EXPERT VIEW/REVIEW PAPER

Magnesium Sulphate Prophylaxis in Severe Preeclampsia-lessons Learnt from Recent Trials Conducted in Low-Middle-Income-Countries – A Systematic Review

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Abstract

Aim and background: Searching is ongoing to find an alternative prophylactic magnesium sulphate regimen for severe preeclampsia despite 24 hours recommendation of the World Health Organization (WHO). This review finds the provision of any such substitute prophylactic instead of the recommended ones searching through the recently published trials.

Objectives: To endorse any alternative prophylactic magnesium sulphate regimen effective for severe preeclampsia.

Methods: *Data sources:* Studies are retrieved from the bibliographic databases of PubMed, Scopus, and Cochrane Library.

Eligibility Criteria, Participants, and Interventions: Included studies are recently published trials intended to compare the efficacy of different modified regimens of magnesium sulphate prophylaxis for women with severe preeclampsia in contrast to the standard regimen.

Results: Out of a total of Fifteen, eight studies evaluated different abbreviated regimens of magnesium sulphate prophylaxis. A lower maintenance dose of magnesium sulphate as preeclampsia-prophylaxis was assessed by two. In addition, four studies evaluated the efficacy of only loading doses of magnesium sulphate as prophylaxis. Finally, one study estimated a placebo in the postpartum period compared to the standard regimen.

No incidence of eclampsia was reported in any group of eight studies. Even in the rest seven studies, eclampsia incidences did not appear significantly higher in the study group allocated for either abbreviated or low dose or loading-dose regimens. However, a statistically significant number of women in the study groups needed extension/reinstitution of prophylaxis. Low-dose and loading dose prophylaxis are found unsuitable for a recommendation. Apart from the established safety potential, abbreviated/short-course prophylaxes of magnesium sulphate have been found to generate different secondary benefits.

Conclusions: The abbreviated postpartum regimen of magnesium sulphate can be recommended as prophylaxis for severe preeclampsia instead of recommended schedule if applied judicially.

Keywords: Eclampsia, Low dose, Magnesium sulphate, Preeclampsia, Prophylaxis.

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Introduction

Rationale

Hypertensive disorders of pregnancy are among the three top causes of maternal jeopardy worldwide.[1] As per recent data from World Health Organization (WHO), 3–10% of pregnant women suffer from hypertensive disorders during pregnancy, which is a 14% contributor to worldwide maternal mortality.[2] Preeclampsia, a spectrum of hypertensive disorders of pregnancy, is characterized by hypertension (140/90) with proteinuria, which usually develops after 20 weeks of gestation.[3] In World Bank-classified low-middle-income countries, preeclampsia can be complicated in 10% of cases as severe preeclampsia.[4,5] Severe preeclampsia is defined when the blood pressure of preeclamptic women rises more than 170/110, along with the development of different features of upper quadrant epigastric pain, thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, unexplained new-onset headache or visual disturbances.[4] Among all cases of 5% severe preeclampasia can progress to life-threatening eclampsia, characterized by the onset of generalized convulsions and/or coma.[6] Low-middle-income countries (LMIC) have a higher rate of eclampsia, amounting to 16–69 cases per 10,000 births, in contrast to Europe, where the rate is 2–3 per 10,000 births.[7]

Whereas there is limited scope to prevent the development of preeclampsia, obstetricians target to prevent the progression of life-threatening complications.[8] To achieve this, WHO recommends 24 hours of magnesium sulphate prophylaxis in all severely preeclamptic women but at the same time acknowledges the possibility of difficulties that can arise if the total dose of 24 hours postpartum has to be administered, especially, to all severely preeclamptic women of LMIC.[9,10] Magnesium sulphate, being a drug with a narrow therapeutic index, has several complications in a higher dosage ranging from sweating, nausea, vomiting, lethargy, hypotension, loss of deep tendon reflexes, respiratory depression,

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coma, cardiac arrest, and ultimately death.[11] In a practical scenario, most women of LMIC are of low body weight in contrast to the Western world, and most of the delivery units there are devoid of intensive care facilities to combat unacquainted drug toxicity if it occurs.[12] Over and above, those facilities are either understaffed and/or overburdened, which makes it often unworkable to administer total magnesium sulphate routine prophylaxis for 24 hours postpartum to all severely preeclamptic women, irrespective of their disease severity. Considering these realities, some authors thus rightfully concluded that routine full-dose administration of magnesium sulphate to all severely preeclamptic women might generate potential adverse effects that may outweigh the risk of seizure, keeping in their mind the fact that 129 women with asymptomatic preeclampsia and 35 women with severe preeclampsia needed to be treated with magnesium sulphate to prevent one case of eclampsia.[13]

Thus, there is always a search for an alternative magnesium sulphate regimen applicable to a mass population of preeclamptic women that is safe and effective in preventing the progression toward eclampsia. However, a Cochrane review of alternative magnesium sulphate regimens for eclampsia and preeclampsia, published in 2000, expressed that the evidence needed to be adequate to establish whether the alternative regimens are as efficacious and safe as standard regimens.[14] Our research question has been initiated from there.

Objectives

The objective of this research is to find answers to whether an adjusted low dose or an abbreviated regimen, or even a single loading dose of magnesium sulphate prophylaxis is capable of preventing eclampsia in severe preeclamptics instead of applying complete traditional dosing and, if so, which regimen among them can be suggested safely and finally, even if chosen, can any of this modified regimen be applicable for all severely preeclamptic women indiscriminately?

With the above context, we have done a systematic review of available studies that compared the effectiveness of different magnesium sulphate regimens applied to severely preeclamptic women of LMIC aiming to prevent eclampsia.

Implementing this study result might be helpful to re-evaluate or strengthen the present guidelines and recommendations of prophylactic magnesium sulphate application in severely preeclamptic women of LMIC who are often under-cared and, thus, susceptible to developing toxicity of magnesium sulphate.

Methods

Eligibility Criteria, Information Sources, Search Strategy

The review followed guidelines detailed in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[15]

We have searched the bibliographic databases since 2000: PubMed, Scopus and Cochrane Library. As the present review deals with the existing published studies, we sought no ethical clearance.

The review protocol is registered in INPLASY register with the registration number INPLASY202340031, and the DOI number is 10.37766/inplasy2023.4.0031

Eligibility Criteria

The inclusion criteria of the studies are mentioned below. Studies were chosen if all five of the following criteria met;

1. Randomized controlled trials or quasi-experimental studies where the study and control group enrolled only severely preeclamptic women.
2. Comparing magnesium sulphate regimens of low dose or abbreviated durations, loading dose, or placebo with any standard magnesium sulphate regimens.
3. The trials' Primary or secondary outcome was "incidences of eclampsia" or "occurrence of fit".
4. Conducted in LMIC and published on or after 2000.
5. Full-text articles with an entire manuscript in English.

The specification of LMIC countries follows the recent new World Bank country classifications.[4] We categorically avoid or are technically compelled to avoid low-income countries because we could not find a single study from any designated 28 low-income countries.

Search Strategy

The following search items were used using combinations of MeSH and free text terms.[16] The search terms were:

- "Eclampsia".
- "Pre-eclampsia".
- "Eclampsia hypertension".
- "Eclampsia pre-eclampsia".
- "Eclampsia gestational hypertension".
- "Eclampsia pre-eclampsia magnesium sulfate".
- "Magnesium sulfate".
- "Eclampsia pre-eclampsia severity symptoms-headache, visual disturbance, epigastric pain, vomiting".
- "Type of eclampsia-antepartum,intrapartum, post-partum, late post-partum".
- "Pregnancy induced hypertension".

The selected search terms were combined alternatively with the Boolean logic (AND, OR and NOT).

We have limited our searches to English (both American and UK English spelling). Records retrieved were subsequently reviewed and duplicates were removed. Additional studies were identified manually from the reference lists of eligible studies and similar review articles.

Study Selection

After screening the abstracts and full-text articles retrieved from the search, two reviewers independently chose the studies according to inclusion criteria and, after corroboration, prepared the final list of eligible studies following the exclusion of the common ones. Finally, they extracted the data from those studies using a standardized form.

Data Extraction and Data Items

We included trials where primary or any secondary outcome measure is incidences of eclampsia and, thus, enrolled the incidences of the same. In addition, we evaluated other effective outcomes like essential side effects of magnesium sulphate (nausea, vomiting, flushing, respiratory depression, and oliguria) and some secondary outcomes (time to start ambulation, breastfeeding, and duration of hospital stay) as retrieved from some studies.

Assessment of Risk of Bias

We have evaluated the ''risk of bias'' in studies according to the Cochrane Handbook and considered each study's selection, performance, detection, attrition, reporting, and other biases.[17]

Data Synthesis

Two reviewers performed the data extraction individually, and any discrepancy was sorted out by discussion. If required, third and fourth reviewers consulted to conclude. Qualitative data were described by using textual narrative synthesis.

Results

Study Selection

The initial parallel search generated 110 and 124 citations by two authors (Fig. 1). About 34 full texts were reviewed by them respectively, of which 13 were retrieved as eligible after discussion and meeting all inclusion and exclusion criteria. In addition, two studies retrieved from the included trials' references were identified later as appropriate and added.

Study Characteristics

The characteristics of the 15 included studies are represented in Table 1.[18–32] All the studies were conducted in LMIC. Four studies were retrieved, from India, whereas three were from Brazil, and two were from Nigeria. In addition, we have recovered one study each from Panama, Iran, Thailand, Pakistan, and Nepal and included a multicentre trial conducted in Latin America.

Eight studies have been found to compare different abbreviated regimens of magnesium sulphate with standard prophylaxis (Conventional vs short maintenance). Two studies compared a lower maintenance dose of magnesium sulphate with regular maintenance (Conventional vs low dose). Four studies evaluated the efficacy of only loading doses of magnesium sulphate as prophylaxis (Conventional vs loading dose). One study evaluated placebo in the postpartum period in contrast to the standard regimen (Conventional vs Placebo).

We have included only those studies that enrolled severely preeclamptic women as their study subjects. However, as depicted in Table 1, an in-depth search revealed 11 studies registered

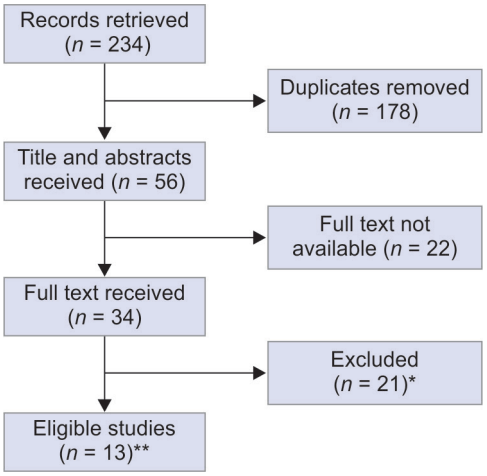

Fig. 1: Flow diagram of statistical analysis

Table 1: Study characteristics

No.	*Study name and year*	*Country*	*Type of study*	*Enrollment type*	*Number*	*Protocol of magsulph*	*Primary objective*
1.	P Vigil[18] 2014–15	Panama	Multicentre open RCT	Stable severe PE	284	Conventional vs short maintenance	Incidence of eclampsia
2.	Emmaneul[19] 2014	Nigeria	RCT (non-inferiority)	″	80	″	″
3.	Shahhen AS[20] 2012–14	India	RCT	″	119	″	″
4.	RUBI[21] 2008–10	India	RCT	″	150	″	″
5.	Sabina B Maia[22] 2011	Brazil	Open RCT	″	120	″	Duration of anticonvulsant TX
6.	Idown B[23] 2015	Nigeria	RCT	″	116	″	Incidence of Eclampsia
7.	Leal NV[24] 2014	Brazil	Open RCT	,,	120	″	Incidence of Eclampsia
8.	Maryam[25] 2012–13	Iran	RCT	All severe PE	182	″	Incidence of eclampsia
9.	Ana CF[26] 2015–2016	Brazil	Triple blind RCT	Stable severe PE	62	Conventional vs low dose	Serum magnesium level
10.	Dhiarapatara[27] 2011–12	Thailand	RCT	All severe PE	60	″	″
11.	Shoaib[28] 2004–06	Pakistan	Quasi experimental study	″	100	Conventional vs Loading dose	Incidence of eclampsia
12.	Surya Prasad[29] 2014–15	Nepal	RCT	″	60	″	″
13.	Anish[30] 2011–13	India	RCT	Stable severe PE	402	″	″
14.	Hethysi[31] 2014	India	RCT	″	100	″	″
15.	P Vigil[32] 2014–15	Latin A	Multicentre open RCT	″	1113	Conventional vs Placebo	″

specifically those severely preeclamptic women who are stable. In addition, there was a categorical exclusion of those severely preeclamptic with any complications or a history of eclampsia in the previous pregnancy. However, the enrolment criteria of 4 studies were found not to have incorporated such exclusion norms regarding disease severity or concomitant morbidity status.[25,27–29]

Risk of Bias Within Studies

Risks of bias were assessed according to the Cochrane EPOC criteria (Table 5).[17] Random sequence generation was found of low Risk in nine studies whereas it was found unclear or undescribed in five studies. Blinding regarding allocation was performed in six studies, whereas this process remains unclear in the rest of the studies. "Blinding of women and personnel" was followed in 4 studies and not done (HR) in three studies. Blinding of outcome assessment appears HR in all studies as it appears "not possible to blind outcome for the assessors". We consider this statement appropriate. All studies had a low risk of "baseline outcome similar" as there is "no outcome at the beginning of studies". All studies had a low risk of incomplete outcome data reporting and were free of selective reporting (all stated outcomes were reported). All studies were deemed to have a low risk of contamination because the arms adhered to allocated interventions. Lastly, all studies demonstrated no significant baseline differences among the study groups and thus had a low risk of bias associated with different baseline variability.

Synthesis of Results of a Group of Studies

Incidences of Eclampsia

Out of 15 enrolled studies, in eight studies, no incidence of eclampsia was reported among preeclamptic women in any group. In 7 studies, out of 1535 severely preeclamptic women in the study and 1513 women in the control group, 13 women developed eclampsia in a study group in contrast to 9 women in the control. The incidence appears statistically insignificant (Table 2 and Fig. 2).

Need to Reinstitute/Prolong Prophylactic Magnesium Sulphate Therapy

All studies except one declared the number of women who needed extension or reinstitution of magnesium sulphate prophylaxis in both groups. In 6 studies, it was found that no women needed reinstitution or extension of prophylaxis in any group. Eight studies categorically mentioned the number of women requiring extensions/reinstitutions.[21–26,30,32] The composite result shows, overall, 36 women out of 1535 in the study group and 6 women out of 1513 in the control group needed an extension of the prophylaxis. This result appears statistically significant (Table 2 and Fig. 3).

Side Effects and Toxicity Features

Nausea, Vomiting

Pascoal et al. in their study, showed the incidence of nausea or vomiting or both appear statistically insignificant.[26] In contrast, Shoaib et al. showed women receiving a standard dose regime complained of statistically significantly higher incidences of the same (Table 3).[28]

Flushing

Three studies compared the incidences of flushing, but in none of the studies, the incidence appears statistically significant in any group (Table 4).[19,26,28]

- Respiratory depression: In two studies, the incidence of respiratory depression is compared but not found to reach any statistical significance (Table 4).[18,32]
- Absent/diminished Knee Jerk: In two studies, the incidence of diminished/absent knee jerk was found to be statistically higher in women receiving the standard Pritchard regimen with respect to the loading dose group.[29,31] In the other two studies, however, the incidence appeared statistically insignificant (Table 4).[19,26]
- Oliguria: In both the studies by Rimal and Hethysi, the incidence of oliguria is found to be statistically higher in the control group (Table 4).[29,31]

  However, incidences of oliguria do not reach statistical significance in any groups of the studies conducted by Pascoal et al. and SB Maia.[22,26]

Secondary Outcomes

Time to Start Ambulation

Vigil-De Gracia et al. in their two studies, and Sabina Maia, in her research, showed similar results that the women who received brief regiment therapy could be ambulatory much earlier than those receiving standard regimen, and this data is statistically significant (Table 4).[18,22,32]

Time to Start Breastfeeding

In their similar studies, the same authors showed women who received brief regiment prophylaxis can be able to breastfeed much earlier than those receiving a standard regimen, and this data is statistically significant (Table 5).[18,22,32]

Duration of Hospital Stay

In their respective studies, three authors found no statistical differences regarding the duration of hospital stay between the two groups of women.[19,23,29] Shaheen Anjum et al., however, compared this outcome-data sub-classifying according to the mode of delivery.[20] She showed that the women who received short-course postpartum therapy were discharged earlier than those who received conventional prophylaxis, irrespective of the mode of delivery (Table 5).

Discussion

Principal Findings

Summary of Evidence

The occurrences of fits measure the efficacy of any prophylaxis of convulsion after initiation of therapy. Thus, while evaluating the effectiveness of any low dose or abbreviated regimen, quite expectedly, most of the studies found fixed this criterion as a primary outcome measure to assess and compare the efficacy of the same.

According to the Magpie trial, the incidence of eclampsia is 3–4% among women with untreated preeclampsia, whereas the rate drops to 0.8–1% in those receiving prophylactic magnesium sulphate.[33,34]

Sibai M also concluded that receiving magnesium sulphate lowers the frequency of eclampsia to 0.6%, with a range of 0.3–0.9%.[35] In this review, out of 15 enrolled studies, no single incidence of eclampsia was reported in any groups of 8 studies. Among the other seven studies, the reported incidences of eclampsia were not found to be statistically higher in any groups in contrast to expected incidences except in those studies assessing the efficacy

Table 5: Bias among the studies

Study	*Random sequence generation*	*Allocation concealment*	*Blinding of women and personnel*	*Incomplete outcome data*	*Blinding of outcome assessment*	*Baseline outcome similar*	*Free of contamination*	*Baseline variable similar*
P Vigil[18]	LR "Randomization done with a computerized program"	LR Sealed envelope was used	LR Coordinators or investigators of each hospital did not have access to the randomization sequence	LR Completed follow up as per protocol	HR Not possible to blind outcome for the assessors	LR No outcome at the beginning of studies	LR All arm received allocated intervention	
Emmanuel M[19]	LR	LR "Allocation were labelled and concealed in sealed envelope"	LR "Allocation concealed from doctors and research-staffs and investigators"	LR	HR	LR	LR	
Shahhen A[20]	LR Randomly divided into two groups	UR Not mentioned	UR Not mentioned	LR	HR	LR	LR	
Rubi[21]	LR The randomization was done in block generated by RALLOC software	UR Not mentioned	UR Not mentioned	LR	HR	LR	LR	
Sabina B Maia[22]	LR "randomly allocated using a sequential number of sealed envelope"	LR "Group allocation was concealed in sealed. opaque envelope"	UR	LR	HR	LR	LR	
Idown B[23]	UR Process of randomization was not mentioned	UR	UR	LR	HR	LR	LR	
Leal NV[24]	UR	UR	HR "intervention was not masked"	LR	HR		LR	
Maryum[25]	UR Process of randomization was not mentioned	UR	UR	HR ********	HR	LR	LR	
Ana CF[26]	LR "A randomization list was prepared using the allocation software program"	LR "Only the pharmacist was aware about the content of the ampoules"	HR "Blinding was removed"	LR	HR	LR	LR	

(Contd...)

Table 5: *(Contd...)*

Study	*Random sequence generation*	*Allocation concealment*	*Blinding of women and personnel*	*Incomplete outcome data*	*Blinding of outcome assessment*	*Baseline outcome similar*	*Free of contamination*	*Baseline variable similar*
Dhiarapatra[27]	UR Method of randomization was not mentioned	UR	UR	LR	HR	LR	LR	
Shoaib[28]	HR "Sampling technique was non-random purposive"	HR	HR	LR	HR	LR	LR	
Suryaprasad[29]	UR Method of randomization was not mentioned	UR	UR	LR	HR	LR	LR	
Anish[30]	LR "Randomization was done by a predetermined schedule"	LR "Randomization schedule and allocation concealment was done by a person unrelated to the study"	LR	LR	HR	LR	LR	
Hethysi[31]	LR "Randomly allocated by computer generated random number"	UR	UR	LR	HR	LR	LR	
P Vigil[32]	LR	LR Sealed envelope was used		LR	HR	LR	LR	

*******Due to, some colleague's disapproval, to discontinue MgSO4 after 12 hours of delivery (in 12 cases), in these women, Mg sulphate was continued up to 24 hours, but these 12 women were excluded from the study altogether. LR, low risk; HR, high risk; UR, unknown risk

Table 2: Dosing pattern and comparison between incidences of eclampsia and need to reinstitute/extend therapy

No	*Study*	*Enrollment*		*Loading dose IV (gm)*	*Maintanence dose (gm/hr)*	*Hour postpartum*	*Incidence of eclampsia*	*Need to reinstitute/ extend therapy*
1.	P Vigil[18]	S	141	4	1	6	0	0
		C	143*			24	0	0
2.	Emmanuel M[19]	S	40	4	1	12	0	0
		C	40			24	0	0
3.	Shaheen A[20]	S	76	4	1	6	0	NM
		C	43			24	0	NM
4.	Ruby[21]	S	75	NM	1 OR 4GM IM 4 HRLY	6	0	1
		C	75	NM		24	0	0
5.	Sabina B Maia[22]	S	56	6	1	12	0	3
		C	56			24	0	0
6.	Idown B[23]	S	58	Pritchard	Pritchard	12	1	2
		C	58			24	2	0
7.	Leal NV[24]	S	60	NM	NM	12	0	3
		C	60	NM	NM	24	0	0
8.	Maryam[25]	S	79	Pritchard	Pritchard	12	1	1
		C	91			24	0	0
9.	Ana C F[26]	S	31	6	1	24	0	3
		C	31		2		0	2
10.	Dhirapatra[27]	S	30	5	1	24	0	0
		C	30		2		0	0
11.	Shoaib[28]	S	50	Pritchard	–	–	0	0
		C	50		Pritchard	24	1	0
12.	Suryaprasad[29]	S	30	Pritchard	–	–	2	0
		C	30		Pritchard	24	1	0
13.	Anish[30]	S	201	Dhaka regimen	–	–	6	18
		C	201		Dhaka regimen	24	3	4
14.	Hethysi[31]	S	50	4gm IV + 8GM IM	–	–	1	0
		C	50		4gm 4 hrly	24	1	0
15.	P Vigil[32]	S	558	4	–	–	2	5
		C	555		1	24	1	0
	Total	S	1535				13	36
		C	1513				9	6

C, control group; S, study group

Group I Incidence rate	0.008469
95% Confidence interval	0.004509–0.014482
Group II Incidence rate	0.005948
95% Confidence interval	0.00272–0.011292
Incidence rate difference	0.002521
95% Confidence interval	–0.003512–0.008553
p-value	$p = 0.4128$
Incidence rate ratio	1.4237
95% Confidence interval	0.5630–3.7739
p-value	$p = 0.4240$

Fig. 2: Pictorial representation of incidences of eclampsia

Group I Incidence rate	0.02345
95% Confidence Interval	0.01643–0.03247
Group II Incidence rate	0.003966
95% Confidence interval	0.001455–0.008632
Incidence rate difference	0.01949
95% Confidence interval	0.01115–0.02782
p-value	$p < 0.0001$
Incidence rate ratio	5.9140
95% Confidence interval	2.4680–17.172
p-value	$p < 0.0001$

Fig. 3: Need to reinstitute/prolong prophylactic magnesium sulphate therapy

Table 3: Comparison of side effects and toxicty features

Study	Number (hour of prophylaxis)	Nausea, vomiting	p-value	Flushing/ hot flush	p-value	Res. Dep.[@]	p-value	Ab/d. Knee jerk[#]	p-value	Oliguria	p-value
P Vigil[18]	141 (6)					1	0.5				
	143 (24)					1					
Emmanuel M[19]	40 (12)			9	0.793			18	0.502		
	40 (24)			10				21			
Sabina B[22]	56 (12)									1	0.5
	56 (24)									0	
Ana C F[26]	31 (1)	4	ns	0	0.5			3	0.66	9	0.65
	31 (2)	11		1				3		8	
Shoaib[28]	50 (L)	5	0.01	35	<1						
	50 (P)	17		40							
Suryaprasad[29]	30 (L)							0	0.001	0	0.001
	30 (P)							16		5	
Hethysi[31]	50 (L)							0	0.012	0	0.022
	50 (P)							6		5	
P Vigil[32]	558 (x)					4	0.5				
	555 (24)					5					

[@]Respiratory depression; [#]Absent/Diminished Knee Jerk

Table 4: Comparison of secondary outcomes

Study	Number (hour of prophylaxis)	Time to start ambulation (hour)	p-value	Time to start breast feeding (hour)	p-value	Hospital stay (days)	p-value	t-test	
P Vigil[18]	141 (6)	10.9 ± 5.3	0.001	25.7 ± 19.8	0.001				
	143 (24)	24.9 ± 3.9		36.5 ± 16.8					
Emmanuel M[19]	40 (12)					6.1 ± 3.03	0.129	1.534	
	40 (24)					5.15 ± 2.12			
Shaheen A[20]	6			VD*	76	2.73 ± 0.76	<0.001	4.2	
	24				43	4.04 ± 1.47			
	6			CS**	76	7.5 ± 1.6	<0.001	4.6	
	24				43	11.11 ± 3.147			
Sabina B Maia[22]	56 (12)	18.8 ± 4.9	<0.001	29.6 ± 14	0.03				
	56 (24)	25.8 ± 6.9		35 ± 10.6					
Idown B[23]	58 (12)					8.8	0.029		df
	58 (24)					10.6		2.2	105.9
Suryaprasad[29]	30 (L)					4.2 ± 1.15	0.11		
	30 (S)					4.77 ± 1.54			
P Vigil[32]	558 (x)	11.8 ± 10.8	0.001	17.1 ± 16.8	0.0001				
	555 (24)	18.1 ± 10.6		24 ± 17.1					

*VD, vaginal delivery; **CS, cesarean section

of the loading dose regimen. While evaluating a composite outcome, 13 (1.26%) women out of 1,534 women in the study group and 9 (0.86%) women out of 1,516 in the control group developed eclampsia. Neither is the incidence found statistically higher in the study group nor do these incidences appear different from the average incidences of eclampsia developed among severely preeclamptic women receiving a recommended regimen of prophylactic magnesium sulphate. Thus, modified prophylaxis might not lessen the potential benefit of magnesium sulphate to prevent eclampsia.

Interestingly, in two studies, though statistically insignificant, the number of incidences of eclampsia is noted higher in the control group receiving the conventional regimen.[23,28] In one study, it was found to be equal in both groups.[31]

Idowa B et al. pointed out that eclampsia was developed in a woman of the control group within 10 minutes of administration

of the loading dose and expressed the opinion that there was non-achievement of the therapeutic level at that time.[23]

We also agree with their explanations which are in concurrence with the thoughts of Lu JF, who concluded that a substantial period of three to four hours after initiation of therapy is needed to achieve a constant serum level of magnesium sulphate in the range of 0.250–0.431 L/kg.[36] Another explanation was put by Shoaib et al., who opined, that magnesium sulphate could not altogether abolish the chance of eclampsia with an appreciable failure rate of approximately 1%, and seizures are possible on some occasions even when the recommended therapeutic level of serum magnesium has been achieved.[28,37,38]

Women who needed reinstitution or/and further prolongation of the therapy are also an estimate of the regimen's efficacy. A composite outcome shows a considerable number of women need reinstitution of treatment ($p < 0.0001$). This finding, on the one hand, reflects the consciousness of the caregivers, who were motivated to restart the therapy at any time without any form of bias; on the other hand, it strengthens the statement that recommendations of dose adjustment can be made while keeping all possibilities open to follow the recommended guidelines if needed.

Advantages Acknowledged by Curtailing the Duration of Prophylaxis

We have consolidated three secondary outcome measures that are supposed to be influenced by the duration of magnesium sulphate therapy. Outcome measures like early ambulation and early breastfeeding are co-related to better maternal-neonatal outcomes. In contrast, index like duration of hospital stay is allied with bed occupancy rate and hospital expense.

Three studies showed, as expected that women receiving abbreviated regimens or placebo were ambulatory earlier and started nursing earlier than those women receiving conventional regimens.[18,22,32] However, as a parameter, the duration of hospital stays was not found to be influenced either abbreviating the period of prophylactic therapy or applying only loading doses.[19,23,29] It is quite explainable as several other determining factors like mode of delivery, the status of the new-born, local practices, and policies related to obstetric service also play vital roles in determining the duration of hospital stay. Interestingly, in one similar study, to rule out this bias, this outcome was classified according to the mode of delivery, and the authors concluded that the women who received a short course of postpartum therapy were discharged earlier than those who received conventional prophylaxis irrespective of the mode of delivery.[20]

Thus, apparently, it is evident that attenuation of the duration of the prophylactic dose of magnesium sulphate has a beneficial effect on severely preeclamptic women.

Thus, Can Duration-curtailment be Endorsed?

Eight studies compared the efficacy of different abbreviated regimens of 6–12 hours in contrast to 24 hours postpartum therapy and revealed a cluster of beneficial outcomes as mentioned above. This curtailment also signifies the need for less intense monitoring in postpartum hours and could be an opportunity for an early shifting of women to the general ward. However, these abbreviated protocols were evaluated by us in detail, and we found a hidden dilemma. None of them had taken into account that most of the study objects being diagnosed in the antenatal period had already received magnesium sulphate before delivery. Thus, the total duration of magnesium sulphate therapy received by study groups is probably much more and does not remain confined only within 6 or 12 hours. Eventually, this fact incites a substantial risk of bias, which most studies did not address. However, in one study, investigators found to put a criterion of recruitment of specifically those who had received prophylaxis during the antenatal period for less than 8 hours probably to rule out this form of bias.

Can Prophylaxis Dose Dilution or Applying only a Loading Dose Reduce Magnesium Sulphate's Side Effects and Toxicity Features?

Because potential side effects of a drug with a narrow therapeutic margin remain correlated with the duration of administration and the dosing pattern, it is apparent that women receiving lesser strength dosing or of abbreviated duration should experience lesser side effects. Keeping this fact in mind, we have chosen for evaluation one subjective and one objective symptom of toxicity, two crucial signs of toxicity, and one clinical parameter related to the pharmacokinetics of magnesium sulphate among the retrieved studies.

Nausea, vomiting, a feeling of warmth, and flushing are early symptoms of magnesium sulphate toxicity and usually occur between the range of 3.8 and 5 mmoL/L.[39,40] Data retrieved from the two studies show incidences of nausea and vomiting are statistically found lower in the loading dose group in one study but not in another, considering the low dose regimen.[26,28] Contrary to our expectation, the incidences of hot flushes have not been found to be statistically lower in study groups in those studies and even in another study comparing an abbreviated regimen.[19,26,28] We conclude that as nausea, flushing or hot flushes are subjective symptoms and can be due to diverse reasons like staying in overcrowded labor rooms in hot, humid countries, more women reported it promptly when asked a close-ended question, even if the symptom did not attribute from the magnesium sulphate itself.

The development of two signs of toxicity, loss of patellar reflexes and respiratory paralysis, were evaluated among six enrolled studies.[18,19,26,29,31,32] Loss of patellar reflex is evidenced at magnesium plasma concentration at 3.5–5 mmoL/L, whereas respiratory paralysis occurs in the range of 5–6.5 mmoL/L[36] and as per consensus, these complications are rare even when recommended full-strength dosing schedule is considered.[40]

We retrieved a few confusing reports while evaluating the incidences of absent or diminished knee jerks/hyporeflexia. For example, two studies comparing the loading dose with the Pritchard regimen found a statistically high occurrence in women receiving the latter.[29,31] Whereas, though statistically insignificant, another study found unexpectedly high incidences of the same in each group receiving 12 vs 24 hours of therapy.[19] This documentation of the unusually high prevalence of hyporeflexia could be due to subjective error in assessing the optimum response of knee jerk. In our opinion, multiple time examinations of knee jerk in the standard regimen or low dose group might cause a bias towards positive results, whereas, in the loading dose group, the investigator was psychologically assured and thus never repeated the examination.

Respiratory depression is uncommon even in recommended dosing regimens, and likewise, no study found any statistically comparable higher incidence in any group.[18,32]

About 90% of the Magnesium sulphate dose is cleared mostly through the renal route during the first 24 hours.[36] Different studies likewise compared postpartum urine output as a potential

criterion that might remain indirectly related to the development of toxicity. Among the four studies, in two studies, the incidence of oliguria was found to be comparably higher in the control group receiving the standard Pritchard regimen.[29,31] However, oliguria is an element of the disease process and not an adverse effect of the drug. However, the inclusion of this parameter in those studies follows our thought that oliguria could indicate whether the disease process is recuperating or worsening or even a determinant of the development of side effects and toxicity among study subjects. Thus, assessing this factor and any documentation of the onset of diuresis can be a guide to taper or withdraw the prophylaxis when the parturient is otherwise found stable. This review shows lowering the strength of prophylaxis or applying only loading dose prophylaxis does not help much concerning lessening the common side effects and toxicity of magnesium sulphate.

Who Are the Ddeal Candidates for the Abbreviated Regime?

The outcome of this review showed that the incidences of eclampsia were not found elevated in women receiving any form of modified regimens in contrast to complete recommended dosing. As a result, through an apparent look, an idea could float up that either duration curtailment or dose reduction does not seem to reduce the efficacy of magnesium sulphate prophylaxis and a duration curtailment can have some accessory secondary benefits, the next question invariably ascends that can we recommend this modified regimen for all severely preeclamptic safely?

To find a justified answer, an in-depth search into the study designs revealed that 11 of the 15 studies enrolled only stable severely preeclamptics as study subjects (Table 1). Those study protocols categorically excluded severely preeclamptics who either have features of impending eclampsia, associated renal or heart failure or had a history of eclampsia in a previous pregnancy. This exclusion provokes a question of whether any form of modified regimen can be applied unanimously to all severely preeclamptic or selectively only to those, who are stable, devoid of complications at the time of diagnosis and can be monitored throughout with essential gadgets. In response to this query, we come to an inference that if all severely preeclamptics, irrespective of disease severity, were enrolled in those studies, the overall incidences of eclampsia would be much higher or at least different and might question the potentiality/safety of these abbreviated or low dose regimens to prevent eclampsia.

Comparison with Existing Literature

Alternative magnesium sulphate dosing for eclamptic women was evaluated earlier, and few studies established the safety and efficacy of low dose and loading dose in treating eclampsia.[41–43] In a systematic review comprising two randomized trials (451 women with eclampsia) and four (415 women with preeclampsia), Duley L et al. opined that the trials are too small for reliable conclusions regarding the efficacy and safety of alternative regimens (loading dose, low dose, and short maintenance) of magnesium sulphate used for the care of women with preeclampsia or eclampsia, or both.[14]

But almost no review exists regarding the provision of any alternative prophylactic magnesium sulphate regimen applicable to severe preeclampsia.

In another review, Pratt JJ et al. assessed data from five non-randomized studies on alternative magnesium sulphate regimens' comparative efficacy and safety for managing preeclampsia and eclampsia.[44] Considering the quality of the five studies as low to very low, the authors have concluded that lower-dose and loading bolus dose-only regimens could be as safe and efficacious as standard regimens.

Our study result corroborates with them though our review deals exclusively with severely preeclamptic women without including eclampsia and tries to evaluate the scope of any alternative prophylactic dosing for them.

Strengths and Limitations

This review is an extensive assemblage of 15 similar studies conducted exclusively on women with severe preeclampsia. Included trials are conducted over a vast geographic area and thus could represent a large population with ethnic diversity.

While considering the pros and cons of different prophylactic regimens, the studies were sub-grouped according to the regimens they tested, and each regimen was individually assessed in terms of its efficacy, safety, and feasibility.

All similar reviews of alternative magnesium sulphate regimens are over the studies that included both eclamptic and preeclamptic women as study subjects and were thus deficient regarding the specific opinion about the preeclamptic-prophylactic-dosing. These are the strengths of this review, and thus, the results of this review can be considered clinically applicable, keeping in mind all of the limitations.

The reviewers' searches were limited to English-language, and one quasi-experimental study was also included. We must also express that this evidence has been generated from the studies of which few are inherently low or very low in quality. These facts can be considered as the limitations of this review.

Conclusions and Clinical Significance

To conclude, curtailment of the duration of prophylaxis or application of lesser strength of magnesium sulphate appears as a safe alternative to prevent eclampsia in stable preeclamptics instead of applying the total dose.

Lowering the dose strength only without altering the duration could not be found to minimize the usual side effects in low-dose groups or generate any specific beneficial secondary outcomes. This is quite explainable as already recommended dosing has been standardized to be devoid of any significant side effects even when trialed in LMIC. Considering these facts, we do not find any rationality to take the risk by lowering only the dosing of the prophylaxis while keeping the duration the same, as this low dose also has to be delivered, keeping the parturients in high dependency units requiring the same intense monitoring.

Adopting the policy of applying only a loading dose of the magnesium sulphate to prevent fits, as tried in 4 studies, appears promising as it has been found statistically effective. However, through in-depth research, we found documentation of much higher absolute incidences of eclampsia in both groups ranging from 1.49 to 6.7% in one study.[29] The comparative analysis appears statistically insignificant as there are higher incidences in both groups, which in turn, imparts a safety profile of this loading dose regimen which is not. Probably for this also, in one study, 18 (8.9%) parturients of the loading dose group need dose extension/reinstitution.[30] These observations question the safety as well as the sensibleness of this regimen.

Considering another aspect, caregivers will be tempted, as well as receivers, if, after a single administration, the risk could be abolished and the patient can be transferred to the general ward

devoid of IV accesses and catheters. But in a practical scenario, we do not shift these high-risk cases so soon under any circumstances and suggest keeping postpartum vigilance for at least 6 hours, even in uncomplicated cases. So, there arises practically no advantage to embracing this loading dose policy concerning secondary outcomes. We thus conclude that the loading dose regimen cannot be recommended as prophylaxis as there remain safety concerns lack of any apparent benefits as well as a higher probability of the need for dose extension.

On the other hand, an abbreviated postpartum regimen of either 6 or 12 hours was found effective, though we could not reach any such consensus that for a total of how many hours the prophylaxis should be considered adequate if the prophylaxis needs to be initiated from the antenatal period. Abbreviated regimens otherwise could generate other advantages like early initiation of breastfeeding and early ambulation of women and might need shorter hospital stay.[18,20,22,32] Our study findings found this abbreviated regime could be an alternative to full-dose prophylaxis considering these particulars that the woman is stable and at the same time, caregivers are open-minded enough to prolong the prophylaxis at any time if needed.

Authors' Contribution

SKB: carried out the concept and design of the study; SKB and DNS: participated in the searching of the studies, data retrieval and manuscript drafting; SB and AH: performed the statistical analysis and helped to draft the manuscript; RB and PM: participated in the drafting of the manuscript and acted as the third and fourth reviewers; All authors read and approved the full manuscript.

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