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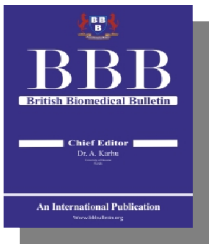

Original

Antenatal Phenobarbitone in Preventing Intraventricular Haemorrhage and Neonatal Convulsions in Preterm Babies

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A R T I C L E I N F O

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A B S T R A C T

The present Randomized control trial was conducted to assess the effect of antenatal phenobarbitone in preventing intraventricular haemorrhage and neonatal convulsions in preterm babies. It was conducted among women with preterm labour admitted in R.G. Kar. Medical College, Kolkata, India. 100 pregnant women with high risk of preterm labour were selected as study group and treated with Inj. Phenobarbitone (10mg/kg) after admission and if the patient did not deliver within 24hrs, another additional dose of 100mg of phenobarbitone orally was given. Control group of 100 pregnant women with high risk of preterm labour in the same time period were taken as controls and were not given Phenobarbitone but received a placebo. This study compared the incidence of neonatal convulsion and intra-ventricular haemorrhage in neonates of preterm mothers receiving phenobarbitone versus mothers who did not receive phenobarbitone. We found Neonatal convulsions occurred in 9% of the study group and 12% among the control group. IVH occurred in 9% among the study group compared to 11% among the control group. Our study supports the use of antenatal phenobarbitone in preventing intraventricular haemorrhage and neonatal convulsion in preterm babies.

Introduction

Incidence of preterm labour ranges from 10 to 15% in India. IVH remains a significant problem, since improved survival of extremely premature infants has resulted in a greater number of survivors with this injury[1]. Intraventricular haemorrhage occurs due to fluctuations in blood pressure and cerebral perfusion around birth and during early postnatal adaptation might also be involved[2]. IVH characteristically initiates in the periventricular germinal matrix[3]. The germinal matrix, located on the head of caudate nucleus and underneath ventricular ependyma, is a highly vascular collection of glial and neuronal precursor cells[3]. This periventricular region is selectively vulnerable to haemorrhage in premature infants predominantly in the first 48 h of life[2]. When the haemorrhage in the germinal matrix is substantial, the ependyma breaks, and the cerebral ventricle fills up with blood. Phenobarbital is a potential neuroprotective agent that might act by preventing ischemic injury or by reducing the fluctuations in blood pressure and cerebral perfusion (Goddard 1987; Wimberley 1982). Phenobarbital has been suggested as a postnatal treatment. Phenobarbital prior to preterm birth for preventing neonatal periventricular haemorrhage and has been the subject of another Cochrane review (Whitelaw 2007). In the study conducted by De Carolis S *et al*[4], Intraventricular haemorrhage was significantly less frequent in the treated group. As many haemorrhages are thought to originate close to the time of birth, prophylactic prenatal rather than postnatal treatment may be preferable. Therapeutic interventions to prevent periventricular, intraventricular, and cerebral haemorrhages in preterm infants include the administration of drugs such as Phenobarbital or indomethacin either before birth or immediately after delivery. Postnatal treatment can reduce the frequency and severity of these haemorrhages, but up to 50 percent occur before postnatal therapy can be initiated. Furthermore, events associated with premature delivery, including labour and neonatal resuscitation, may play a part in the pathogenesis of intracranial haemorrhage. For these reasons, antenatal therapy should be a more effective preventive strategy than postnatal therapy. Several studies and a recent meta-analysis[9,10] have suggested that antenatal administration of Phenobarbital decreases the frequency and severity of intracranial hemorrhage[5]. This study was intended to evaluate whether antenatal phenobarbitone given to preterm mother can reduce the risk of intra-ventricular haemorrhage and neonatal convulsions in preterm babies.

Materials and Methods

Shankaran S *et al*[6]. Showed beneficial effects of antenatal phenobarbital therapy on neonatal intracranial haemorrhage in preterm infants[3]. Our study was a Prospective randomized single blinded interventional study Conducted between July 2011 and June 2012. Patients admitted for institutional delivery in the Department of Gynaecology & Obstetrics of R.G.Kar Medical College and Hospital, Kolkata, were taken as subjects for study. This study was designed to compare the incidence of neonatal convulsion and intra-ventricular haemorrhage in neonates of preterm mothers receiving phenobarbitone versus mothers who did not receive phenobarbitone. The study got clearance from the institutional ethical committee. Written consent was taken from all the mothers. For every woman to be included in the study a detailed history taking, clinical examination and relevant investigations were carried out and investigation reports noted if available with the client.

Women fulfilling the criteria as singleton pregnancy, gestational age between 30 and 36 weeks were included in the study. Mothers with multifetal gestation, gestation- <30, and >36 week, polyhydramnios, congenital malformation, antepartum haemorrhage, severe pregnancy induced hypertension (160/110), eclampsia, previous Caesarean section, previous myomectomy, epilepsy, diabetes, heart disease, renal disease and non-vertex presentation and the babies with Severe asphyxia and gross congenital anomaly were excluded from the study.

Primary outcome measure was to decrease the incidence of Intra-ventricular haemorrhage in preterm neonates. Secondary outcome measure was to reduce the incidence of Neonatal Convulsions in preterm neonates and to reduce the Perinatal Mortality Rate due to IVH in preterm neonates.

Total 200 pregnant women with high risk of preterm labour admitted for institutional delivery in the department of Obstetrics and Gynaecology during the study period were randomized equally to one of the following group:

Study group

Pregnant women with high risk of preterm labour were given with Inj. Phenobarbitone (10mg/kg) after admission and if the patient did not deliver within 24hrs, another additional dose of 100mg of phenobarbitone orally was given.

Control group

Pregnant women with high risk of preterm labour in the same time period were taken as controls and were not given Phenobarbitone but received a placebo.

All women included in the study group were treated with 10mg/kg intramuscular phenobarbitone when the mothers were in early stage of labour. All women included in the control group received distilled water. After delivery, the neonates were observed and the APGAR score noted at 1min and 5 min. Neonates with cardio-respiratory depressions were resuscitated with CPR and intubated with ET tube. Some neonates got admitted in NICU for further management. Neonates were observed in NICU, some babies were put on mechanical ventilation, observed for any convulsions. Neonates cranial USG was done within72 hrs of birth, looked for any intra-ventricular haemorrhage. Neonates were closely observed for any convulsion during the stay in NICU. Neonates were monitored in the NICU by the on duty paediatrician and we collected all the vital data from them for further analysis. Ultimately the number of stay of the neonates in NICU and neonatal death within 72 hrs were noted.

Results

Primary data collection and recording were done regarding details of obstetric history, examination, age, parity, gestational age assessment, blood pressure, other basic investigations, mode of delivery in the mother. After delivery, APGAR score at 1min and 5 min noted, intubation with ET tube was done in cardio-respiratory depressed neonates, some were admitted in NICU, in NICU some were put in mechanical ventilation. The neonates were closely observed for any convulsions, within 72 hrs of birth the neonates cranial USG were done for any intra-ventricular haemorrhage. Number of day in NICU was noted and any neonatal death within 72 hrs was noted. Statistical analysis was assisted by Graph pad in stat 3. Ink of san diago Chicago software. The clinical characteristics of the mothers and infants in the two groups were compared by, Fisher's exact test, two tailed t-tests. All analysis was

two tailed with P value less than 0.05 was considered to indicate a statistically significant difference. Treatment effects were estimated on the basis of relative risks and 95 percent confidence intervals.

Discussion

In this randomized control trial 200 Preterm mothers were randomized of which 100 were in the study group and another 100 in the control group. They were selected by proper analysis of inclusion and exclusion criteria. Those who received Phenobarbitone were called study group, and those who did not, were enlisted under control group. After delivery the neonates were followed in the NICU for any convulsions and cranial USG was done within 72 hrs of birth for any intra-ventricular haemorrhage and the neonatal death within 72 hrs of birth were noted. Neonatal convulsions occurred in 9% of the study group and 12% among the control group, RR is 0.75, 95% CI is 0.3307-1.701, P value was 0.645(NS- not significant), which implies that there is no significant decrease in neonatal convulsion by using antenatal phenobarbitone. IVH occurred in 9% among the study group compared to 11% among the control group, RR was 0.8182, 95% CI was 0.3545-1.888, P value was 0.8143(NS- not significant), thus it implies that there is no significant decrease in the incidence of IVH with antenatal phenobarbitone in the study by Seetha sankaran *et al*[7], 23% among the phenobarbitone group and 23% among the placebo group had Intraventricular Haemorrhage, relative risk, 1.0; 95 percent confidence interval, 0.8 to 1.4. There was no difference in the severity of intracranial haemorrhage. Neonatal death within 72hrs occurred in 7% among the study group compared to 10% in the control group, RR is 0.70, 95% is 0.277 to 1.766, P value is 0.613 (NS- not significant). In this prospective interventional study in a setting with low resource centre, antenatal phenobarbitone given to preterm mothers was not statistically significant in reduction of intraventricular haemorrhage in preterm babies. Also it was not associated with significant reduction of neonatal seizures due to intraventricular haemorrhage in preterm babies. It also does not significantly reduce the perinatal mortality rate. However it has been observed that in case of intraventricular haemorrhage the study group has fewer incidences than the control group. Also neonatal convulsion and PNMR is less in the study group than the control group. Comparing with the other study by Seetha sankaran[8], perinatal mortality is in our study is more, it may be attributed to poor resources, high rates of cross infections. This observation though not statistically significant but, indicates that further research studies in this aspect can be done particularly with a large sample size which may lead to statistically significant results. Also multiple studies in different institutions with a meta-analysis can produce significant results. This study also is interesting because minimal facilities are required to do the study as also the intervention is minimal. Moreover this study is mainly a clinical observational study requiring minimum of tools and gadgets. Also due to the restricted time period of study (1 year only) the long- term follow- up could not be done. Long-term follow-up study is suggested for further assessment in this subject. As in our study, most of the early studies were not supporting the use of antenatal phenobarbital for preventing IVH. There is one study in 1980s which showed significant decrease in IVH, but they also gave phenobarbitone to the neonates. This study again can be another area of research activity. In case of future trials, additional area of focus can be the assessment of neuro-developmental status of follow-up studies of these preterm babies.

Conclusion

This study which includes 100 cases of study group and 100 cases of control group, shows that however the results are not statistically significant, Incidence of IVH and Neonatal convulsion is less in the study group (those who received antenatal phenol-barbitone). So this study concludes that antenatal Phenobarbitone can be given to reduce the Intra-ventricular Haemorrhage and Neonatal convulsion in Preterm neonates.

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Table 1. Baseline maternal parameters

Parameters	Study group (n=100)	Control group (n=100)
Maternal age(yrs)	18.72 + 0.46	18.88±0.33
>19	21.04 + 1.2	21. 16± 1.04
20-24	26 + 1.5	25 + 1.3
25-30	31.6± 2.08	33.75±1.89
>30		
Parity	42%	39%
Primi	58%	61%
Multi		
Gestational Age(wks)	30 + 0.6	30 + 0.6
30-32	32 + 0.4	32 + 0.5
32-34	34 + 0.3	34 + 0.05
34-36		
Injection-Delivery interval(hrs)		
<24hrs	74%	78%
>24hrs	26%	22%
Maintenance dose		
Required	26%	22%
Not required	74%	78%
Mode of delivery		
Vaginal delivery	78%	85%
LUCS	22%	15%

Table 2. Parameters of the neonates

Parameters	Study group (n=100)	Control group (n=100)
Birth Weight(kg)		
1.5-2	1.79 + 0.18	1.78± 0.16
2.1-2.5	2.17± 0.10	2.19± 0.09
APGAR score		
<3		
1 min	22%	13%
5 min	6%	4%
Intubation in Delivery		
Room		
Required	44%	38%
Not Required	56%	62%
NICU Admission		
Required	61%	55%
Not Required	39%	45%

Table 3. Outcome of interventions in the study

Parameter	Study Group (n=100)	Control Group (n=100)	RR	P value
Neonatal convulsion	9	12	0.75	0.645(NS)
IntraVentricular Haemorrhage	9	11	0.81	0.81(NS)
Neonatal Death <74hrs	7	10	0.70	0.613(NS)