USE OF PHENYTOIN SODIUM AND NIFEDIPINE IN TREATMENT OF ECLAMPSIA : A PRELIMINARY STUDY

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SUMMARY

In a preliminary study 36 patients of eclampsia admitted from August 1987 to February 1989 to a major referral hospital were subjected to the following therapeutic regime. Phenytoin sodium in a loading dose of 800-1000 mg intravenously effectively controlled convulsions in virtually all cases. Nifedipine 10 mg sublingually or intrarectally was used to lower the blood pressure when it was higher than 160/110 mm Hg in order to prevent a cerebrovascular accident and other life-threatening complications arising from severe hypertension. Sedatives were not used as part of the regime. Occasionally, a restless patient was administered minimal doses of promethazine (12.5 - 25 mg parenterally). Diuretics were avoided.

Pregnancy was terminated aggressively and most patients responded to Oxytocin infusion and artificial rupture of membranes and delivered by vaginal route (88%). Only two maternal deaths occurred. At the time of hospital admission both these patients had already developed potentially lethal complications; one had cerebrovascular accident and the other acute renal failure. No major maternal complication was encountered. Thirty-four patients were discharged after an average hospital stay of 9.8 days without any significant sequelae. No deleterious effect of the regime was noted in the newborn. The corrected perinatal mortality in babies weighing more than 1000 gm at birth was 435/1000 total births. This initial study justifies wider clinical application and larger clinical trials.

INTRODUCTION

Eclampsia remains a major cause of maternal and fetal death in the third world countries. The multitude of therapeutic regimes practised indicates that no method is satisfactory. Any regime for treatment of eclampsia includes measures directed at protection of maternal airway, control of convulsions, reducing the high blood

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pressure and termination of pregnancy at its earliest. For the present study, we formulated a protocol which includes the use of a high dose of phenytoin sodium as anticonvulsant, sublingual nifedipine as antihypertensive and early intervention for termination of pregnancy.

Intravenous infusion of phenytoin sodium has been for treatment of status epilepticus in pregnancy and there is no evidence to suggest that it has any adverse effect on the fetus (Dalessio 1985). Nifedipine which has rapid antihypertensive effect when given sublingually is currently being used in the treatment of hypertensive crisis. It has been shown to lower the blood pressure without any reduction in uteroplacental blood flow (Lindow et al 1988).

This preliminary study attempts to establish the clinical efficacy of such a regime in the management of eclampsia in present day obstetrics.

MATERIAL AND METHODS

Thirty six patients of eclampsia admitted to the Department of Obstetrics and Gynaecology, L. N. J. P. N. Hospital from August 1987 to February, 1989 were included in the study. The hospital serves as a major referral centre with an annual delivery rate of approx. 4000/year.

Patients were given an initial loading dose of 800/1000 mg of phenytoin sodium intravenously in 100 cc of normal saline over a period of 1 hour or 200 mg of phenytoin sodium intravenously given 3-4 minutes every 20 minutes (total 4-5 doses). This was followed by maintenance dose of phenytoin 100 mg intravenously 8 hourly.

Sublingual/intrarectal nifedipine was used to lower the blood pressure whenever the diastolic blood pressure was 110 mm of Hg. or more. Initially a 10 mg capsule of nifedipine was punctured and placed under the tongue of the patient, the blood pressure was recorded every 5-10 minutes, until the diastolic B.P. came down to 90 mm Hg. A repeat dose was given whenever required. Alpha methyl dopa and hydralizine were used for subsequent control of blood pressure. Fluid intake was not restricted. Diuretics & sedatives were not used as part of the regime.

Pregnancy was terminated aggressively. Artificial rupture of membrane performed whenever feasible at this time and concurrently labour was induced/augmented with intravenous diluted oxytocin infusion.

All neonates born alive were thoroughly examined immediately after birth to look for any evidence of central nervous system depression. All babies were given Vit. K. injection i.m. at birth. Babies were kept under observation in the neonatal until for atleast 24-28 hours.

RESULTS

Out of 36 patients of eclampsia studied 24 were primiparous with a mean age of 20 years and 12 patients were multiparous with a mean age of 27. Twenty eight patients were unbooked and 8 patients had paid 1 or 2 visits to the antenatal clinic before the onset of eclampsia. In 75% of the patients, onset of eclampsia was before delivery and 25% of the patients were admitted with post-partum eclampsia. The mean arterial pressure was less than 100 mm Hg in only one patient, between 101-120 mm Hg in 12 patients, between 121-140 in 21 and more than 140 mm Hg in 2 patients. Heavy proteinuria i.e. 3 + and above was present in ten patients and in 2 patients proteinuria was absent. Only 5 patients had generalised edema. The mean gestational age was 31.7 weeks.

Twenty six patients had no convulsions after the initial bolus dose of phenytoin sodium, 6 patients had one or two convulsions within 1 hour and none subsequently. Two

patients had 1 convulsion between 1-8 hour of the bolus dose and only two patients had more than two tonic-clonic convulsions after the initial bolus dose. However, no patient had convulsions 8 hours after the initial bolus dose. These 10 patients were given an intravenous dose of 10 mg of diazepam at each convulsion. The two patients who had more than 2 convulsions were put on intravenous diazepam drip. However one of them developed apnoea and diazepam had to be stopped (This particular patients had neither apnoea nor convulsion subsequently and ultimately recovered).

Table I

Change in level of consciousness with therapy in the first 24 hours

Level of consciousness	At time of admission	6 hours after admission	24 hours after admission
Full conscious	8	7	11
Drowsy	6	13	19
Stuporose - Delirious	2	14	4
Comatose	1	2	Both died*

* One patient had evidence of cerebrovascular haemorrhage at time of admission and other developed after 6 hours

Table II

Maternal complications in the first twenty four hours

Maternal complications*	At time of admission	6 hours after admission	24 hours after admission
1. Respiratory Depression	0	1**	0
2. Excessive throat secretion	19	11	2
3. Hyperpyrexia	1	2	2
4. Cerebrovascular haemorrhage	1	2	Both died
5. Renal failure	1	1	Died
6. Pumanary edema haemorrhage	1	0	0
7. Jaundice (Hemolytic)	1	1	1
8. Hematuria	1	2	3
9. Disseminated intravascular coagulation	0	0	0

* Twenty eight patients had no complications except for excessive throat secretion.

** This patient had received diazepam drip.

Bradycardia or hypotension was not observed in any of these 36 patients who received a bolus dose of phenytoin sodium. Table I and II summarises the maternal complications occuring in these patients. Average duration of stay was 9.8 days (6-26 days). Average duration of labour was 13.6 hours (6-28 hours). Two patients had caesarean section (Table III). One patient had postpartum haemorrhage controlled with oxytocin and bimanual massage. One patient required manual removal of placenta under general anaesthesia.

There were only two maternal deaths. One patients was a primigravida, 35 weeks gestation admitted with history of convulsions for 24 hours. Patient was in coma with right hemiplegia and 7th nerve palsy at the time of admission and expired after 24 hours. The 2nd patient an unbooked case of postpartum eclampsia with onset of convulsions 10 hours earlier. The patient was in renal failure at the time of admission, she had 3-4 convulsions over 6 hours, she went into deep coma with evidence of CVA and expired 22 hours after admission.

Table III

Method of termination of pregnancy in 27 patients who had eclampsia before delivery

Vaginal Deliveries	24
Spontaneous Vaginal Deliveries	20
Forceps application	4
Caesarean sections	2
Destructive operation (Craniotomy)	1

Neonatal outcome

Table IV summarises the outcome of fetuses of 27 patients admitted before delivery. Details of 4 intranatal deaths and 2 neonatal deaths is given in Table V.

The average 1 minute Apgar score was 5.1 and 2/3rd of neonates and subnormal Apgar at one minute i.e. less than 7. However, all except 1 baby was easily resuscitated (mean 5 minute Apgar was 7). Coagulation defects were not recorded in any of the newborns.

DISCUSSION

The agents currently used for treatment of eclampsia have been reviewed by Davey (1986). Magnesium sulphate is

Table IV

Outcome of 29 fetuses of 27 patients of eclampsia*

Status of fetus infants	Birth Weight					Total
	< 1 kg	1-1.5 kg	1.51 - 2 kg	2.1 - 2.5 kg	> 2.5 kg	
All	6	5	9	4	5	29
Alive when admitted	0	4	8	3	4	19
Born Alive	0	4	6	2	3	15
Discharged Alive	0	2	6	2	3	13

* Two patients had twin delivery.

Table V

Details of 6 perinatal deaths among 19 fetuses alive when eclampsia was diagnosed (Birth weight ≥ 1000 gms)

Birth weight (gm)	Comments
1. 1000 gm	Labour induced; vaginal delivery; maturity 34 weeks; A/S-0, 5, 5, died on 2nd Day of hyaline membrane disease.
2. 1100 gm	Labour induced; breech vaginal delivery; II twin; maturity 36 weeks SGA; A/S 7, 8, 8; died on 2nd day of pulmonary haemorrhage.
3. 1700 gm	Labour induced; vaginal delivery; still born; convulsions in mother not controlled with phenytoin, patient started on diazepam intravenous infusion. Patient had apnoea and fetal heart disappeared in labour.
4. 2000 gm	Labour induced; vaginal delivery; still born; maturity 36 weeks, fetal heart disappeared with onset of labour 6 hours after admission.
5. 2400 gm	Labour augmented with oxytocin; vaginal delivery; still born, patient had thick meconium, fetal heart 60-80/minute at time of admission, caesarean not done in view of very irregular and slow fetal heart. FHS (Fetal Heart) disappeared at the end of 1 stage of labour.
6. 2700 gm	Labour induced; vaginal delivery; still born; patient had icterus at time of admission, fetal heart irregular at onset of labour. Caesarean not done to avoid maternal morbidity.

A/S - Apgar Score.

effective and widely used but has relatively close therapeutic and toxic plasma levels and there is need for close supervision. Clonazepam and diazepam are said to be very effective in stopping fits but less effective in preventing them. They produce sedation of mother and fetus with the risk of neonatal hypothermia, hypotonous and apnoea (Davey, 1986). On the other hand, when phenytoin sodium is used in the peripartum period for control of convulsion it is not known to cause any respiratory depression in the newborn (Donaldson et al 1978). Anticonvulsant effects are evident after 10 to 20 minutes of the start of phenytoin infusion (50 mg/minute to a total of 18 mg/kg body weight). Seizures stop in 30% of patients after approximately 400 mg has been administered i.e. about 10 minutes after the start of infusion. Maximal anticonvulsant effects appear only after full dose of phenytoin has been administered i.e. 20 to 30 minutes after the start of the infusion (Delgado et al 1982). Phenytoin given intra-

venously at a rate of 50 mg/minute to a total dose of 18 mg/kg body weight alongwith intravenous diazepam has been recommended as the treatment of status epilepticus. A similar protocol has been advised for treatment of grandmal seizures in pregnancy (Dalessio 1985). Occurrance of congenital malformations (fetal hydantioin syndrome) have been reported by Hansen et al (1976) in fetuses born to mothers who have been taking phenytoin throughout pregnancy but not confirmed by later studies (Nakane et al, 1980). However there is no evidence that intravenous administration of anticonvulsant drugs which may be employed in status epilepticus has any adverse effect on the fetus (Dalessio 1985 & Moore and Redman 1987).

In the present study, phenytoin effectively controlled convulsions in majority of the cases (32 out of 36 patients were fully controlled within 1 hour). Only two patients (5.5%) required additional therapy in the form of diazepam infusion. In Pritchard series (1985) with magnesium sulphate 5 out of 245 patients required additional treatment for control of convulsions (2.04%). The fit recurrence rate has been reported to be 6.85% with lytic cocktail therapy and 1.98% with magnesium sulphate (Nagar et al, 1988). As is evident from Table I, 20 patients were either fully conscious or just drowsy 6 hours after admission and only four patients took longer than 24 hours to regain consciousness. This indirectly prevented the complications such as excessive throat secretions, maternal aspiration and chest complications arising from prolonged unconsciousness. Only one patient had respiratory depression and this particular patient was receiving diazepam infusion as convulsions were not controlled with phenytoin sodium.

Nifedipine, a calcium channel blocker given orally in pregnancy induced hypertension has been shown to be effective antihypertensive agent with no adverse fetal effects (Lindowet at 1988). In the present series of patients of eclampsia nifedipine lowered severe maternal hypertension sufficiently to prevent complications arising from hypertension per se i.e. cerebrovascular accidents, renal failure and cardiac failure. Fetal heart rate changes during labour (which could be due to decreased placental blood flow due to hypertension) was encountered in only four babies and all 4 were stillborn. Although Nifedipine is used to arrest preterm labour, all cases left for vaginal delivery (88%) responded to induction/augmentation of labour with oxytocin infusion and no patients required caesarean section because of non-progress of labour.

Maternal mortality of 5.5% (2 out of 36 patients) in our series is higher than that reported by Pritchard (1985) i.e. 0.45% (1 out of 245 patients) and no maternal death by Nagar S et al (1988) with magnesium sulphate therapy. But the two maternal deaths that occured in our series were moribund patients who were admitted with potentially lethal complications and these were not excluded from the study and cannot strictly be called treatment failure.

In our series, the perinatal mortality is still very high i.e. 435/1000 births (316 per 1,000 in the fetuses alive on admission) Still births contribute appreciably to high perinatal mortality but in large percentage (40%) fetus was already dead when the diagnosis of eclampsia was made and treatment initiated (Table IV).

The results of this preliminary study suggest that the regime used is able to control convulsions effective, bring down the blood pressure safely and rapidly, and prevent complications in the mother without unduly jeopardising the well being of the fetus. This initial analysis has encouraged

us to not only continue this study but also to extend the application of this regime to patients of severe hypertension to prevent the onset of eclampsia.

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