MANAGEMENT OF ECLAMPSIA BY $MgSO_4$ LOADING DOSE VS STANDARD REGIMEN: A COMPARATIVE CLINICAL TRIAL

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Summary

Eclampsia is a life threatening obstretic emergency, the second leading cause of maternal death in Bangladesh. The high maternal morbidity and mortality in Eclampsia is related to multiple or recurrent seizures mostly. Magnesium Sulphate ($MgSO_4$) is the gold standard drug to control and prevent recurrent fits. To compare the occurrence of recurrent seizures with loading dose and standard regimen of $MgSO_4$ (Loading plus maintenance dose). This prospective comparative study was carried out in Department of Obstetrics & Gynaecology of Chittagong Medical College Hospital (CMCH) from January 2011 to December 2011.It was a comparative clinical trial. Study subjects were selected who had eclampsia regarding age, parity, gravidity and gestational age or after recent delivery. Then subjects were categorized into two in alternating method, i.e if first patient was in Group A then next patient was in Group B. Patients who had already received $MgSO_4$ from outside,convulsion due to other causes and having contraindication of $MgSO_4$ therapy were excluded from this study. With written informed consent, Group A received loading dose of inj. $MgSO_4$ and Group B was treated with loading dose plus maintenance dose (standard regimen). The primary outcome was to measure the number of recurrent seizures among the both groups. Secondary outcomes were the side effects, toxicity, Intensive Care Unit (ICU) support, regain of consciousness, normalization of blood pressure and protenuria. The test statistics used to analyze the data were Chi Square test (χ^2) and unpaired student's t-test. P values of < 0.05 were considered statistically significant The rate of recurrent seizure was 13.3% in loading dose vs 6.3% in standard regimen Group A (O<0.05, RR 2.207, 95% CI 1.089-4.470). Side effects of $MgSO_4$ were higher in Group B (71.1% vs 93%, P<0.01). Considering toxicity 3% was found in loading dose vs 3.8% in standard regimen of $MgSO_4$ i.e almost same (P>0.05). Women who received the standard regimen of $MgSO_4$ are less likely to develop recurrent seizures than those who received loading dose only. Toxicities of $MgSO_4$ are almost same and very little in both the regimen.

Key Words: $MgSO_4$; Eclampsia; Recurrent Seizures.

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Introduction

Eclampsia, the occurrence of seizure in association with preeclampsia, one of the grave diseases peculiar to pregnancy still remains a major killer in the field of obstetrics [1,2]. There were over 4 million cases of preeclampsia and eclampsia globally, of which 63,000 resulted in a maternal death [3]. Estimated case fatality rates, mainly on hospital based studies show that the risk of dying from eclampsia is approximately 14 times higher in a developing country compared to a developed country [3]. Nigeria, one of the highest rates of maternal mortality in the world having most common cause of maternal death is Eclampsia [4]. Incidence of Eclampsia is extraordinarily high in Bangladesh which is about 7.9% [5].

In general, aim of treatment in eclampsia is prevention of further fits as it is the recurrent fits that leads to significant cerebral anoxia and associated with adverse outcome [6]. On the basis of high quality evidences, World Health Organisation (WHO) has recommended Magnesium Sulphate ($MgSO_4$) is the most effective, safe and low cost drug for the management of severe preeclampsia and eclampsia [7,8,9].

There is currently a better understanding of the mechanisms of action of $MgSO_4$ in regulating the neuromuscular excitability by acting directly on the myoneural junction by antagonizing N-methyl-D-aspartate receptor activation [10].

The two most widely used dosage regimens of $MgSO_4$ are Pritchard's regimen (intramuscular) and Zuspan's regimen (Intravenous) [10,11,12]. But controversy exists regarding the optimum maintenance dose in the IV regimen [13,14,15]. Assessment of serum magnesium level is also needed side by side clinical monitoring in Zuspan's regimen. While in the Pritchard's regimen as it is intramuscular, side effects and toxicity are less, so only clinical monitoring is enough. Moreover, intramuscular regimen is 8 times more effective than intravenous regimen in prevention of convulsion. Maternal mortality was also 2.5 times greater in the women who received intravenous regimen [13,14,16].

The concept of using just loading dose of $MgSO_4$ in eclampsia was suggested by Boyd and Brower. Sibai and Ramanthan found that about 10% of eclamptics experience a further convulsion after receiving only loading dose [15,16]. The rationale for the maintenance regimen is the belief that it will reduce the risk of further convulsion, which will improve the outcome. In Eclampsia Collaborative trial, it was showed hat recurrent convulsion rate 13.2% and 5.7% with standard regimen of $MgSO_4$ in two controlled trials, Magpie trial showed that preventive $MgSO_4$ for all cases of pre-eclampsia reduces the risk of development of eclampsia related to maternal death by 58% and 45% respectively [2,16,17,18]. In Bangladesh $MgSO_4$ has been used as anti convulsant from 1998 after commencement of its production locally and replaced diazepam [5,19,20]. As a result death rate between the years 1998 and 2000 was also lower compared with that in 1997 (16% to 8%), when diazepam was used for controlling convulsion [5,19].

The choice of which regimen to use depends on a number of factors such as availability of staffs to monitor the patients as well as the expertise of staffs [4]. In the resource constrained settings, like Bangladesh intramuscular maintenance therapy maybe easier to administer and also clinical monitoring is enough.

Considering the high morbidity and mortality related with recurrent seizures, this comparative clinical trial was designed with $MgSO_4$ dosage (Loading dose vs standard regimen) for the management of eclampsia in Chittagong Medical College Hospital, Chittagong, Bangladesh, where the major cause of maternal death was eclampsia (52% in 2010).

Materials & methods

This study was carried out from January 2011-December 2011 in Obstetric & Gynaecology Department, CMCH. This was prospective comparative clinical trial, subjects were selected all eclamptic patients regardless of age. parity, gravidity and gestitional age. Considering the inclusion & exclusion criteria 340 eclamptic patients were enrolled. Patients who had already received $MgSO_4$ from outside, convulsion due to other causes and having contraindication of $MgSO_4$ therapy were excluded from this study. With written informed consent study populations were selected in two groups. Group A was received loading dose of $MgSO_4$ & Group B was received standard regimen i.e loading plus maintenance dose. Then frequent monitoring was done during first 2 hrs of therapy (Every 15 min interval), hourly for 6 hrs, then 4 hourly for 48 hrs. Follow up should be done till discharge. The efficacy of the both regimen was assessed by measuring the occurrence of recurrent convulsion (Primary outcome). Convulsion recurred 6, 12, 24, 48hrs after the initial dose was evaluated. If the convulsion recurred after 30minutes of initial therapy then we treated the patient with further inj. of 2.47gm/5ml $MgSO_4$ IV slowly over 5-10 min (Recurrent dose). Secondary outcome i.e side effects, toxicities, regain of consciousness, ICU support and perinatal outcomes were also evaluated. Besides,with $MgSO_4$, patients of both groups were managed by giving supportive care, controlling BP and managing labour & delivery. During study all the patients were assured that their confidentiality would be maintained strictly. The study was approved by institutional review board & also by the ethical review committee of Bangladesh Medical Research Council of Chittagong Medical College, Chittagong. All the data were checked & edited after collection. Then statistical analysis was done by Chi Square Test (χ^2) & unpaired t-test.

Results

Among the study populations 180 patients were in loading dose Group A & 160 patients belonged to standard regimen Group B.

Majority of the patients were in 20-25 year age group (61.7% in Group A, 54.3% in Group B). In teenage 19.4% belong to Group A and 18.8% in Group B considering the socio-economic status most of the eclamptics were in lower class 56.7% in Group A, 55.0% in Group B. Regarding distribution of gestational variables, no significant

statistical difference was found in relation to gestational age into 2 groups. (P>0.05) Primiparous were pre-dominant in both the study group. (73.3% in Group A, 69% in Group B). Half of the patients having irregular Ante Natal Care (ANC) (56.1% & 56.2% in Group A & B respectively). In both the groups the rate of caesarean delivery was higher (66.6% & 80.6%). Vaginal delivery was 27.8% and 14.4% in Group A and Group B respectively.

Clinical presentation of eclampsia was almost same in both the groups. Of them 54.5% and 58.1% patients had ante-partem eclampsia in Group A & Group B respectively. 24.4% & 25.0% had intrapartum eclampsia, 21.1% & 16.9% had post partum eclampsia in Group A & B respectively. Majority of the patient had convulsion 1-5 in number.

The primary outcome was to measure the rate of recurrent seizures after intervention of inj. $MgSO_4$. This was statistically significant between two groups (P<0.05, RR 2.207, 95% CI 1.089 - 4.470). 24 patients having recurrent seizures in Group A which is about 13.3%. Where as in Group B the rate of recurrent seizure was only 6.3% i.e 10% out of 160 eclamptics. Most of the seizure occur within 6 hours of $MgSO_4$ therapy (12 in Group A and 5 in Group B). Gradually the rate of Seziure declined. With 48 hours of therapy, it is only 2 in number in loading dose and no or 0 in standard regimen.

Almost all the patients developed side effects like headache, drowsiness but a few presented with flushing. Side effects were observed 71.7% in Group A and 93.1% in Group B. Considering toxicity, there was no significant differences between loading dose and standard regimen (3.3% vs 3.8%, P>0.05 Relative Risk (RR) 0.889, 95% CI 0.292-2.701). Among the total 12 eclampics (6 in Group A vs 6 in Group B) 3 had absent patellar reflex (2 in Group A vs 1 in Group B) 4 had oliguria followed by anuria (2 in Group A vs 2 in Group B) 2 had respiratory depression (1 in Group A vs 1 in Group B) and rest of the 3 had cardiac arrest (1 in Group A vs 2 in Group B).

Most of the patients regained conscious level within 48 hrs after intervention of $MgSO_4$ (94.9% in Group A and 92.9% in Group B). Blood pressure was also normal within 48 hrs. Proteinuria was absent on third day of therapy. 4.4% in Group A, 3.1% in Group B patients needed ICU support (P>0.05).

Regarding maternal outcomes among 340 eclamptics, 329 patients cured with $MgSO_4$ therapy i.e cure rate was 96.8%. The maternal death rate was 3.9% in loading dose compared to 2.5% in standard regimen (P>0.05).

Table 1 : Distribution of gestational variables among the study groups (with χ^2 test significance)

Gestational Variables		Study Groups				Total		Sig
		Group A		Group B				
		n	%	n	%	n	%	
Gestational Age in Groups	< 28 Wks	02	1.1	01	0.6	03	0.9	P > 0.05
	29-32 Wks	21	11.7	26	16.3	47	13.8	Not
	33-36 Wks	102	56.6	83	52.0	185	54.4	Significant
	> 36 Wks	55	30.6	50	31.1	105	30.9	
	Total	180	100.0	160	100.0	340	100.0	
Parity	Primipara	132	73.3	111	69.4	243	71.5	P > 0.05
	Multipara	48	26.7	49	30.6	97	28.5	Not
	Total	180	100.0	160	100.0	340	100.0	Significant
Ante Natal Care (ANC)	Regular	70	38.9	66	41.3	136	40.0	P > 0.05
	Irregular	101	56.1	90	56.2	191	56.2	Not
	Nil	09	5.0	04	2.5	13	3.8	Significant
	Total	180	100.0	160	100.0	340	100.0	
Mode of Delivery	Vaginal Delivery	50	27.8	23	14.4	73	21.5	P < 0.01
	Instrumental Delivery	10	5.6	08	5.0	18	5.3	Significant
	Caesarian Section	120	66.6	129	80.6	249	73.2	
	Total	180	100.0	160	100.0	340	100.0	

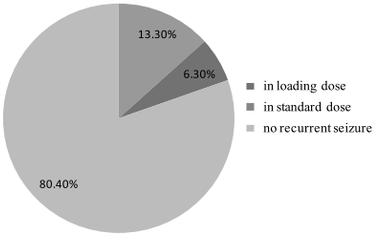

Fig 1 : Pie Diagram Showing Distribution of recurrent seizures among study groups

Table II : Distributions of recurrent seizures among the study groups (with χ^2 test significance)

		Study Groups				Total		Sig
		Group A		Group B				
		n	%	n	%	n	%	
Recurrent Seizures	Yes	24	13.3	10	6.3	34	10.0	P < 0.05
	No	150	86.7	156	93.7	306	90.0	
	Total	180	100.0	160	100.0	340	100.0	Significant
	< 6 Hours	12	50.0	05	50.0	17	50.0	
	< 12 Hours	06	25.0	03	30.0	09	26.5	
Recurrent Seizures	Within 24 Hours	04	16.7	02	20.0	06	17.6	P < 0.05 Significant
	Within 48 Hours	02	8.3	00	0.0	02	5.9	
	Total	24	100.0	10	100.0	34	100.0	

Table III : Risk estimation of maternal morbidity & mortality related variables along with the study group

		Group A n (%)		Group B n (%)			
Recurrent Seizures	Yes	24	(13.3)	10	(6.3)	$\chi^2 = 4.722$ P = 0.030 Significant	2.207 (1.089 – 4.470)
	No	150	(86.7)	150	(93.7)		
Side Effects	Maternal Study	Variables Groups	χ^2 Test Significance		Relative Risk (95% Confidence Interval)	$\chi^2 = 26.159$ P = 0.000 Highly Significant	0.0.769 (0.696 – 0.851)
					(93.1) (6.9)		
Toxicity	Yes	06	(3.3)	06	(3.8)	$\chi^2 = 0.043$ P = 0.835 Not Significant	0.889 (0.292 – 2.701)
	No	174	(96.7)	154	(96.2)		
Maternal Death	Yes	07	(3.9)	04	(2.5)	$\chi^2 = 0.522$ P = 0.470	1.555 (0.464 – 5.216)
	No	173	(96.1)	156	(97.5)		

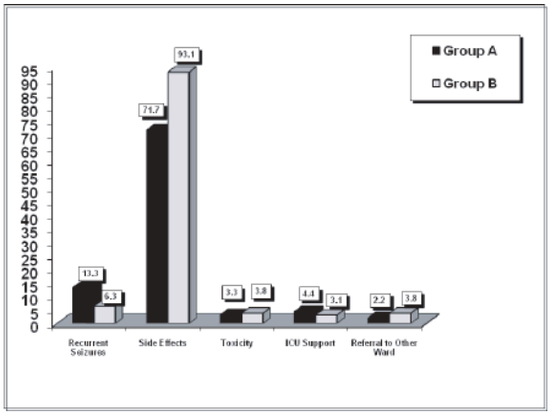

Fig 2 : Distribution of positive maternal morbidities among the study groups

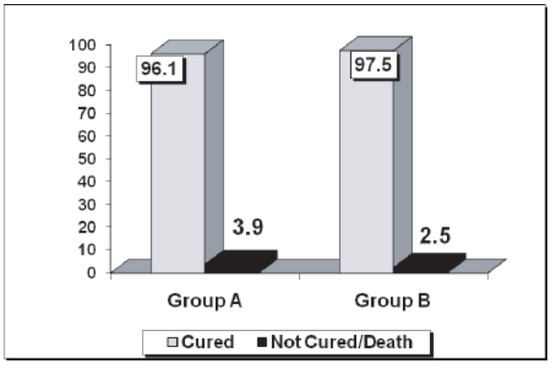

Fig 3 : Distribution of maternal outcomes among the study groups

Discussion

A total 340 eclampsia patients were studied. In our study the rate of recurrent seizure in Group A (Loading dose) was 13.3% and in Group B (Standard regime) was 6.3%. Our data demonstrated that patients in Group B having lower rate of recurrence of fit than the Group A. The difference in Group A & Group B was statistically significant (P value < 0.05). There was clear difference between the two groups in Relative Risk (RR) of recurrent convulsion (RR 2.207, 95% confidence interval CI 1.089-4.470). In a previous randomized study conducted in our country at Dhaka Medical College Hospital by M.R. Begum who found the rate of recurrent seizures was 4.0% in loading dose vs 3.5% in standard regimen [12,13,16]. In our study it was found 6.3% in standard regimen which is slightly higher than 3.5% in the study conducted by M.R. Begum. The result of collaborative eclampsia trail shows that recurrent convulsion rate,13.2% (60/453) and 5.7% (22/388) in two controlled trials with standard regimen of $MgSO_4$ which is almost similar with our study [2,10,21]. A study carried out by Mohan C. Regmi et al (2009) in Nepal found that there was no recurrent seizure in standard regimen but it was 4.6% in loading dose [22].

Considering socio-demographic profiles the mean age of the study population was 22.68 ±4.08 years in Group A and 23.53 ±4.85 years in Group B.

Primiparous had highest risk with developing eclampsia. Majority of the eclamptics (71.5%) among the total in our study were primigravida, of them 132 in Group A and 111 in Group B patients. In our experience, more than half of the eclamptics (56.2%) had irregular antenatal care compared with 40.0% and 3.8% had regular and no antenatal care respectively. Furthermore, our finding was 56.7% in Group A and 55.0% in Group B belonged to poor socio economic status.

There was statistically no significant difference in gestational age, parity, ANC and mode of delivery and also in socio demographic profiles in the two groups (P>0.05). This is consistent with the findings of a randomized trial conducted by Mohan C. Regmi et al. who found that mean gestational age 35.42 ±3.78 weeks and 37.03 ±2.41 weeks in standard regimen and loading dose group respectively, while in our study we found 36.06 ±2.77 weeks in Group A and 35.82 ±2.85 weeks in Group B. Because of the peculiarity of these patients, more than half of the women had irregular or no ANC, gestational age was either estimated in months or extrapolated from the fundal height measurement at the time of examination [22].

The clinical types of eclampsia was almost similar to the series reported by Talat Naz et al. and Mehr-un-nisa et al. who found that 63.4% had antenatal fits, 17.3% intrapartum and 19.2% had postpartum eclampsia [23]. The findings of our study were 56.2% antepurtam eclampsia, 24.7% intrapurtam and 19.1% were postpurtam eclampsia. There was no significant difference with types of eclampsia between two groups. However, the proportion of cases of postpartum eclampsia was significantly higher in the UK and USA. Antenatal screening and appropriate treatment of patients with preeclampsia maybe responsible for this difference. The ratio of antepartum to postpartum fit may be a reflection, not only of the availability and quality of ANC but of the use of these facilities.

After intervention with $MgSO_4$ most of our patients had side effects like headache, drowsiness (71.7% in loading vs. 93.1% in standard regimen) (RR 0.769, CI 0.696-0.851) while a few patient had flushing. Considering the $MgSO_4$ toxicity, there were 3.3% in loading dose vs. 3.8% in standard regimen. This was not statistically significant (P>0.05, RR 0.889, CI 0.292-2.701). This is consistent with the study of them. They also did not find any significant difference between the two groups in the risk ratio of oliguria (RR 0.20, 95% CI 0.03 to 1.59) and absent tendon reflexes (RR 0.25, 95% CI 0.06 to 1.06) [24]. But this toxicities were whether due to dose related or any anesthetic hazards or may be due to eclampsia related complications not known.

In our evaluation most of the patients regained consciousness within 48 hours (94.9% and 92.9% in Group A and Group B repectively). This is inconsistent with the study of M.R. Begum et al. in Dhaka who found that most of them regained consciousness 10.94±8.29 hrs in loading vs. 11.24±8.37 hrs in standard regimen [25]. In the study conducted by Shikha seth et al. reported that 76% eclamptics regained consciousness within 6 - 12 hours [14].

The rate of maternal mortality was 3.9% in loading vs. 2.5% in standard regimen in this current study. These observations of our study are in accordance with that of M.R. Begum et al. who found that maternal death rate was 4.45% in the loading and 5.02% in the standard regimen group [13]. Although the rate was slightly higher in the loading dose but statistically not significant, P>0.05. This is consistent with our study findings but in contrast with the maternal mortality in the study of M.C. Regmi et al which was low i.e. 2.3% in loading dose and no death in standard regime [22]. Further evaluation is necessary regarding maternal death whether this was due to anesthetic hazard or fluid overload or lack of supportive care or availability of ICU during management of the patients of Eclampsia related complecations. The Eclampsia Trial Collaborative group showed a reduction in the risk of recurrent seizure of 52.0% and 62.0% with $MgSO_4$ compared with diazepam and phenytoin [18,26]. We see that the maternal death is not related to the dosage regime of $MgSO_4$ other than it may be due to the complications of eclampsia, related to organ damage.

Conclusion

The high maternal mortality reported from the developing countries is primarily among the patients who has multiple seizures.

In eclampsia recurrent seizures more controlled who received standard regimen than only loading dose of $MgSO_4$. The toxicities of MgS04 are less and almost similar in both the dosage regimen.

Disclosure

All the authors declared no competing interest.

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