Magnesium sulphate *versus* phenytoin in eclampsia – Maternal and foetal outcome – A comparative study

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RESEARCH

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Abstract

Background

Eclampsia manifests as seizures and is unique to the pregnant state. It remains an important cause of maternal mortality especially in resource-challenged countries that lack access to prenatal care.

Aims

The aim of our study was to compare maternal and foetal outcomes in mothers with eclampsia with the administration of either magnesium sulphate or phenytoin in a resource- challenged situation.

Method

The work was conducted from January 2012 to December 2012. A total of 80 patients were assigned alternately to two groups – one group was treated with magnesium sulphate (Group-M; n=40), and the other treated with phenytoin (Group-P; n=40) (Figure 1). The magnesium sulphate was administered according to Pritchard's regimen; phenytoin administered according to Ryan's regimen. With either regimen, anticonvulsant therapy was continued for 24 hours postpartum or 24 hours after the last convulsion, whichever was later.

Results

Fifty-four per cent of patients regained consciousness within eight hours of treatment onset in Group-P compared to 5.3 per cent in Group-M ($p=0.0001$, $\chi^2=19.24$). Seven patients in Group-P had recurrence of convulsions as compared to none of the 40 women assigned to Group-M ($p=0.032$, $\chi^2=4.62$). The incidence of Caesarean section was greater (62.5 per cent) in Group-M compared to Group-P (25 per cent; $p=0.001$, $\chi^2= 9.96$). No statistically significant differences were found in the foetal outcomes between the two groups.

Conclusion

Phenytoin use may be reconsidered in selective cases in low and middle income countries (LMIC) as it has been found simpler to use, has several benefits and also curtails treatment cost. Magnesium sulphate is substantially more effective than phenytoin with regard to recurrence of convulsions. Proper training in the management of eclampsia should be given to all health care workers to ensure appropriate management of eclamptic mothers. Thus, the treatment of this disease calls for more research especially in resource-challenged settings.

Key Words

Eclampsia; magnesium sulphate; phenytoin; low and middle income countries; resource challenged; maternal mortality; comparison;

What this study adds:

1. Magnesium sulphate is more effective than phenytoin with regard to recurrence of convulsions.
2. The time taken for return to consciousness was significantly earlier and patients delivered earlier in the phenytoin group compared to those in the magnesium sulphate group, pointing to the fact that phenytoin has an edge over magnesium sulphate in the bed-turnover rate of eclampsia patients from the labour room eclampsia-turret to the post-partum ward. These findings could be particularly useful in the resource challenged hospitals of low- and middle income countries (LMIC) that have a high

ratio of eclamptic patients to the number of railed cots available, in addition to a perennial paucity of skilled nursing staff trained to manage eclampsia patients. Also, the Caesarean section rate was significantly less in the phenytoin group, implying again the decreased need for skilled workers in the delivery of such patients compared to the magnesium sulphate group.

3. In LMIC, where eclampsia is rampant and labour rooms are overflowing with such critical patients, the concept of having earlier delivery, decreased number of Caesarean delivery, increased bed turn-over (from the eclampsia turret to the labour ward), and lower cost of therapy with phenytoin looks to have practical implications. Hence, in resource poor situations, and in patients having a lesser degree of disease severity, the option of using phenytoin needs reconsideration. Also, the majority of mothers in LMIC have a low body mass index (BMI) and magnesium sulphate administration is a painful experience since it often leads to gluteal abscesses – an iatrogenic condition that causes more mental and physical trauma than the whole disease event itself. The use of phenytoin in eclampsia cannot be rejected outright yet.

Background

Eclampsia is an affliction that manifests with seizures which is unique to the pregnant state and remains one of the major direct causes of maternal mortality worldwide.[1,2] Though it is a rarity in developed countries, in low and middle-income countries (LMIC), where appropriate and prompt intervention cannot be meted out, delays in seizure treatment can result in hypoxic brain damage and potentially in maternal or infant death.

There are 144 LMICs according to the World Bank classification of countries.[3] Countries are categorised according to income based on the 2011 Gross National Income (GNI) per capita. The groups are: low income ($1,025 or less); lower middle income ($1,026–$4,035); and upper middle income ($4,036–$12,475). There are 36, 54 and 54 low-income, lower middle-income and upper middle-income countries, respectively.[3] The World Health Organisation (WHO) ranks pre-eclampsia and eclampsia as the second leading direct cause of maternal morbidity and mortality in LMICs, closely following postpartum haemorrhage. Also in LMICs, there is a three times greater risk of pre-eclampsia progressing to eclampsia and those presenting with eclampsia have approximately a 14 times greater risk of death.[4]

Eclampsia is a Greek word coined by Hippocrates in the 17th century meaning "to shine forth" or "flash of lightning". Many studies[5-8] have questioned the current paradigm of eclampsia as a predictable and potentially preventable disease. Because hypertension is usually recognised after an eclamptic fit, the duration of hypertension before the fit may be relatively short and eclampsia can occur unwarranted like the "flash of lightning". The LMICs have a very high incidence of eclampsia and neither the occurrence of antenatal visits nor hospitalisation have prevented its occurrence.[9,10]

Maternal age, nulliparity, and pregnancy-induced hypertension (PIH) have been found to be independent risk factors for eclampsia.[11] Studies show that the risk of eclampsia decreases by three per cent per one-year increase in maternal age, whereas it increases 2.6-fold and 35.4-fold in nulliparous women and women with PIH, respectively.[11]

Anti-convulsants such as magnesium have a generalised central nervous system (CNS) depression that serves to attenuate seizures. The pharmacodynamics of magnesium helps mitigate the cerebral complications of eclampsia by dilating the cerebral arteries that help rescue the brain from developing ischaemia. Magnesium also has tocolytic activity and a mild antihypertensive effect.[12] However, it is not without side-effects – the most serious of which is respiratory depression which is usually seen only with magnesium overdose when the serum levels exceed >10mEq/L. The first clinical sign of magnesium toxicity is loss of deep tendon reflexes, which should be elicited in patients prior to its administration.

Phenytoin acts by rendering a stabilising effect on neuronal membranes. After an intravenous infusion, it rapidly crosses the blood-brain barrier, is non-sedative, and has a long half-life. Phenytoin is not without serious side-effects and includes dysrhythmias and hypotension[13] that can occur at levels >50 mcg/ml.

Our goal in this study was to evaluate the efficacy of magnesium sulphate (Pritchard Regimen)[14] and phenytoin (Ryan Regimen)[15] in eclampsia in a resource-challenged setting. Direct comparison of maternal and perinatal outcomes was used to evaluate the advantages and disadvantages of one regimen over the other.

Method

The study was conducted in the department of obstetrics and gynaecology of a teaching hospital with approximately 220 and 190 patients presenting with convulsion in pregnancy and eclampsia respectively per year between January 2012 and December 2012 after obtaining institutional ethics committee approval and written informed consent from the patient's attendant. Patients

with a diagnosis of eclampsia, regardless of age, parity, gestational age, singleton or multiple pregnancies, whether delivered or undelivered, were included in the study. A total of 80 such patients were studied during a one-year period.

Data was collected for a period of eight months. Three days per week – that were the principal author's admission and on-call days i.e. Tuesday, Thursday and Saturday – were pre-selected for data collection. A patient data register was formulated from admitted eclampsia patients, who were identified by a serial number for the duration of the study. Patients with even serial numbers were treated with magnesium sulphate and odd numbered serials were treated with phenytoin. With our allocation method there was no significant bias in any of the demographic parameters of the patients (Table 1). Ninety-nine pregnant women with convulsion were screened for eligibility, of which eight patients were excluded as per the exclusion criteria given below; 91 patients were invited for the study of which three would not give consent; the remaining 88 patients satisfying the inclusion criteria were included in the study (Figure 1). A thorough antenatal history was taken and a full neurological examination was completed to confirm the diagnosis. Patients with other causes of convulsion such as epilepsy, cerebral malaria, meningitis, encephalitis, ingestion of poisonous substances or medications, intracranial haemorrhage resulting from head injury or any form of trauma, hysteria, postpartum psychosis or coma caused by endocrine disorders (such as myxoedema, diabetes or adrenal disorders) were excluded from the study.

In Group-M, the patients received magnesium sulphate according to the Pritchard regimen with a loading dose of 4g intravenously (IV) over five minutes that was immediately followed by 5g intramuscularly (IM) into each buttock, with further 5g IM every four hours (provided the respiratory rate was >16/min, urine output >25ml/h, and knee jerks were present) until 24 hours after the last convulsion or after the onset of therapy, whichever was later. The intramuscular injections were given in the upper outer quadrant of each buttock by a three-inch long 20-gauge needle. One patient was excluded from the study as she had decreased urine output <25ml/h. Patients in Group-P, received phenytoin according to the Ryan regimen in a loading dose of 15mg/kg body weight by IV (split as 10mg/kg initially over a period of 30 minutes and then 5mg/kg two hours later over 10 minutes) followed by a maintenance dose of 300mg by IV over 10 minutes until 24 hours had passed since the last seizure. The dose of phenytoin was given in 70-100ml of normal saline at the rate of 25mg/min. Phenytoin, as similar to magnesium sulphate, was also continued for either 24 hours postpartum or 24 hours after the last convulsion, whichever was later. In the event of recurrence of convulsion after treatment with phenytoin, magnesium sulphate 5gm IM was given in each buttock. Seven patients had recurrence of convulsions and required magnesium sulphate and were excluded from the study (Figure 1).

Patients were admitted to a quiet and dark labour room in the eclampsia turret in a railed cot. An airway tube was inserted in unconscious patients and high-flow oxygen administered, intravenous infusion with injection Ringer's lactate (RL) was started and Foley's catheterisation was done. Oropharyngeal suction and eye care, along with checking for nystagmus, was done hourly.

Parameters recorded were: systolic and diastolic blood pressure, urine output, respiratory rate, patellar reflex, level of consciousness (according to Glasgow Coma Scale), and number of convulsions on admission and every four hours. The investigations completed on admission and every four hours were as follows: serum platelets, serum urea, serum creatinine, liver function test (LFT), and urine albumin. Complications such as acute renal failure (ARF), cerebrovascular accident (CVA), and hepatic failure, if present, were also recorded. Foetal parameters including birth-weight of foetus and Apgar score at one and five minutes were noted. Injection RL was given at the rate of 80-100ml/hour intravenously for fluid maintenance and its rate was adjusted according to urine output.

When SBP was more than 160 mmHg and/or DBP more than 110mmHg in the patients of either group, primarily sublingual nifedipine in the dose of 10–20mg was used as the anti-hypertensive. IV labetalol was also administered if nifedipine treatment alone failed.

Pregnancy was terminated either by Caesarean section or by vaginal delivery according to the Bishop's score[16] and after the convulsions and blood pressure came under control. If Bishop's score was unfavourable, Caesarean section was performed. In Group-M, CS was avoided for two hours of starting therapy.

For statistical analysis, students 't' and chi-square tests were used. A p-value of <0.05 was regarded as statistically significant, <0.01 as very significant and <0.005 as highly significant. If any one or more cells contained a value of less than 5, then the p-value taken was from Fisher's exact (2-tailed) and $\chi 2$ taken from Yates corrected. For cost analysis independent t-test was used.

Results

Of the 80 patients selected for the study, the overall incidence of antepartum eclampsia was 51.3 per cent, the rest presented in the intrapartum (35 per cent) or postpartum period (13.8 per cent). Most of the patients were 16-25 years of age. The incidence of eclampsia was highest in the unregistered (80 per cent) and primigravida (80 per cent) categories. In Group-M and in Group-P, 87.5 per cent and 80 per cent of the patients were illiterate and 42.5 per cent and 50 per cent were poor (modified BG Prasad social class V; 17), respectively. The socio-demographic distribution of the patients in the two groups showed there was no significant difference on these aspects between patients of the two groups (**Table 1**).

Table 1: Distribution of patients in the two groups according to the socio-demographic profile

Patient profile	**Group M** (%)	**Group P** (%)	p Value	χ^2
Age group (in yrs.)				
16-25	30 (75)	31 (77.5)	0.79	0.07
26-35	10 (25)	9 (22.5)		
Literacy				
Illiterate+ primary education	35 (87.5)	32 (80)		
Secondary+ graduate	5 (12.5)	8 (20)	0.36	0.83
Social group				
BG Prasad scale III to V	31 (77.5)	34 (85)		
I & II	9 (22.5)	6 (6)	0.39	0.74
Parity				
P=0	33 (82.5)	31 (77.5)		
P>0	7 (17.5)	9 (22.5)	0.57	0.31
Number of antenatal visits				
0 TO <3 ANC visits	33 (82.5)	31 (77.5)		
≥ 3 ANC visits	7 (17.5)	9 (22.5)	0.57	0.31
Gestational age				
< 34weeks	4 (10)	2 (5)		
≥ 34weeks	36 (90)	38 (98)	0.67	0.13
Type of eclampsia				
Antepartum eclampsia	23 (57.5)	18 (45)		
Intrapartum eclampsia	12 (30)	16 (40)		
Postpartum eclampsia	5 (12.5)	6 (15)	0.52	1.27

Table 2 and Figure 2 show that the patients' distribution into two groups according to their morbidities was uniform and statistically non-significant thus maintaining homogeneity between the groups.

Table 3 and Figure 3 show that 54.1 per cent of patients became conscious within eight hours of treatment onset in Group-P compared to 5.3 per cent in the Group-M. However, in the Group-M, 63 per cent of patients regained consciousness within 9-16 hours. This finding was statistically significant (p= 0.0001, $\chi 2$ = 19.24, CI = 0.13 – 0.51).

Table 2: Distribution of patients in the two groups according to their morbidities

	Group M (%)	**Group P** (%)	p Value	χ^2
DBP				
90 to 110mmHg	27 (67.5)	26 (65)		
>110mmHg	13 (32.5)	14 (35)	0.81	0.06
Number of convulsions				
1 to 5 convulsions	25 (62.5)	26 (65)		
≥ 6 convulsions	15 (37.5)	14 (35)	0.81	0.05
Level of consciousness				
Unconscious	29 (72.5)	28 (70)		
Conscious & semi-conscious	11 (27.5)	12 (30)	0.8	0.06
Convulsion to treatment interval				
< 6hrs	20 (50)	26 (65)		
≥ 6hrs	20 (50)	14 (35)	0.17	1.84

The incidence of recurrence of seizures in Group P was 14.9 per cent of 47 patients while none in Group M had a recurrence (Table 3). This result has been found to be statistically significant (p-value by 2-tailed Fisher's exact=0.032, $\chi 2$ by Yates corrected= 4.62; incidence of recurrence of seizure was 14.9 per cent with 95 per cent CI as 7.091 and 28). A majority of the patients delivered within 12 hours of onset of convulsions (Table 3), Group-P (77.5 per cent) versus Group-M (60 per cent), including 35 per cent of patients in the phenytoin group who delivered within six hours of the first seizure compared to 25 per cent patients in the magnesium sulphate group, though the result was not statistically significant (p=0.148, $\chi 2$=2.095). A total of 20 per cent in Group-M and 35 per cent in Group-P had a normal vaginal delivery. The incidence of Caesarean section was higher in Group-M compared to Group-P (62.5 per cent vs 25 per cent, respectively), which was highly statistically significant (p=0.001, $\chi 2$=9.96, CI=2.14 – 3.41), the two groups being comparable in the on-admission Bishop's score (Table 3; Figure 3).

Table 3: Distribution of the patients and newborns in the two groups according to the differences in the outcome

	Group M (%)	**Group P** (%)	p-value	χ^2
Return of consciousness				
≤ 8hrs	2 (5.3)	20 (54.1)		
> 8hrs	36 (95)	17 (46)	0.0001	19.24
Recurrence of seizures				
Recurrence of seizures	0 (0)	7 (14.9)		
No recurrence of seizures	40 (100)	40 (85.1)	0.032	4.62
First convulsion to delivery interval				
≤ 12hrs	24 (60)	31 (77.5)		
> 12hrs	16 (40)	9 (22.5)	0.148	2.095
Mode of delivery				
Caesarean	25 (62.5)	10 (25)		
Others	15 (17.5)	30 (75)	0.001	9.96
Post-partum morbidity				
Post-Partum Haemorrhage (PPH)	4 (10)	0 (0)		
No PPH	36 (90)	40 (100)	0.11	2.37
Apgar score				
≥6	21 (65.6)	23 (82.1)	0.14	2.08
<6	11 (34.4)	5 (17.9)		
Distribution of new-borns according to the stillbirth rate				
Alive	32 (88.9)	28 (82.4)	0.43	0.61
Still born	4 (11.1)	6 (17.6)		
Distribution of new-borns according to neonatal morbidity				
Hypotonia	0 (0)	2 (7.1)	0.12	2.36
No hypotonia	32 (100)	26 (92.9)		
Distribution of new-borns of according to early neonatal mortality				
≤7days old babies dead	6 (15.8)	2 (6.7)	0.34	1.34
Live births	32 (88.9)	28 (82.4)		

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Group-M patients' newborns had lower Apgar scores compared to Group-P patients' newborns (34.4 per cent compared to 17.9. per cent) as shown in Table 3, but the results were not statistically significant (χ2=2.08, p=0.14). Hypotonia was present in 7.1 per cent newborns of mothers who received treatment with phenytoin while none of the infants in Group-M suffered from this problem. A total of 61.1 per cent infants in Group-M and 76.5 per cent of infants in Group-P had an uneventful perinatal period. The study showed that the difference in the perinatal mortality distribution between the two groups was not statistically significant (p=0.46), with Group-M having an early neonatal mortality rate of 188 per 1000 live births while Group-P had 69 per 1000 live births, which was also not significant (adjusted chi square=1.34; p value=0.34) (Table 3 and Figure 3).

Group-M showed a 7.5 per cent incidence of gluteal abscess which was nil in Group-P and this problem was specific to Group-M due to the mode of delivery of magnesium sulphate by deep IM injections in the buttocks. Seventy-five per cent patients in Group-M and 90 per cent of patients in Group-P had an uneventful recovery and the maternal morbidities were comparable in both the groups (p=0.36, χ2=0.81).

Upon admission in both Group-M and Group-P patients had platelet count that was within the normal range. The renal function test (urea, creatinine), liver function tests (bilirubin, AST, ALT, alkaline phosphatase), and serum uric acid level showed comparable results, with the values of uric acid, urea, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase usually above the normal range but not markedly raised. Bilirubin levels remained within normal limits in both the groups. None of the patients in either group developed HELLP syndrome.

Our study, fortunately, had no maternal mortality. There was a slight increase in maternal morbidity in the Group-M compared to Group-P (p=11, χ2= 2.37). Two patients in the Group-M suffered from aspiration pneumonia following prolonged unconsciousness and postpartum haemorrhage,

respectively.

Of the 81 babies delivered by 80 patients, 41 were in Group-M as one mother delivered twin babies. Of these five mothers with singleton delivery and presenting with post-partum eclampsia were excluded so that 36 children remained in Group-M including a pair of twin babies. Similarly, in Group-P six mothers with singleton delivery were excluded to include 34 children in this group. 34.4 per cent of the babies in Group-M were born depressed (Apgar score <6) of which six babies needed resuscitation and positive pressure ventilation compared to 37.2 per cent of babies with ≤3 Apgar score in Group-P of which four babies needed additional respiratory support. This finding was not statistically significant (p=0.83, $\chi 2$=0.04). Moreover, the five-minute Apgar scores (7-10) were comparable in both groups (60.5 per cent in Group-M vs 62.8 per cent Group-P).

Of the 60 live born babies (excluding the 11 babies of mothers with postpartum eclampsia and 10 stillborns), 15.8 per cent of infants in Group-M and 6.7 per cent in Group-P died within seven days of birth (p=0.34, $\chi 2$=1.34). Prematurity and its complications (pneumonia and septicaemia) were the major causes of neonatal deaths. Intrauterine growth restriction (IUGR) accounted for the most common cause of neonatal morbidity (6.3 per cent), closely followed by birth asphyxia, septicaemia, prematurity and meconium aspiration.

Almost half (48.8 per cent) of the patients were mildly anaemic. A total of 12.5 per cent of patients in Group-M and five per cent of patients in Group-P had severe anaemia (<6.5mg) on admission. The anaemia was not aggravated by the use of either magnesium or phenytoin for their treatment. The other haematological parameters were not altered in either group. None of the patients exhibited thrombocytopenia or gross deterioration of liver and renal function tests. One patient in the Group-P showed a temporary rise in the blood urea and creatinine levels which returned to normal upon correction of dehydration.

The direct and indirect costs incurred during the course of therapy, propelled us to formulate a cost analysis between the two groups. The direct costs taken into account were the cost of medicines, cost of the hospital stay and cost of transport. The indirect cost included the loss of daily wage. Since our hospital is run by the government there was no added cost of hospital stay in either groups. Also, as most of the patients were from nearby villages the transport cost was negligible. We therefore concentrated on the cost of medicines and the monetary loss incurred from loss of daily wage due to hospital stay. The analysis yielded the following results depicted in Table 4.

We found that the cost of therapy was significantly high in Group-M patients (t – statistics: 27.61, p value: 0.0000) compared to Group-P.

Table 4: Cost analysis between the two groups

	Group M	Group P
Mean cost of therapy (direct cost + indirect cost)	Rs. 1489.10 (23.90 USD)	Rs. 751.33 (12.06 USD)
Standard deviation	Rs. 152.25 (2.44 USD)	Rs. 73.28 (1.18)
t-statistics: 27.61, p value: 0.00000 test value		

Discussion

Eclampsia is a dreadful complication of pregnancy occupying the centre stage of obstetric attention.

A study indicated a higher incidence of eclampsia in young nulliparous women (<20 years) and a higher mortality in women older than 25 years.[18] In our study the maximum number of women presenting with eclampsia were in the 16-25 years age-group with 42.5 per cent of the patients being less than 20 years of age. Another study[19] stated that 64 per cent of the eclamptic patients were primigravidae. The above trend matches our study with 80 per cent amongst them being primigravidae. In Group-M and in Group-P 42.5 per cent and 50 per cent of the patients respectively belonged to social class V of the Aggarwal modification of B.G Prasad's socioeconomic status classification.[17] This strong correlation between low standards of living and incidence of eclampsia suggests that poor nutritional factors might be associated with the mothers' low socio-economic class and may have an important effect on the genesis of eclampsia.[14] Women with a past history of the disease have also been shown to be at risk of recurrence. Studies have reported the role of relevant family history with an inheritance pattern suggestive of a single gene model.[21] In Group-M 57.5 per cent and in Group-P 45 per cent had antepartum eclampsia and this is in accordance with literature that has indicated antepartum eclampsia constituted 50 per cent of all eclamptics.[1]

A total of 35 per cent and 42.5 per cent in the Group-P delivered within 0-6 hours and 7-12 hours respectively compared to 25 per cent and 35 per cent of patients in

Group-M, with both groups having comparable Bishop's scores. Most of Group-P patients delivered earlier than the Group-M with an equal number of patients in each group having favourable Bishop's score (p=0.32). This finding is supported by Friedman et al.[21] who reported a more rapid cervical dilatation (3.3cm/hour versus 1.5cm/hour) with phenytoin than magnesium sulphate and hence a reduced time interval between time to delivery and the first fit. The definitive treatment of eclampsia being delivery of the foetus, the patients in Group-P with unfavourable Bishop's score or non-progress of labour could be delivered by Caesarean section immediately under general anaesthesia unlike the two hour waiting time required after magnesium sulphate administration in the Group-M, thus reducing the treatment-delivery time interval. Although the Bishop's scores were comparable on admission, the number of deliveries by Caesarean section was significantly lower (25 per cent) in Group-P compared to Group-M (62.5 per cent), the difference being statistically highly significant (p=0.001). Our study is in accordance with Duleyet al.[2] who reported a statistically significant increase in the risk of Caesarean section in patients treated with magnesium sulphate compared to phenytoin. Also, research has reported[8] increased length of labour and Caesarean delivery with magnesium sulphate treatment. However, some studies[22,23] differed in their opinions, stating that magnesium sulphate did not affect labour outcome nor did it increase the rate of caesarean section. Another study comparing labour aftermath with phenytoin showed that magnesium sulphate given for intra-partum treatment of pregnancy-induced hypertension did not significantly affect labour outcome,[22] but did necessitate a higher dose of oxytocin.[24] Though the Caesarean section rates have been increasing over the last decade, the major indications have remained unchanged. According to a study[25] done in the southern parts of India, absolute indications for Caesarean section constituted 7.74 per cent and non-absolute indications comprised of 92.26 per cent, which is similar to our hospital statistics as well. The Caesarean section for eclampsia and pre-eclampsia constituted approximately 6.4 per cent of all the Caesarean sections performed. This data is similar to the operative deliveries performed for eclampsia and pre-eclampsia in our hospital. Our study showed that compared to phenytoin, magnesium sulphate significantly increases the need for Caesarean delivery. This increase has major implications on the limited health care resources[25] as well as there is a higher incidence of morbidity and mortality for both mother and baby arising from Caesarean section when compared with vaginal delivery.[26] Also, the individual cost of therapy due to the use of magnesium sulphate rises because of the added cost of caesarean section in the Group-M. Thus it may be said that in low resource set-up where vaginal delivery is preferred, use of phenytoin served the purpose to our advantage with the added benefit of showing significant reduction of the cost of therapy.

The time taken for return to consciousness in the Group-P within eight hours of start of treatment was 54.1 per cent compared to 5.3 per cent of patients in the Group-M. Two patients in the Group-M and three in the Group-P were omitted deliberately since they were fully conscious on admission. Here it was seen that phenytoin had an edge over magnesium sulphate in the bed-turnover rate of eclampsia patients from the labour room eclampsia-turret to the post-partum ward. This finding was statistically significant and is similar to a study by Raman et al (p=0.0001)[27]. Of the 47 eclamptic patients treated with phenytoin 14.9 per cent of patients showed a recurrence of convulsion within four hours of onset of treatment compared to no recurrences in the Group-M (p-value by 2-tailed Fisher's exact=0.032, $\chi 2$ by Yates corrected= 4.62; 95 per cent CI= 7.091 and 28). This study is in accordance with several other studies.[6,19,23] Naidu et al.[28] stated that magnesium sulphate relieves cerebral vasospasm compared with phenytoin and therefore may be the better drug for prevention of eclamptic convulsions. In another comparative study, the women randomised to receive magnesium sulphate compared to phenytoin had a 67 per cent reduced incidence of recurrent convulsions.[29] Maternal morbidity was lower in the magnesium group compared with the phenytoin group in our study. The single incidence of vescico-vaginal fistula that occurred in Group-M was due to the removal of Foley's catheter inadvertently instead of continuously draining the bladder for 10 days in a patient presenting with obstructed labour. Postpartum haemorrhage occurred in 10 per cent of patients in the M-group and this finding corroborates with a study[8], which reported an increased incidence of postpartum bleeding and respiratory depression with magnesium sulphate. One patient in the Group-P had oliguria, which had been corrected by the third postpartum day. This was due to dehydration and probably not due to the result of side effects of phenytoin.

The first clinical sign of magnesium toxicity is loss of deep tendon reflexes. Therefore, serial neurologic examinations were completed in patients receiving magnesium therapy. If there had been an episode of magnesium overdose then it would have been treated with 10 per cent calcium gluconate or chloride solution and cardiorespiratory support.[12] In the management of treatment failure, further 2gm IV magnesium sulphate may be given over five minutes after the measurement of serum magnesium levels to detect whether an increased dosage might be of benefit.[30] In our study, one patient receiving magnesium sulphate

suffered from magnesium overdose and was eliminated from the study but none had treatment failure. The toxic effects of phenytoin can be detected initially by the occurrence of nystagmus. Hence, hourly checks for nystagmus were conducted along with the routine eye care. In case of convulsion recurrence due to treatment failure with phenytoin, magnesium sulphate 10gm IM was given as per protocol. There were seven cases of 47 who had treatment failure p=0.032) and none suffered from the problems of phenytoin overdosage.

The one-minute Apgar score of babies of mothers in Group-M was lower than in the babies of mothers of Group-P such that 26.3 per cent of infants in Group-M were born depressed (Apgar score 0-3) compared to 22.9 per cent in Group-P, but the values stated are not statistically significant (p=0.83). This increased incidence of intubation in babies in Group-M compared to babies in Group-P having the initial zero-minute Apgar score of ≤3 is incongruent with a few studies[18,28] that have stated the frequency of intubation in the magnesium sulphate group was 11 per cent less compared to the phenytoin group and also fewer babies died or were in SCBU for more than seven days.[31] However, the five-minute Apgar score between 7 and 10 was comparable in both the groups suggesting that the respiratory depressant effect of magnesium sulphate was only temporary. The causes of neonatal morbidity in both the groups in the descending order were IUGR, birth asphyxia, septicaemia, prematurity, and meconium aspiration. The most common cause of morbidity was IUGR that constituted 6.3 per cent of all cases. In Group-P there was an increased incidence of hypotonia in newborns (p=0.12). Perinatal mortality rate (PNMR) in Group M was 278 per 1000 births, slightly more than PNMR of Group-P with 235 per 1000 births. This finding was corroborated by Buckshee et al.[32] who mentioned PNMR of 23.3 per cent in the phenytoin treated group. However, another study[31] found out that fewer babies died to mothers treated with magnesium sulphate. Stillbirths were higher in the Group-P than in the Group-M. Our study suggested that babies of mothers treated with phenytoin had a better neonatal outcome than the babies of the Group-M with Group-P having an early neonatal mortality of 69 per 1000 live births compared to Group-M with 188 per 1000 live births (p=0.34).

A recent study[33] analysed the data from 24 LMIC on the side-effects related to the use of magnesium sulphate in eclampsia and pre-eclampsia. Despite the compelling evidence for its use concern has been expressed amongst health care providers, particularly in low- and middle-income countries, regarding the safety and potential for toxicity of magnesium sulphate, particularly in clinical environments where the capacity for patient monitoring is limited.[33,34] Of the serious adverse effects mentioned, maternal death directly attributable to magnesium sulphate administration is one of them. The authors reported that the death was caused by severe respiratory depression.[35] Still, if concerns about drug toxicity can be set aside, additional concerns continue to be expressed about the impact on health systems and services, when magnesium sulphate is prescribed as therapy and particularly so by health care administrators and providers who serve in lower-resource settings.[34,35] Treatment approaches may differ in higher-resource settings due to the use of intravenous infusion pumps rather than intramuscular administration, low threshold/mandatory post-caesarean admission to intensive care units, accessibility to better anaesthetic equipment and frequent blood and blood-gas parameters monitoring facilities. Also, the lower patient-staff ratios typically enable more vigilant patient monitoring in these settings, unlike that in resource challenged hospitals.

Conclusion

The advantages of a high rate of bed turnover and decreased number of Caesarean delivery that has been found with phenytoin are useful practical points that need re-evaluation of its use in selective cases of eclampsia, in patients clinically presenting with the disease of lesser degrees of severity, and in hospitals lacking in adequate number of eclampsia beds, and also in the number of skilled caregivers. Several alternative magnesium sulphate regimens are being used by providers that comprise of the use of single only loading dose, or reducing the size of the maintenance dose, or increasing the interval between maintenance doses. However, there is insufficient evidence about the efficacy of these modified regimens. Hence the use of phenytoin, which has been widely studied, may be reconsidered in these circumstances also. Hand in hand, it cannot be forgotten that magnesium sulphate is still substantially more effective than phenytoin with regard to recurrence of convulsions. Thus, apart from the need to provide training to all health care workers in the management of patients of eclampsia, the treatment of this disease calls for more research work, especially in the resource challenged settings where unregistered antenatal mothers that present with eclampsia are unable to give adequate history of the past illness and also have no booking blood tests done. Their future management calls for a plan to devise a new formulation that would combine the beneficial effects of phenytoin and magnesium sulphate and reject their adversities keeping in mind the cost effectivity, to help manage this deadly disease more efficiently.

References

1.Cooray SD, Edmonds SM, Tong S, Samarasekera SP, Whitehead CL. Characterization of Symptoms Immediately Preceding Eclampsia. Obstet Gynecol. 2011 Nov;118(5):995-9.

2. Duley L. The Global Impact of Pre-eclampsia and Eclampsia.SeminPerinatol. 2009;33:130-137.

3.Tabassum N, Umber A, Khan S. Eclampsia: A Major Cause of Feto – Maternal Mortality and Morbidity? Annals. 2010;16(3):202-205.

4. The World Bank. How we classify countries. Available from: http://data.worldbank.org/about/country-classifications. Accessed May 2013.

5. Katz VL, Farmer R, Kuller JA. Preeclampsia into eclampsia: Towards new paradigm. Am J Obstet Gynecol. 2000 Jun;182(6):1389-96.

6.Odendaal HJ, HallDR. Magnesium sulfate prophylaxis. J MaternFetal Invest. 1996;6:14-18.

7. Burrows RF, Burrows EA. The feasibility of a control population for a randomized control trial of seizure prophylaxis in the hypertensive disorders of pregnancy. Am J Obstet Gynecol. 1995;173:929-35.

8.Witlin AG, Sibai BM. Magnesium sulphate therapy in preeclampsia-eclampsia. Obstet Gynecol. 1998;92(5):883--889.

9.Urassa DP, Carlstedt A, Nyström L, Massawe SN, Lindmark G. Eclampsia in Dar es Salaam, Tanzania – incidence, outcome, and the role of antenatal care. ActaObstetGynecol Scand. 2006;85:571– 578.

10.Mcdonagh M. Is antenatal care effective in reducing maternal morbidity and mortality? Health Policy Plan. 1996 Mar;11(1):1-15.

11.Morikawa M, Cho K, Yamada T, Yamada T, Sato S, Minakami H. Risk factors for eclampsia in Japan between 2005 and 2009. Int J Gynaecol Obstet. 2012 Apr;117(1):66-8.

12. Stead LG. Seizures in Pregnancy/Eclampsia. Emerg Med Clin N Am 2011; 29: 109–116.

13. Mackenzie E, Greer IA. Preventing eclampsia. Current Obstet Gynecol. 1996;6:159-164.

14. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol. 1984;148:951-963.

15. Ryan G, Lange IR, Naugler MA. Clinical experience with phenytoin prophylaxis in severe preeclampsia. Am J Obstet Gynecol. 1989;161:1297-1304.

16.Bujold E, Blackwell SC, Hendler I, Berman S, Sorokin Y, Gauthier RJ. Modified Bishop's score and induction of labor in patients with a previous cesarean delivery. Am J Obstet Gynecol. 2004 Nov;191(5):1644-8.

17.Aggarwal AK. Social classification - the need to update in present scenario. Indian J Community Med. 2008;33(1):50-51.

18. Vigil-De Gracia P, García-Cáceres E. Thrombocytopenia, hypertension and seizures in eclampsia. Int J Gynaecol Obstet. 1998 Apr;61(1):15-20.

19. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet. 1995 Jun 10;345(8963):1455-63. Erratum in: Lancet 1995 Jul 22;346(8969):258.

20.Odent M. Plea for a new generation of research in eclampsia. Clinical Effectiveness in Nursing. 2006;9 Suppl:2:e232–e237.

21.Repke JT, Robinson JN. The prevention and management of pre--eclampsia and eclampsia.Int J Gynaecol Obstet. 1998 Jul;62(1):1-9.

22. Friedman SA, Lim KH, Baker CA, Repke JT. Phenytoin versus magnesium sulfate in preeclampsia: A pilot study. Am J Perinat. 1993;10:233– 238.

23.Leveno KK, Alexander JM, McIntire DD, Lucas MJ. Does magnesium sulphate given for prevention of eclampsia affect the outcome of labour? Am J Obstet Gynecol. 1998;178:707-712.

24. Atkinson MW, Guinn D, Owen J, Hauth JC. Does magnesium sulfate affect the length of labor induction in women with pregnancy – associated hypertension? Am J Obstet Gynecol. 1995;173:1219 –1222.

25.Witlin AG, Friedman SA, Sibai BM. The effect of magnesium sulfate therapy on the duration of labor in women with mild preeclampsia at term: a randomized, double--blind, placebo--controlled trial. Am J Obstet Gynecol. 1997 Mar;176(3):623-7.

26.Unnikrishnan B, Rakshith P, Aishwarya A, Nithin K, Rekha T, Prasanna P, Ankita A, et al. Trends and Indications for Caesarean Section in a tertiary care Obstetric Hospital in Coastal South India. Australas Med J. 2010;3(12): 821-825.

27.Snyman L. Is the high caesarean section rate a cause for concern? ObstetGynaecol Forum 2002; 12(2):8–13.

28. Raman NV, Rao CA. Magnesium sulfate as an anticonvulsant in eclampsia. Int J Gynaecol Obstet. 1995 Jun;49(3):289-98.

29. Naidu S, Payne AJ, Moodley J, Hoffmann M, Gouws E. Randomised study assessing the effect of phenytoin and magnesium sulphate on maternal cerebral circulation in eclampsia using transcranial Doppler ultrasound. Br J ObstetGynaecol. 1996 Feb;103(2):111-6.

30.Lipstein H, Lee CC, Crupi RS. A Current Concept of Eclampsia. Am J Emerg Med. 2003 May;21(3):223-6.

31. Walker JJ. Severe pre-eclampsia and eclampsia.BaillieÁ re's Clinical Obstetrics and Gynaecology. 2000;14(1):57--71.

32.Duley L, Henderson-Smart DJ, Chou D. Magnesium sulphate versus phenytoin for eclampsia. Cochrane

Database Syst Rev. 2010 Oct 6;(10):CD000128.
33. Buckshee K, Patwardhan VB, SoonawalaRP(eds): Principles and Practices of Obs and Gynae for Postgraduates. Jaypee Brothers: New Delhi, 1996; 47.
34. Smith JM, Lowe RF, Fullerton J, Currie SM, Harris L, Felker-Kantor E. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. BMC Pregnancy Childbirth. 2013 Feb;5:13:34.
35.Barua A, Mundle S, Bracken H, Easterline T, Winikoff B: Facility and personnel factors influencing magnesium sulfate use for eclampsia and pre-eclampsia in 3 Indian hospitals. Int J Gynecol Obstet. 2011; 115(3):231–234.
356.Malapaka SV, Ballal PK: Lose-dose magnesium sulfateversus Pritchard regimen for the treatment of eclampsia and imminent eclampsia. Int J Gynaecol Obstet. 2011;115(1):70–2.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

ETHICS COMMITTEE APPROVAL

The COMJNMH Institutional Ethics Committee approved this study.

Figure 1: Consort diagram of the study

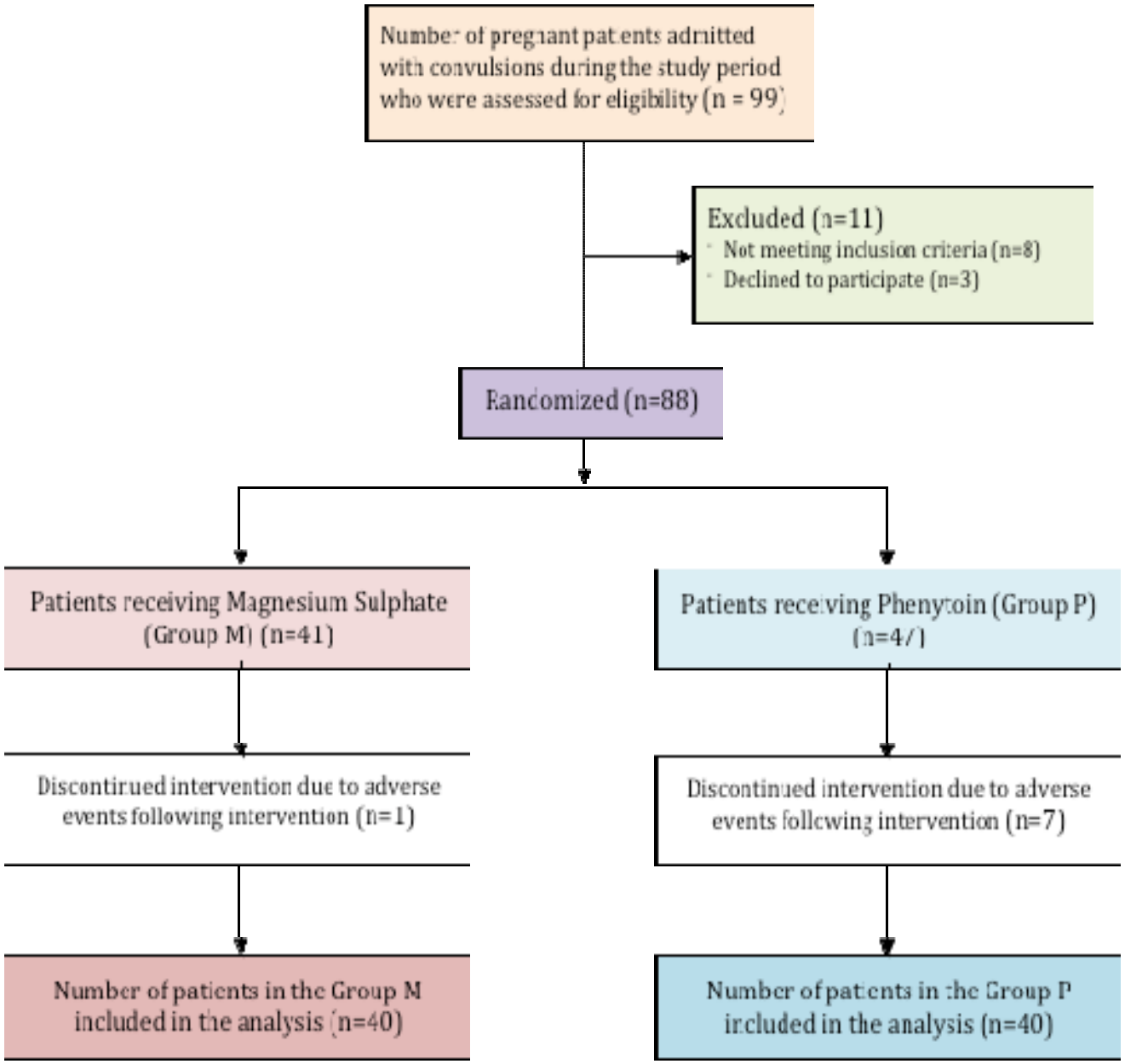

Figure 2: Distribution of patients in the two groups according to their morbidities

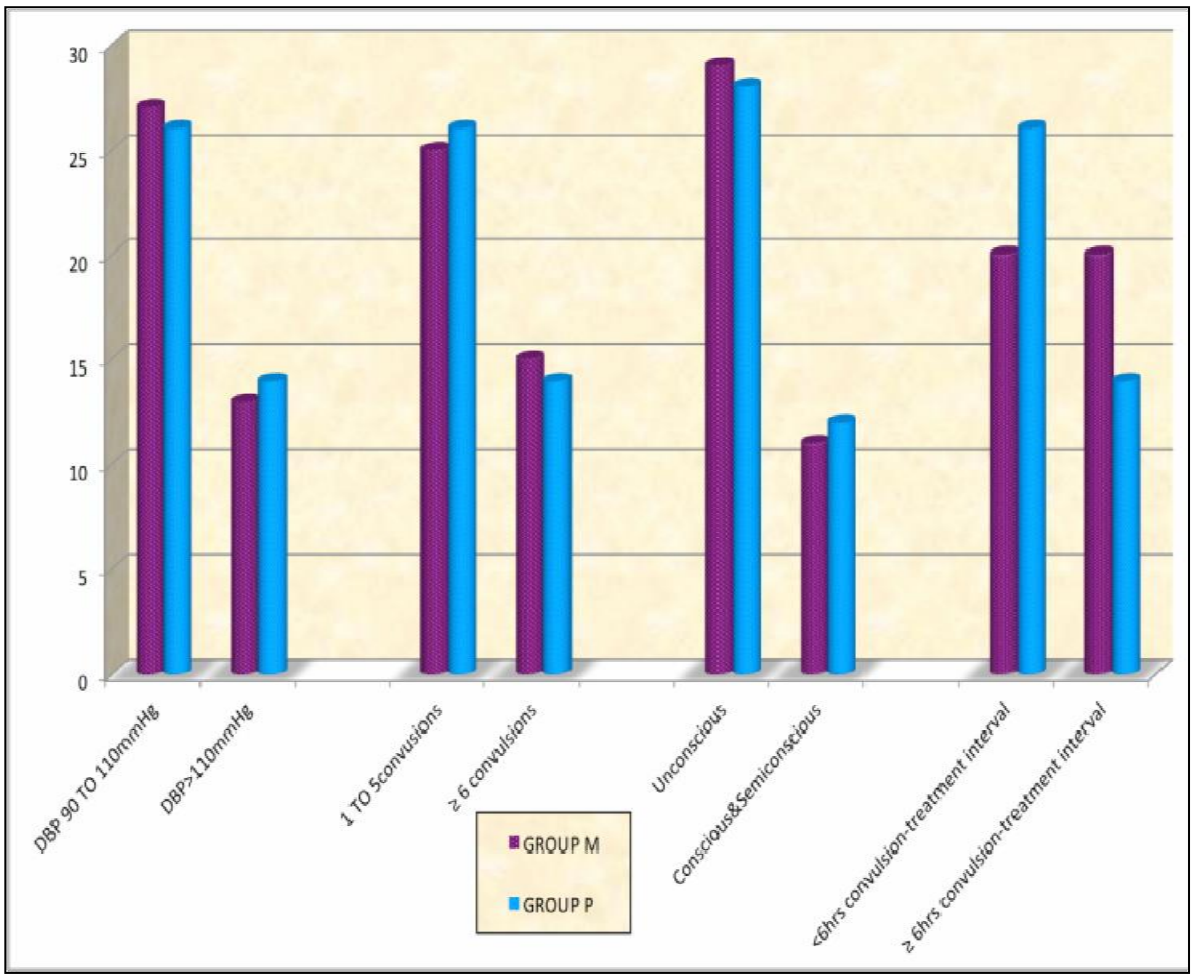

Figure 3: Distribution of the patients and newborns in the two groups according to the differences in the outcome