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ORIGINAL ARTICLE

Posterior Reversible Encephalopathy Syndrome (PRES): Evolving the Mystery of Eclampsia!

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Abstract

Background With the availability of neuroimaging, it is possible to know the exact underlying CNS pathology in eclampsia, and thus, the therapy can be targeted at the same. The present study was undertaken to find out the neurological changes in cases of eclampsia and to find the incidence of PRES in association with eclampsia and to study the role of Inj. Mannitol in cases of eclampsia with PRES who do not respond to Inj. $MgSO_4$ alone.

Methods This is a referral hospital-based prospective study of 110 consecutive cases of eclampsia who were subjected to MRI/CT scan brain without contrast. All 110 women with eclampsia were treated with routine principles of management of eclampsia. Inj. $MgSO_4$ was the drug of choice as anticonvulsant. Inj. Mannitol was added as antiedema agent in patients who did not respond to $MgSO_4$ alone.

Results All patients of eclampsia showed PRES on neuroimaging. 40 (36.36%) patients received inj. Mannitol as they had either recurrent convulsions or extreme irritability or deep coma after multiple convulsions and did not recover consciousness after convulsions were controlled.

Conclusion PRES is the core component of the pathogenesis of eclampsia, and the incidence is 100% in our study. Inj. $MgSO_4$ is the drug of choice, and addition of Inj. Mannitol in cases with recurrent convulsions, extreme irritability, visual symptoms and severe headache plays a dramatic role in control of convulsions and recovery of the patients.

Keywords Eclampsia · PRES · Inj. $MgSO_4$ · Inj. Mannitol

Introduction

Eclampsia is defined as occurrence of one or more convulsions in pregnant women with hypertension and proteinuria that cannot be attributed to any other cause. Eclampsia occurs in 0.5% of patients with mild preeclampsia and 2–3% in those with severe preeclampsia. However, what triggers the occurrence of convulsions in preeclamptic patients still remains a mystery!! But one thing is certain that some neurological changes occur in cases of preeclampsia which lead to eclamptic seizures. These cerebral complications of eclampsia account for many of the deaths due to eclampsia.

Our earlier knowledge of neurological changes in eclampsia depended on the autopsy findings of eclamptic patients, and the commonest findings were intracranial hemorrhages, cortical/subcortical petechial hemorrhages, cerebral edema, etc [1]. Autopsy series provides information regarding the CNS abnormality in patients dying of eclampsia. But this information is not necessarily indicative of the CNS

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abnormality present in the majority of patients who survive the condition.

With the availability of neuroimaging, it is now possible to know the exact underlying CNS pathology in eclampsia, and thus, the therapy can be targeted at the same. On neuroimaging CT/MRI, the neurologic manifestations of eclampsia are very similar to hypertensive encephalopathy which shows subcortical edema predominantly in occipital lobes, parietal lobe which was named by Hinchey et al as posterior reversible encephalopathy syndrome i.e PRES. The edema usually completely reverses. MRI permits noninvasive evaluation of these patients and provides physiologic information without the need of a contrast agent.

An association between eclampsia and PRES was first described by Hinchey et al. in 1996 [2]. This condition is marked by headache, altered mental status, visual changes and seizures. These patients were found to have extensive posterior cerebral edema. PRES has been associated with many other conditions besides eclampsia as in severe hypertension, autoimmune disease, treatment with cytotoxic drugs, sepsis, after organ transplant, etc. Generalized seizures are often the most common clinical manifestations of PRES.

Neuroimaging findings of PRES have been described in scores of eclamptic patients as a single case report or small case series, but exact association of PRES and eclampsia is unknown. The present study was undertaken to find out the neurological changes in 110 consecutive cases of eclampsia and to find the incidence of PRES in association with eclampsia.

PRES (Posterior Reversible Encephalopathy Syndrome)

PRES is a clinico-radiological entity that presents with neurological symptoms and signs in conjunction with unique neuroimaging findings of vasogenic edema involving the posterior circulation. The term PRES is a misnomer as the syndrome can involve or extend beyond the posterior cerebrum. It occurs secondary to failure of autoregulatory response to acute changes in blood pressure. As term suggests, it resolves completely if treated appropriately, but some can progress to develop permanent neurological defects.

Pathophysiology of PRES

The pathophysiology of PRES is poorly understood. Two main theories have been proposed.

1. High blood pressure leading to loss of autoregulation, hyperperfusion and vasogenic edema.
2. Endothelial dysfunction leading to vasoconstriction, and hypoperfusion resulting in cerebral ischemia and subsequent vasogenic edema.

Eclampsia is one of the most common situations described in association with PRES. In MRI/CT imaging, the brain typically demonstrates focal regions of symmetric hemispheric edema. The parietal and occipital lobes are most commonly affected followed by frontal lobes, inferior temporal–occipital junction and cerebellum [3].

Aims and Objectives

1. To study the neurological changes in patients of eclampsia and to know the incidence of PRES in patients of eclampsia.
2. To study the role of Inj. Mannitol in cases of eclampsia with PRES who do not respond to Inj. $MgSO_4$ alone.

Materials and Methods

This is a prospective study of 110 consecutive cases of eclampsia who were subjected to neuroimaging CT/MRI over a period of five years from 2012 to 2017. The study was conducted in the Dept. of OB–GYN in an institution which is a tertiary referral center. Ethical approval was obtained from Ethical committee.

All patients, once diagnosed as eclampsia, were stabilized first with anticonvulsant and antihypertensive drugs. A detail history was elicited. After stabilization of patient, induction/augmentation of labor was done. LSCS was done for obstetric indications. All 110 patients were subjected to neuroimaging CT/MRI without contrast after delivery or after stabilization with anticonvulsant and antihypertensives if delivery was not imminent. In the initial part of the study, CT scan without contrast was done but later as per advice of the neurophysician, MRI without contrast was performed.

The diagnosis of PRES was made by radiologist using the standard radiological criteria for PRES. Neurophysicians were involved after the CT/MRI study with the neuroimaging diagnosis of PRES.

The criteria for diagnosis of PRES on CT were hypoattenuation of the occipital and parietal regions. On MRI, the signal characteristics of affected areas include:

(a) T1 Hypointense in affected regions.
(b) T1 C + Patchy variable enhancement.
(c) T2 Hyperintense in affected regions.

These signs of PRES persist for several days to weeks [4].

Treatment Protocol

Inj. $MgSO_4$ All patients received $MgSO_4$ regime in the form of either low-dose regime and Pritchard regime or Zuspan regime.

Table 1 Patient demographics

Demographic	No. of patients	Percentage
Registered	4	3.64
Unregistered	106	96.36
Urban	63	57.27
Rural	47	42.73
Primigravida/para	80	72.73
Multigravida/para	30	27.27
Age 17–19 years	13	11.82
Age 20–25 years	87	79.09
Age 26–30 and more	10	7.09

Inj. Mannitol Inj. Mannitol was administered in cases who did not respond to Inj. $MgSO_4$ alone and had either recurrent convulsions, extreme irritability, visual disturbances or severe or deep coma.

Dose Inj. Mannitol was administered 100 cc of 20% IV. 6 hourly for 48 h, and then, it was tapered 8 hourly for next 24 h, 12 hourly for next 24 h and then omitted.

Recurrent Convulsions The conventional treatment for recurrent convulsions has been to give additional two doses of Inj. $MgSO_4$, and if convulsions are not controlled, then add one more anticonvulsant like Inj. Phenytoin or Inj. Levetiracetam. In the present study, inj. Mannitol was added if there were recurrent convulsions which were not controlled with additional doses of $MgSO_4$.

Antihypertensive Antihypertensives like Inj. Labetalol, Tab Labetalol and Tab Nifedipine were used for control of severe hypertension if systolic blood pressure of more than 160 mm Hg or diastolic blood pressure of > 105 mm Hg was observed. Gradual correction to target level of 140–150 systolic and 90–100 mm Hg diastolic are advisable to protect mother and avert the uteroplacental blood flow.

Results

Maternal Characteristics

Most of cases are unregistered (96.36%), primigravida (72.73%) and in age group 20–25 yrs (79.09%) (Table 1).

Type of Eclampsia and No. of Convulsions

75.66% had antepartum eclampsia and 50.9% had more than three convulsions (Table 2).

Table 2 Type of eclampsia and no. of convulsions

Type of eclampsia	No. of patients	Percentage
Antepartum eclampsia	83	75.66
Postpartum eclampsia	27	24.54
No. of convulsions		
1–2	54	49.09
3–5	43	39.09
> 5	13	11.82

Table 3 Presenting symptoms and blood pressure levels

Premonitory symptoms	No. of patients	Percentage
Headache	87	79.09
Visual disturbances	40	36.36
Vomiting	22	20.00
Epigastric pain	7	6.36
Altered mental state	5	4.54
BP on admission		
130/90 or less	21	19
> 140/100	34	31
> 160/110	55	50

Table 4 Anticonvulsant treatment given

Treatment given	No. of patients	Percentage
Inj. $MgSO_4$ + Inj. Mannitol	70	63.63
Inj. $MgSO_4$ alone	40	36.36

Presenting Symptoms and Blood Pressure Levels

Majority of the patients had preictal history, and they presented with symptoms of headache (79.09%) and BP on admission > 160/110 (50%) (Table 3).

Anticonvulsant Treatment (Protocol) Given

63.63% patients received Inj. $MgSO_4$ with Inj. Mannitol (Table 4).

Indications for Inj. Mannitol

Recurrent convulsions (23.63%) was the most common indication for Inj. Mannitol (Table 5).

Table 5 Indications for Inj. Mannitol

Indications	No. of patients	Percentage
Recurrent convulsions	26	23.63
Extreme irritability	8	7.27
Deep coma	6	5.45

Table 6 Site of lesion on CT/MRI

Variables	No. of patients	Percentage
Imaging modality		
CT scan without contrast	30	27.27
MRI without contrast	80	72.73
MRI–CT findings		
No. of patients with PRES*	110	100
Site of lesion		
Occipital lobe	71	64.54
Parietal lobe	69	62.72
Frontal lobe	33	30
Temporal lobe	13	11.81
Cerebellum	8	7.27
Multiple areas	5	4.54

*$P > 0.05$ insignificantly different

Site of Lesion on CT/MRI

Cerebral edema is often widespread but predominates in parietal and occipital regions. MRI is safe in pregnancy, and its utilization is important in diagnosis of PRES in pregnant women. Appropriate treatment can be executed in these cases, and it results in speedy recovery of the patients without residual neurological defects.

In imaging modality, MRI without contrast was done in 72.73% patients and CT without contrast in 27.27% patients. All patients (100% patients) were found to have PRES on MRI CT. Occipital lobe (64.54%) was the most common site of lesion followed by parietal lobe (62.72%) (Table 6).

Mode of Delivery and Perinatal Outcome

Vaginal delivery occurred in 65.44% patients, and LSCS was done for obstetric indications in 34.54% patients. In the present study, live birth occurred in 83.64% patients.

Maternal Mortality There was not a single maternal death in this study of 110 pts. of eclampsia. All patients were treated in ICU. There were four cases who had HELLP syndrome along with severe preeclampsia/Eclampsia. Inj. Dexamethasone was given to all these patients.

Discussion

Eclampsia is a major cause of maternal mortality and morbidity in India along with hemorrhage and sepsis. The maternal mortality in eclampsia is reported to be 3–5%. $MgSO_4$ has played an important role in reducing maternal and perinatal mortality and morbidity. In spite of the availability of intensive care unit and state-of-the-art technology, some patients still die from eclampsia. Common cause of death in these patients is CNS complication such as intracerebral hemorrhage or massive cerebral edema.

Studies have been reported—two retrospective studies by Justin Brewer [5] (N- 47), Steven Wagner [3] (N-7) and two prospective studies by Fatima Mubarak [6] (N-11) and Nazli Husain [7] (N-22). Though small in sample size, all these four studies reported PRES on MRI in eclampsia patients. These imaging studies have added to our knowledge regarding CNS abnormalities in eclampsia. These transient neurologic abnormalities are probably due to temporary insult such as hypoxia, ischemia or edema.

In the present study, neuroimaging in patients diagnosed as eclampsia showed PRES. Probably, this would be the largest study of neuroimaging in eclampsia so far. Patil Mithil has reported an incidence of PRES/cerebral edema/hypertensive encephalopathy in almost 60% cases of atypical or refractory eclampsia [8].

Eclamptic seizure may occur in patients with minimal elevation of BP. In pathogenesis of eclamptic seizures, blood pressure alone is not the only cause but endothelial dysfunction is a hallmark of preeclampsia as a contributing factor. Pregnancy itself may decrease the threshold at which an elevation in BP may lead to cerebral hyperperfusion and brain edema.

$MgSO_4$, which clearly controls eclamptic seizures, has now been shown to reduce cerebral perfusion pressure (CPP) in women with elevated CPP, and thus, it has been hypothesized that the reduction in CPP following Inj. $MgSO_4$ results in prevention of seizures [3].

In patients with eclampsia, if the convulsions are not controlled with $MgSO_4$ alone, then there is a definite role of a stronger antiedema agent like mannitol along with $MgSO_4$ as suggested by neurophysicians. Our study has proved that addition of another antiedema agent like mannitol helps in selected cases in whom there is recurrent convulsions, extreme irritability or deep coma, blindness, etc. Bilge Demir has reported a retrospective study comparing $MgSO_4$ and mannitol in treatment of eclamptic women with PRES [9].

Our experience of a prospective study of 110 cases definitely suggests Inj. Mannitol may not be superior to Inj. $MgSO_4$ but in cases where there is recurrent convulsions, extreme irritability (extensive cerebral edema) or deep coma, addition of Inj. Mannitol will have an equally important role in dramatic recovery and prevent the possible development of permanent neurologic deficits.

We propose that addition of Inj. Mannitol is to be considered in selected cases of eclampsia.

Study Raises Another Important Question, Should Patients with a Classical Clinical Presentation of Eclampsia Routinely Undergo Imaging Studies if the Result May or May Not Affect Their Treatment?

The answer to this question is NO. Our study of 110 cases of eclampsia patients investigated by MRI/CT and diagnosed clinically by convulsions, hypertension and premonitory symptoms are insignificantly different $P > 0.05$. So there is no need of MRI in every patient of eclampsia. This study and previous studies have proved that PRES or cerebral edema is the core component of eclampsia and inj. $MgSO_4$ in the drug of choice. An additional antiedema agent like Inj. Mannitol should be definitely considered if convulsions are not getting controlled with $MgSO_4$ alone or in patients of severe preeclampsia who have severe headache and visual disturbances.

However, there is a definite role of MRI in cases of doubtful diagnosis of eclampsia where there is focal neurologic sign or prolonged coma.

Conclusion

The present study has helped us to know the exact neurological changes in eclamptic patients. It was found that PRES is the core component in all 110 (100%) patients on MRI/CT. This is the largest prospective study done so far and gives ample evidence that there is no need to do MRI/CT in patients of eclampsia as a routine.

Inj. $MgSO_4$ is the drug of choice to control the eclamptic convulsions but in selected cases of eclampsia where there is recurrent convulsions, deep coma, extreme irritability or visual disturbances, an addition of strong antiedema agent like Inj. Mannitol would help to revert the neurological signs like cerebral edema and result in dramatic recovery.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standard All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Informed Consent Informed consent was obtained from all patients for being included in the study.

Human and Animal Rights This article does not contain any studies with human or animal subjects.

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Dr. Suman Sardesai graduated from Topiwala National Medical College and Nair Hospital, Mumbai, and did postgraduation in OBST and GYN at Nowrosjee Wadia Hospital and Seth G.S. Medical College, Mumbai, in 1975. She joined Dr. Vaishampayan Govt. Medical College, Solapur, Maharashtra, and pursued her teaching career for thirty-two (32) years. She has many original research projects to her credit. She received "FOGSI CORION AWARD" First Runner-up for her research paper "Low-dose $MgSO_4$ Regime for Preeclampsia and eclampsia" in 1998 at AICOG, Hyderabad (AP). She received FOGSI CORION AWARD First Prize for her original research on "Tobacco Handling in Pregnant Bidi workers: As Hazards as smoking 25 cigarettes per day" in 1999 at AICOG, Lucknow (UP). She also presented poster on various conservative surgeries for prolapse at FIGO held at Washington. Her other subjects of interest are conservative surgical procedure for genital prolapse, reversal of sterilization and surgery for genital malignancies.