in the local market. There

are also variation between the internationally recommended dosage regimen and route for the drug and those that are practiced in Pakistan at the tertiary level of care. This is reflective of the need for notification and communication of standardized protocols as well as training of health staff. While there is awareness among health practitioners on the effectiveness of the drug, however due to lack of training, there is a tendency at the basic and secondary levels of care to refer cases of preeclampsia and eclampsia to tertiary level without the management of convulsions.

In order to create wider acceptability for the use of magnesium sulphate, there is a need to create ownership, commitment and dedication among concerned policy and decision-making circles. Wider adaption of magnesium sulphate needs to be positioned as priority policy recommendation in public health spheres. Technical assistance in the form of preparation of standard guidelines and protocols for the use of magnesium sulphate as well as in case of referrals from one level of care to another is also needed. There should be a uniform policy for the dosage regimen and referral mechanisms. Uninterrupted supply from multiple pharmaceutical companies, literature in local language and availability of prefilled dosage are among a few steps needed to achieve the goal of making magnesium sulphate a norm for the treatment of preeclampsia and eclampsia in Pakistan. For Pakistan, the challenge is the integration of the use of magnesium sulphate into existing clinical practices and procedures for the management and prevention of the disease.

2. INTRODUCTION

The estimated number of annual maternal deaths for the world is in excess of 500,000 of which 99% occur in developing countries. Pakistan has the third highest number of maternal deaths after India and Nigeria followed by Democratic Republic of Congo, Ethiopia and Tanzania. Pakistan is among the 13 countries of the world that account for little more than two-thirds (67%) of all maternal deaths. In terms of highest maternal mortality ratios, however, Sierra Leone, Afghanistan and Malawi are the worst ranking countries. Globally, preeclampsia / eclampsia is among the five leading causes of maternal deaths and morbidity. The incidence of preeclampsia is estimated at 3.2% of all live births, giving a total number of over 4 million cases each year, of which over 72,000 are fatal accounting for 13% of all maternal deaths.¹ The prevalence of preeclampsia, however, varies in developing countries and ranges from 1.8% to 16.7%.²

Maternal health in Pakistan has been in a deplorable state for the indefinite past. At 276 per 100,000 live births, the maternal mortality ratio is well short of the 140 per 100,000 target set for

2015 under the Millennium Development Goals. In Pakistan slightly more than half of all maternal deaths are attributed to postpartum haemorrhage, puerperal sepsis, and eclampsia. According to Pakistan Demographic and Health Survey conducted in 2006 – 2007, out of every ten maternal deaths, one is attributed to eclampsia. Some small-scale facility based studies have found eclampsia to be responsible for as much as 16% to 30% maternal deaths in different settings of Pakistan.³ Importantly, many of the antepartum stillbirths are also associated with preeclampsia and eclampsia in Pakistan.⁴ Eclampsia cannot be effectively treated at home once it occurs. Symptoms of eclampsia need to be identified during antenatal care and treated by trained medical practitioner and monitored carefully. Effective prevention and treatment of preeclampsia/eclampsia, by and large, depend on antenatal care, functioning referral system and deliveries by skilled birth attendants.⁵ For effective treatment also, there is now firm evidence supporting the introduction of magnesium sulphate for significantly reducing the risk of eclampsia among women with severe preeclampsia.⁶

Despite compelling evidence, magnesium sulphate use in Pakistan is negligible. This article reviews and summarizes available evidence, in the context of Pakistan, on the efficacy, accessibility and acceptability of magnesium sulphate as a drug of choice in the prevention and treatment of preeclampsia and eclampsia. The article takes stock of existing research to explore barriers on adaption and usage of the drug as an internationally recommended treatment. It also brings forth recommendations in overcoming existing barriers in making magnesium sulphate a norm for prevention and treatment of preeclampsia and eclampsia in Pakistan. It is the purpose of this article to highlight existing barriers and behaviours among health practitioners and concerned professional in respect to the use of magnesium sulphate and to provide concrete recommendations which could help preparing a plan of action, messages and policy briefs for creating wider acceptance and usage of the drug in Pakistan.

3. METHODOLOGY

A three-pronged process is followed for the purpose of this literature review.

First, relevant literature both published and available in the grey literature, i.e. technical reports, policy briefs, and working papers, was collected. A variety of search engines, including PUB MED, Google Scholar, POP LINE and Reproductive Health Archive were used for finding relevant literature. Various combinations of search terms were utilized to access relevant literature, primary combinations of search strings contained ‘Pakistan,’ ‘Eclampsia’ and ‘Magnesium Sulphate.’ Articles written specifically in the context of Pakistan and those that

discussed barriers to the use of magnesium sulphate in general were included in the review.

Second, searched published literature was retrieved through using JStor, ScienceDirect, EBSCOHost, Elsevier Science, Oxford and Cambridge Journals electronic portals. Both published and grey literature was then thematically arranged. Relevant published and unpublished material available online and produced since 1990 was indexed and reviewed for the purpose of this article.

Third, the selected literature was further arranged according to its overall relevance to the literature review, i.e. common elements, innovations and implications in the context of Pakistan. Around 150 articles were reviewed and 90 are cited in this report.

4. PREECLAMPSIA AND ECLAMPSIA

Hypertensive disorders of pregnancy (HDP) represent a group of conditions associated with high blood pressure during pregnancy, proteinuria and in some cases convulsions. For the mother and the baby, the most serious consequences result from preeclampsia and eclampsia. These are associated with vasospasm, pathologic vascular lesions in multiple organ systems, increased platelet activation and subsequent activation of the coagulation system in the microvasculature. In pregnancy, if hypertension occurs before 20 weeks gestation, it is classified as chronic hypertension. Hypertension occurring after 20 weeks gestation is called pregnancy-induced hypertension, and the presence of proteinuria changes the diagnosis to preeclampsia. Eclampsia is usually a consequence of preeclampsia consisting of central nervous system seizures, which often leave the patient unconscious; if untreated it may lead to death. The long-term sequelae of both preeclampsia and eclampsia are not well evaluated, and the burden of HDP stems mainly from deaths.⁷ The diagnosis of Eclampsia is secure in the presence of generalized edema, hypertension, proteinuria, and convulsions. However, women in whom eclampsia develops exhibit a wide spectrum of signs, ranging from severe hypertension, severe proteinuria, and generalized edema to absent or minimal hypertension, no proteinuria, and no edema.⁸ Therefore, several clinical symptoms are potentially helpful in establishing the diagnosis of eclampsia. These symptoms may occur before or after the onset of convulsions, and they include persistent occipital or frontal headaches, blurred vision, photophobia, epigastric and/or right up- per-quadrant pain, and altered mental status.⁹ The onset of eclamptic convulsions can be antepartum, intra-partum, or postpartum, however, almost all cases (more than 90%) of eclampsia develop at or beyond 28 weeks. The remaining cases occur between 21 and 27 weeks of gestation (7.5%) or at 20 weeks of gestation or earlier (1.5%) (See table 1).¹⁰

Pathogenesis of eclampsia is not fully known and therefore its prevention strategies are limited. It is done primarily through the preventing the development of preeclampsia or secondary by using pharmacologic agents to prevent convulsions in women with established preeclampsia. Prevention can also be tertiary by preventing subsequent convulsions in women with established eclampsia. Currently, there is no preventive therapy for preeclampsia. During the past decade, several randomized trials reported on the use of protein or salt-restricting zinc, magnesium, or fish oil supplementation, low-dose aspirin, calcium, and vitamin C and E in women with various risk factors to reduce the rate or severity of preeclampsia, results of which have shown minimal or no benefit in reduction of preeclampsia.¹¹

**TABLE 1: TIME OF ONSET OF ECLAMPSIA IN RELATION TO DELIVERY
[PERCENTAGES]**

	Douglas and Redmanc ¹² (N = 383)	Katz et al ¹³ (N = 53)	Mattar and Sibai ¹⁴ (N = 399)	Chames et al ¹⁵ (N = 89)
Antepartum	38	53	53	67
Intra-partum	18	36	19	
Postpartum	44	11	28	33
≤48h	39	5	11	7
>48h	5	6	17	26

Current management schemes designed to prevent eclampsia are based on early detection of gestational hypertension or preeclampsia and subsequent use of preventive therapy in such women. Some of the recommended preventive therapies have included close monitoring (in-hospital or outpatient), use of antihypertensive therapy to keep maternal blood pressure below a certain level (less than severe range or to normal values), timely delivery, and prophylactic use of magnesium sulphate during labour and immediately postpartum in those considered to have preeclampsia. It is also assumed that appropriate and timely standard preventive therapy will avert eclampsia in virtually all patients with gestational hypertension-preeclampsia. In the treatment of preeclampsia and eclampsia, the role of anticonvulsants is crucial for managing seizures during pregnancy.¹⁶ As for the choice between different drugs, much of the controversy has subsided under ever-growing and irrefutable evidence on the greater efficacy of magnesium sulphate.

5. MAGNESIUM SULPHATE AS A DRUG OF CHOICE

Magnesium sulphate is an anticonvulsant drug recommended by the World Health Organization as the most effective, safe, and low-cost treatment available for severe preeclampsia and eclampsia. While severe preeclampsia is a common cause of maternal death, the efficacy and low-cost of magnesium sulphate make this condition a highly treatable one. Although its exact mechanism of action is unclear, magnesium sulphate is thought to treat eclampsia through affecting a series of cardiovascular and neurological functions and by altering calcium metabolism. In terms of administering the drug, magnesium sulphate is a solution that can be administered intramuscularly or intravenously, at a recommended concentration of 1.8 to 3.0mmol/L. For intramuscular administration, an initial 4g dose is given intravenously, followed immediately by a 10g intramuscular dose, and then 5g intramuscular doses every four hours in alternating buttocks. For intravenous administration, an initial 4g dose is given intravenously, followed by a 1-2g/h maintenance infusion given by a controlled infusion pump.

Magnesium sulphate has been on the World Health Organization's essential medicines list since 1996 and is highly affordable (a typical dosage costs US\$0.35 per ampoule). However, magnesium sulphate has not achieved widespread usage in developing countries. This is due to lack of public awareness of the drug, lack of adequate service-provider training, and lack of availability of magnesium sulphate in these areas. Magnesium sulphate is rarely globally manufactured because its low cost leaves little profit-based incentive for pharmaceutical companies to produce it for international market. For service providers or distributors to acquire magnesium sulphate, it is advisable to contact the local Ministry of Health and local pharmaceutical companies (or comparable entities) for information on how to do so. As of January 2012, WHO regulatory authorities had not yet prequalified manufacturers of magnesium sulphate. It was, however, placed on their 2010 Expression of Interest list as a drug for which they will accept requests for prequalification. There are no existing global public-sector price agreements for magnesium sulphate.¹⁷

6. EVIDENCE ON THE EFFICACY OF MAGNESIUM SULPHATE

One of the landmark studies to test the evidence supporting magnesium sulphate as the drug to evaluate for preeclampsia to prevent eclamptic convulsions is known as the Magpie [Magnesium Sulphate for Prevention of Eclampsia] Trial. The study was on a randomised placebo controlled trial that was conducted in 33 countries and included over 10,000 eligible women. The study effectively found that magnesium sulphate halves the risk of eclampsia, and probably reduces the

risk of maternal death. Furthermore, in the study there did not appear substantive harmful effects to mother or baby in the short term.¹⁸ In 2003, a systematic review showed that magnesium sulphate is substantially more effective than diazepam for eclampsia.¹⁹ A series of studies had already firmly established that magnesium sulphate is a better anticonvulsant than other available drugs, i.e. diazepam and phenytoin.²⁰ While magnesium sulphate has been the drug of choice in the United States, in Britain, for instance, Diazepam and phenytoin were favoured. However, by mid 1990s, a network of researchers – the collaborative eclampsia trial -reported the first large randomised trial comparing the three drugs and firmly setting new standards by producing compelling support for the use of magnesium sulphate. The trial reported that women were 52% and 67% less likely to suffer recurrent fits after treatment with magnesium sulphate than with, respectively, diazepam or phenytoin.²¹ A review article published in 1996 collated evidence on the use of magnesium sulphate from randomised trials and comes to a conclusion that the drug is superior in preventing the recurrence of seizures in eclampsia and seizure prophylaxis for preeclampsia.²² In a build-up to the Magpie Trial, several small-scale randomized control trials several small-scale randomized control trials were conducted which firmly established the efficacy of magnesium sulphate over other drugs for the treatment of preeclampsia and eclampsia.

In country-specific studies, a Population Council project on introducing magnesium sulphate in the hospitals of Kenya resulted in reducing the maternal mortality due to eclampsia by two-thirds and the overall maternal mortality by 40% in research sites.²³ A hospital-based prospective study conducted in Dallas, Texas found that selective magnesium sulphate prophylaxis results in an increased overall incidence of eclampsia because of more seizures in women with non-severe gestational hypertension who are not given magnesium sulphate prophylaxis.²⁴ A study involving 450 women managed at the Maternity Hospital in Kuwait found magnesium sulphate to be effective in preventing recurrence of eclamptic fits and safe for both mother and foetus.²⁵ In India, a small-scale study conducted on 30 patients with preeclampsia and 15 with eclampsia conclusively found that administration of magnesium sulphate to these patients was beneficial in relieving severity of the disease.²⁶ In a study comparing results arrived through randomized control trial with the real outcomes in Bangladesh, India, Pakistan and Nigeria, it was observed that improvements in maternal outcome with magnesium sulphate for preeclampsia/eclampsia in real world settings are comparable to those reported in trials.²⁷

In Pakistan, a cross-sectional study conducted at the Sobhraj Maternity Hospital over a period of two years from 1999 to 2000 with an objective to evaluate the use of magnesium sulphate as an anticonvulsant in the management of eclamptic patient found eclampsia to be well-controlled by

the use of MgSO₄. In its findings, convulsions were controlled in 94% patients despite lack of monitoring facilities of serum magnesium level.²⁸ Another study conducted at District Headquarter Hospital of Faisalabad in 2007 found MgSO₄ to be a better anticonvulsant in terms of total morbidity, recurrence of fits, maternal deaths and respiratory depression as well as in terms of total foetal morbidity and perinatal deaths when compared with Diazepam.²⁹ A study conducted over a period of four years from 2004 to 2008 at the Hayatabad Medical Complex in Peshawar reached at the conclusion that eclampsia, a major cause of maternal mortality and morbidity in Pakistan, can be effectively controlled with the administration of MgSO₄ for preventing recurrent fits and is safe for both mother and foetus.³⁰ Similarly, a study conducted at the Sandeman Hospital in Quetta in 2006 with an obstetric population of 3,050 deliveries found MgSO₄ to be a therapeutically effective consultant agent. In the same study, in 10% cases of recurrent convulsion, however, Midazolam was administered.³¹ A study conducted at the Punjab Medical College and in its affiliated hospitals on 60 patients divided equally as control and intervention groups found that magnesium sulphate is an effective drug for prevention of fits in patients of severe preeclampsia.³² In addition, there are a number of other small-scale studies, mostly relying on hospital records, conducted in Pakistan showing greater efficacy of magnesium sulphate in the treatment of preeclampsia and eclampsia and recommending magnesium sulphate as a drug of choice for reducing the rate of eclampsia.³³

In light of the findings of several large- and small-scale studies, also through randomized controlled trials, there is now wide consensus among health practitioners and public health experts that magnesium sulphate is more effective in reducing convulsions and maternal deaths, compared to other anticonvulsants, i.e. Diazepam or Phenytoin. In the case of mild preeclampsia, the consensus is that no anticonvulsant treatment is needed. However, either in the case of severe preeclampsia or eclampsia, magnesium sulphate is now considered as standard of care to treat convulsions.³⁴ In Pakistan too, role of magnesium sulphate in the prophylaxis of eclampsia is well proven.³⁵

7. BARRIERS TO THE USE OF MAGNESIUM SULPHATE

As mentioned above that despite compelling evidence magnesium sulphate use is below desired levels.³⁶ In an international call to governments and nongovernmental organizations, among similar initiatives taken by other advocacy groups, EngenderHealth urged all parties to prioritize magnesium sulphate as a life-saving treatment for eclampsia in the developing world. In 2007, EngenderHealth and University of Oxford brought together scientists, advocates, researchers, and representatives of various international nongovernmental organizations to identify country-

specific barriers to the availability and use of magnesium sulphate, as well as factors that facilitate its utilization in settings where the drug is not the treatment of choice within public health systems. The Call for Action identified lack of national priority and guidelines, lack of education and training and supply shortages, in countries like Pakistan, as the primary barriers to the use of magnesium sulphate.³⁷ In terms of supply and affordability it is important to note that analysis on data gathered through the Magpie trial showed that magnesium sulphate for preeclampsia costs less and prevents more eclampsia in low income countries and its cost-effectiveness substantially improves if it is used only for severe preeclampsia, or the purchase price is reduced.³⁸

Among studies that have originated from developing countries, Aaserud et al come to a conclusion in their case study on the policy and practice gap on the use of magnesium sulphate for the treatment of preeclampsia and eclampsia that “despite robust evidence from a landmark trial and systematic review of the effectiveness of magnesium sulphate for the treatment of preeclampsia, the drug is still not available...” and that “licensing, importation and production are probably not the most important barriers in most settings to translating this research evidence into practice.”³⁹ Duley, in order to promote evidence-based care for the treatment of eclampsia, recommends that key strategies in removing barriers to the use of magnesium sulphate are facilitating easy access to the drug, increasing understanding of how to evaluate health care interventions and the levels of evidence, and raising awareness of the evidence supporting the use of the drug. Furthermore, once the drug is available and clinicians are convinced of the need to use it, they need training and support in its administration as they gain experience and confidence.⁴⁰ A study conducted in Zambia found that the major barrier to the availability of MgSO₄ within the public health system was lack of procurement by the Ministry of Health. Other barriers identified by the study included a lack of demand by health professionals at the health centre level and a lack of in-service training in the use of MgSO₄. The study further found that where there was demand by obstetricians, magnesium sulphate injection was being procured from the private sector by the hospital pharmacy despite not being registered and licensed for use for the treatment of severe preeclampsia and eclampsia by the National Pharmaceutical Regulatory Authority.⁴¹ In Nigeria, while national protocol has been developed on the use of magnesium sulphate, there is need for further training of health workers on how to use this important drug.⁴² In Zimbabwe, it was found that delays in the availability of magnesium sulphate for the treatment of eclampsia were caused by poor communication between central medical stores and obstetricians, as well as by delays in adding magnesium sulphate to the WHO list of essential drugs.⁴³

Unavailability of the Drug: Among Pakistan-specific research, a study with an objective to observe pregnancy outcomes in eclamptic and to explore the avoidable factors contributing to the adverse outcome was conducted at the Hayatabad Medical Complex in Peshawar. The study was conducted over a period of 15 months in years 2001 and 2002 and noted that out of the 71 patients developed eclampsia, only 12 could be administered with MgSO₄ due to limited availability of the drug, which exhausted thereafter. The study further noted that mean stay for patients treated with magnesium sulphate is significantly less than to those treated with Diazepam. The study reaches at the conclusion that non-availability of ideal anticonvulsant – Magnesium Sulphate – for the majority of the patients has resulted in higher mortality as it was found higher at 18.6% in patients given parenteral Diazepam compared with 8.3% among those given MgSO₄.⁴⁴ The observation is consistent with the findings of other studies as in Dhaka mortality rates had fallen from 16% to 8% with the introduction of MgSO₄.⁴⁵ Similar was the observation of Sawhney et al who reported a significant reduction of maternal mortality with MgSO₄.⁴⁶

TABLE 2: AVAILABILITY OF MAGNESIUM SULPHATE IN PUBLIC HEALTH FACILITIES, SELECTED STUDIES

Sources	First Level Care Facilities, i.e. BHU, RHC	Secondary Level Care Facilities, i.e. THQ	Tertiary Level Care Facilities, i.e. DHQ
NPPI Baseline Survey Sindh, 2009	-	20%	3%
Fikree et al, 2006 – Multan	0% (n = 38; n = 8)	0% (n = 2)	0% (n = 1)
Shah and Pervaiz, 2006 – DG Khan ⁴⁷	0% (n = 35; n = 8)	0% (n = 1)	100% (n = 1)
WHO, 2010 – Kohat and Swabi ⁴⁸	40% (n = 4; n = 3)	-	50% (n = 2)
			5% (n = 21; n = 2; n = 0; n = 2)
NARI, 2009 – Dadu ⁴⁹			13% (n = 20; n = 1; n = 1; n = 1)

The issue of unavailability of drugs in health facilities is directly linked to its supply. On the lack of supplies of magnesium sulphate in health facilities, a baseline study conducted under Norwegian-Pakistan Partnership Initiative in Sindh in 2009 confirms this finding. The study reveals that only 3% district-headquarter facilities and 20% tehsil-headquarter facilities have the supplies of magnesium sulphate.⁵⁰ A study conducted in Multan covering 49 public health

facilities that included basic health units, rural health centre, and tehsil and district headquarter hospitals found that no facility had the supplies of magnesium sulphate.⁵¹ Importantly, clear policies concerning what level of facilities, health centres or hospitals, receive which drugs are vital for availability of sufficient stock. This is true of magnesium sulphate and its antidote calcium gluconate as lower level facilities might not receive the drugs because their staffs, including physicians, are not adequately trained in their use, or because regulations may restrict provision by certain cadres of staff (see table 2).⁵²

Availability of the Antidote: In terms of availability of drug and its antidote, several studies in Pakistan have reported severe lack of supplies of not only magnesium sulphate but also of its antidote. Together with magnesium sulphate, it is also extremely important that calcium gluconate is always available as an antidote for magnesium sulphate toxicity.⁵³ There is no comprehensive study conducted to-date to assess the availability of both the magnesium sulphate and calcium gluconate at different levels of public and private health facilities.

Capacity of Health Care Providers: In terms of training of health practitioners and availability of training-aid on the use of magnesium sulphate at the healthcare facilities, existing evidence shows that only those health practitioners who were either part of donor-funded projects, i.e. Pakistan Initiative for Mothers and Newborns, or participated in any randomized control trials, i.e. Magpie Trial, have received training and training-aid on the use of magnesium sulphate for.⁵⁴ Otherwise, health practitioners in Pakistan generally lack training on administering magnesium sulphate and are more comfortable in using anticonvulsants, i.e. Diazepam, that they have been using in the past.

As for the curriculum of midwives and nurses, table 3 provides brief overview of the present status. The curriculum of community midwives, which has been developed not too long ago, mentions magnesium sulphate as a drug to be taught for the prevention of eclampsia and to be injected only as a loading dose. A few studies that have explored level of knowledge of community midwives about preeclampsia/eclampsia and about the use of magnesium sulphate for its treatment are generally negligible. While curriculum for nurses, prepared Pakistan Nursing Council, does not contain any reference to magnesium sulphate as a drug of choice for the prevention and treatment of preeclampsia/eclampsia and only refers to anticonvulsants for the treatment of pregnancy-induced hypertension.

HEALTH PROVIDERS	CURRICULUM	KNOWLEDGE
Community Midwives	Drugs to be taught include magnesium sulphate to be injected only as a loading dose in cases of impending eclampsia. ⁵⁵	An assessment by Technical Resource Facility on behalf of the Program finds 62% of CMWs do not know how to advise mothers or the management of mild preeclampsia, while 68% also did not know what action to take in the case of severe preeclampsia before referral. ⁵⁶ Similar findings are made by a Population Council study in which only 19 CMWs knew how to administer MgSO ₄ out of a total of 106. ⁵⁷
Nurses	Unit III includes pregnancy-induced hypertension (eclampsia and preeclampsia) under safe motherhood and its referral, while anticonvulsants are part of unit V. ⁵⁸	No study available

Knowledge and Recognition of Preeclampsia/Eclampsia at the Household and Community Levels: At the household and community levels, knowledge and recognition of danger signs of preeclampsia and eclampsia are non-present or otherwise extremely limited. A review of literature conducted on maternal health issues in Pakistan in 1997 suggested that not only married women and their mothers-in-law had no knowledge of preeclampsia/eclampsia, extensive training on its danger signs is also needed for traditional birth attendants.⁵⁹ According to the most recent Pakistan Demographic and Health Survey, one-third of pregnant women in Pakistan receive no prenatal care at all. Of the two-thirds (61%), with at least one prenatal visit, consulting a skilled provider, only quarter learns about the symptoms of complications during pregnancy. Similarly, in qualitative formative research carried out in 2006 by the Pakistan Initiative for Mothers and Newborns, a USAID-funded project, bleeding, prolonged labour, retained placenta and fever were reported as threatening conditions during the entire duration of pregnancy. In ten districts, where baseline study was conducted, no where the knowledge about three or more danger signs was found to be more than one-third, while in six districts it was even less than 10%. In better-off districts, i.e. Rawalpindi, knowledge regarding pregnancy-induced hypertension as one of the danger signs was around one-quarter in rural areas and around one-third in urban areas. In predominantly rural districts, i.e. Buner and Upper Dir, the same was found to be around 10%.⁶⁰ These figures are indicative of general lack of knowledge among

married women in Pakistan about symptoms related to preeclampsia and eclampsia and increasing role of community-based health workers to share information about pregnancy-related danger signs in their respective catchment areas.

Health Care Delivery System: Perhaps one of the most relevant study conducted to date is an unpublished work by Hafiz and Rizwan where they have used both qualitative and quantitative approaches to study the barriers to the use of magnesium sulphate in Pakistan for the purpose of developing an informed policy.⁶¹ The review of findings from different studies conducted in Pakistan and those at which Hafiz and Rizwan arrived are arranged in table 4 connecting levels of health care delivery system.

LEVELS	BOTTLENECKS
Policy, Guidelines, Registration	There is only one pharmaceutical company in Pakistan – Zafa – that is manufacturing the medicine. In addition, the dosage recommended in EmNOC is different from latest recommendations.
Procurement and Distribution	Procurement of MgSO ₄ is mostly dependent upon the demands by the Health Departments and is therefore reflective of policies of respective facilities rather than of a central procurement policy. The Provincial Medical Store Depot manages the acquisition, storage and distribution of medicines.
Cost and Production	MgSO ₄ is low-cost drug; does not have incentives for pharmaceutical companies to manufacture and not used for other purposes and thus has limited demand.
Dosage Regimen and Route	There is variation in dosage quantities and regimens at the facility level. The study found only one facility using the internationally recommended regimen and that was due to the fact that the obstetrician was trained on essential surgical skills and emergency maternal and child health.
Availability	The availability of drug is considerably less in Sindh and Balochistan and if available in other provinces then it is only at the level of teaching hospitals. The drug is usually unavailable in private hospitals but larger pharmacies in major cities do have available stock. Similar problems of availability exist for the antidote and local anaesthesia.
Training	Pharmacists do not have dosage preparation training and the dosage was prepared in obstetric departments. Clinical guidelines are not always followed and in some settings diazepam and magnesium sulphate is administered together making the treatment dangerous. Most of the hospital staff administering treatment through magnesium sulphate does not have training and knowledge of recommended protocols and guidelines.

LEVELS	BOTTLENECKS
Awareness and Practices of Health Professionals	At the teaching hospital level, while there is awareness of the usefulness of magnesium sulphate, health professionals are mostly using other anticonvulsants in which they have been trained. Knowledge regarding usefulness of the drug during severe preeclampsia is also limited. At the tertiary care level and below patients are being referred without any emergency management. There are no referral guidelines and health professionals

8. ADDRESSING BARRIERS TO EXPAND ACCESS TO MAGNESIUM SULPHATE:

The National Essential Drug List, first prepared by the Ministry of Health in 1994 in partnership with the World Health Organization and most recently revised in 2007, includes magnesium sulphate as an essential drug at the primary, secondary and tertiary levels for the treatment of eclampsia and severe preeclampsia. However, the status of the National Essential Drug List remains murky with the passing of the eighteenth amendment to the constitution whereby health is now a devolved subject and a prerogative with provinces. The province of Punjab has adopted the National Essential Drug List as it is and sets itself the target of its yearly review, according to the needs of the population of Punjab, under the Punjab Health Sector Strategy for 2012 – 2020. One of the targets set under the Strategy for the revision of essential drug list is the inclusion of magnesium sulphate.⁶² In view of the eighteenth amendment, provinces can start by adopting the national essential drug list or the World Health Organization’s model list of essential drugs, both of which includes magnesium sulphate, and overtime revise it to their specific needs.

A study prepared for the United Nations Commission on Commodities for Women and Children’s Health explores the current landscape and available evidence on the use of magnesium sulphate for the prevention and treatment of preeclampsia and eclampsia identified eight key areas where there are potential barriers and gaps. These eight key areas have been summarized in table 5.⁶³ In addition to inclusion of magnesium sulphate in essential medicines lists in all provinces, there is also a need to develop and of endorsement by provinces of a standard treatment guidelines, including protocols on administering the drug, according to different levels of health care delivery and health practitioners. Once the drug is included in the essential medicines, it will require quality control and quality assurance measures for both public and private sectors. This would then be the federal prerogative under the four subjects that remain within the purview of health’s ‘national roles’—information, regulation, international commitments, and several elements of policy. More specifically it would be the task of the Drug

Regulatory Authority, whose bill has just been passed in the national assembly. As for its manufacturing, pharmaceutical companies will respond to demand from health facilities even if profit margins are thin. The manufacturing of drug could be made even more attractive for pharmaceutical companies by ensuring the widespread availability and appropriate utilization of affordable, ready-to-use “eclampsia treatment packs” for the administration of magnesium sulfate.

TABLE 5: ADDRESSING THE BARRIERS AND GAPS TO EXPANDING ACCESS TO MAGNESIUM SULPHATE

Barriers / Gaps	Description
Policy	Inclusion of MgSO ₄ in the essential medicines lists of all provinces and regions and similarly development and endorsement by provinces of standard treatment guidelines and protocols on administering magnesium sulphate.
Regulatory	Once registered, MgSO ₄ requires quality control and quality assurance measures within the public and private sectors, such as quality testing and post-marketing surveillance.
Manufacturing	Magnesium sulphate is rarely globally manufactured because its low cost that leaves little profit-based incentive for pharmaceutical companies.
Supply Chain Management	Earmark funds for the procurement of MgSO ₄ .
Demand by Providers	Ensure health providers are prescribing MgSO ₄ ; education and training is a key here that strongly influence the quality and level of provider care as well as acceptable standards of practice.
Demand by Consumers	Train staffs in the use of magnesium sulphate to shed any doubts about its utility and safety; and to address concerns hospitals might have about their reputation in the event of overdose and maternal deaths.
Information System	Implementation of a management information system (MIS) for logistics and to ascertain availability, accessibility, and appropriate use of medicine.
Financing	Address health costs, apparent and hidden, and financial barriers that may be prohibitive to providing or receiving treatment.

Importantly, demand by health providers for magnesium sulphate can only be increased if they are given adequate education and training, along with establishing standards of practice, for prescribing and administering MgSO₄. Side-by-side there is also a need to engage in a concerted communication with healthcare staff and with the management of health facilities to shed any doubts about drug’s utility and safety. Their apprehensions in the event of overdose and maternal deaths need to be addressed.

In addition to the study conducted by Hafiz and Rizwan, other research work in Pakistan that has come out with specific recommendations that has policy implications on the use of magnesium sulphate for the prevention of preeclampsia and eclampsia are:

1. Siddiqui et al. come to a conclusion that pharmacist intervention in the management of pregnancy-induced hypertension patients is needed to prevent pregnant mothers from preeclampsia and eclampsia.⁶⁴ This implies that not only health staff but pharmacists too, at public dispensaries or private pharmacies, need training on dosage preparation.
2. Fikree et al. find that with regards to eclampsia, physical examination by nurses and doctors were mainly 'poor,' however management, especially among doctors, depicted a better trend reflecting the need to build the capacity of health care provider on the prognosis of the disease.⁶⁵
3. Bhutta et al. make a recommendation on the basis that there is strong evidence of the benefits of magnesium sulphate for the prevention and management of eclampsia, it should be included in the repertoire of management strategies in first-level health facilities.⁶⁶ This would need guidelines for referral and protocols on drug's administration for first-level health facilities as well as extensive training and monitoring.
4. Spurrett and Cook, while reviewing the management practices in the Asia-Oceania region, recommend that the use of traditional birth attendant is a resource that needs to be utilised.⁶⁷ In Pakistan, where two-thirds of the births are still administered in non-medical setting, cannot be ignored for improving maternal health in general and reducing maternal mortality in particular.
5. Sheraz, Boota and Shahzad, besides highlighting the importance of an improvement in antenatal care, also come to a conclusion in their prospective study that upgrading the neonatal facilities and early delivery by caesarean section, in case of eclampsia, can improve the perinatal outcome.⁶⁸ This, however, remains, inconclusive.
6. An observational study conducted at the Department of Physiology at the Liaquat University of Medical and Health Science Jamshoro found evidence that magnesium has an important role for safe maternal and foetal outcome.⁶⁹ Magnesium supplementation is important for prevention of pregnancy-associated complications.

9. AREAS FOR FURTHER RESEARCH

Optimal Regimen: While there seems to be a general consensus in the scientific community on its efficacy, existing evidence is inconclusive about the optimal regimen for the administration of magnesium sulphate for the prevention and treatment of preeclampsia and eclampsia. A Cochrane review comparing different regimens for administration of magnesium sulphate used for the care of women with preeclampsia or eclampsia, or both, comes to a conclusion that although strong evidence supports the use of magnesium sulphate for prevention and treatment of eclampsia, trials comparing alternative treatment regimens are too small for reliable conclusions.⁷⁰ Though, there is evidence that loading dose of magnesium sulphate is a good alternative for standard Pritchard regimen as it avoids multiple painful injections of magnesium Sulphate.⁷¹ Although use of MgSO₄ is preferred to be through intravenous route, an alternative intramuscular regimen has also shown effectiveness. Accordingly, this regimen advocates a loading dose of combined intravenous and intramuscular administration followed by four hourly intramuscular maintenance therapies.⁷² A study in Bangladesh has also shown that administration of a loading dose of MgSO₄ at the community level before referral to hospital improved the maternal and perinatal outcomes of patients with eclampsia and preeclampsia at the hospital.⁷³ A study conducted in India comparing the efficacy of low dose magnesium sulphate (Dhaka) regime with the widely used Pritchard Regime in eclampsia found both to be equally effective. However, the study found that maternal and perinatal outcome was better in low dose magnesium sulphate (Dhaka) regime as compared to Pritchard regime.⁷⁴ In the context of Pakistan, any study that intends to look into preferable regimen for administering MgSO₄ will also have to explore acceptability and adaptability factors from the perspective of health practitioners.

Effect on Stillbirths: Further research is also needed to determine the effect of magnesium sulphate on stillbirths when administered in pregnancies with hypertensive disorders. A study by Jabeen et al. arrives at a conclusion that antihypertensive and magnesium sulphate supplementation for hypertensive disorders in pregnancy reduce morbidity and mortality associated with these disorders however their role in reducing stillbirths is not clear for which further research is needed.⁷⁵

Prophylactic Agent: Administering prophylaxis for mild preeclampsia is controversial. Recommendation for magnesium sulphate therapy for seizure prophylaxis is for all women with severe preeclampsia during induction or labour. American Congress of Obstetric and

Gynaecologists recommends magnesium sulphate in severe preeclampsia only.⁷⁶ Anthony et al. comes to a general conclusion that though magnesium sulphate is now the drug of choice for treating eclamptic patients, further studies are required to establish its role as a prophylactic agent in the prevention of eclampsia.⁷⁷ This has strong implications for Pakistan, especially when standardized health practitioners' and referral guidelines are yet to be developed.

Effects on Perinatal Morbidity and Mortality: Also, while available research has firmly established that the use of magnesium sulphate in comparison with other anticonvulsant for the treatment of eclampsia reduces the risk of maternal death and recurrence of seizures but its other effects on maternal morbidity, or perinatal morbidity and mortality are still not clear.⁷⁸ Further research is needed for establishing the effectiveness of the drug not just for the expecting mother but for her newborn as well.

9. POLICY RECOMMENDATIONS

- In general, there is a need for preparation of standard national treatment guidelines for the use of magnesium sulphate. Such a guideline could also include Pakistan-specific standard of care and protocols needed for administering MgSO₄. Guidelines developed by the World Health Organization and recommended through several best practices could be adapted.
- Together with standard national treatment guidelines, there is a need for a policy shift to focus more on cost-effective high-impact prevention and treatment to improve maternal health in Pakistan, i.e. through the use of magnesium sulphate. Such a policy shift would have to go beyond the Ministry of Health and needs to includes medical association, public health alliances, national programmes, civil society organisations, provincial and district governments, pharmaceutical companies and teaching hospitals. This will help make the drug a norm for the treatment and prevention of preeclampsia/eclampsia.
- There is also a need to ensure uninterrupted supply of the drug together with its antidote. More suppliers should be encouraged to manufacture and supply the drug locally in ready-to-use injections with usage instructions in local language. A prefilled dosage available with pharmacists could also help increasing the acceptability of the use of the drug by health practitioners. However, this would have to be backed-up by demand from health facilities for the drug.

- At the facility level, simplified protocols, referral guidelines, regular trainings and refreshers of health staff will increase the use as well as efficacy of the drug. Trainings and material needs to be specific different levels of healthcare delivery and the roles of the practitioners.
- Leading professional and local champions could also be engaged to encourage the use of magnesium sulphate in comparison with other available drugs in hospitals. This could be coupled with a monitoring and reward mechanism, which encourages hospitals in adapting magnesium sulphate as a standard of care for preeclampsia and eclampsia.
- Finally, simplified protocols that recommends standard dosage regimen and are available in one treatment box will help health staff in non-teaching facilities to use magnesium sulphate.

10. CONCLUDING WORDS

While there is now firm evidence on the efficacy of magnesium sulphate in the treatment of preeclampsia and eclampsia, early referral of patients or at-risk patients to a tertiary care institution would be needed to reduce morbidity and mortality. In addition, early referral to a facility providing basic essential obstetric care or comprehensive essential obstetric care is equally important. Another important factor is the correct diagnosis of preeclampsia during antenatal and postpartum care by screening, noting blood pressure levels, performing urinalysis for protein and asking about warning signs such as headache, blurred vision, epigastric pain, etc.⁷⁹ Prevention of eclampsia in Pakistan remains a challenge. This challenge can be met only, if there is a multipronged approach from investing more in maternal health and improved antenatal care in general to early detection and aggressive management of severe preeclampsia. Such measures can then help reducing incidence of eclampsia and its dreadful complications.⁸⁰ It is also important to note that the exact mechanism of action of magnesium sulphate remains largely hypothetical. Though the specific mechanisms of action remain unclear, the effect of magnesium sulphate in the prevention of eclampsia is likely multi-factorial.⁸¹ A review of the physiology of magnesium sulphate is essential to understanding pharmacodynamics actions, dosing guidelines, and safety requirements.⁸² For Pakistan, in the backdrop of firm evidence supporting the criticalness and importance of magnesium sulphate as a clinical tool to reduce the burden of eclampsia, the commitment to reduce high rates of maternal mortality will be assessed by the extent to which the use of magnesium sulphate is integrated into existing clinical practices and procedures⁸³

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