RESEARCH ARTICLE

A Randomized Parallel Non-inferiority Trial to Evaluate the Safety and Efficacy of Levetiracetam in Comparison to Magnesium Sulfate in the Management of Severe Preeclampsia

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Abstract

Aim: The study aimed to compare the safety and efficacy of levetiracetam to magnesium sulfate for the prevention of convulsions in preeclampsia.

Materials and methods: A total of 60 women with preeclampsia with severe features were randomized to receive either levetiracetam or magnesium sulfate. In the levetiracetam group, a loading dose of 1000 mg/day (500 mg 12th hourly for 24 hours) was administered slowly over 5 minutes intravenously followed by an oral tablet of levetiracetam 500 mg 12th hourly for 5 days. In the magnesium sulfate group, 4 gm of magnesium sulfate was given IV over 3–5 minutes followed by a maintenance dose of 1 gm/hour for 24 hours. Magnesium sulfate solution was given in dilution via infusion pump.

Results: This study shows that levetiracetam is non-inferior to magnesium sulfate as none of the patients in both arms had any convulsions.

Conclusion: Levetiracetam is non-inferior to magnesium sulfate in the prevention of convulsions in preeclampsia. It can be used as an alternative to magnesium sulfate, especially when magnesium sulfate is contraindicated.

Keywords: Anticonvulsants, Levetiracetam, Magnesium Sulfate, Preeclampsia, Seizure.

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Introduction

Hypertensive disorders affect 10% of all pregnancies and the incidence of preeclampsia is 8–10%. These include gestational hypertension, chronic hypertension, preeclampsia, eclampsia, and superimposed preeclampsia. Preeclampsia stands out as a major cause of maternal morbidity and mortality about 8%.[1,2] Some of the complications of preeclampsia can be prevented like eclampsia. Timely administration of an anticonvulsant drug in severe preeclampsia can prevent eclampsia which in turn can reduce the morbidity and mortality of the mother and baby. The standard anticonvulsant used is magnesium sulfate. It is considered a first-line drug for prophylaxis against convulsions. The standard regime to administer the magnesium sulfate is Prichard's regime, which consists of magnesium sulfate being administered 4 gm intravenously (IV) followed by 5 gm intramuscularly (IM) in alternating buttocks totaling 14 gm. A further 5 gm IM every 4 hours for 24 hours is administered. Another regimen is an intravenous regime which comprises magnesium sulfate being administered 4 gm IV followed by 1–2 gm IV/hour for 24 hours.[3,4] Other low dose regimes like the Dhaka regime have been used.[5] However, the loading dose of magnesium sulfate as 4 gm IV and 10 gm IM (5 gm in each buttock) can be cumbersome and painful to the patient. Moreover the maintenance dose of 5 gm IM 4th hourly is also painful to the patient. Before administering each dose, signs of magnesium sulfate toxicity have to be checked namely reduced respiratory rate, decreased patellar reflexes, and reduced urine output. A gluteal abscess is a known complication of intramuscular magnesium sulfate.[3,4] Phenytoin has also been used to prevent seizures in preeclampsia. However, its efficacy has been shown to be lesser than that of magnesium sulfate. Many centers do not have facilities to monitor serum magnesium levels.[6,7]

On the other hand, newer anticonvulsant drugs have been less studied in the prevention of convulsions in preeclampsia patients. Levetiracetam is a newer anticonvulsant. It has been used extensively in pregnancy as an anticonvulsant drug in epileptic women.[8] It has been proven to be safe in pregnancy and has shown not to have any adverse effects on the fetus. Levetiracetam has a 12 hourly dosage and does not need extensive monitoring as in comparison to magnesium sulfate. It has been used as a second-line anticonvulsant

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in eclampsia. Hence this study proposed to use levetiracetam as a prophylactic anticonvulsant in severe preeclampsia.

Materials and Methods

The study was conducted at BLDE (DU) Shri BM Patil Medical College Hospital and Research Center, Vijayapura, Karnataka, India. Ethical clearance was obtained on December 27, 2019, by the Institute Ethical Clearance Committee.

The study was registered in the Clinical Trials Registry of India, the registration number being CTRI/2020/02/023194.

Study design: Randomized parallel non-inferiority trial.

Consenting pregnant women having gestational age above 28 weeks presenting with preeclampsia with severe features were recruited during the study period. Pregnant women with chronic hypertensive disorders, pregnant females with fetal anomalies detected on USG, patients who were diagnosed with other causes of convulsions in pregnancy like cerebral malaria and epilepsy were excluded from the pregnancy.

Method of Collection of Data

The study commenced on February 8, 2020, and was completed on November 30, 2020. Informed and written consent was obtained from all participants. The study protocol and possible adverse effects of the drug were explained to the patient. On admission, a detailed history was taken and a thorough clinical examination of the patient was done. The fundoscopic examination was done as well. Laboratory investigations for complete blood count, liver function tests, and renal function tests were done.

Patients were randomly allocated by means of a computerized random number generator into one of two categories of anticonvulsant treatment:

Group I: Magnesium sulfate: A loading dose—4 gm of magnesium sulfate was given IV over 3–5 minutes followed by a maintenance dose of 1 gm/hour for 24 hours. Magnesium sulfate solution given in dilution via infusion pump.

Group II: Levetiracetam: Levetiracetam was administered 500 mg 12th hourly for 24 hours intravenously. It was administered slowly over 5 minutes. This was followed by an oral tablet of levetiracetam 500 mg 12th hour for 5 days.

Hypertension was controlled with oral nifedipine and if required oral/intravenous labetalol. Any convulsions after administration of magnesium sulfate or levetiracetam were noted. Any adverse effects or toxicity of magnesium sulfate or levetiracetam were noted.

Sample Size

- With the anticipated proportion of primigravida vs multigravida 68.3 and 18.4%[(ref)], the minimum sample size per group is 30 patients with 80% power and 5% level of significance.

  Formula used

$$n = \frac{(z_\alpha + z_\beta)^2 2p^* q}{MD^2}$$

  Where
  Z = Statistic at a level of significance
  MD = anticipated difference between two proportions
  p = common proportion
  $q = 100 - p$
  Total sample size = 30 + 30 = 60

Sample Size Estimation

$$Z = \frac{E}{\sigma/\sqrt{n}} \text{ this implies } n = Z(\alpha/2) \times \sigma^2/E^2$$

In this study, $Z(\alpha/2) = 1.96$ @ 5% level of significance and $\sigma = 0.51$ (from pilot study) and $E = 20\%$ i.e., expected change are Improvement due to new treatment (levetiracetam).

Test statistics used

- Z statistics are used to assess the significance of the difference in averages associated with $MgSO_4$ and levetiracetam.
- p values are mentioned to know the level of significance of the difference between the two treatments.
- Odds ratio is calculated to assess the change of effectiveness of one with the other.
- Confidence intervals are used to identify the range of the values of the parameters within which the parameters are expected to lie with a $1-\alpha$ level of confidence

Results

A total of 1,942 women were delivered during the study period of which 255 had preeclampsia. A total of 191 women had severe preeclampsia with severe features. Sixty women fulfilled the inclusion criteria and were randomized according to a computer-generated randomization list.

Women were randomized to either group one which received magnesium sulfate or group II which received levetiracetam.

There was no statistically significant difference in age, duration of gestation, and parity in both groups (Tables 1 and 2). Imminent symptoms were more in the magnesium sulfate group (Tables 3 and 4).

The blood pressure and heart rate were recorded 4th hourly for 24 hours in both the groups. There was no statistical difference in both groups (Table 5). There was no statistically significant difference between the two groups' blood parameters (Table 6). There was no statistically significant difference with respect to the mode of delivery in the groups though the number of cesareans sections was more in the levetiracetam group (Table 7). The neonatal outcome was comparable in both groups (Table 8). In two patients on magnesium sulfate, the urine output was low and hence the drug was stopped.

Discussion

Prevention of seizures in a patient who suffers from severe preeclampsia is of paramount importance. These patients need to be treated as a medical emergency. Various drugs have been used to treat convulsions in eclampsia such as magnesium sulfate, phenytoin, diazepam, and lytic cocktail (chlorpromazine, promethazine, and pethidine).[9,10] Magnesium sulfate and phenytoin have been used in the prevention of preeclampsia. Magnesium sulfate has been shown to be superior to phenytoin in preventing convulsions.[11] However it has significant adverse effects. The commonly observed adverse

Table 1: Data on age and period of gestation

	Magnesium sulfate		*Levetiracetam*		
	Mean	*SD*	*Mean*	*SD*	*p-value*
Age	24.0	3.7	24.2	3.9	0.766
Period of gestation	38.26	2.30	38.20	2.50	0.3174

Table 2: Data on gravid, para, and living

	Gravida			*Para*			*Living*		
Drugs	*No*	*Frequency*	*%*	*No*	*Frequency*	*%*	*No*	*Frequency*	*%*
Magnesium sulfate	1	10	0.33	0	14	0.47	0	17	0.57
	2	11	0.37	1	12	0.40	1	12	0.40
	3	06	0.20	2	04	0.13	2	01	0.03
	4	03	0.10						
Levetiracetam	1	20	0.67	0	20	0.67	0	20	0.67
	2	07	0.23	1	08	0.27	1	8	0.27
	3	02	0.07	2	01	0.03	2	1	0.03
	5	01	0.03	4	01	0.03	3	1	0.03

Table 3: OR of presence and absence of various symptoms under two treatments

	Imminent signs			*Headache*			*Nausea*			*Vomiting*		
Drugs	*OR*	*p-value*	*CI*	*OR*	*p-value*	*CI*	*OR*	*p-value*	*CI*	*OR*	*p-value*	*CI*
Magnesium sulfate	0.30	0.084	0.07–1.14	1.63	0.73	0.33–8.76	0.48	1	0.01–126–25	0.17	0.19	0.57–283
Levetiracetam	3.33	0.084	0.88–14.03	0.61	0.73	0.11–2.98	2.04	1	0.007–9.87	5.8	0.19	0.003–1.7

Table 4: Table showing imminent symptom and drug used

Drugs	*Headache*	*Nausea*	*Vomiting*	*Abdominal pain*
Magnesium sulfate	6 (20%)	2 (6%)	5 (16%)	2 (6%)
Levetiracetam	4 (13%)	0	1 (3%)	1 (3%)

Table 5: Comparison of heart rate, systolic blood pressure, diastolic blood pressure between magnesium sulfate and levetiracetam

	Magnesium sulfate		*Levetiracetam*				*95% CI ($MgSO_4$)*		*95% CI (Levetriacetam)*	
	Mean	*SD*	*Mean*	*SD*	*Z value*	*p-value*	*Lower bound*	*Upper bound*	*Lower bound*	*Upper bound*
Systolic BP										
At admission	166	16.43	161	13.2	3.55	0.001	160.11	171.89	156.27	165.73
At 4 hours	135	14.60	140	14.1	3.61	0.001	129.77	140.23	139.65	140.35
At 8 hours	134	13.10	137	11.3	2.35	0.01	129.31	138.69	136.69	137.31
At 12 hours	1133	10.10	134	11.2	0.83	0.406	129.38	136.62	133.76	134.24
At 24 hours	132	11.50	135	14.9	2.26	0.01	127.88	136.12	134.73	135.27
Diastolic BP										
At admission	102	8.90	104	6.80	1.96	0.05	98.81	105.19	103.79	104.21
At 4 hours	87	8.60	91	8.70	3.72	0.001	83.92	90.08	90.79	91.21
At 8 hours	87	9.35	85	9.90	1.76	0.078	83.65	90.35	84.78	85.22
At 12 hours	88	11.70	84	6.30	3.65	0.001	83.81	92.19	83.72	84.28
At 24 hours	86	8.60	84	9.50	1.82	0.684	82.92	89.08	83.79	84.21

effects are flushing, respiratory depression, reduced urine output, and depressed reflexes.[10,12] In our study two patients had reduced urine output for which magnesium sulfate had to be stopped. On the contrary, newer anticonvulsant drugs like levetiracetam and lamotrigine have been less studied in pregnancy for preventing convulsions in preeclampsia or in eclampsia. Classic antiepileptic drugs like sodium valproate, phenytoin, and carbamazepine are all known to have teratogenic effects on the fetus and hence their use in pregnancy has been discouraged. Levetiracetam has been used extensively in pregnant epileptic women for the prevention of seizures. It has not been shown to be associated with a higher risk of teratogenics effect on the fetus. Levetiracetam is a relatively safer drug with no need for strict monitoring of adverse effects as required in magnesium sulfate. It has a 12th hourly dosage, making it easy to administer.[13] In our study, there were no convulsions in both groups. There were two patients on the magnesium sulfate arm who developed adverse effects, however, there are nine in the levetiracetam group. There were no adverse neonatal outcomes in either of the groups through magnesium sulfate is known to cause neonatal depression.[14] A retrospective study conducted in the US showed that levetiracetam was being used in the prevention of convulsions in preeclampsia more so in those patients who had contraindications to the administration of magnesium sulfate like rising serum creatine and serum magnesium sulfate, pulmonary edema, reduced urine output or symptoms like headache, vision changes.[15] In another retrospective study conducted in Mumbai, India, it was seen that levetiracetam was administered in eclamptic patients who had low urine output or who had convulsions after the administration of magnesium sulfate. They have shown favorable results with levetiracetam.[16] Levetiracetam has been mentioned as a drug that can be used in eclampsia where magnesium sulfate is contraindicated.[17] There have been no known randomized control

Table 6: Comparison of blood parameters between magnesium sulfate and levetiracetam

	Magnesium sulfate		*Levetiracetam*				*95% CI ($MgSO_4$)*		*95% CI (Levetiracetam)*	
	Mean	*SD*	*Mean*	*SD*	*Z value*	*p-value*	*Lower bound*	*Upper bound CI 95%*	*Lower bound*	*Upper bound CI 95%*
HB	11.89	1.73	10.99	1.54	1.93	0.053	11.27	12.51	10.44	11.54
Leukocyte count	11744.8	4667	12304.96	5143.8	21.90	0.0001	10072.53	13417.07	12193.48	12416.44
Platelet count	2.17	0.66	2.04	0.83	0.41	0.681	1.93	2.41	2.02	2.06
Serum bilirubin	0.77	0.37	0.61	0.56	0.64	0.522	0.64	0.90	0.60	0.62
S. Protein	6.06	0.51	5.06	0.95	3.21	0.001	5.88	6.24	5.05	5.07
Blood urea	17.46	6.83	19.73	9.56	2.17	0.03	15.01	19.91	19.57	19.89
Serum creatinine	0.60	0.14	0.66	0.32	0.34	0.733	0.55	0.65	0.66	0.66

Table 7: Comparison of mode of delivery between magnesium sulfate and levetiracetam

	Magnesium sulfate	*Levetiracetam*		
	NO (%)	*NO (%)*	*Z value*	*p-value*
LSCS	9 (30%)	14 (47%)	1.37	0.170
Vaginal delivery	21 (70%)	16 (53%)	1.08	0.280

Table 8: Comparison of baby parameters between magnesium sulfate and levetiracetam

	Magnesium sulfate		*Levetiracetam*				*95% CI ($MgSO_4$)*		*95% CI (Levetiracetam)*	
	Mean	*SD*	*Mean*	*SD*	*Z value*	*p-value*	*Lower bound*	*Upper bound CI 95%*	*Lower bound*	*Upper bound CI 95%*
Baby weight in kg	2.50	0.57	2.63	0.52	−0.48	0.6312	2.30	2.70	2.44	2.82
Apgar 1 minute out of 10	6.71	0.61	6.8	0.60	−0.32	0.749	6.49	6.93	6.79	6.81
Apgar 5 minutes out of 10	8.73	0.57	8.6	0.70	0.45	0.6474	8.53	8.93	8.59	8.61
Baby mother side	0.4	0.45	0.5	0.50	−0.40	0.6892	0.24	0.56	0.49	0.51
Baby admitted to NICU	0.6	0.50	0.5	0.50	0.39	0.6966	0.42	0.78	0.49	0.51
Birth asphyxia	0.4	0.50	0.10	0.30	1.30	0.1936	0.22	0.58	0.09	0.11
Prematurity	0.1	0.3	0.13	0.34	−0.15	0.8808	−0.01	0.21	0.12	0.14
Growth restriction	0.06	0.24	0.03	0.18	0.18	0.8572	−0.03	0.15	0.02	0.04

trials on comparison of levetiracetam and magnesium sulfate to the best of our knowledge. Larger studies would be required in this field. Levetiracetam may be of great use in remote places where monitoring of the adverse effects of magnesium sulfate may not be possible. It may be of great importance in those patients who already have clinical features that are contraindicated for the administration of magnesium sulfate. This study shows that levetiracetam is non-inferior to magnesium sulfate as none of the patients in both arms had any convulsions.

Conclusion

Magnesium sulfate has been the gold standard drug in the treatment of eclampsia and in preventing convulsions in preeclampsia. However, it is not without adverse effects. There is a need to explore other options of anticonvulsant drugs which are as effective as magnesium sulfate and are safe for the mother and the fetus. Levetiracetam has been studied extensively in pregnant epileptic women. This study concludes that levetiracetam is non-inferior to magnesium sulfate in preventing seizures in preeclampsia. Larger and extensive studies are required in this field to study the newer anticonvulsant drugs.

Limitation of the Study

As it is a pilot study, larger studies are required in his field.

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