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Comparison of Effect of Phenytoin & Phenobarbitone in Neonatal Seizures

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ABSTRACT

Introduction: Neonatal seizures are the most frequent clinical manifestation of neurological dysfunction in the newborn. Most physicians treat neonatal seizure with phenobarbitone as first line and then phenytoin as second line drug. Both drugs are effective in most of the neonatal units but limited studies have been conducted regarding their comparative clinical efficacy. **Aims & Objectives:** The aim of the study was to compare the clinical efficacy of phenytoin and phenobarbitone in controlling neonatal seizures for more than 24 hours irrespective of the cause. **Place and duration of study:** The study was conducted in Pediatrics Department, Shaikh Zayed Medical Complex Lahore, from January 2016 to Dec 2016. **Material & Methods:** A total of 150 cases were enrolled in this study based on stringent inclusion and exclusion criteria, a written informed consent and approval from the hospital ethical committee. At the time of enrollment, the neonates were randomly assigned to receive one of two anticonvulsant drugs using lottery method. Both drugs were administered intravenously over a 5 to 15 minute period once daily. The loading doses of both drugs were 20mg / kg/ day with the maintenance dose of 4mg/ kg/ day. Patients were divided into two groups, comprising of 75 patients in each group (group A was given phenytoin and B was given Phenobarbitone). All the demographics and outcome variables were entered in a pre-defined questionnaire. **Results:** In our study, mean neonatal age in Group A and B was 13.88 $\pm$ 7.47 and 12.11 $\pm$ 6.47 days respectively with a gender distribution of 48(M):52(F) in Group-A and 46.67(M):53.33(F) in Group-B. The mean seizure control time was found to be 31.23 $\pm$ 11.41 hours in Group-A and 25.64 $\pm$ 10.84 hours in Group-B. Group-A showed less efficacy of 16% (n=12) than in Group-B 78.67% (n=59). P value was calculated as 0.000 showing a significant difference. **Conclusion:** Our study showed phenobarbitone to be more efficacious in controlling neonatal seizures than phenytoin when administered intravenously over a 5 to 15 minute period once daily in a loading dose of 20mg / kg/ day and maintenance dose of 4mg/ kg/ day.

Key words: Neonatal seizures, management, phenytoin and phenobarbitone, efficacy.

INTRODUCTION

Neonatal seizure is a medical emergency. Hypoxic ischemic encephalopathy is a most common cause of neonatal seizures. Incidence of neonatal seizure is 1-5 per 1000.[1]

Neonatal seizures show some underlying brain disorder e.g. Birth asphyxia, intraventricular hemorrhage and metabolic disorders.[2]

Most neonates with seizures are treated with phenobarbitone as first line drug, although its efficacy in the emergency setting has not been unequivocally demonstrated.[3] It is used in most of the developing countries due to its low cost. Its agonist action on GABA Cl channel receptor complex results in activation and longer duration of opening of the chloride channels. Thus decreasing glutamate triggered excitability. Its lypophilic nature results in large distribution and brisk depression of the CNS, which results in excellent seizure control.[4]

In comparison phenytoin is used as second line anti seizure drug. Its action is through blockage of voltage dependent neuronal sodium channels and it is useful in controlling neonatal seizures resistant to phenobarbitone.[5]

The rationale of our study was to check the effect of phenytoin and Phenobarbital on neonatal seizures. There is no data available for this topic to check the

effect of both drugs in local population. There was only one study Published in England with small sample size and we wanted to conduct this study with a larger sample size in our population as ethnicity may have impact on efficacy.

MATERIAL AND METHODS

Sample Size

The required sample size was 150 cases total calculated as (75 subjects in each group) considering 5% level of significance and study power 80% and expected percentage efficacy in both groups i.e. phenytoin is 78%[7] and phenobarbitone as16%.[7]

Sampling Technique

Non-probability, consecutive sampling

Study Design

Randomized controlled trial

Sample Selection

Inclusion Criteria

Neonates till 30 days of life both male/female with seizures.

Exclusion Criteria

Neonates with respiratory distress liver dysfunction, assessed by liver function, (Serum Alkaline Phosphatase, SGOT, SGPT, Prothrombin time and Albumin). Renal insufficiency by renal function test (Blood Urea Nitrogen, Creatinine) Cardiac abnormalities assessed by electrocardiogram, chest x-ray and echocardiography were excluded

Data Collection Procedure

A total of 150 cases were enrolled in this study after fulfilling inclusion/exclusion criteria, a written informed consent and approval from hospital ethical committee. At the time of enrollment, the neonates were randomly assigned group A and B using lottery method.

Phenobarbital and phenytoin were administered intravenously over a 5 to 15 minute period once daily.

Patients were divided into two groups, comprising of 75 patients in each group (group A was given phenytoin and B was given Phenobarbitone). All the demographics and outcome variables were entered in a pre-defined questionnaire. Clinical efficacy was labeled as neonate free of seizures for period of 24 hours after giving anticonvulsant.

Ethical Consideration

- Informed consent was taken by the parents regarding study protocol
- All the neonates had been provided the standard of care treatment of available setting in addition to that of the treatment drug was given to Group A and B.
- All participating neonates were closely monitored for adverse effects and in case of failure of treatment shifted to 2nd line of drugs according to standard protocol.

Statistical analysis:

The data was entered on computer software SPSS version 15. Quantitative data like age and time taken to control seizures were presented by mean and standard deviation. Qualitative data like gender and clinical control of seizure efficacy. Chi square test was used to determine the significance of efficacy in between both groups and p value $\leq$0.05 was considered as significant. The data was stratified for gender, cause of seizure, gestational age and birth weight to address the effect modifiers. Post stratification chi square test was applied with p value $\leq$0.05 as significant.

RESULTS

A total of 150 cases fulfilling the inclusion/ exclusion criteria were enrolled for the comparison of efficacy of phenytoin and phenobarbitone in controlling neonatal seizures. Age distribution of the patients were done, it showed that 57.33%(n=43) in Group-A and 73.33%(n=55) in Group-B were between 1-15 days of life while 42.67%(n=32) in Group-A and 26.67%(n=20) in Group-B were between 16-28 days of life, mean$\pm$sd was calculated as 13.88$\pm$7.47 and 12.11$\pm$6.47 days in Group-A & B. (Table-1).

Patients were distributed according to gender, it showed that 46.67% (n=35) in Group-A and 48%(n=36) in Group-B were male while 53.33%(n=40) in Group-A and 52%(n=39) in Group-B were females. (Table-1)

Mean time taken to control seizures was compared it showed that 31.23$\pm$11.41 hours in Group-A and 25.64$\pm$10.84 hours in Group-B. (Table-1)

Comparison of efficacy in both groups showed that 16% (n=12) in Group-A and 78.67%(n=59) in Group-B had efficacy while 84%(n=63) in Group-A and 21.33% (n=16) in Group-B had no findings of efficacy, p value was calculated as 0.00 showing a significant difference. (Table-1)

The data was stratified for gender, cause of seizure, gestational age and birth weight to address the effect modifiers. Post stratification chi square test was applied with p value ≤0.05 as significant. (Table-1)

Age Distribution N=150	**Age (in days)**	**Group –A (n=75)**		**Group –B (n=75)**	
		No. of patients	**%**	**No. of patients**	**%**
	1-15	43	57.33	55	73.33
	16-28	32	42.67	20	26.67
	Total	75	100	75	100
	Mean +SD	13.88+7.47		12.11+6.47	
Gender Distribution N=150	**Gender**	**Group –A (n=75)**		**Group –B (n=75)**	
		No. of patients	**%**	**No. of patients**	**%**
	Male	35	46.67	36	48
	Female	40	53.33	39	52
	Total	75	100	75	100
Mean Time taken control seizures N=150	**Time taken control seizures**	**Group –A (n=75)**		**Group –B (n=75)**	
		Mean	**SD**	**Mean**	**SD**
		31.23	11.41	25.64	10.84
Comparison of Efficacy in Both Groups (n=150)	**Efficacy**	**Group –A (n=75)**		**Group –B (n=75)**	
		No. of patients	**%**	**No. of patients**	**%**
	Yes	12	16	59	78.67
	No	63	84	16	21.33
	Total	75	100	75	100
Stratification for efficacy with regards to gender	**Female**	**Efficacy**			**P value**
		Yes		**No**	0.00
	Group A	7		28	
	Group B	28		8	
	Male				**P Value**
	Group A	5		35	0.95
	Group B	31		8	
Stratification for efficacy with regards to cause of seizures	**Causes**	**Group –A**		**Group-B**	**P Value**
	Meningitis	6		29	0.95
	Intracranial bleed	4		18	
	kernicterus	2		12	
< 37 Weeks					
Stratification for efficacy with regards to gestational age	**Group**	**Yes**		**No**	**P value**
	A	3		19	0.000
	B	22		4	
	>37 weeks				
	Group	**Yes**		**No**	**P value**
	A	9		44	0.000
	B	37		12	
Low birth weight					
Stratification for efficacy with regards to birth weight	**Group**	**Yes**		**No**	**P value**
	A	4		16	0.003
	B	11		5	
	Normal Birth weight				
	Group	**Yes**		**No**	**P value**
	A	8		47	**0.000**
	B	48		11	

Table-1: comparison of clinical efficacy of phenytoin and phenobarbitone in treatment of neonatal seizures.

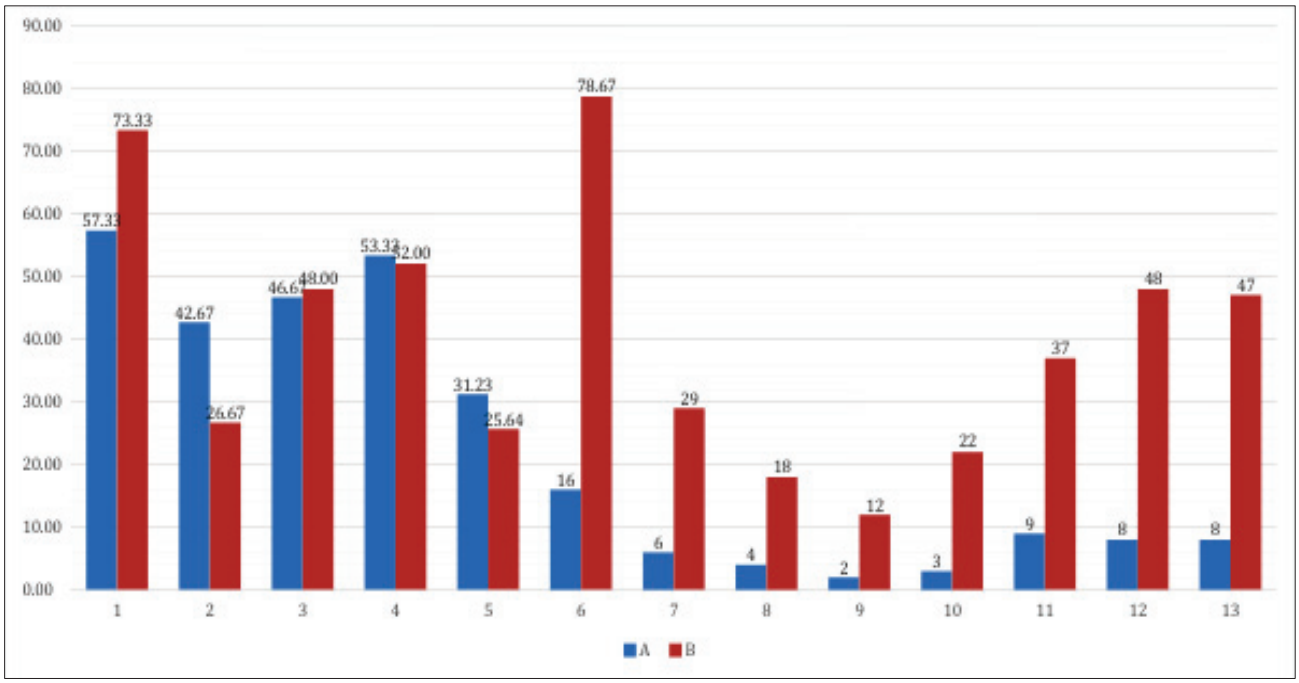

Fig-1: Graphical representation of comparison of the clinical efficacy of phenytoin and phenobarbitone in treatment of neonatal seizures.

DISCUSSION

Neonatal seizures are the most important and common presentation of significant neurological dysfunction.[6] The incidence of seizure in neonates born at term is 0.5 to 3/thousand and preterm is 1 to 13/thousand in very low birth rate.[7]

Phenobarbitone is first drug of choice in treating neonatal seizures in most of the countries.[8] This drug achieved clinical control in only 30 to 40% cases.[9] Phenytoin is added as second line when fits are not controlled. Its use is limited because of effect on cardiac contractility.[10]

Phenobarbitone and Phenytoin have traditionally been most common drugs in controlling neonatal seizures despite only 50% efficacy.[11] Only few studies showed comparable data regarding their efficacy. In one randomized prospective trail by Painter et al. in 1999 was done which showed initial control of seizures by Phenobarbitone 45% Phenytoin 43% (p=1). The complete seizure control was 57%. Neonates were monitored for side effects. The main side effect was on liver function test. These liver function test were monitored 24 hourly for any abnormalities but no side effect was noted at that time. Challenge we faced during study was with 5 neonates in whom seizures were not controlled by assigned drugs and were then shifted to other antiepileptics. Those patients were excluded from study. In our study the comparison of efficacy showed 16% seizures controlled with phenytoin and 78.67% control with phenobarbitone.

The findings of our study is consistent with the study of Painter et al showing that phenobarbitone is more effective than phenytoin for controlling of neonatal seizures.

Our study differed from Boylan, et al,[11,12] which showed that although phenobarbitone controlled fits in 25% of cases and used it as first line of drug but EEG background remains abnormal and Phenytoin was more effective about 27% in controlling fits and EEG background became normal after the use of phenytoin.

PHB is cheaper and used in developed and under developed countries as first line of drug having few side effects like sedation and cognitive disability. Our results express that “There is a difference in efficacy of phenytoin & phenobarbital in treatment of neonatal seizures”, however, in absence of local data, we are of the view that some other multi centre trials are required to validate our findings.

CONCLUSION

We concluded that the efficacy of phenobarbitone is significantly higher when compared with phenytoin in treatment of neonatal seizure.

As there are multiple controversies regarding the best standard first line of drug for the treatment of neonatal seizures. There is need for developing consistent evidence based guideline regarding the first line drug for controlling neonatal seizures. Further studies are required to develop the standard protocol regarding first, second and third line of drugs for controlling neonatal seizures.

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