Magnesium Sulphate for the Management of Preeclampsia and Eclampsia in Low and Middle Income Countries: A Systematic Review of Tested Dosing Regimens

Rebecca Gordon, BSc,[1] Laura A. Magee, MD, FRCPC,[1,2,3] Beth Payne, BSc,[1,3] Tabassum Firoz, MD,[2] Diane Sawchuck, RN, PhD,[1,3] Domena Tu, BBA,[3] Marianne Vidler, BA, MPH,[1] Dane de Silva, BMLSc,[1] Peter von Dadelszen, MBChB, DPhil, FRCSC[1,2,3]; for the Community Level Interventions for Pre-eclampsia (CLIP) Working Group

[1]Department of Obstetrics and Gynaecology, University of British Columbia, Vancouver BC

[2]Department of Medicine, University of British Columbia, Vancouver BC

[3]Child and Family Research Institute, University of British Columbia, Vancouver BC

Abstract

Objective: To review systematically the magnesium sulphate ($MgSO_4$) dosing regimens tested in low and middle income countries (LMICs) for women with preeclampsia (prevention) and/or eclampsia (treatment).

Data Sources: We searched Medline, EMBASE, IPA, CINAHL, CDSR, and CENTRAL databases for relevant English language publications.

Study Selection: Our search yielded 753 publications, of which 26 (10 randomized controlled trials and 16 observational studies) evaluated $MgSO_4$ for preeclampsia and/or eclampsia in World Bank-classified LMICs.

Data Extraction: Independent, by two authors.

Data Synthesis: Twenty-five studies were conducted in hospital settings and one in the community. Rates of eclampsia were usually < 5% (median 3.0%, range 0.0% to 26.5%) even when $MgSO_4$ was administered for eclampsia. When dosage varied from the standard Pritchard or Zuspan regimens, almost all (n = 22) reduced the dose or duration of treatment, most commonly because of concerns about maternal safety, cost, or resource availability. Four trials of a loading dose only (4 g IV + 10 g IM) versus loading plus maintenance dosing of 5 g/4 hr IM found no difference in eclampsia recurrence (RR 1.64; 95% CI 0.48 to 5.65, n = 396). One study documented less eclampsia recurrence associated with community administration of a $MgSO_4$ loading dose before referral to a care facility versus treatment in a care facility (RR 0.23; 95% CI 0.11 to 0.49, n = 265).

Conclusion: Use of $MgSO_4$ for eclampsia treatment and prevention has been well-studied in LMICs, but concern remains about potential toxicity. Further studies are needed to identify the minimum effective dosage of $MgSO_4$ for management of preeclampsia and eclampsia and whether $MgSO_4$ loading can be safely administered in the community.

Key Words: Preeclampsia, eclampsia, developing countries, magnesium sulfate, anticonvulsants

Competing Interests: None declared.

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Résumé

Objectif : Procéder à une analyse systématique des schémas posologiques de sulfate de magnésium ($MgSO_4$) mis à l'essai dans des pays à revenu faible ou intermédiaire (PRFI) chez des femmes présentant une prééclampsie (prévention) et/ou une éclampsie (traitement).

Sources de données : Nous avons mené des recherches dans les bases de données Medline, EMBASE, IPA, CINAHL, CDSR et CENTRAL afin d'en tirer les publications anglophones pertinentes.

Sélection des études : Notre recherche nous a menés à 753 publications, dont 26 (10 essais comparatifs randomisés et 16 études observationnelles) ont évalué l'utilisation de $MgSO_4$ dans des cas de prééclampsie et/ou d'éclampsie au sein de PRFI identifiés par la Banque mondiale.

Extraction de données : Indépendante, menée par deux auteurs.

Synthèse des données : Vingt-cinq études ont été menées en milieu hospitalier et une étude l'a été en milieu communautaire. Les taux d'éclampsie étaient habituellement inférieurs à 5 % (médiane : 3,0 %, plage : 0,0 % - 26,5 %) même lorsque du $MgSO_4$ était administré pour contrer l'éclampsie. Lorsque les posologies utilisées s'éloignaient des posologies standard Pritchard ou Zuspan, pratiquement chacune d'entre elles (n = 22) réduisait la dose de $MgSO_4$ ou la durée du traitement, la raison

la plus couramment citée étant la présence de préoccupations au sujet de la sûreté maternelle, des coûts ou de la disponibilité des ressources. Quatre essais ayant comparé le seul recours à une dose de mise en charge (4 g IV + 10 g IM) au recours à une dose de mise en charge et à une dose d'entretien de 5 g/4 h IM n'ont constaté aucune différence en matière de récurrence de l'éclampsie (RR, 1,64; IC à 95 %, 0,48 - 5,65, n = 396). Une étude a constaté une récurrence moindre de l'éclampsie associée à l'administration d'une dose de mise en charge de $MgSO_4$ en milieu communautaire avant l'orientation vers un établissement de soins, par comparaison avec l'administration d'un tel traitement au sein d'un établissement de soins (RR, 0,23; IC à 95 %, 0,11 - 0,49, n = 265).

Conclusion : Bien que l'utilisation de $MgSO_4$ aux fins de la prévention et de la prise en charge de l'éclampsie ait bien été étudiée au sein des PRFI, des préoccupations subsistent quant à sa toxicité potentielle. La tenue d'autres études s'avère requise pour identifier la posologie minimale efficace de $MgSO_4$ pour la prise en charge de la prééclampsie et de l'éclampsie, ainsi que pour déterminer si une dose de mise en charge de $MgSO_4$ peut être administrée en toute sûreté en milieu communautaire.

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INTRODUCTION

Together, preeclampsia and eclampsia are among the top three causes of maternal death globally.[1] Ninety-nine percent of these maternal deaths occur in low and middle income countries, in which 10% to 25% of maternal deaths are due to preeclampsia or eclampsia.[2] The major burden of maternal death is in sub-Saharan Africa and South Asia, where the risk of death is nearly 200 times greater than in high income countries.[3] In addition to their catastrophic impact on mortality rates, preeclampsia and eclampsia cause life-threatening and life-altering morbidities that increase the burden of these diseases substantially in both high and low income countries.[2]

Preeclampsia is traditionally defined as new hypertension (diastolic BP ≥ 90 mm Hg) and significant proteinuria in women at ≥ 20 weeks' gestation. Preeclampsia is thought to be a pregnancy- and placenta-specific form of systemic inflammation that affects multiple organ systems.[4] One of the most severe and characteristic complications of preeclampsia is eclampsia, defined as the occurrence of one or more tonic-clonic seizures in the presence of symptoms, signs, and/or laboratory findings of preeclampsia.[5] In low-resource settings, where access to health care is limited, eclampsia occurs with greater frequency.[6,7]

In 1925, magnesium sulphate was introduced into clinical practice to treat eclampsia.[8] Since then, $MgSO_4$ has been proven to more than halve the risk of occurrence of eclampsia in women with preeclampsia and of recurrence in women with eclampsia.[9–12] A Cochrane review of alternative $MgSO_4$ dosing regimens included four randomized controlled trials from LMICs, three from India, and one from South Africa.[13] $MgSO_4$ is recognized by the World Health Organization and the United Nations as both a priority medicine and a life-saving commodity for the treatment of severe preeclampsia and/or eclampsia.[14]

$MgSO_4$ is generally administered parenterally in a loading dose (IV with or without additional IM dosing) followed by maintenance dosing (by continuous IV infusion or intermittent IM injections). The two most commonly used regimens are the Zuspan regimen (a loading dose of 4 g IV, and maintenance dosing of 1 g/hr IV) and the Pritchard regimen (loading doses of 4 g IV and 10 g IM, and maintenance dosing of 5 g IM/4hr).[15,16]

Although well-studied and widely used in high-income countries, $MgSO_4$ is underutilized in LMICs. This is because of many barriers, such as:

1. unreliable supply of the compound and the materials required for its administration,
2. lack of training of health care providers about $MgSO_4$ administration, and
3. lack of political will to change procurement of and licensing protocols for $MgSO_4$.[17]

$MgSO_4$ for treatment of severe preeclampsia and eclampsia was listed on only 50% of 89 countries' Essential Medicines Lists in a recent review.[18] Another major challenge to the effective use of $MgSO_4$ is the lack of prenatal care received by women in LMICs, which leads to late (if any) presentation to the tertiary health care facilities where $MgSO_4$ is most commonly available. All of these barriers may result in suboptimal use of $MgSO_4$. The global health community has recognized the barriers to use of $MgSO_4$ for eclampsia prevention and treatment as a key issue. Consequently, the United Nations Population Fund is addressing the issues of variability in formulation and the potential for mixing errors by mapping $MgSO_4$ manufacturers and moving towards a standardized formulation and presentation of $MgSO_4$.

Our primary aim in this study was to review the $MgSO_4$ dosing regimens that have been evaluated in LMICs for eclampsia prevention or treatment, and to document

ABBREVIATIONS

BP	blood pressure
IM	intramuscular
IV	intravenous
LMIC	low or middle income country
$MgSO_4$	magnesium sulphate
RR	relative risk

the associated maternal side effects and maternal and perinatal mortality. A secondary aim was to gain further understanding of barriers to $MgSO_4$ use and trends in research involving this compound in LMICs.

METHODS

We searched the following databases for English language publications: Medline (from 1946), EMBASE (from 1974), IPA (from 1978), CINAHL (from 1982), CDSR (from 2005) and CENTRAL (from 1991), up to January 3, 2013. We included all studies investigating the use of $MgSO_4$ for preeclampsia and/or eclampsia in any of the 144 LMICs.[19] Observational studies and RCTs were included. Two authors independently reviewed the database search results for eligible studies and relevant extracted data; disagreement was resolved by consensus.

We abstracted the following outcomes: eclampsia occurrence or recurrence (depending on the study population), maternal mortality, perinatal mortality (and stillbirth and neonatal death separately), and serious maternal side effects directly related to $MgSO_4$ use. In the case of RCTs comparing $MgSO_4$ with other anticonvulsants, we collected only information from the $MgSO_4$ arm(s) of each trial, as our interest was limited to dosing regimens, outcomes, and maternal side effects, rather than the effectiveness of $MgSO_4$ (which has been proven compared with other agents[9–11,20,21]).

Both qualitative and quantitative analyses were performed. The effectiveness of loading dose-only studies, in comparison with loading plus maintenance therapy, was analyzed using Cochrane Review Manager 5.1 software (Nordic Cochrane Centre, Copenhagen, Denmark). A relative risk for recurrent seizures was calculated for:

1. community administration, and
2. loading dose-only studies compared with the standard Pritchard dosing regimen.

RESULTS

Of 753 studies identified, we included 26, and of these 10 were RCTs.[6,15,16,22–44] Four RCTs were included in the relevant Cochrane review.[13] The majority of studies were excluded because they did not evaluate $MgSO_4$ in an LMIC. Two studies were excluded because they were published in Spanish.[45,46]

The 26 studies included were from 10 different LMICs (Bangladesh, Brazil, India, Nepal, Nigeria, South Africa, Thailand, Turkey, Pakistan, and Zimbabwe), representing all World Bank regions except the Middle East and North Africa. In total, the studies enrolled 4688 women, ranging from 17 to 736 per study (Table 1). Reported definitions of the hypertensive disorder of enrolled women varied in availability and detail. Eclampsia was defined most often as "symptoms of eclampsia" (n = 15), and was not defined at all in four other studies. The definition of preeclampsia was hypertension and proteinuria (n = 5), "imminent eclampsia" (n = 3), or was not defined at all (n = 6).

The only community-based $MgSO_4$ study was from Bangladesh. Women with eclampsia or "severe preeclampsia" were administered a loading dose of $MgSO_4$ before referral to a care facility, where all women received "maintenance treatment" (not further explained).[6]

Twenty-five studies were conducted in hospital settings in which $MgSO_4$ was usually administered for eclampsia treatment (n = 14 studies), rather than prevention (n = 4); in the seven other studies, $MgSO_4$ was used for eclampsia treatment and prevention in a mixed population of women with eclampsia and preeclampsia.

Outcomes associated with $MgSO_4$ treatment for eclampsia prevention and/or treatment are shown in Table 1. Eclampsia rates were < 5% in most studies (shaded dots), and < 10% in all but three others (shaded lines). Eclampsia occurred in seven women administered a 10 g IM $MgSO_4$ loading dose (13%), compared with the standard Pritchard regimen.[43] There were three cases of eclampsia (15%) in a small study of low-dose $MgSO_4$.[16] Recurrent eclampsia occurred in 35 women referred to hospital for eclampsia (26.5%), compared with eight women (6%) who received a loading dose of $MgSO_4$ in the community before transfer to hospital.[6]

At least one maternal death was seen in 17 of the studies, with a median of 1.5% maternal deaths (range 0% to 10.6%); the authors attributed none of the deaths to magnesium toxicity. Rates of perinatal mortality (median 20%, range 2% to 65.4%), and stillbirth (median 11.4%, range 1.5% to 55.4%) and neonatal death (median 10%, range 4.6% to 30.8%) were also high.

The reported dosing regimens are summarized in Table 2. The 26 studies described 39 regimens. All studies administered loading doses, usually by a combination of IV and IM routes (n = 31 regimens), but also by IV only (n = 7) or IM only (n = 1).[43] The Pritchard (n = 12) and Zuspan regimens (n = 3) were most commonly used. The most common IV loading dose was 4 g (n = 32), although others used 2 g (n = 3) or 3 g (n = 2); this was usually followed by two IM loading dose injections of $MgSO_4$ (i.e., one into each buttock) of 5 g IM every 4 hours (n = 14).

Table 1. Characteristics of included studies

Study	Region (country)	RCT	Type of HDP	Definition	Women n	Timing of treatment relative to delivery (women), n			Eclampsia* n (%)	Maternal death n (%)	PNM n (%)	SB n (%)	NND n (%)
						AP	IP	PN					
Abbade et al. (2010)[15]	Latin American and Caribbean (Brazil)	●	PET/E	"symptoms of eclampsia"	29	—	—	—	—	—	—	—	—
Adewole et al. (2000)[23]	Sub-Saharan Africa (Nigeria)		E	"symptoms of eclampsia"	21	18	1	2	1 (4.8)	1 (4.8)	3 (14.3)	—	—
Begum et al. (2001)[24]	South Asia (Bangladesh)		E	"symptoms of eclampsia"	65	63	—	2	1 (1.5)	0	11 (17.0)	8 (12.3)	3 (4.6)
Bhalla et al. (1994)[25]	South Asia (India)	●	E	"symptoms of eclampsia"	45	34	5	6	1 (2.2)	0	4 (8.8)	1 (2.2)	3 (6.6)
Bhattacharjee et al. (2011)[26]	South Asia (India)	●	E	"symptoms of eclampsia"	67	37	16	14	5 (7.5)	1 (1.5)	10 (15.0)	5 (7.5)	5 (7.5)
					70	38	16	16	6 (8.6)	3 (4.3)	13 (18.6)	6 (8.6)	7 (10.0)
Chatterjee and Mukheree (1997)[27]	South Asia (India)		E	"symptoms of eclampsia"	16	14		2	—	0	4 (25)	2 (12.5)	2 (16.0)
Chinayon (1998)[28]	East Asia and Pacific (Thailand)		E	"symptoms of eclampsia"	90	50	25	15	—	3 (3.3)	9 (10.0)	4 (4.4)	5 (5.5)
Chissell et al. (1994)[29]	Sub-Saharan Africa (South Africa)	●	Severe PET	dBP ≥110mmHg Proteinuria ≥1+	9	—	—	—	0	0	—	1 (11.1)	—
				Other symptoms	8	—	—	—	0	0	—	1 (12.5)	—
Chowdury et al. (2009)[30]	South Asia (India)		E	"symptoms of eclampsia"	480	312	86	82	16 (3.3)	24 (5.0)	108 (22.5)	47 (9.8)	61 (12.7)
					150	100	15	35	3 (2.0)	5 (3.3)	23 (15.3)	10 (6.6)	13 (8.7)
Coetzee et al. (1998)[31]	Sub-Saharan Africa (South Africa)	●	Severe PET	2 or more of: dBP≥110mmHg, significant proteinuria, signs of imminent eclampsia	345	—	—	—	1(0.3)	0 (0)	—	38 (11)	—
Crowther (1990)[32]	Sub-Saharan Africa (Zimbabwe)	●	E	"symptoms of eclampsia"	24	—	—	—	1 (4.2)	1 (4.2)	—	—	2 (8.3)
Ekele and Ahmed (2004)[34]	Sub-Saharan Africa (Nigeria)		E	—	33	—	—	—	2 (6.1) within 30 min	—	—	—	—
Ekele et al. (2009)[33]	Sub-Saharan Africa (Nigeria)		E	Tonic-clonic convulsions, elevated BP, proteinuria	121	29	79	166	9 (7.4) within 4 hrs	12 (9.9)	—	67 (55.4)	—
Gr et al. (2012)[44]	South Asia (India)		Imminent E/E	—	100	—	—	—	1 (1.0)	0 (0)	20 (20)	—	—
					100	—	—	—	3 (3.0)	3 (3)	37 (37)	—	—
Malapaka and Ballal (2011)[22]	South Asia (India)	●	Imminent E/E	—	75	57	5	10	6 (8.3)	1 (1.4)	23 (31.9)	7 (9.7)	4 (7.4)
					54	39	7	5	0 (0)	1 (1.9)	22 (40.7)	8 (14.8)	8 (14.8)
Mahajan et al. (2009)[35]	South Asia (India)		E	"symptoms of eclampsia"	58	80		15	6 (8.3)	1 (1.4)	27 (28.4)	11 (11.6)	16 (16.8)
					37				0 (0)	1 (1.9)			
Nagar et al. (1988)[36]	South Asia (India)		E	"symptoms of eclampsia"	101	66	16	19	2 (2.0)	0 (0)	10 (9.9)	—	—

Continued

Table 1. *Continued*

Study	Region (country)	RCT	Type of HDP	Definition	Women n	Timing of treatment relative to delivery (women), n			Eclampsia* n (%)	Maternal death n (%)	PNM n (%)	SB n (%)	NND n (%)
						AP	IP	PN					
Noor et al. (2000)[37]	South Asia (India)		PET/E	"symptoms of eclampsia"	133	76		4	2 (1.5)	9 [8 E, 1 PE] (6.8)	25 (18.8)	—	—
Okusanya et al. (2012)[43]	Sub-Saharan Africa (Nigeria)	●	Severe PET/E	Severe PET: BP>160/110mmHg and 2+ proteinuria, E: severe PET and convulsions	54	—	—	—	7 (13.0)	4 (7.4)	12 (22.2)	—	—
					49	—	—	—	2 (4.0)	0 (0)	1 (2.0)	—	—
Orji et al. (2012)[42]	Sub-Saharan Africa (Nigeria)	●	Severe PET	—	85	—	—	—	0 (0)	0 (0)	2 (2.4)	—	—
					85	—	—	—	0 (0)	0 (0)	6 (7.1)		
Raman and Rao (1995)[39]	South Asia (India)		Imminent E/E	"symptoms of eclampsia/imminent eclampsia"	736	676		60	21 (2.9)	21 (2.9)	263 (32.1)	144 (19.6)	—
Regmi et al. (2010)[38]	South Asia (Nepal)	●	E	"symptoms of eclampsia"	37	33		4	0 (0)	0 (0)	—	—	—
					43	36		7	2 (4.7)	1 (2.3)			
Seth et al. (2010)[16]	South Asia (India)		PET/E	Preeclampsia: proteinuria detected by dipstick with blood pressure over 140/90 mmHg after 20 weeks GA. Eclampsia: appearance of convulsions	26	26	0	0	2 (7.7)	2 (7.7)	17 (65.4)	9 (33.3)	8 (30.8)
					20	20	0	0	1 (5.0)	0 (0)	8 (40.0)	6 (28.8)	2 (10)
					20	20	0	0	3 (15.0)	1	8 (40.0)	6 (30)	2 (10)
Shamsuddin et al. (2005)[6]	South Asia (Bangladesh)		Severe PET/E	—	133†	—	—	—	8 (6.0)	3 (2.3)	—	14 (10.5)	—
					132				35 (26.5)	14 (10.6)		21 (1.5)	
Shoaib et al. (2009)[40]	South Asia (Pakistan)		Severe PET	BP >140/100, 2+ proteinuria, symptoms of imminent eclampsia	100	—	—	—	0 (0)	0 (0)	—	—	—
									1 (2.0)	0 (0)			
Taner et al. (1996)[41]	Europe and Central Asia/Turkey		E	"symptoms of eclampsia"	444	397		47	5 (1.1)	42 (9.5)	265 (60.0)	171 (38.5)	94 (21)

*For eclampsia, cell shading reflects the eclampsia rate: dots (< 5.0%), white (5.0% to 9.9%), and lines (≥ 10.0%).

†This group was referred to hospital; their treatment course followed local standards and was not tracked.

AP: antepartum; dBP: diastolic blood pressure; E: eclampsia; HDP: hypertensive disorder of pregnancy); IP: intrapartum; NND: neonatal death; PET: preeclampsia; PNM: perinatal mortality; PN: postnatal; SB: stillbirth.

Table 2. Summary of $MgSO_4$ dosing regimens

			Loading dose										Maintenance dose†														Dosing if seizure occurred after start of treatment
			IV (g)				IM (g)‡						IV (g/hr)						IM (g)					IM frequency (per n hr)				
	RCT*	women, n	2	3	4	6	4	5	6	8	9	10	0.67	1	2	2.5	4	5	2	2.5	4	4.5	5	3	4	5	6	8	
Abbade et al. (2010)[15]	•	14			•									•															—
	•	15			•									•															—
Adewole et al. (2000)[23]		21			•																		•			•			2 g IV
Begum et al. (2001)[24]		65			•				•											•					•				10 mg diazepam
Bhalla et al. (1994)[25]§	•	45			•					•											•				•				1.5 g IV
Bhattacharje et al. (2011)[26]	•	67			•																		•					•	2 g IV
	•	70			•							•											•		•				2 g IV
Chatterjee and Mukheree (1997)[27]		16			•							•											•				•		—
Chinayon (1998)[28]		90		•								•											•		•				—
Chissell et al. (1994)[29]	•	9			•							•											•		•				—
	•	8				•									•														—
Chowdury et al. (2009)[30]		480			•							•											•		•				2 g IV
		150			•																		•		•				2 g IV
Coetzee et al. (1998)[31]	•	345			•									•															—
Crowther (1990)[32]	•	24			•							•											•		•				2 g IV
Ekele and Ahmed (2004)[34]		33			•							•											•		• (12 hr.)				2 g IV
Ekele et al. (2009)[33]		121			•							•																	"initiate maintenance protocol"
Gr et al. (2012)[44]		100	•										•																2 g IV
		100			•								•																2 g IV
Malapaka and Ballal (2011)[22]	•	72			•														•					•					2 g IM or IV
	•	54			•							•											•		•				2 g IM or IV
Mahajan et al. (2009)[35]		58	•							•							•								•				—
		37	•				•										•								•				Repeat loading dose
Nagar et al. (1988)[36]		101			•							•											•				•		—
Noor et al. (2000)[37]		133			•							•																	5 g IM
Okusanya et al. (2012)[43]	•	54										•																	—
	•	49			•							•											•		•				—
Orji et al. (2012)[42]	•	85			•							•											•		•				—
	•	85			•							•																	—
Raman and Rao (1995)[39]		736			•							•											•		•				2 g IV; 10mL diazepam iv if still not stopped

Continued

Table 2. *Continued*

	RCT*	women, n	Loading dose: IV (g) 2	3	4	6	Loading dose: IM (g)‡ 4	5	6	8	9	10	Maintenance dose†: IV (g/hr) 0.67	1	2	2.5	4	5	Maintenance dose†: IM (g) 2	2.5	4	4.5	5	IM frequency (per n hr) 3	4	5	6	8	Dosing if seizure occurred after start of treatment
Regmi et al. (2010)[38]	•	37			•							•											•		•				2 g IV
	•	43			•							•																	Initiate maintenance protocol
Seth et al. (2010)[16]		26			•							•											•		•				—
		20			•																								—
		20			•			•									•							•					—
Shamsuddin et al. (2005)[6] ‖		133			•				•																				—
Shoaib et al. (2009)[40]		50			•							•																	—
		50			•							•													•				—
Taner et al. (1996)[41]		444		•							•							•				•						—

* When only one arm is presented, the treatment in the other arm was $MgSO_4$. Some observational studies had two different treatment regimens studied and both are presented here, when relevant.

† Maintenance therapy was continued for 24 hours after delivery or last convulsion (whichever was later) unless otherwise stated.

‡ The IM loading dose was administered by two injections, one into each buttock.

§ Only the $MgSO_4$ + nifedipine arm of this trial was included, as the other treatment arm was lytic cocktail + nifedipine.

‖ This group received maintenance therapy in facility but the dosage was not reported. This group was compared against a group that received treatment in facility after referral from the community. The treatment in hospital was not reported and therefore the group was omitted from this table.

As shown in Table 2, lower doses or abbreviated durations were frequently used (n = 22 regimens from 20 studies), compared with the standard Pritchard or Zuspan regimens, either by decreasing the administered dose in grams (n = 21) or by decreasing the duration of therapy (n = 1). Two studies decreased only the loading dose, while the majority decreased the maintenance therapy dose (n = 10) or both loading and maintenance doses (n = 9). When stated (n = 10), the reasons for dosing modification were:

1. the small size of women reflecting the potential for Mg toxicity (n = 4),
2. other concerns about toxicity (n = 6),
3. inconsistent supply of the drug (n = 3),
4. cost-effectiveness (n = 3),
5. lack of resources required for consistent and effective monitoring of patients (n = 3), and
6. difficulties with repeated IM injections for the patient (n = 1);

multiple reasons were often stated in a single paper. Only one study investigated a higher IV maintenance dose (2 g/hr vs. 1 g/hr) with the rationale that serum magnesium concentrations on the standard Zuspan (1 g/hr) regimen had been "low" and possibly ineffective.[29]

Seven studies (26.9%) administered only a loading dose of $MgSO_4$; in five of these studies, the loading dose was compared with a loading dose plus maintenance therapy regimen.[16,33,37,38,40,42,43] Five studies were RCTs and two were observational. Four RCTs compared a 14 g Pritchard loading dose (4 g IV + 10 g IM) with the full Pritchard regimen (of the same loading dose plus 5 g/4 hr IM maintenance therapy)[16,38,40,42]; the loading dose-only regimen was associated with a similar risk of eclampsia, but the 95% CIs were wide (RR 1.64; 95% CI 0.48 to 5.65, n = 396 women). In a fifth RCT of 103 women with eclampsia or severe preeclampsia, a loading dose of 10 g IM (without the 4 g IV) was compared with the standard Pritchard regimen (of loading and maintenance dosing)[43]; there was no significant difference between groups in eclampsia occurrence ($P = 0.142$) or recurrence ($P = 0.195$).

In the only community-based study of $MgSO_4$ administration (in Bangladesh), 265 women with eclampsia received either a 10 g loading dose (4 g IV + 6 g IM) in their own home or no treatment followed by referral (for all women) to an emergency obstetric care facility with $MgSO_4$ availability.[6] This

study involved task shifting from the care facility into the community, through training of field workers (to create community awareness and identify eclampsia and severe preeclampsia cases) and focal point persons (such as general practitioners, to evaluate women, administer $MgSO_4$ as appropriate, and refer as soon as possible to the nearest care facility). Community administration of a $MgSO_4$ loading dose before transfer was associated with a lower rate of eclampsia recurrence (RR 0.23, 95% CI 0.11 to 0.49) than transfer and $MgSO_4$ administration in the care facility.

As also shown in Table 2, 19 of the regimens reported treatment with $MgSO_4$ for recurrent seizures, usually 2 g IV (n = 11) or "IV or IM" (n = 2), or initiation of maintenance therapy in loading dose-only studies (n = 3). Two studies, one in 1995 and the other in 2001 (after publication of the 1995 Collaborative Eclampsia Trial[20]), included diazepam as a treatment for recurrent seizures.[24,39]

Reports of severe maternal adverse effects directly attributed to $MgSO_4$ administration were rare: "magnesium toxicity" (3/152 women from 2 studies[26,29]), "adverse reaction" (1/685 from one study[33]), and "respiratory depression or distress" (4/346 from three studies[23,25,38]).

DISCUSSION

In this systematic review, we found a large number of studies in LMICs of use of $MgSO_4$ for eclampsia prevention and treatment. Although the hypertensive disorder was often not well defined, eclampsia occurred infrequently in most studies, even among those that enrolled women with eclampsia. This is consistent with the effectiveness of $MgSO_4$ as demonstrated in the controlled setting of RCTs.[13] It should also be noted that maternal and perinatal mortality were high in the included studies, reflecting the severity of disease and the health care systems in which these studies were conducted. Maternal adverse events were unusual, and no maternal death was attributed by any authors to the use of $MgSO_4$.

Despite insufficient evidence about their effectiveness, alternative $MgSO_4$ dosing regimens (of varying types) have been studied in LMICs.[13] The dose or duration of treatment has been reduced in almost all cases because of concerns about $MgSO_4$ toxicity or availability.

The safety of $MgSO_4$ use in LMICs has also been highlighted by a recent review focused on safety (24 studies, 9556 women)[47]; maternal respiratory depression occurred in 1.3% of cases (range 0% to 8.2%), calcium gluconate was used in less than 0.2%, and only one maternal death was attributed to $MgSO_4$ (associated with a serum Mg level of 24 mEq/L).

All but one of the studies included in our review were conducted in hospital settings. This is consistent with the fact that $MgSO_4$ is generally administered in a care facility, but this presents a challenge in rural areas where transportation can take hours, and the resulting delay in administering $MgSO_4$ could tip the balance between a positive and a negative outcome for mother and baby. The only study of community administration of $MgSO_4$ in women with eclampsia[6] suggested that such early treatment followed by transport to a care facility may be beneficial for mothers. It will be important to see if these results can be replicated, and perhaps extended to women with preeclampsia and a high risk of adverse outcomes.

The strength of this review is the comprehensive description of dosing regimens and major outcomes. The review also has limitations. First, our literature review was limited to six major databases and did not search for articles not indexed in these databases or in grey literature. We also excluded non-English language publications (n = 2) for practical reasons, and we recognise that studies from LMICs may be missed by such a strategy. Second, most studies did not adequately describe the hypertensive disorder suffered by their study subjects.

CONCLUSION

Administration of $MgSO_4$ has been widely studied in LMICs for eclampsia prevention and treatment, with ensuing low rates of eclampsia and a favourable safety profile. The tendency to use lower doses or shorter durations of treatment than have been proven effective in RCTs suggests concerns about $MgSO_4$ toxicity. Further studies of both reduced-dosing regimens and community administration of $MgSO_4$ are required, given that delays in triage, transport, and treatment at a care facility have been targeted for improvement in order to decrease maternal mortality.

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