"A PROSPECTIVE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LEVETIRACETAM IN COMPARISON TO MAGNESIUM SULPHATE IN THE MANAGEMENT OF ECLAMPSIA"

By

Dr. SINDHU MANNE

Dissertation submitted to BLDE (Deemed to be University), Vijayapura.

In partial fulfilment of the requirements for the award of the degree of

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IN

OBSTETRICS AND GYNAECOLOGY

Under the guidance of

Dr. Sailaja R Bidari

Professor Department of **OBSTETRICS AND GYNAECOLOGY**

BLDE (DEEMED TO BE UNIVERSITY)

SHRI B.M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA, KARNATAKA.

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LIST OF ABBREVIATIONS

MgS04	**MAGNESIUM SULPHATE**
LEV	**LEVETIRACETAM**
SGOT	**SERUM GLUTAMIC OXALOACETIC TRANSAMINASE**
SGPT	**SERUM GLUTAMIC PYRUVIC TRANSAMINASE**
ALP	**ALKALINE PHOSPHATASE**
BSUA	**BEDSIDE URINE ALBUMINE TEST**
LSCS	**LOWER SEGMENT CESAREAN SECTION**
HELLP	**HEMOLYSIS, ELEVATED LIVER ENZYMES AND LOW PLATELETS**
AED's	**ANTI-EPILEPTIC DRUGS**
NICU	**NEONATAL INTENSIVE CARE UNIT**
ACOG	**AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS**
sFlt-1	**CIRCULATING SOLUBLE fms-LIKE TYROSINE KINASE-1**
PGF	**PLACENTAL GROWTH FACTOR**
VEGF	**VASCULAR ENDOTHELIAL GROWTH FACTOR**
AT_1-AA	**ANGIOTENSIN II TYPE 1 RECEPTOR AUTOANTIBODIES**
TX	**THROMBOXANE**

INTRODUCTION

Eclampsia; a perplexing enigma. To this day it continues to alarm the Obstetrics and Gynecology community as how best to predict, diagnose and treat the disorder. It is is defined as the development of seizures that cannot be attributed to other causes and/or unexplained coma during pregnancy or puerperium in a woman with pre-eclampsia.[1]

It is an unpredictable, multisystem, life threatening emergency disorder that affects the lives of a mother and her unborn child, making it an important cause of morbidity and mortality.[2] Approximately 1 in 2000 deliveries are complicated by eclampsia in developed countries, whereas the incidence in developing countries varies from 1 in 100 to 1 in 1700 cases.[1] In India, the disorder is still prevalent with a high case fatality rate and an incidence that remains unchanged in the last 40 years.[3] The overall prevalence is reported to be about 1% of the overall population, with a higher prevalence among the rural population (1.9%) than in the urban population (0.6%). Although there are few incidence studies from India, the most recent one suggests an age-standardized incidence rate of 27.3 per 100,000 per year.[4]

Oftentimes the development of an eclamptic fit is without prior warning. In India, the initial contact with hospital care, especially among the rural population, is at a regional level. These centers have substandard care and poor knowledge in the management of eclampsia due to poorly trained hospital staff and a lack of basic resources such as a team of skilled obstetricians and anesthetists. These

regional centers also lack proper resuscitation equipment to give immediate life-saving care necessary for eclampsia patients.

The majority of the patients are sent to tertiary care hospitals after administering a loading dose of Magnesium Sulphate (MgS04). Magnesium Sulphate is the drug of choice for prevention and treatment of convulsions in eclampsia patients.[5] MgS04 has been irrefutably supported as a superior anticonvulsant compared to diazepam and phenytoin in the treatment and prevention of recurrent seizures in women with eclampsia.[6] The exact mechanism of its action is unclear, however, MgS04 seems to trigger cerebral vasodilation leading to reduction in ischemia that occurs during an eclamptic event as a result of cerebral vasospasm.[7] The drug is associated with several minor and major adverse effects. Minor effects such as flushing, nausea and vomiting, myalgia and irritation at the injection site. More serious side effects include the loss of patellar reflexes (seen at serum concentrations of 8-10 mEq/L) and respiratory depression (>13 mEq/L).[8] Administration of MgS04 requires careful monitoring. This is lacking in rural areas. The drug is often administered without proper evaluation of hematological, renal and liver profiles of the patient and then immediately referred to higher centres due to a lack of proper infrastructure, ICU set up or unavailability of trained obstetricians and anesthetists. Routine monitoring of a woman undergoing magnesium sulphate therapy requires assessment of the general neurological state of the patient such as alertness, presence of patellar reflexes, respiratory rate and urinary output. Careful vigilance is required in avoiding more serious side effects. This allows for delaying the administration of the next dose or administering calcium gluconate correction in cases of magnesium toxicity. Despite the compelling evidence for usage of magnesium sulphate, there is still a growing concern about the safety of its administration and use in clinical environments where the capacity to monitor the patient is limited.[8]

This demands the further exploration of a drug that can be safely administered, is inexpensive, readily available and requires less monitoring than the current magnesium sulphate regimen. Levetiracetam (LEV) is an effective antiepileptic drug that is relatively safe in pregnancy and free of teratogenic side effects.[9] This drug has the potential to be used in the treatment of eclampsia.[10] It does not require intensive monitoring, is easily accessible, inexpensive, and easy to administer. This newly marketed antiepileptic drug has been around since 2000 and has many pharmacological advantages such as a nearly complete absorption rate, rapid onset of action, minimal binding to plasma proteins, no activity on enzyme induction, absence of interactions with other drugs, no cognitive side effects, complete excretion by the kidneys and does not require blood-level monitoring.[11]

Keeping in mind the potential for Levetiracetam to be a safe alternative to Magnesium Sulphate in the treatment of eclampsia, this study has been undertaken to determine the safety, efficacy and perinatal outcome associated with both of these drugs.

AIMS

- To determine if Magnesium Sulphate is a safe alternative to using Levetiracetam in the treatment of eclampsia
- If Levetiracetam can be proven to be as effective as Magnesium sulphate and relatively safe in patients than further studies and assessment can be done on the use of the drug

OBJECTIVES

- To evaluate the demographics of patients with eclampsia at BLDE Medical College, Vijayapura, Karnataka
- To evaluate the efficacy of Levetiracetam as an alternative to Magnesium sulphate in the management of eclampsia
- To evaluate the neonatal outcome in babies exposed to Levetiracetam and Magnesium sulphate

ECLAMPSIA: PATHOPHYSIOLOGY

Eclampsia, is the end point to a number of pathophysiological and hypertensive changes that culminate to produce this life threatening event. The targeted place for the development of the disease is in the placenta. There is an alteration in the normal pathophysiological changes occuring in the developing placenta. These minute changes lead to large scale disturbances that clinically affect the mother and baby.

The human placenta is a discoid-shaped structure important for the transmission of blood and nutrients between mother and fetus throughout pregnancy. It is made up of a maternal side, developed from decidua basalis, and a fetal side that develops from chorion frondosum. Blood flow in the placenta is divided into two systems, uteroplacental and fetoplacental circulation. Uteroplacental circulation is the system through which blood flows from the maternal vessels into the intervillous spaces and around the villi. This blood perfuses through the villi and delivers oxygen and nutrients to the fetal blood and drains back across the intervillous space into the maternal circulation via the uterine veins. This continuous movement is facilitated by the low resistant nature of maternal arterial pressure in the uteroplacental vessels.

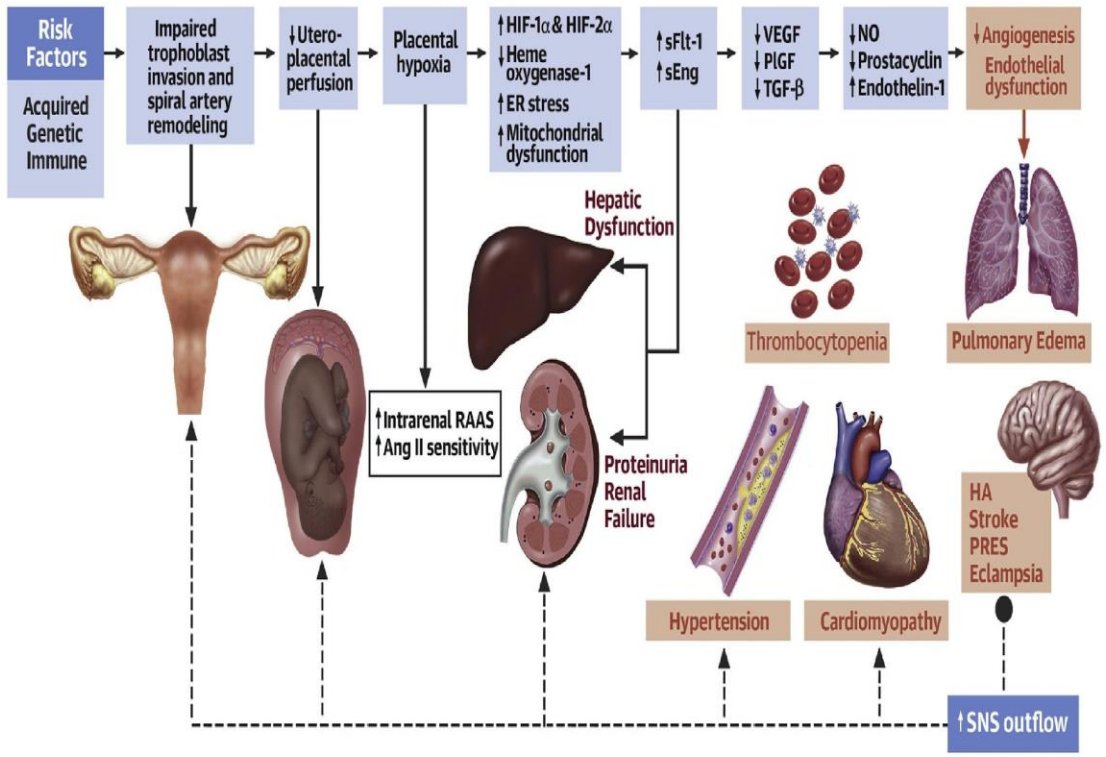
In hypertensive disorders of pregnancy, this well developed system is altered. There is an absence of spiral artery remodelling and increased production of antiangiogenic factors that lead to vasospasm, reduced organ perfusion, increased

endothelial dysfunction and activation of the coagulation system. These changes affect the placenta, kidneys, liver and the brain. In the placenta, problems arise from defective spiral artery remodeling. There is a failure of invasion of cytotrophoblast into the inner third of the myometrium, at the junction between the decidua and the myometrium. Normal invasion allows for replacement of the vascular endothelial and muscular linings of the decidual vessels and deeper myometrial arterioles that causes an enlargement of the vessel diameter for increased placental perfusion. In this pathologic state, the endothelial lining and muscular elastic tissue of the deeper myometrial arterioles is not replaced. These abnormally narrow spiral arteries result in decreased blood flow and high resistant pressure. It prevents adequate time for oxygen exchange to occur across the intervillous space and turbulent flow damaging the villi that leads to placental ischemia and poor perfusion. The inner lumen of blood vessels, known as the endothelium, senses these ischemic/hypoxic changes and signals the release of vasoactive mediators such as soluble fms-like tyrosine kinase-1 (sFlt-1), TNF-α, IL-6, angiotensin II type 1 receptor autoantibodies (AT_1-AA) and thromboxane (TX). These mediators reduce nitric oxide and increase reactive oxygen species leading to widespread pathological changes in the maternal vasculature. These changes are reflected in the kidneys where they cause alterations in the renin-angiotensin system such as increased sensitivity to angiotensin II, reduction of renal pressure and increased total peripheral resistance that ultimately culminates to cause hypertension.

Further progression of these changes can lead to altered pathology in the brain causing severe vasospasm of cerebral arterioles and an over-dilatation of vessels.

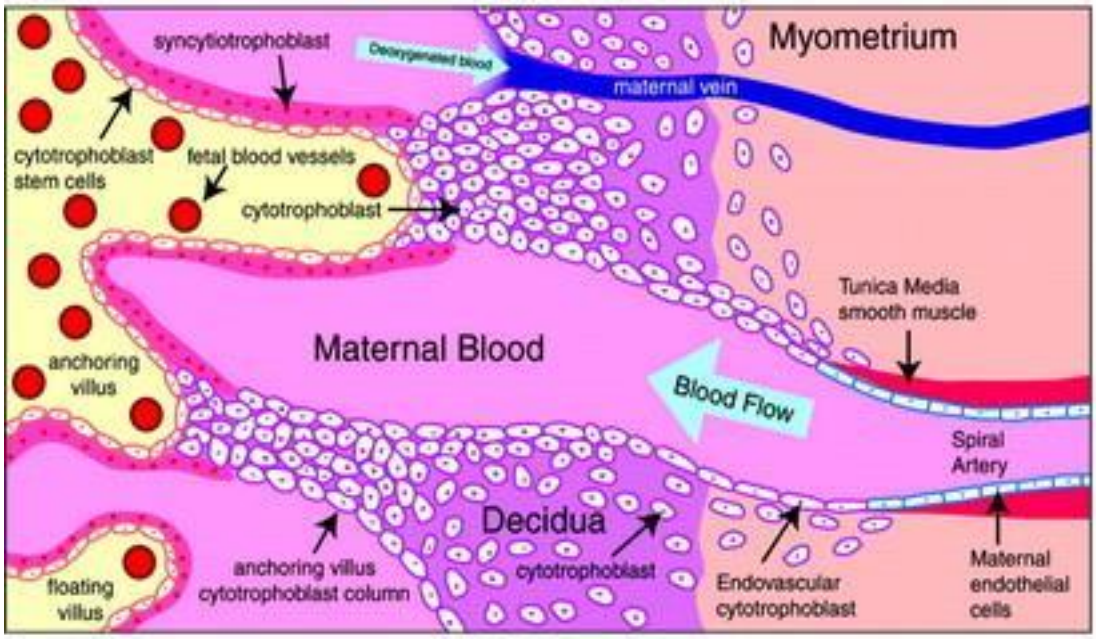
Vasospasm of cerebral arteries is an autoregulatory response by the body to severe hypertension. This vasoconstriction leads to cytotoxic ischemia, edema and infarction of the brain. As the disease progresses, this autoregulatory response is lost and vessels dilate resulting in hyperperfusion and worsening of the cerebral edema. There is also a release of certain molecules from the placenta such as neurokinin B, inflammatory cytokines, endothelins and tissue plasminogen activator which are reported to have excitatory action on neuronal receptors. An interplay of these different pathological changes can ultimately cause excessive release of excitatory neurotransmitters like glutamate that cause large scale depolarization of neurons that manifest as generalized tonic-clonic seizures. This in the presence of severe hypertension is called eclampsia.

CENTRAL ILLUSTRATION: Pathogenesis of Preeclampsia

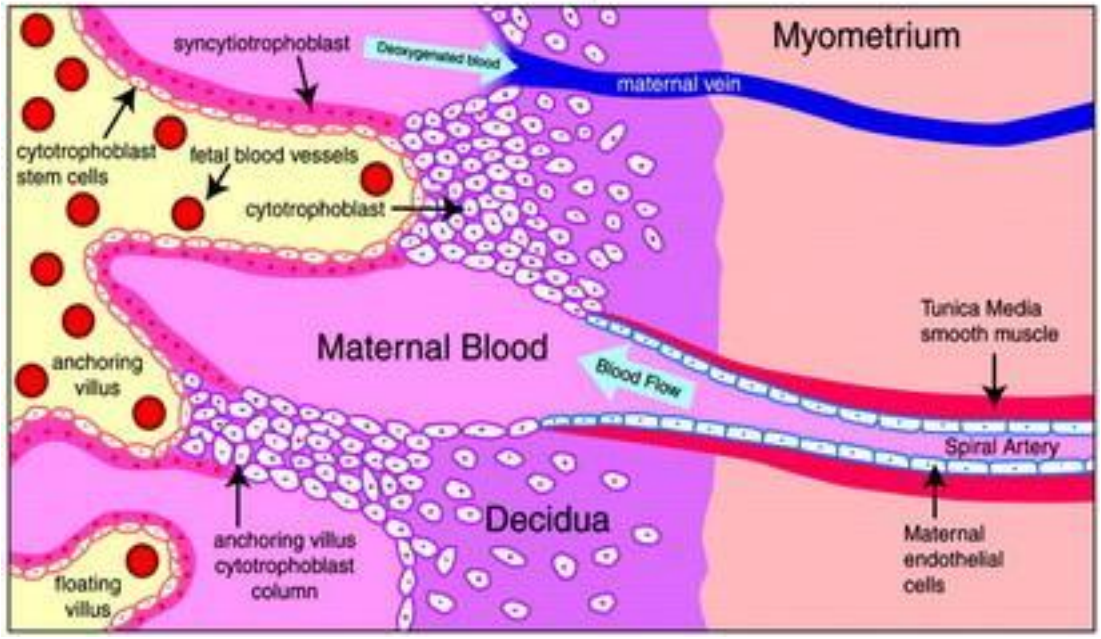


Ives, C.W. et al. J Am Coll Cardiol. 2020;76(14):1690-702.

Normal



Preeclampsia

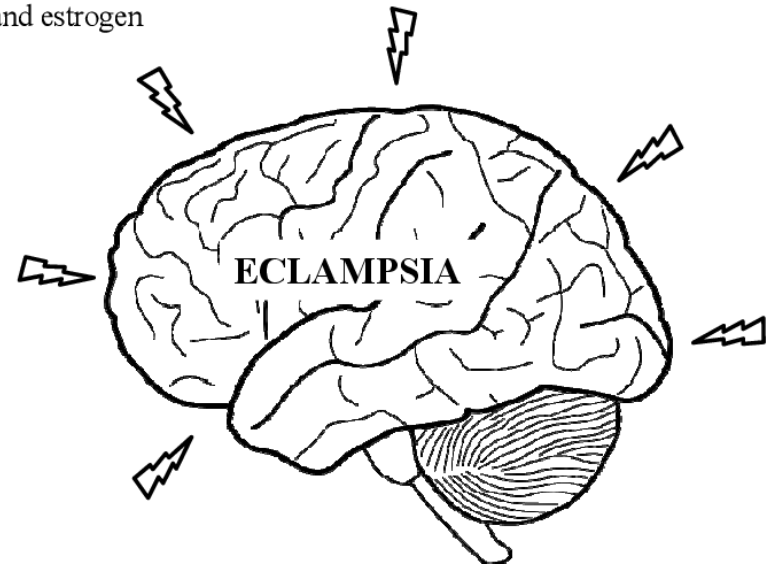


Blood-Brain Barrier Disruption

- Increased permeability factors
- Failure of efflux transporters
- Endothelial dysfunction
- Autoregulatory breakthrough
- Edema formation

Change in Neurosteroids

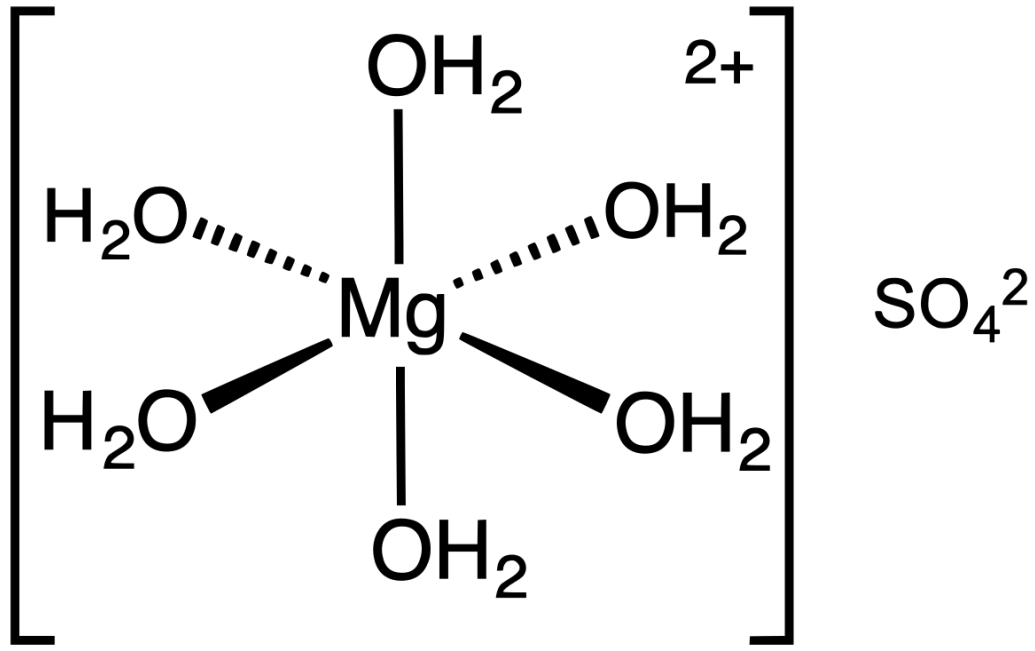
- Decreased $GABA_AR$ subunits
- Pro-convulsive effects of estradiol
- Imbalance of progesterone and estrogen
- Others



Inflammation & Infection

- Microglial activation
- Local cytokine production
- Others

MAGNESIUM SULPHATE: PHARMACOLOGY



Magnesium Sulphate (MgSO4) is a chemical compound containing magnesium minerals and sulphate salts. It is used in pregnancy as a safe, inexpensive anticonvulsant agent that acts on the central nervous system to prevent and treat generalized tonic-clonic seizures without causing CNS depression in the mother or fetus.

MgSO4 is used in pregnancy for the main purpose of anticonvulsant therapy but has a number of other uses. Its actions on the cardiovascular system help to reduce systemic vascular resistance which helps to reduce blood pressure. In the uterus, it exerts a tocolytic action that causes relaxation of the uterine myometrial muscles. The drug is

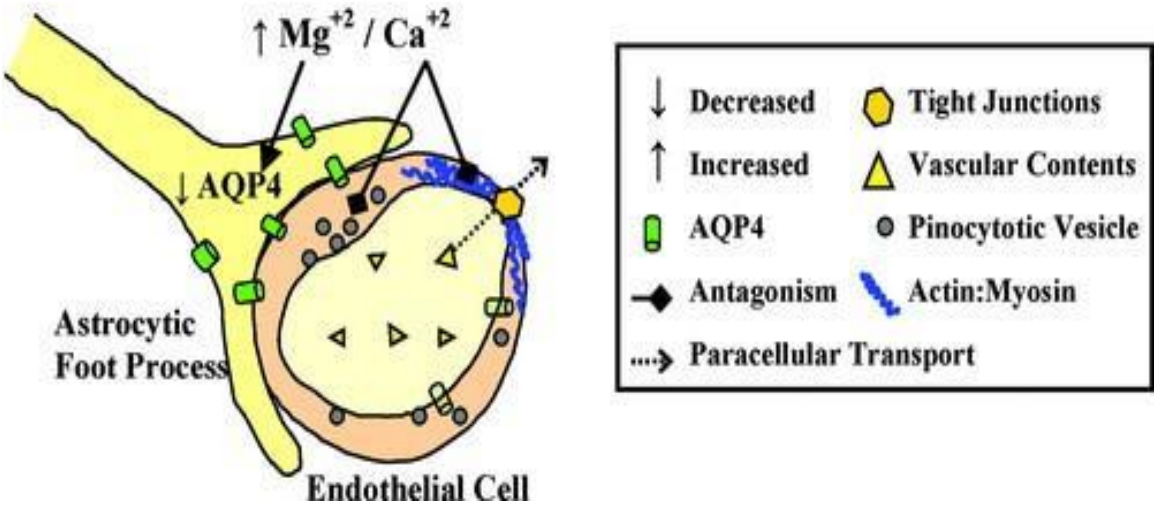
also beneficial in the prophylaxis and treatment of hypomagnesemia and in magnesium deficient patients receiving total parenteral nutrition.[12]

The structure of magnesium structurally resembles that of calcium, making it a competitive antagonist of calcium. Increased concentration of calcium has been shown to induce vasospasm of cerebral arteries. Thus, the administration of magnesium sulphate helps to reduce the concentration of calcium through competitive inhibition and helps in alleviating the effects of vasospasm on cerebral vessels. Although the exact pathogenesis of cerebral vasospasm that leads to eclampsia is unknown, it is well understood that calcium plays an important role.

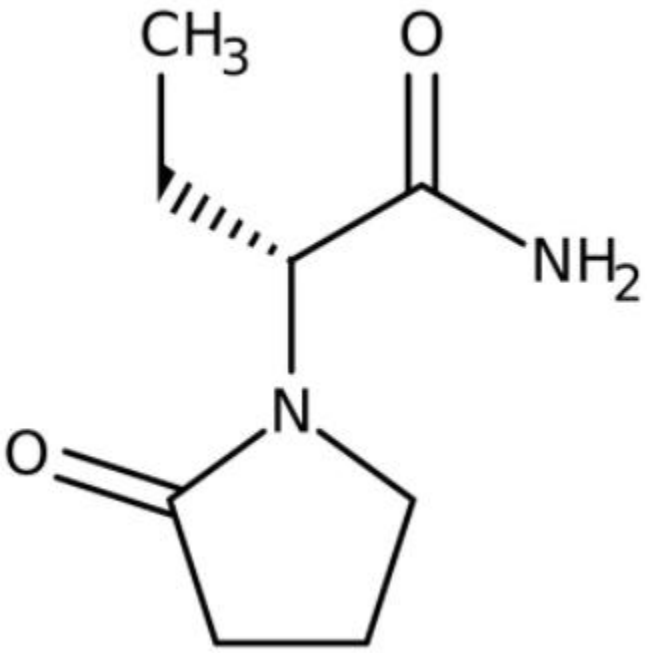
The drug is administered intravenously or intramuscularly and has a half-life of four hours in a person with normal renal function. It is contraindicated in patients with reduced glomerular filtration, as it can increase the half life of the drug. Measurement of serum creatinine and a vigilant watch on urine output is needed to assess adequate glomerular functioning as the drug has a narrow therapeutic window. The serum magnesium levels should be maintained within a therapeutic level of 4-7 mEq/L, 4.8-8.4 mg/dL, or 2.0 to 3.5 mmol/L. Increases in these levels can produce loss of reflexes, respiratory depression or cardiac arrest. To prevent toxicity, monitoring of knee jerk reflexes, respiratory rate, chest auscultation and urine output should be intermittently checked.

Effect of Magnesium Sulfate on Cerebral Edema and the Blood-brain Barrier.

Cellular Target	Mode of Action	Possible Mechanism
Cerebral Endothelium	Decreased Blood-brain Barrier (BBB) disruption ↓ Limited Cerebral Edema Formation Via Paracellular Transport	Calcium Antagonism ↓ Decreased Cell Contraction ↓ Decreased Tight Junction Permeability
	Limited Transcellular Transport	Decreased Pinocytosis
Astrocyte	Limited Cerebral Edema	Decreased Aquaporin 4 (AQP4) Expression



LEVETIRACETAM: PHARMACOLOGY

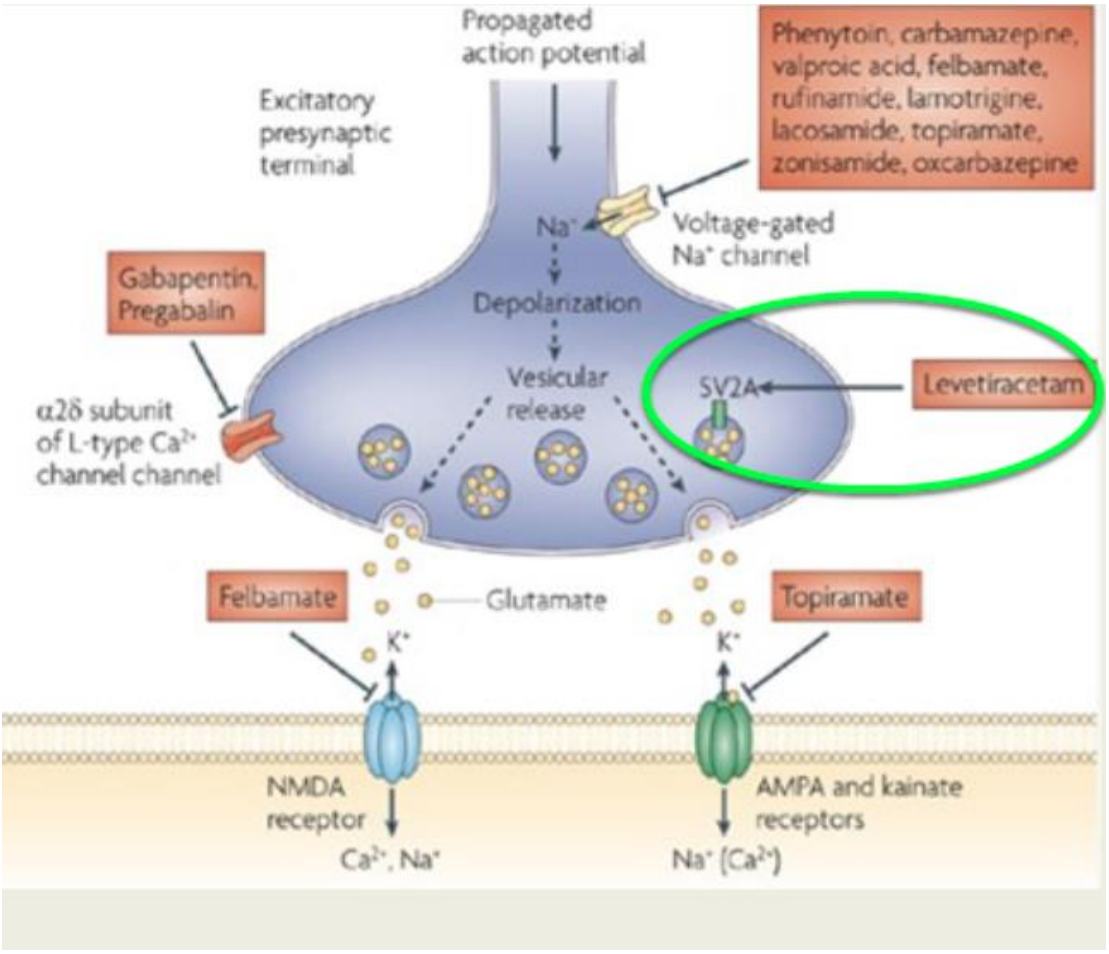


Levetiracetam, a recently marketed antiepileptic drug, was approved in the year 2000 for the treatment of partial onset, myoclonic, and primary generalized tonic-clonic seizures. Recently, it has been also used in a smaller number of status epilepticus cases and as seizure prophylaxis in patients with subarachnoid hemorrhage.[13]

The drug has more than a 95% bioavailability when taken orally. Its plasma half life is between 6-8 hrs with a duration of action for 24 hours. Peak plasma concentration can be reached within 5 to 15 minutes with the intravenous form of the drug. Patients with altered renal functioning require a dose adjustment. As the drug is not dependent on

hepatic metabolism and has minimal protein binding activity, it can be safely administered with other drugs as there are no pharmacokinetic interactions.

The mechanism of action of Levetiracetam is still not clearly defined. It is hypothesized that the drug binds with a protein called SV2A, also known as synaptic vesicle protein 2A. This secretory vesicle protein is present on calcium dependent vesicles that release neurotransmitters. The interaction of the drug with this vesicle protein reduces the release of neurotransmitters, thus reducing the chance of a convulsion.



REVIEW OF LITERATURE

LITERATURE ON ECLAMPSIA

Thomas S.V. looked at the neurological aspects of eclampsia in an article published in the Journal of Neurological Sciences. He classifies eclampsia according to the onset of symptoms. Convulsions starting before the onset of labor in a pregnant woman with preeclampsia is referred to as antepartum eclampsia. About three quarters of all eclampsia occur antepartum. Intrapartum eclampsia is the onset of convulsions after the beginning of labor in a preeclampsia pregnant female. Postpartum eclampsia is a convulsion occurring within seven days of delivery of the fetus and placenta in a patient with preeclampsia. Seizures are the hallmark of eclampsia. Generally they are generalized tonic clonic types that start over the face and progress over the rest of the body. The average frequency of seizures was found to be three in a 12 hour duration. About 6.5% of patients with eclampsia develop neurological complications such as cortical blindness, aphasia, limb weakness, psychosis, coma or cerebrovascular accident. Raised intracranial pressure is another major complication which requires emergent management. Control of seizures is a major task in the management of eclampsia. Different protocols are available in different parts of the world. Magnesium sulphate is a popular drug to manage convulsion in eclampsia. Serious toxic symptoms can develop with magnesium overdose, especially in the presence of compromised renal functioning. Early signs are loss of knee and ankle jerk at MgSO4 levels of 8-12 mg/dl. Paralysis of respiratory muscles at levels around 15-17 mg/dl. Cardiac arrest can occur at 30-35 mg/dl. The article discusses studies comparing the efficacy of magnesium sulphate to

other antiepileptic drugs such as phenytoin and diazepam in the management of eclampsia. Results of those studies concluded that the magnesium sulphate group had a lower mortality rate or risk of artificial ventilation and pneumonia. Results of the studies show that magnesium sulfate therapy is superior to the phenytoin and diazepam in the management of eclamptic seizures. The article calls for further studies which would be useful to develop suitable solutions to prevent eclampsia.[14]

Imaralu et al wrote about the etiology of eclampsia. In their journal titled "Evolution of Magnesium Sulphate for Eclampsia," they looked at the etiopathogenesis of eclampsia. The exact mechanism by which preeclampsia develops in eclampsia remains unclear. Most often, eclampsia still occurs suddenly without overt features of severe preeclampsia. Described as a "flash of lightning" by Veradeus. Although the exact mechanism remains elusive, there are several abnormalities consistently observed in patients progressing to eclampsia. These include evidence of cerebral ischemic necrosis. It is made evident by findings of vasospasm detected with computed tomography (CT) and magnetic resonance imaging (MRI). There is also a consistent finding of edema formation in patients with eclampsia. This results from a sudden increase in blood pressure through areas of vasoconstriction in the cerebral arteries and arterioles. These features are reversible and possibly hint at eclampsia being a form of hypertensive encephalopathy or posterior reversible encephalopathy syndrome (PRES). This explains why the use of anti-hypertensive drugs and resolution of hypertension post delivery in eclampsia patients leads to reversibility of symptoms such as headache, persistent vomiting, cortical blindness and seizures. The article further looked at the history of

eclampsia treatment. The disease was differentiated from epilepsy in the 18th century. Initially it was thought that a circulating toxin was acting on the nerve centers causing the onset of seizures. This led to initial therapy focusing on measures to remove the toxin. Measures such as phlebotomy, gastric lavage and catharsis were used then. Slowly, as it was believed that convulsions disrupted functioning of system organs, sedation became a popular treatment choice. Although MgSO4 has been a remedy used since the early twentieth century and scientifically proven to help treat eclampsia, fits have still been observed during its administration. This is largely due to inadequate knowledge on the exact mechanism of action of how the drug alleviates and prevents seizures. Mortality associated with magnesium sulphate is mainly because of toxicity. Toxicity is especially observed during patient transfers and in areas of chaotic environments such as the labor room. Monitoring is key to preventing toxicity, close observation of a patient's clinical condition is important as some patients can develop toxicity even at therapeutic serum magnesium levels. A respiratory rate of 16 cycles per minute or more, normal deep tendon reflexes, urine output during treatment of at least 25 ml/hour, should all be monitored carefully. Fetal heart rate should also be closely monitored in mothers being administered magnesium sulphate. High fetal levels of magnesium can impair fetal breathing movements.[15]

LITERATURE ON MAGNESIUM SULPHATE IN ECLAMPSIA

Sadeh M published an article titled "Action of Magnesium Sulfate in the Treatment of Preeclampsia-Eclampsia." They have suggested that one of the actions of MgSO4 when given in preeclampsia-eclampsia patients is preventing vasospasm by its antagonistic action on calcium. Magnesium (Mg^{2+}) is a bivalent ion with structural similarities to Calcium (Ca^{2+}) that allows it to compete with calcium for binding at the presynaptic membrane. This leads to an inhibition of acetylcholine-Ca^{2+}-dependent release. This action can be terminated by increasing the concentration of calcium at the presynaptic junction. This is given in the form of calcium gluconate, which is commonly used as an antidote for magnesium sulphate toxicity. These two ions also have opposing effects on vascular tone. While calcium plays a role in inducing vasospasm of isolated cerebral arteries, magnesium causes decreased cerebral vascular tension and can help reverse vasospasm. The article also mentioned about the role of MgSO4 on blood pressure. It states that the transient minor effect of magnesium sulphate treatment on blood pressure can be explained by its varying level of sensitivity to antagonizing calcium in cerebral and systemic arteries. During preeclampsia-eclampsia pathogenesis, ischemia of cerebral vessels leads to an increase in the intracellular concentration of Ca^{2+}. A reduction of transmembrane potential opens up calcium channels and releases Ca^{2+} from the mitochondria and endoplasmic reticulum. This calcium activates phospholipase enzymes that hydrolyze the membrane phospholipids leading to injury of the cell membrane and further releases calcium that continues to worsen the process. High concentrations of calcium deplete the ATP reserve leading to irreversible cell damage. One of the routes of

calcium influx during ischemia is through N-methyl-D-aspartate (NMDA) receptors. Mg^{2+} helps block this inward flow of Ca^{2+}. This study analyzes that a large part of magnesium sulfate action in eclampsia might be due to its action on blocking these NMDA receptors.[16]

Salha et al discussed the impact of eclampsia in their article titled "Modern management of eclampsia." The article states that the occurrence of seizures in association with preeclampsia are important causes of maternal mortality and morbidity. Even though the disease has been around for ages, there is still a consistent lack of management practices. The answer to poor management of eclampsia lies in better education and training of obstetricians, anesthetists and midwives in the diagnosis and treatment of eclampsia. The study points out the importance of higher level hospital care for eclampsia patients. It states that transporting a pregnant woman with eclampsia is difficult and dangerous. The ambulance journey can precipitate further incidence of seizures. The purpose of anticonvulsant therapy is to stop the present convulsion and prevent recurrence of convulsions. Eclampsia patients administered MgSO4 showed a reduction in maternal mortality, need for ventilatory support and admission to an intensive care unit. Use of magnesium sulphate is because of its vasodilatory and membrane stabilizing actions. When given through an intramuscular route, MgSO4 was associated with pain and abscess formation in 0.5% of cases. This is why the IV route is more preferred. Monitoring in cases administered by MgSO4 requires hourly measurement of patellar reflexes and respiratory rate. If any signs of magnesium toxicity are present, further doses should be withheld until these disappear.[17]

Bain et al observed the antenatal magnesium sulphate regimens. They reported that while the many adverse effects following antenatal administration of magnesium sulphate are well known, the risk of each event individually is unknown. Life-threatening maternal adverse effects such as respiratory arrest, cardiac arrest and even death are extremely rare but have still been reported in case reports. The more commonly reported adverse effects include flushing, increased warmth and sweating due to peripheral vasodilatory action of magnesium sulphate, nausea, vomiting headaches, muscle weakness, blurred vision and intravenous or intramuscular site pain or discomfort. Though these adverse effects are considered minor, they have been associated with early cessation of therapy with magnesium sulphate. The study also concludes that vigilance of MgSO4 is necessary to ensure safety for mothers. It states that errors associated with the administration of magnesium sulphate represent a significant and perhaps unappreciated risk of harm.[18]

LITERATURE ON LEVETIRACETAM IN PREGNANCY

Khalil B described the mechanism of action of Levetiracetam. The mechanism by which the drug acts is different from other antiepileptic drugs. Although it is still not clearly defined how the drug helps in reducing seizures, its main action is through binding to the synaptic vesicle protein SV2A. By binding to this protein LEV reduces the rate of vesicle release. Other mechanisms include inhibition of neuronal GABA and glycine gated channels and partial depression of the N calcium current. Khalil B also reported data on the safety of LEV in pregnancy and breastfeeding. Although limited data is available, the

UK Epilepsy and Pregnancy Registry showed that there were no minor malformations in the LEV monotherapy group that included 39 monotherapy exposures. Other smaller reports also reported similar findings of lack of LEV-related malformations. The mean birth weight for infants exposed to LEV was within a normal range. These preliminary reports seem to show that LEV is a favorable choice and additional reports can help further establish the safety of LEV therapy in pregnancy. In regards to breastfeeding, although LEV is transferred to infants through breast milk, serum levels in infants were very low suggesting that breastfeeding is not contraindication in patients using LEV monotherapy.[19]

Yang et al wrote how "Prolonged Exposure to Levetiracetam Reveals a Presynaptic Effect on Neurotransmission." The article suggests that it is possible that LEV binding with SV2A enhances the inhibition of abnormal bursting in epileptic circuits. The SV2 family of proteins contains 12 potential transmembrane regions. Although their precise function is still not established, their structure resembles transport proteins suggesting an involvement in pumping of calcium. Interestingly, LEV was more effective in diminishing late synaptic responses during rapid stimulus. This leads to a selective effect of the drug on epileptic activity leaving normal neurological functioning intact. This is an extremely desirable quality in an antiepileptic drug. LEV requires long exposure compared to other antiepileptics that act on ligand and voltage gated channels. The drug is unique in that it requires access to an intracellular component, SV2 proteins. Because of this, the drug requires more time to pass through the plasma membrane and into the presynaptic cytoplasm before binding to the SV2A protein. This results in a longer

latency before physiological effects of the drug can be observed. This typically ranges from 20-60 minutes according to a number of in vivo and in vitro studies. The article concludes that LEV and its benefits in patients with intractable seizures or intolerable side effects of other AEDs makes it an attractive target for future drug development and research.[20]

Satia et al conducted a retrospective observational study, which showed that 9 out of 10 patients who were given levetiracetam did not develop any convulsions after treatment was started. The one out of the 10 patients that continued to have convulsions despite levetiracetam therapy had 'status eclampticus'. Thus, in spite of a smaller number of cases there were no obvious side effects noted and a favourable outcome was seen in cases given Levetiracetam. The study calls for further evaluation of the anti-epileptic drug to further investigate its use in eclampsia.[21]

Longo et al did a case series showing that women with epilepsy that were given levetiracetam monotherapy had positive outcomes. The study showed encouraging results. All three patients delivered healthy babies with no evidence of cognitive alterations, medical problems or birth defects prenatally, at birth, or 3 and 6 months postpartum. Testing of the drug done in the third trimester on animals showed that there were no adverse effects of Levetiracetam at doses up to six times the maximum recommended human dose (MRHD) of $\geq$ 3600 mg/kg/day.[22]

Bansal et al conducted a study on Levetiracetam in pregnant women with epilepsy. In the study, they did not find any fetal malformations in women with epilepsy who were exposed to LEV during pregnancy. Their results were similar to those seen in Australian, UK and Ireland pregnancy registers and a population-based cohort study from Denmark. They concluded that in utero, the exposure to LEV is relatively safe in regards to causing any major congenital malformations in neonates.[23]

Koubeissi M did a study titled "Levetiracetam: More evidence of safety in pregnancy." The study notes that pharmacokinetic attributes of LEV have facilitated its wide clinical use. For example, LEV has linear pharmacokinetics and rapid onset of action, is completely excreted by the kidneys, doesn't interact with other drugs, has no cognitive side effects and does not require blood-level monitoring. These attributes make it a preferable choice for first line antiepileptic drug (AED) treatment. Thus, it is of great importance to assess the safety of levetiracetam in pregnancy.[24]

MATERIALS AND METHODS

A hospital based interventional study was done to determine and compare the effects of administering either Magnesium Sulphate or Levetiracetam in pregnant females diagnosed with eclampsia.

Source & place of study: Patients admitted to the labour ward in the 'Department of Obstetrics and Gynecology' in **B.L.D.E. (Deemed to be University) Shri B.M. Patil's Medical College, Hospital and Research Centre, Vijayapura**

Field of study: Tertiary teaching hospital

Study duration: 1st of October 2019 - 30th June 2021

Study design: Hospital based prospective interventional study

Inclusion criteria

1. All patients presenting with features of eclampsia during the study duration (1st of October 2019 - 30th June 2021) were recruited into the study.
2. All patients diagnosed with antepartum, intrapartum and postpartum eclampsia
3. Gestational age ≥ 24 weeks
4. Patients giving informed and written consent for investigations

Exclusion criteria

1. Patients who were diagnosed with other causes of convulsions in pregnancy such as:
    a. Epilepsy
    b. Trauma
    c. Cerebral malaria
    d. Cerebrovascular accidents
    e. Stroke
    f. Subarachnoid hemorrhage
    g. Space occupying lesions
    h. Metabolic abnormalities (hypoglycemia)
    i. Congenital brain malformations
    j. Drug/substance overdose
2. Chronic hypertensive patients
3. Pregnant females with fetal anomalies detected on USG
4. Patients who withdraw the consent for further participation in the study

Sample Size

- With Anticipated Proportion of primigravida vs multigravida 68.3**%** and18.4%[1] the minimum sample size per group is **38 patients with 80% power and 5% level of significance**.

- Formula used

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

Where Z= Z statistic at a level of significance

MD= Anticipated difference between two proportions

P=Common Proportion

q= 100-p

- Total sample size=38+38=76
    - 38 patients- Magnesium sulphate group
    - 38 patients- Levetiracetam group

Statistical Analysis

- Numerical variables will be presented as Mean ±SD, and categorical variables will be presented as frequency(%) and diagrams
- Comparison of numerical variables between groups will be found using unpaired t test/ Mann whitney U test , and categorical variables by Chi square or Fisher's Exact test

METHODOLOGY

1. Informed and written consent was obtained from all participants or their attendants in the case that participant is unable to give consent. Nature of the intervention and associated risks and side effects were explained and consent was taken for sending of investigations and for the administration of anticonvulsant drugs.
2. On admission, detailed history was taken along with a thorough clinical examination of the patient. Patient's baseline vitals including blood pressure, heart rate, respiratory rate were done. Patient was catheterized if not already catheterized and urine output on admission was recorded.
3. Laboratory investigations for complete blood count, complete urine analysis, liver function tests, renal function tests, coagulation profile and fundoscopic examination were performed.
4. Patients were placed into either the Magnesium Sulphate group or Levetiracetam group based on the history of whether a loading dose of MgSO4 was administered or not. Those that were administered an outside dose of magnesium sulphate were directly allocated into Group A- MgSO4 group and continued with pritchard's regimen. Those that were not administered a loading dose of MgSO4 were then randomly allocated by means of a random number generator into one of the two categories of anticonvulsant therapy as shown below:

2 Sets of 38 Unique Numbers Per Set
Range: From 1 to 76

Set #1

25, 4, 40, 75, 3, 66, 48, 26, 50, 46, 15, 5, 58, 76, 73, 32, 12, 64, 21, 19, 54, 33, 23, 49, 2, 55, 27, 36, 69, 68, 14, 59, 39, 24, 63, 6, 47, 56

Set #2

48, 69, 31, 12, 20, 18, 34, 10, 68, 54, 55, 25, 73, 59, 13, 7, 2, 27, 57, 65, 64, 44, 5, 61, 29, 49, 53, 52, 41, 45, 16, 14, 11, 3, 35, 33, 71, 6

Set #1 and set # 2 were allocated into MgSO4 and Levetiracetam, respectively. Based on the drug administered, regimen given was as follows:

I. Group A- Pritchard Regimen

a. Loading dose of 4 g magnesium sulphate ($MgSO_4 \cdot 7H_2O$ USP) as a 20% solution was given intravenously at a rate not to exceed 1 g/min. Followed promptly with 10 g of 50% magnesium sulphate solution, one half (5 g) injected deeply in the upper outer quadrant of each buttock through a 3-inch-long 20 gauge needle.

b. Maintenance dose was given every 4rth hourly with 5 g of a 50% solution of magnesium sulphate injected deeply in the upper outer quadrant of alternate buttocks

c. At every time of administration of maintenance dose a clinical examination was done to check for presence of patellar reflex, to confirm respirations were not depressed and to assess urine output of the previous four hours had exceeded or was equal to 100 mL. Once these measurements were within normal limits maintenance

dose was continued for 24 hours after delivery or after the onset of first convulsion, whichever came latter.[25]

II. Group B- Levetiracetam

a. Loading dose of 1 g was administered. Two vials of Injection Levera (5 mL each) were diluted with 100 mL of normal saline and administered intravenously as a 15-minute infusion.

b. Maintenance dose of 500 mg intravenously diluted in 100 mL normal saline as a 15-minute infusion was continued BD for two days.[26]

c. After two days of intravenous administration of injection Levera, patient was converted to oral tablets in the form of Tablet Levera 500 mg BD.

5. Blood pressure was controlled with antihypertensives in the form of oral nifedipine or intravenous labetalol was used.

I. Oral Nifedipine

i. Tablet Depin Retard 20 mg 12th hourly for blood pressure ≥160/90 mmHg ≤160/110 mmHg

ii. Blood pressure was monitored 2nd hourly

II. Labetolol

i. Injection Labetolol 20 mg slow IV bolus over 2 minutes for patients with blood pressure recordings ≥160/110 mmHg

ii. Repeated doses were given every 10 minutes if blood pressure remained ≥160/110 mmHg. Additional 20 mg was added each time to a maximum of 4 doses or 300 mg in a 24 hour period.

iii. Once blood pressure was controlled , monitoring of BP was done 2nd hourly

6. Any convulsions after administration of MgSO4 or Levetiracetam were noted
7. After delivery via cesarean section or vaginal delivery, the perinatal outcome of neonate was documented.

RESULTS

Table 1: Distribution of patients according to Age Group (YEARS)

Age (Years)	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
< 20	5	13.2	2	5.3	X^2=7.506	P=0.0674
20 - 24	27	71.1	21	55.3		
25 - 29	6	15.8	11	28.9		
30+	0	0	4	10.5		
Total	38	100	38	100.0		
Insignificant						

It is observed from the above table that the maximum number of participants ie. 27 (71.1%) in the MgSO4 group and 21 (55.3%) from the LEV group were among the age group of 20-24 years. Alternatively, while only 4 (10.5%) of the patients in LEV and none of the patients among the MgSO4 group were more than 30 years of age.

Table 2: Mean distribution of patients according to Age (YEARS)

Age	MAGNESIUM SULPHATE		LEVETIRACETAM	
	Mean	±SD	Mean	±SD
Age(Years)	21.74	2.554	23.79	4.068

It is observed from the above table that the mean distribution of age among patients with eclampsia was 21.74 (+/- 2.5 years) in the Magnesium sulphate (MgSO4) group and

23.79 (+/- 4.0 years) in the Levetiracetam (LEV) group. The difference between the groups is not significant as proved by Chi-square test (P=0.067>0.05)

Figure 1: Distribution of patients according to Age Group (YEARS)

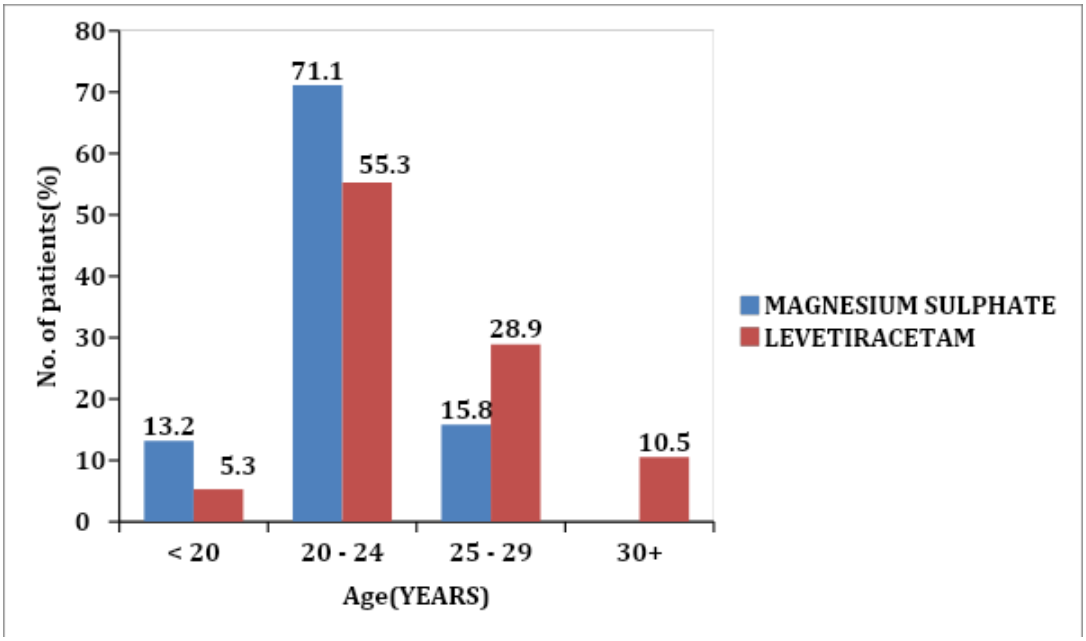


Table 3: Distribution of patients according to basic vitals

Basic variables	MAGNESIUM SULPHATE		LEVETIRACETAM		Mann whitney U test/Unpaired t test	P value
	Mean	±SD	Mean	±SD		
GESTATIONAL AGE	35.81	3.105	34.77	3.592	U=327.000	P=0.159
Systolic BP	150.79	30.079	150.79	30.079	U=668.500	P=0.574
Diastolic BP	98.16	14.492	98.68	20.556	U=715.500	P=0.945
Statistically insignificant						

It is observed from the above table the distribution of patients in each group based on gestational age, pulse rate and systolic and diastolic blood pressure. Study participants on

admission had a mean gestational age of 35.8 (+/- 3.1 years) in the MgSO4 group and 34.7 (+/- 3.5 years in the LEV group. The mean blood pressures among both groups was almost identical. Both MgSO4 and LEV groups had a mean systolic blood pressure of 150 mmHg and a diastolic blood pressure of 98 mmHg with a difference that was statistically insignificant as proved by Mann Whitney U test (P=0.574>0.05) and (P=0.945>0.05) respectively.

Table 4: Distribution of patients according to type of eclampsia

Type of eclampsia	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
ANTEPARTUM	32	84.2	26	68.4	X^2=2.621	P=0.1055
POSTPARTUM	6	15.8	12	31.6		
Total	38	100	38	100		
Insignificant						

It is observed from the above table that majority of the study participants in MgSO4 group (84%) and in LEV group (68%) had antepartum eclampsia. Among the study participants who had postpartum eclampsia were 15.8% in MgSO4 group and 31.6% in LEV group. The difference between the groups is not significant as proved by Chi-square test (P=0.1055>0.05)

Figure 2: Distribution of patients according to type of eclampsia

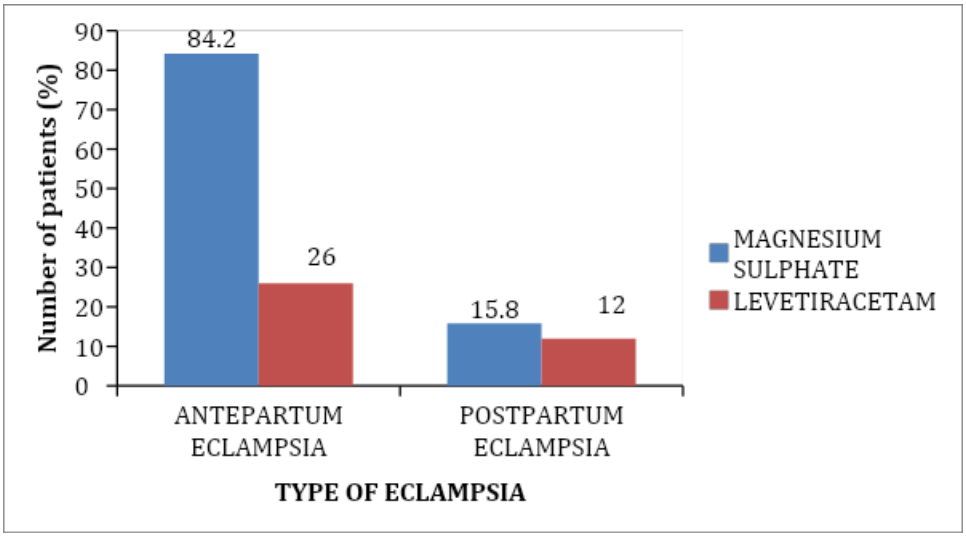


Table 5: Obstetric history

OBSTETRIC HISTORY	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
MULTIGRAVIDA	8	21.1	10	26.3	X^2=8.768	P=0.0125*
PRIMIGRAVIDA	24	63.2	12	31.6		
POST PARTURATION	6	15.8	16	42.1		
Total	38	100.0	38	100.0		
*- Highly significant						

It is observed from the above table that a majority of women ie. 63% and 31.6% of study participants were primigravida in the MgSO4 and LEV group respectively. Among the study participants, 21% in the MgSO4 group and 26% in the LEV group were multigravida. Majority of the patients in the LEV group were admitted during post partum period (42%) whereas in the MgSO4 group only 15.8% of patients were admitted with the diagnosis of eclampsia in the postpartum period. Because of this, the difference between the groups is significant as proved by Chi-square test (P=0.0125<0.05)

Figure 3: Obstetric history

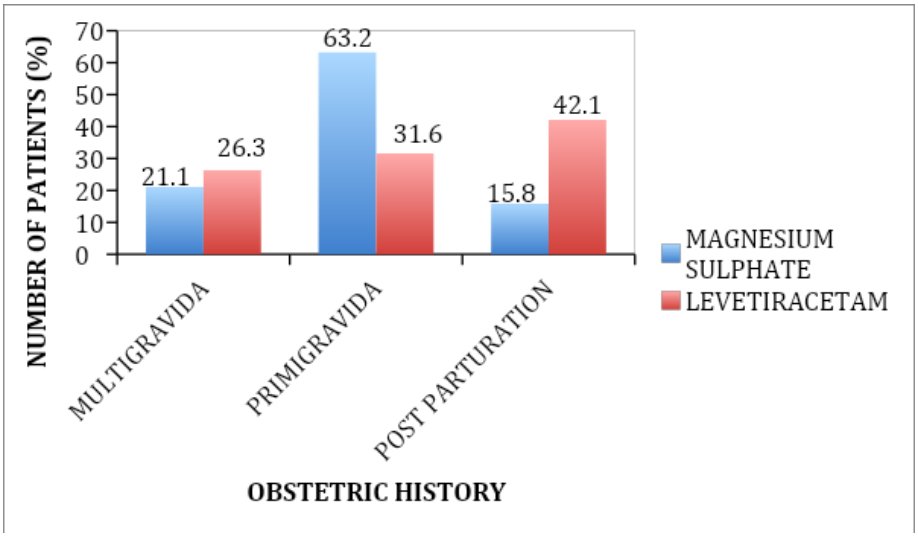


Table 6: Gestational Age

GESTATIONAL AGE	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
Post natal day - IMMEDIATE	3	7.9	1	2.6	X^2=8.961	P=0.0621
Post operative day 1-7	1	2.6	6	15.8		
Post operative day- IMMEDIATE	2	5.3	5	13.2		
Pre term	13	34.2	16	42.1		
Term	19	50.0	10	26.3		
Total	38	100.0	38	100.0		
Insignificant						

We observe in the above table that among the antepartum eclampsia patients, 34.2% in MgSO4 group and 42.1% of patients in LEV group were preterm patients. Whereas, 50% in the MgSO4 and 26.3% in the LEV group were term patients. Among the postpartum eclampsia patients, a total of 13.2% of patients in MgSO4 group were on post operative day immediate or post natal day immediate and 2.6% of patients were on post operative days 1-7. Among the LEV group, a total of 15.8% of patients were on postoperative or

post natal day immediate and 15.8% of patients were on post operative days 1-7. The difference between the groups is not significant as proved by Chi-square test (P=0.0621>0.05)

Figure 4: Gestational Age

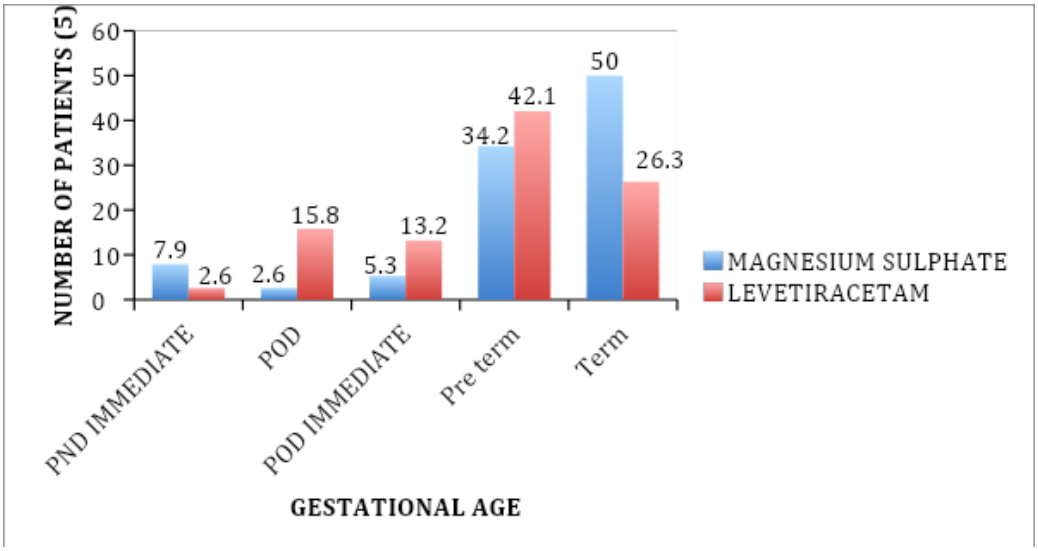


Table 7: Other cofactors associated with eclampsia patients

TYPES OF COMPLICATIONS	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
POST-PARTUM HEMORRHAGE	1	2.6	1	2.6	X^2=1.069	P=0.9829
ABRUPTIO PLACENTA, HELLP SYNDROME	3	7.9	3	7.9		
NO OTHER COMPLICATIONS	28	73.7	30	78.9		
OLIGOHYDRAMNIOS	1	2.6	1	2.6		
PULMONARY EDEMA	1	2.6	1	2.6		
RH INCOMPATIBILITY	3	7.9	1	2.6		
TWIN GESTATION	1	2.6	1	2.6		
Total	38	100.0	38	100.0		
Insignificant						

We observe in the above table the range of cofactors present in eclampsia patients of both groups administered anti-epileptic drugs. Postpartum hemorrhage was associated with patients in both groups equally (2.6%). Abruptio placenta and HELLP syndrome were both the same in both groups (7.9%). The presence of twin gestation, pulmonary edema and oligohydramnios was the same in both MgSO4 and LEV groups at 2.6% in each group. Among the MgSO4 group, 7.9% of patients had Rh-incompatibility differing from LEV group in which only 2.6% had Rh-incompatibility as an associated cofactor to eclampsia. Majority of patients in both groups did not have any associated cofactors along with eclampsia. In the MgSO4 group, 73.7% and in the LEV group 78.9% had no other associated complications. The difference between the groups is not significant as proved by Chi-square test ($P=0.98>0.05$).

Figure 5 : Distribution of other complications associated with patients

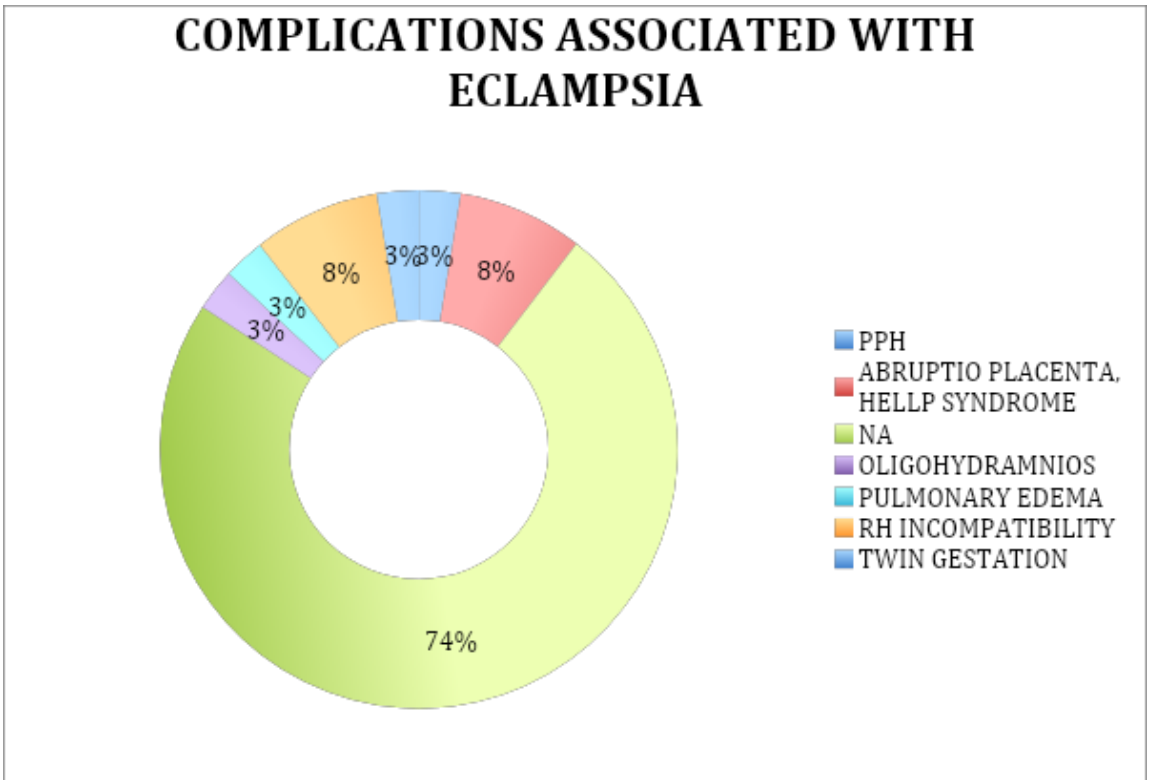


Table 8: Administration of loading dose of MgSO4

WAS LOADING DOSE ADMINISTERED	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
GIVEN	27	71.1	0	0	X^2=41.878	P=<0.001*
NOT GIVEN	11	28.9	38	100		
Total	38	100.0	38	100.0		
*- Highly significant difference						

It is observed from the above table that a total of 71.1% of patients given MgSO4 were already administered an outside loading dose of the drug, whereas 28.9% were not administered any outside loading dose. LEV was only administered in patients that were

not administered an outside loading dose of MgSO4 so 100% of patients administered LEV were not given a loading dose. The difference between the groups is significant as proved by Chi-square test (P= less than 0.001<0.05).

Figure 6: Was loading dose given outside?

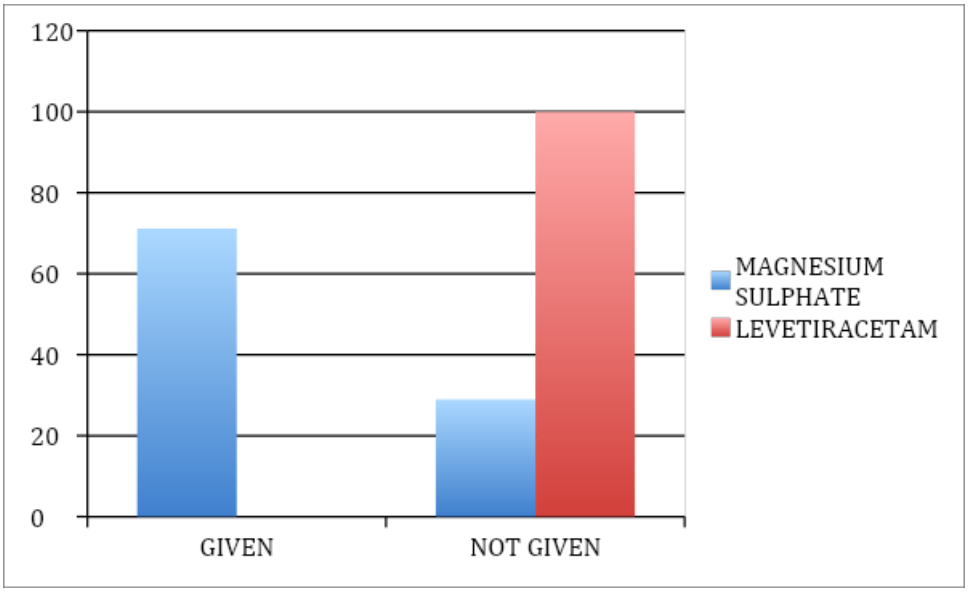


Table 9: Total number of convulsions after intervention

NO. OF CONVULSIONS AFTER INTERVENTION	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
0	33	86.8	34	89.5	X^2=1.682	P=0.6410
1	4	10.5	2	5.3		
2	1	2.6	1	2.6		
3 or more	0	0	1	2.6		
Total	38	100.0	38	100.0		
Insignificant						

It is observed from the above table that in the MgSO4 group, 86.8% had no convulsions after administration of the drug, 10.5% had one episode of convulsion, 2.6% had two episodes of convulsion and no patients had 3 or more convulsions. In the LEV group, 89.5% of patients had no convulsions after administration of the drug. A total of 5.3% of patients threw a single episode of convulsion after administration of LEV, 2.6% had 2 episodes of convulsions and 2.6% had 3 or more convulsions. The difference between the groups is not significant as proved by Chi-square test (P=0.6410>0.05).

Figure 7: Total number of convulsions after intervention

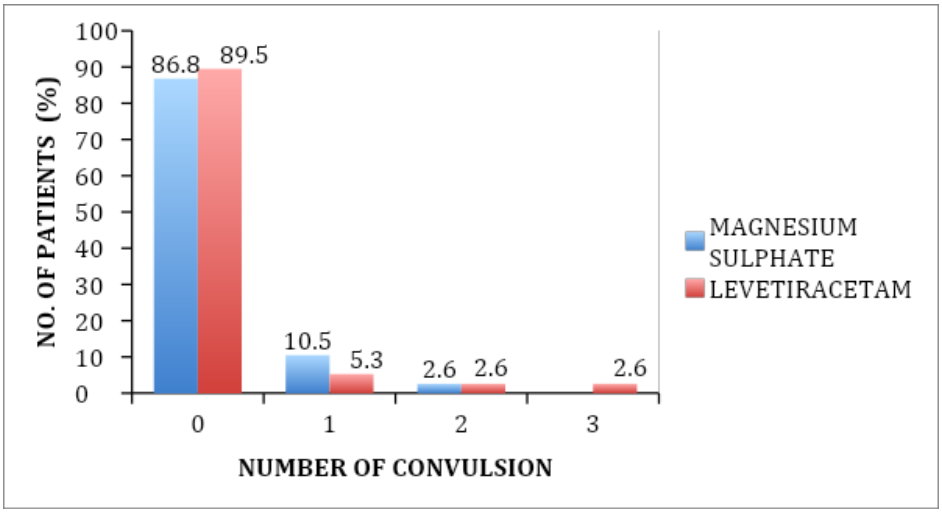


Table 10: Fundoscopic examination

GRADES OF HYPERTENSIVE RETINOPATHY	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
GRADE 1	4	10.5	5	13.2	X^2=3.174	P=0.3656
GRADE 2	2	5.3	0	0		
GRADE 3	1	2.6	0	0		
NORMAL	31	81.6	33	86.8		

Total	38	100.0	38	100.0		
Insignificant						

It is observed from the above table that fundoscopic examination revealed that among the patients administered MgSO4, 10.5% had Grade I, 5.3% had Grade II, 2.6% had Grade III hypertensive retinopathy. 81.6% of patients that were administered MgSO4 had a normal fundoscopy. In the LEV group, 13.2% of patients had Grade I hypertensive retinopathy and none had Grade II or Grade III hypertensive retinopathy. 86.8% of patients in the LEV group had normal fundoscopic examinations. The difference between the groups is not significant as proved by Chi-square test (P=03656>0.05).

Figure 8: Fundoscopic examination

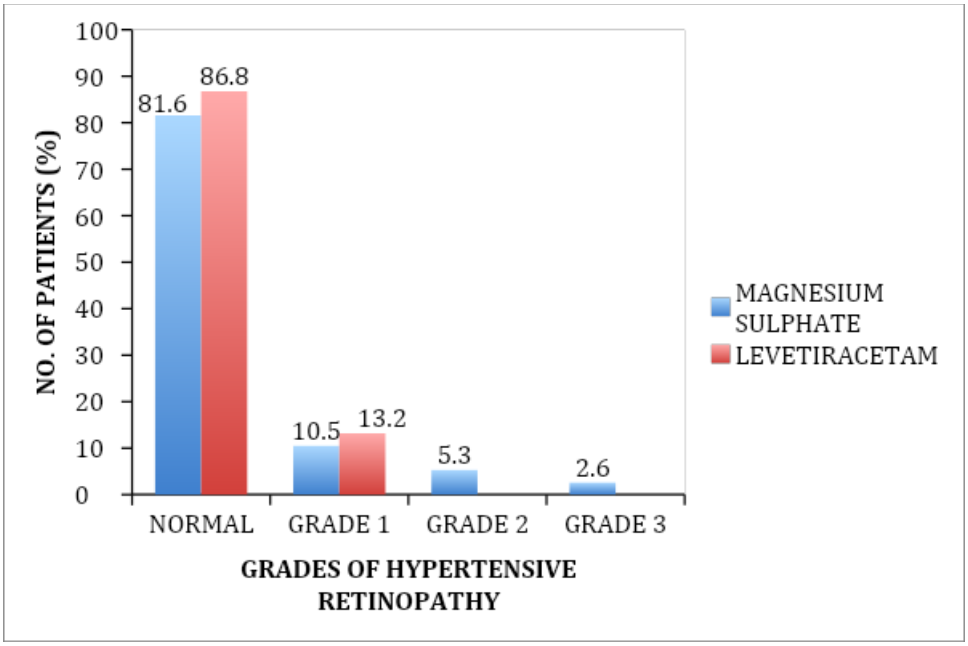


Table 11: Distribution of study subjects as per Mode of Delivery

Mode of Delivery	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
LSCS	27	71.1	29	76.3	X^2=0.2714	P=0.6024
VAGINAL DELIVERY	11	28.9	9	23.7		
Total	38	100.0	38	100.0		
Insignificant						

It is observed from the above table that in patients given MgSO4, 71.1% of them delivered via cesarean section and 28.9% had vaginal deliveries. In the LEV group, 76.3% underwent cesarean sections, while 23.7% had vaginal deliveries. The difference between the groups is not significant as proved by Chi-square test (P=0.624>0.05).

Figure 9: Distribution of study subjects as per Mode of Delivery

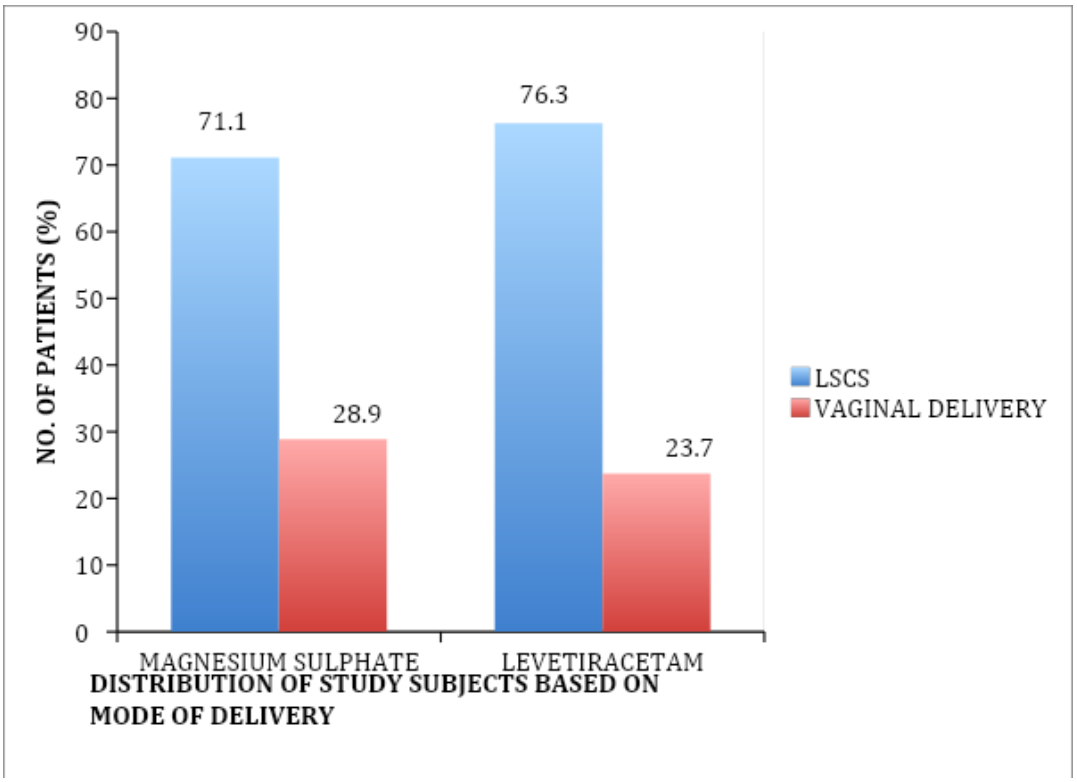


Table 12: Perinatal outcome

Perinatal outcome	MAGNESIUM SULPHATE		LEVETIRACETAM		Chi square test	P value
	N	%	N	%		
MORTALITY	6	15.8	7	18.4	X^2=0.4744	P=0.7888
MOTHERSIDE	11	28.9	13	34.2		
NICU	21	55.2	18	47.4		
Total	38	100.0	38	100.0		
Insignificant						

It is observed from the above table that in the MgSO4 group, 15.8% of babies had mortality, 55.2% were admitted in NICU and later discharged with no further complications, and 28.9% were free of any complications. In the LEV group, 18.4% of babies had mortality, 47.4% were admitted to NICU and later discharged with no further complications, and 34.2% were free of any complications. The difference among the groups was statistically insignificant as proved by Chi-square test (P=0.7888>0.05).

Figure 10: Perinatal outcome

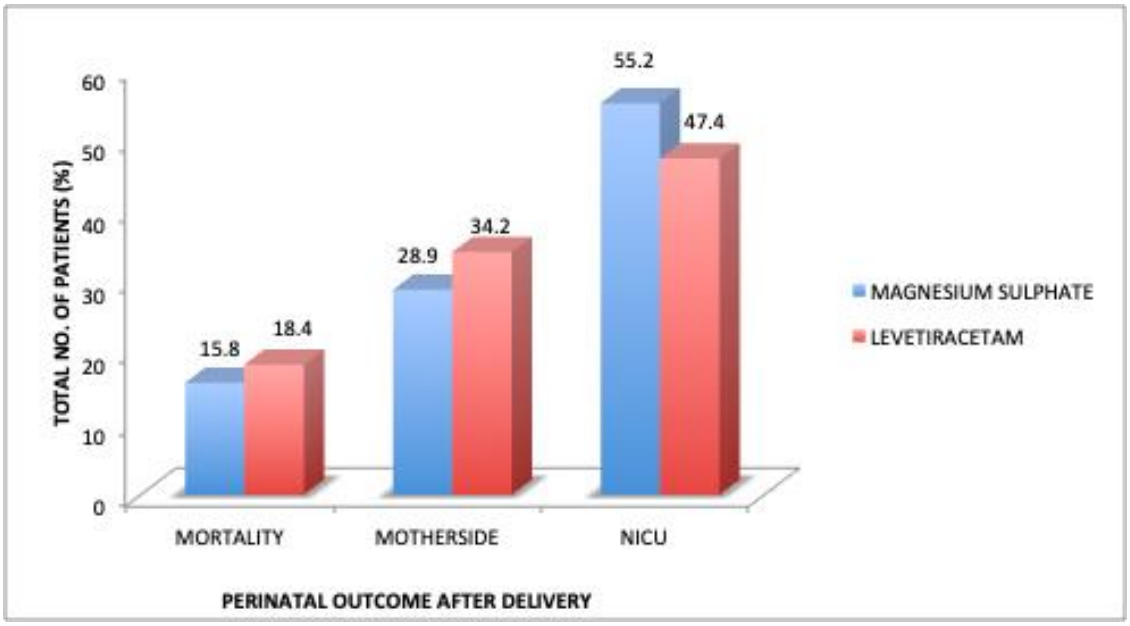


Table 13: Mean distribution and standard deviation of laboratory findings

Basic variables	MAGNESIUM SULPHATE		LEVETIRACETAM		Mann whitney U test/Unpaired t test	P value
	Mean	±SD	Mean	±SD		
WBC's	15621.58	4579.604	17321.61	13228.907	U=680.000	P=0.663
Hb	11.810526	1.4344769	12.107895	2.0268977	U=650.000	P=0.454
Platelet count	2.185526	.7786291	2.156316	1.1181752	U=712.000	P=0.917
SGOT	55.00	85.683	81.63	119.163	U=676.000	P=0.633
SGPT	37.45	56.901	50.05	61.594	U=641.500	P=0.403
Alkaline phosphatase	283.903	105.6705	235.395	208.8910	U=386.500	P=0.000*
Total Serum Bilirubin	1.018421	.9986086	.973684	.6879991	U=648.500	P=0.443
INR	1.015526	.1661276	1.000816	.2201459	U=627.000	P=0.322
Serum creatinine	.642105	.1734103	.731579	.5317514	U=695.500	P=0.779
Blood urea	17.107895	6.9499516	17.107895	6.9499516	U=666.500	P=0.563
Uric acid	7.07	1.811	6.93	2.006	t=0.314	P=0.754
*:Statistically significant						

It is observed from the above table that routine blood investigations reveal that a mean WBC count in MgSO4 group is 15621 ± 4579.6 and in the LEV group is 17321.6 ± 1328.9. The mean hemoglobin is 11.8 ± 1.4 in the MgSO4 group and 12 ± 2 in LEV group. The mean platelet count among the MgSO4 group and LEV group are 2.18 ± 0.77 and 2.15 ± 1.11, respectively. The difference in all three of these values among MgSO4 and LEV was statistically not significant as proved by the Mann Whitney U test.

According to the above table, in the MgSO4 group, liver function tests reveal a mean SGOT of 55 ± 85.6 and SGPT 37 ± 56.9. In the LEV group, mean SGOT is 81.6 ± 119 and mean SGPT is 50 ± 61.5. Alkaline phosphatase (ALP) has a mean value of 283.9 ± 105.6 in the MgSO4 group and 235 ± 208.8 in the LEV group. Total serum bilirubin in the MgSO4 has a mean value of 1.0 ± 0.9 and in the LEV group has a mean value of 0.97 ± 0.68. The difference in SGOT and SGPT values among MgSO4 and LEV was statistically not significant as proved by Mann Whitney U test. However, the values in ALP between the two groups are statistically significant as proved by the Mann Whitney U test.

Coagulation profile, according to the above table, shows a mean INR value of 1.01 ± 0.16 in the MgSO4 group and 1.0 ± 0.2 in the LEV group. The difference in INR values among MgSO4 and LEV was statistically not significant as proved by the Mann Whitney U test.

According to the above table, renal function tests show a mean serum creatinine of 0.6 ± 0.17 in the MgSO4 group and 0.7 ± 0.5 in the LEV group. Blood urea had a mean value of 17 ± 6.9 in both the MgSO4 group and the LEV group. Uric acid has a mean value of 7.0 ± 1.8 in the MgSO4 group and in the LEV group it is 6.9 ± 2.0. The difference in values of serum creatinine and blood urea among both groups was statistically not significant as proved by Mann Whitney U test. The difference in uric acid between the MgSO4 group and LEV group was statistically not significant as proved by the Unpaired T test.

DISCUSSION

Preeclampsia is a unique disorder that is specific to pregnancy. The effects of the disease on multiple organs originates from changes occurring during pregnancy. These changes suggest that preeclampsia is a two-stage disorder. The first stage is asymptomatic and characterized by an abnormal development of the placenta. This prevents normal placental perfusion and proper delivery of nutrients, oxygen and blood to the growing fetus. The series of these pathological changes activate an array of immune mediators that damage the vessel walls and allow the spread of placental debris throughout maternal circulation. This in turn produces the second stage of the disorder, the symptomatic stage. Relative to the damage acquired in different organs, different pathologies can present. These include development of hypertension with or without proteinuria, liver changes that can manifest as HELLP syndrome (hemolysis, elevated liver function enzymes and low platelets), renal impairment, and eclampsia.

Eclampsia, is the final culmination of a series of events that ultimately puts the life of the mother and fetus at risk. It is by definition, the new onset of seizures or coma in a pregnant woman diagnosed with preeclampsia. These events start with changes in the placenta and can progress to changes in the vasculature, particularly in the cerebral vessels. This results in hypoxia and ischemia, ultimately manifesting as convulsions in a pregnant woman. Eclampsia can be subclassified depending on the time of its presentation. Antepartum eclampsia is the onset of seizures in a preeclampsia patient during the antenatal period. This is after 20 weeks of pregnancy but prior to delivery.

Intrapartum eclampsia is the onset of seizures during the process of delivery and postpartum eclampsia is onset of seizures after delivery. Regardless of when the convulsion occurs, prompt response and administration of antiepileptic drugs is crucial to saving the life of the mother.

For many years, MgSO4 has been the undisputed gold standard for treatment and management of eclampsia patients. No alternative AEDs have come close to the effectiveness and safety of MgSO4. As a result, the side effects of the drug and hurdles faced by developing countries, especially in small rural areas when administering and monitoring patients, has been negated.

This is why this study set out to explore the potential of Levetiracetam, one of the newer AEDs on the market. The research behind this drug has been very limited. But the studies done till date have mainly shown safety of the drug when administered in pregnant women. These limited studies have also demonstrated safety of the drug in fetal outcome after delivery. Short term and long term effects have not been observed in babies during the course of LEV therapy. However, it is important to note that due to the novelty of this drug in pregnant females, most of these studies have been conducted on pregnant women with epilepsy, not eclampsia. The single study that has observed the outcome of LEV in eclampsia patients has been utilized as the basis for this study. That study, however, was a retrospective study. Our study is a prospective study done in real time on eclampsia patients presenting to the labor room at Shri B.M. Patil's Medical College, Vijayapura. The purpose of this study was to conduct a comparison between

administering MgSO4 and Levetiracetam and to observe for convulsions present after administration of either of the agents. Overall safety of mother and child after administration was also assessed and recorded.

Age Distribution of the Patients

In our study 13.2% among the patients given MgSO4 and 5.3% of patients given LEV were below the age group of 20 years old. The majority of patients belonged to the 20-24 year old age group. 71.1% patients in this age group were given MgSO4 group and 55.3% were given LEV. The 25-29 year old age group showed 15.8% patients in the MgSO4 group and 28.9% in the LEV group. Only 10.5% of patients belonged to the 30 years and older age. All of these patients were a part of the LEV group. The mean age group of patients was 21.74 (+/- 2.5 years) in the Magnesium sulphate (MgSO4) group and 23.79 (+/- 4.0 years) in the Levetiracetam (LEV) group. This shows that the majority of patients presenting with eclampsia are in the early years of the reproductive age group. Presenting mainly in the age group distribution of 19-26 years of life. This shows that eclampsia is more common in the early years than after 30 years of age.

Thus, our study findings were similar to published literature reporting that eclampsia is primarily a disease affecting younger women. Because of this, teenage pregnant women are at higher risk of developing eclampsia, and their care should be prioritised in clinical practice.[27]

Gestational Age

We found in our study that the majority of the study participants given MgSO4 and LEV were in the third trimester of their pregnancy. The mean gestational age among the MgSO4 group is 35.8 (+/- 3.1 years) and among the LEV group is 34.7 (+/- 3.5 years). Thus, our study findings show that a large number of eclampsia cases are preterm, occurring between 34-35 weeks of gestation. These findings are similar to various published literature which show that a majority of eclampsia cases develop preterm and are associated with a higher incidence of maternal and fetal complications. According to Gupte et al, there is a significance in the gestation of onset of preeclampsia-eclampsia. This leads to a difference in the overall prognosis and management of the patient. Early onset of the disease is more commonly associated with placental pathology as late onset is more likely associated with an underlying maternal pathology such as diabetes, obesity or cardiovascular disease.[28]

Blood Pressure

It is observed from this study that the mean blood pressure in both groups of MgSO4 and LEV was around 150/98mmHg. The range of blood pressures seen in patients included in our study reported blood pressure as high as 200/140mmHg and as low as 90/60mmHg. This shows that there is a wide variation in the presentation of patients to our hospital, this can be attributed to the fact that our hospital is a tertiary centre. Majority of cases are referral patients, who mostly have been given intervention for blood pressure control prior to arrival at our hospital. For those with higher blood

pressures, it suggests that these cases were directly referred from home without any intervention given. Distance of travel might also play a contributory role in higher blood pressure recordings upon arrival to our hospital. This might be attributed to a longer time interval between the last intervention as a result of prolonged travel time to our hospital from a referral hospital.

Type of Eclampsia

Among the MgSO4 group, 84.2% had antepartum eclampsia and 15.8% had postpartum eclampsia. Among the LEV group, 68.4% had antepartum eclampsia and 31.6% had postpartum eclampsia. The majority of participants in both groups were antepartum eclampsia patients. According to a study by Llera M, higher rates of maternal mortality and complications were seen with patients with early eclampsia or antepartum eclampsia. The article divided antepartum eclampsia into two subcategories, early antepartum and intercurrent eclampsia. Early antepartum eclampsia is defined as convulsions appearing in a pregnant woman diagnosed with hypertension or proteinuria before 28 weeks of gestation. Intercurrent eclampsia is defined as convulsions in the presence of hypertension or proteinuria appearing before the initiation of labor. The only difference is that symptoms will stop and subside with clinical improvement in the patient that allows for continuation of pregnancy for more than 7 days. The study found that higher rates of maternal mortality were associated with early eclampsia patients at 22.2% and lower rates were associated with intercurrent eclampsia. Complications such as brain hemorrhage were since at a higher incidence in early eclampsia at 24.1% and

lowest incidence were seen in intercurrent eclampsia at 4.3%. The majority of other complications such as disseminated intravascular coagulation, acute renal failure and abruptio placentae were statistically higher in antepartum eclampsia compared to intrapartum eclampsia. Severe postpartum hemorrhage, another complication associated with eclampsia, was statistically more associated with postpartum than antepartum eclampsia patients. The article further concludes that the worst effects of eclampsia are more obviously associated with antepartum eclampsia than intrapartum or postpartum types of eclampsia.[29] According to a study done by Bembalgi et al, incidence of antepartum eclampsia was 1.19% and postpartum eclampsia was 0.31%. This is comparable to our study which also concluded that incidence of antepartum eclampsia is more than postpartum eclampsia.[30] A study by Leitch et al, showed that the overall rates of eclampsia has declined over a 60 year period due to better availability of antenatal care and use of prophylactic MgSO4 regimens, however, the incidence of postpartum eclampsia has slowly increased. This type of eclampsia is no longer a rare condition.[31] In our study, 10 of the 18 cases of postpartum eclampsia presented within 24 hours of delivery with episodes of convulsions associated with hypertension and/or proteinuria. This was similarly demonstrated by a study conducted by Watson et al. The study reviewed over 132 cases of postpartum eclampsia and concluded that 47% of patients presented within 48 hours with features of postpartum eclampsia.[32]

Parity

We found in our study that the majority of the study participants in both groups of MgSO4 and LEV were primigravida. In the MgSO4 group, 79% of participants were

primigravida. In the LEV group, 73.7% of participants were primigravida. This correlates with other studies that show eclampsia occurs more frequently in primigravida mothers. Grum et al discussed how primigravida is a risk factor for preeclampsia and how the odds were higher for developing the disease (2.68 times higher) compared to those in women who were multigravida. Preeclampsia is often referred to as a disease of first pregnancy because of an abnormal interplay between immunological factors that is seen during the first establishment of fetoplacental and maternal tissue.[33] A study conducted by Harutyunyan, explained that the risk of developing the disease is lower in multiparous women and coincided with milder development of symptoms compared to symptoms seen in primiparous women.[34] According to Luo et al, it is thought that primiparous women are six to eight times more susceptible to preeclampsia than multiparous women. Pregnancy poses a dilemma as the two systems of mother and child must coexist without any immunological rejection. This poses a challenge due to the immunological incompatibility of the fetus with the mother. In order for pregnancy to be normal, a maternal immune tolerance to the fetus must properly develop. The interface between the mother and child should act as a bridge for immunological tolerance but at the same time should act as a barrier to prevent infectious microbes from crossing and harming the fetus. One of these cofactors in helping develop this type of interface is a paradigm shift in the ratio of Th1 (pro-inflammatory T-helper cells) to Th2 lymphocytes (suppressor T-helper cells). Multiparous women tend to have a protective effect due to adaptive changes in the initial pregnancy that favors an established immune tolerance in their subsequent pregnancies. Angiogenic factors play another key role in explaining the higher risk of preeclampsia in primigravida women. Various reports suggest that a higher sFt-1 levels

can predispose women to developing preeclampsia. Circulating soluble fms-like tyrosine kinase (sFlt-1) indicates abnormal angiogenesis might be present. Typically, this marker is an inhibitor of placental growth factor (PGF) and vascular endothelial growth factor (VEGF). The levels of sFlt-1 are suggested to decrease from the first to second pregnancy. Lower levels suggest lower risk of developing preeclampsia in subsequent pregnancies.[35] These various studies suggest strongly that primigravida women have a stronger correlation to developing preeclampsia then multigravida women, as was similar to what we observed in our study.

Other Diseases and Complications Associated with Eclampsia

In our study it was concluded that some complications were associated along with eclampsia in some of the study participants. Among both the MgSo4 group and LEV group, other factors associated with pregnancy included abruptio placenta, HELLP syndrome, postpartum hemorrhage, pulmonary edema, oligohydramnios and Rh negative blood groups. In the MgSo4 and LEV group, the majority of patients had no other associated complications. In the MgSo4 group, 73.7% had no other risk factors detected and in the LEV group, 78.9% had no associated risk factors. Among the complications that were present in association with eclampsia, both MgSo4 and LEV groups had 7.9% of patients who had either abruptio placenta or HELLP syndrome. As eclampsia is a multisystemic disorder, it is not a surprise that patients present to hospitals with other risk factors in association with the disorder. One of the main associated factors was HELLP syndrome. This is a severe form of preeclampsia associated with presence of hemolysis,

elevated liver enzymes and low platelet count. Lipstein et al discussed how HELLP syndrome can complicate up to 10% of eclamptic cases. According to this study, Women that develop eclampsia are at an increased risk for the development of other complications. The most common complication noted was abruptio placenta. Other complications encountered included acute renal failure, cerebrovascular and cardiovascular complications such as cerebral hemorrhage or peripartum cardiomyopathy.[36] Complications such as pulmonary edema or aspiration pneumonia usually developed as a result of poor fluid management leading to fluid overload. These various factors that can ultimately lead to maternal and neonatal mortality, make it more evident to the importance of preventing and treating eclampsia.

Development of Convulsions After Intervention

After the administration of intervention in the form of MgSO4 or LEV, our study concluded that 13.1% of patients administered MgSO4 still developed convulsions after the loading dose of the drug was given. This was more than the LEV group, as 7.9% of those administered LEV continued to have convulsions after loading dose was given. However, the number of convulsions still experienced after therapy was more in the LEV group compared to the MgSO4 group. 2.6% of patients in the LEV group had three or more convulsions compared to the MgSO4 group, which had only one or two episodes of convulsion following therapy. None of the patients in the MgSO4 group had more than two convulsions following MgSO4 therapy. Multiple factors can play a causal role in

why patients continued to experience convulsions after loading dose and/or maintenance dose of MgSO4 or LEV were given. One of the main factors in the MgSO4 group is due to the duration of time between loading dose being administered and patient's arrival to our hospital. In cases where there was a delay in patients coming to our hospital following loading dose given outside, there was a higher chance of them throwing a convulsion. This is due to a large lapse in the time between administration of the loading dose and maintenance dose of the drug. Another factor is the onset of action time required for drugs to take effect. Magnesium sulphate is administered intravenously and intramuscularly. The intravenous dosage has an immediate onset of action and a duration of action of thirty minutes. The intramuscular route has an onset of action within one hour and a duration of action lasting three to four hours. Administering the intramuscular dose prior to intravenous route can delay the action of the anticonvulsant and lead to patients throwing another convulsion. To avoid this from happening the intravenous dose of Pritchard's regimen should always be administered first, followed by the intramuscular dose.[37] On the other hand, Levetiracetam has an onset of action of five to thirty minutes following administration of the loading dose.[38] The loading dose of LEV is given over a period of 15 minutes through intravenous infusion diluted in 100 ml of normal saline. This time period plus the onset of action time requires at least thirty minutes from the time of drug infusion for onset of drug action to occur. This means that there is a potential for convulsions to occur during the initial thirty minutes of a patient being administered LEV that should not be attributed to the efficacy of the drug itself. Overall, from our study we have observed that the efficacy of LEV and MgSO4 was very similar

in the study participants. Both had their positives and negatives, but neither can be concluded as being better than the other.

Fundoscopy

In this study, fundoscopy was done routinely in all patients admitted to our hospital. In both study groups the majority of patients had normal fundoscopy. Both MgSO4 group and LEV groups had 81.6% and 86.8% of patients, respectively, that had a normal fundoscopy. Grade I retinopathy changes were seen in 10.5% of the MgSO4 group and 13.2% in the LEV group. Grade II retinopathy changes were seen in 5.3% of the MgSO4 group and 0% in the LEV group. Grade III retinopathy changes were seen in 2.6% of the patients in MgSO4 group and 0% in patients of the LEV group. Retinal detachment is an anticipated complication after an eclamptic seizure. For this purpose all patients admitted to our hospital were screened for any visual impairment with fundoscopy. While retinal detachment was more commonly associated with antepartum eclampsia, transient neurologic deficits and transient cortical blindness was seen more frequently in postpartum cases of eclampsia.[36]

Mode of Delivery in Eclampsia Patients

The majority of the patients admitted with eclampsia underwent cesarean section rather than vaginal delivery. In the MgSO4 group, 71.1% underwent LSCS (lower segment cesarean section) and 28.9% had vaginal delivery. In the LEV group, 76.3%

underwent LSCS and 23.7% had vaginal delivery. Medical literature supports delivery within 72 hours in patients with pregnancies complicated by severe preeclampsia and eclampsia. However, the optimal route of delivery is still under debate. ACOG and a study by Pritchard et al support vaginal delivery as maternal benefits are said to be better. Other studies suggest immediate cesarean delivery especially in patients with gestational age less than 30 weeks as there is a higher chance of induction failure and fetal intolerance to labor in early gestational ages.[39]

Perinatal Outcome in Eclampsia Patients

In our study, the perinatal outcome after delivery of eclampsia patients was assessed. In the MgSO4 group, 15.8% of the participants had neonatal mortality. In the LEV group, 18.4% of participants had neonatal mortality. Among the babies that had good perinatal outcomes that did not require NICU admission, 28.9% and 34.2% were reported respectively among MgSO4 group and LEV group. Among the babies that required NICU admission, 55.2% were in the MgSO4 group and 47.4% were in the LEV group.

Complete Blood Count

We found in our study that the mean hemoglobin in both groups was around 11-12 grams per deciliter. The highest among our study was a value of 16.8 grams per deciliter and the lowest was 7.6 grams per deciliter. A study by Nasiri et al discussed the importance of measuring hemoglobin values during pregnancy. High levels of hemoglobin can be associated with increased risk of diabetes, preterm delivery and low

birth weight.[40] Multiple studies have observed higher hemoglobin levels in women with preeclampsia than in normotensive pregnant women. Hemoglobin values show a positive correlation with blood pressure and the higher values may be due to hemoconcentration. Some studies suggest that increased values of hemoglobin may be the cause of vasoconstriction in patients with preeclampsia. The physiology behind higher hemoglobin concentrations is due to failure of normal plasma expansion, hypovolemia and inadequate placental perfusion. All of which contribute to pathology of preeclampsia. Hemoconcentration volume leads to hyperviscosity which further hampers blood flow in microvascular sites such as the placenta. This contributes to reduced perfusion and oxygenation at the site of placental tissue. Other factors include the action of free hemoglobin on nitric oxide. Free hemoglobin can inactive nitric oxide, which is a potent vasodilator. This action leads to vasoconstriction and ultimately contributes to hypertension and placental ischemia. Oxidized hemoglobin can produce methemoglobin which in turn can damage the endothelium. Using hemoglobin as an indicative marker of preeclampsia and it's possible role in anticipating the extent of the disease in a patient requires further analysis, but seems promising based on recent studies.[41]

Liver Function Tests

Our study observed the values of liver function tests in patients of eclampsia. Among the investigations, the most notable were liver enzymes like serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) and total bilirubin levels. The mean SGOT in the MgSO4 and LEV groups was 55 U/L and

81.6 U/L, respectively. The mean SGPT was 37.45 U/L in the MgSO4 group and 50 U/L in the LEV group. The mean total serum bilirubin levels in the MgSO4 group was 1.0 mg/dl and in the LEV group was 0.97 mg/dl. In a study done by Munazza et al, abnormalities in liver function tests can be seen in up to 3% of pregnancies. Among the most commonly associated causes is preeclampsia.[42] The onset of these abnormalities sets in during the third trimester and can be associated with symptoms of nausea, vomiting and upper right epigastric tenderness due to irritation of Glisson's capsule, hepatic cell edema or periportal and focal parenchymal necrosis.[43] Elevated liver function tests can indicate a case of eclampsia complicated by other diseases such as HELLP syndrome. In the presence of hemolysis, elevated SGOT, SGPT and hyperbilirubinemia can occur. The cause of elevated liver enzymes is most likely periportal hemorrhagic necrosis. Because the disease of preeclampsia can affect multisystems, it is important to study end organ damage through analysis of tests like liver function tests. These can give us a better idea of the state of organs such as the liver in a patient with eclampsia.

Renal Function Tests

Our study observed renal function tests in both groups of study participants. Among the most important values observed were serum creatinine, blood urea and uric acid. The serum creatinine in both groups had a mean value of 0.6 mg/dL and 0.7 mg/dL in MgSO4 group and LEV group, respectively. The mean value of blood urea was around 17 mg/dL ± 6 mg/dL in both study groups. Uric acid had a mean value of 7 ± 1.8 mg/dL in the MgSO4 group and 6.9 ± 2 mg/dL in the LEV group. During pregnancy, the glomerular filtration rate increases by 30-40%. This rise in baseline during pregnancy

means that even a normal serum creatinine value can reflect renal pathology in a pregnant woman with preeclampsia. Uric acid is an end product of liver metabolism. It can be a proinflammatory marker that causes endothelial dysfunction. Several studies have shown that its concentration can directly correlate with the severity of preeclampsia.[44] According to ACOG guidelines on hypertension in pregnancy, serum creatinine concentrations greater than 1.1 mg/dL or doubling of serum creatinine in the absence of renal disease is significant in patients with preeclampsia or eclampsia.[43] A study by Kuper et al had findings that suggested that serum creatinine values over 0.75 mg/dL were associated with adverse effects in pregnant patients with hypertensive disorders. A study by Tewabe et al concluded that elevated renal function tests can further promote development of hypertension in pregnancy. Early detection of these altered renal function tests can help diagnose preeclampsia and prevent the further development of eclampsia in pregnant mothers. This requires continuous and close monitoring of these end organ tests throughout pregnancy. Ultimately, this can lead to prevention of feto-maternal complications and ensure a safe pregnancy.[45]

SUMMARY AND CONCLUSION

Eclampsia is an amalgamation of a multitude of factors in hypertensive disorders of pregnancy. It is the end-point to a series of events that brings about damaging changes in a mother's life. Preventing this stage is the most important part of reducing feto-maternal morbidity and mortality, but once a convulsion has ensued, the best thing is to properly assess and prevent a repeat convulsion from further endangering the pregnancy. Swift action should be taken to stabilize the patient following a seizure. This includes basic resuscitation, adequate fluid management, controlling blood pressure, administering anticonvulsant therapy and planning the appropriate mode of delivery based on gestational age and fetal outcome. Among these, choosing the appropriate anticonvulsant is a key part of managing these patients. For years the gold standard has been the classic magnesium sulphate therapy using Pritchard's regimen. Many studies have experimented with different regimens of this drug, but till date Pritchard's regimen has been the most effective.

Working in a tertiary care center, we have seen the limitations of this regimen as a result of the patients referred from rural areas and primary health centers to our hospital. Inadequate monitoring post administration of MgSO4 and insufficient administration due to lack of knowledge concerning the proper dosage of the drug are some of the drawbacks we have observed. This has led us to conduct this study in search of a new alternative anticonvulsant that can match the effectiveness and safety of magnesium sulphate but also be cost effective, accessible and easy to monitor and administer. Levetiracetam is a recently approved drug for seizure management in epileptic patients.

As a result of its favorable drug profile, an emerging number of studies have been conducted on the drug's efficacy and safety in pregnant women. These studies have concluded that the drug is relatively safe during pregnancy and has not proven to cause harm in the fetus. With these factors in mind, we wanted to see if this drug was comparable to magnesium sulphate when administered to eclampsia patients in a tertiary hospital setting. This study was conducted in the department of Obstetrics and Gynecology at B.L.D.E (Deemed to be University) Shri B. M. Patil's Medical College, Hospital and Research Centre, Vijayapura after obtaining ethical committee clearance. It was a prospective interventional study conducted over a period of two years with a total of 76 study participants. All patients that were diagnosed with eclampsia (antepartum, intrapartum or postpartum eclampsia) were included in this study. On admission, routine investigation work up was done, sent and collected. Patients were administered one of the two anticonvulsants studied in this trial, either magnesium sulphate according to Pritchard's regimen or Levetiracetam. After administration, patients were monitored and observed for any recurring seizures post administration, any post administration effects of the drugs and perinatal outcome was also assessed. The cases were followed up till the time of discharge which was postoperative day seven in cesarean section patients and postnatal day five in vaginal delivery patients.

The salient findings of our study are as follows:

1. Majority of the eclampsia study participants belonged to a young age group (between 20-24 years of age).
2. Majority of the eclampsia patients included in our study were primigravid women.

3. Although the disease is associated with many complications, the majority of our patients did not have comorbidities or other associated pregnancy complications such as HELLP syndrome, gestational diabetes, abruptio placenta and oligohydramnios.
4. The overall administration of magnesium sulphate was safe and continues to be effective in treating eclampsia patients. Among the cases that had to be discontinued with magnesium sulphate, the main reason was due to low urine output after initiating therapy, magnesium toxicity in one case and presence of recurrent seizures
5. The administration of Levetiracetam proved to be safe in eclampsia patients and had no adverse effects in neonates before or after delivery. Administration of the drug was simple and can be easily taught to hospital workers. Patients tolerated the drug well with no reported side effects. Whether it is safer than magnesium sulphate is still inconclusive. The main reasons for discontinuing the drug were due to recurrent seizures. An increase in dosage might prove to be beneficial and further studies can help assess whether this can help prevent the reported recurrent seizures. This can help negate the possibility of drug ineffectiveness due to the current dosage used in this trial.

Thus, from our study we can conclude that the overall efficacy of magnesium sulphate is good, similar to what was reported by previous studies. Moreover, the overall efficacy of Levetiracetam is still under question, but this study shows promising development that the drug has a possibility for becoming a good alternative to magnesium sulphate. Further studies on dosage can help to further assess its efficacy.

LIMITATIONS

1. Smaller sample size prevents an accurate representation of the general population. A larger sample would have allowed for better representative inferences.
2. As many cases of eclampsia were referred cases, documentation and history taken from patient's relatives was the only evidence for knowing patients had been given a loading dose at an outside hospital. If we had taken patients who came to our hospital first following a convulsion, it would have given us complete control in administering the drug properly. This would have better allowed us to study the effectiveness of magnesium sulphate against levetiracetam.

Further studies which can be conducted from this study are:

1. Comparative study on various dosing of Levetiracetam and its effectiveness in treating eclampsia patients
2. Comparing the efficacy of Magnesium Sulphate versus Levetiracetam in different types of eclampsia: antepartum and intrapartum versus postpartum eclampsia.
3. Studying the long-term effects of Levetiracetam on babies born to eclampsia mothers.

INFORMED CONSENT FOR PARTICIPATION IN DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that Dr. SINDHU MANNE of Shri. B. M. Patil Medical College Hospital and Research Centre has examined me thoroughly on _____ at _____ (place). Further Dr. SINDHU MANNE informed me that he/she is conducting dissertation/research titled "A PROSPECTIVE STUDY TO EVALUATE THE SAFETY AND EFFICACY OF LEVETIRACETAM IN COMPARISON TO MAGNESIUM SULPHATE IN MANAGEMENT OF ECLAMPSIA" under the guidance of Dr. S. R. Bidri requesting my participation in the study. Further, Doctor has informed me that my participation in this study will help in evaluation of the results of the study which is a useful reference for treatment of other similar cases in near future.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me. The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment. I am giving consent for the routine investigations and administration of the drugs in the trial.

I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness:

1.

2.

Date:

Place

PROFORMA

Name: IPNo:

Age: Case.no:

Address: Occupation:

DOA: Contact no:

DO Study:

1. Obstetric History :

1. Obstetric score : G P L A
2. Gestational age:

2. Past History:

History of hypertension : YES ☐ NO ☐

History of eclampsia : YES ☐ NO ☐

3. Family History:

1. HYPERTENSION YES NO

4. BLOOD PRESSURE ON ADMISSION:

5. CATEGORY OF HYPERTENSION:

- Pre eclampsia :
  - Mild
  - Severe
- Eclampsia**:**

1. **Any other complication:**

   (eg: HELLP , Asphyxia , oligohydraminos , IUGR)

7. STUDY PARAMETERS :

- Pulse rate, Blood pressure monitoring
- Complete blood count
- Liver function test
- Renal function test
- Fundoscopic examination
- Bedside test for proteinuria
- Serum magnesium level (optional)

8. MODE OF DELIVERY:

- Vaginal delivery:
- Instrumental delivery:
- LSCS: Indication:

9. PERINATAL OUTCOME:

- Mother side:
- NICU:
- Mortality:

REMARKS:

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