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Research Article

ROLE OF PHENOBARBITONE PROPHYLAXIS IN NEONATAL JAUNDICE IN LATE PRETERM NEONATE

***Venkatesh S and Srinivas K**
Department of Paediatrics, MVJ Medical College and Research Hospital
**Author for Correspondence*

ABSTRACT

Background: Hyperbilirubinemia is a common problem in neonates with an incidence of 70-80%. Premature babies have higher incidence of neonatal jaundice requiring therapeutic intervention than term new-borns.

There are very few studies regarding use of prophylactic phenobarbitone in the late preterm neonates hence we intend to evaluate the efficacy of prophylactic phenobarbitone in reducing the peak serum bilirubin levels, duration and the need of phototherapy in this vulnerable group thus prevent complications and enable early discharge. *Aims and Objectives:* This prospective study was performed to asses if prophylactic phenobarbitone can reduce peak serum bilirubin levels, duration of phototherapy and need of exchange transfusion in late preterm infants. *Materials and Methods*: 106 preterm born between 34 to 36 weeks meeting inclusion and exclusion criteria were included, they were randomised into 2 groups, prophylactic phenobarbitone and control group. Prophylactic phenobarbitone of 10 mg/kg within 6 hours of life was given followed by 5m/kg for first 5 postnatal days. This study was done in the department of paediatrics at MVJMC&RH over a period of 1 year. *Results***:** Among 106 neonates, demographic data was comparable among both the groups. Serum bilirubin levels were lesser in group 1 when compared to group 2, which was not statistically significant (p=0.001). The duration of phototherapy and requirement of exchange transfusion was lesser in the phenobarbitone group and was statistically significant (p value<0.05). *Conclusion*: Jaundice remains one of the main treatable problems with low birth weight babies being at higher risk. With very few studies available on the Postnatal prophylactic use of Phenobarbitone in neonatal jaundice in low birth weight babies, Our study concludes with decrease in need of Phototherapy and Exchange transfusion in neonatal jaundice among low birth weight babies when used prophylactically

Keywords: *NICU, Phenobarbitone, Phototherapy, Hyperbilirubinemia*

INTRODUCTION

Hyperbilirubinemia is a common problem in neonates with an incident of 70-80% (Chung *et al.,* 2004). Neonatal hyperbilirubinemia (NH) is a cause of concern for the parents as well as for the paediatricians (Mishra *et al.,* 2008).

Jaundice occurs more frequently in late preterm infants than term infants. The duration of jaundice is often more prolonged and peak concentrations of indirect bilirubin frequently are higher than found in term infants. The primary factors causing physiological indirect hyperbilirubinemia are delayed maturation and lower concentrations of uridine diphosphoglucuronate glucuronosyltransferase, the rate-limiting enzyme for conjugation of bilirubin. The enterohepatic circulation of bilirubin also contributes to bilirubinaemia in late preterm infants, especially those infants whose feeding skills are insufficient or whose gastrointestinal motility is slow or impaired. Late preterm infants are twice as likely as term infant to have significantly elevated bilirubin values during birth hospitalization. In addition, the peak in bilirubin concentration may occur 5 to 7 days after birth in late preterm infants, a time when many such infant are at home (Korkmaz *et al.,* 2004).

In addition, the neurological immaturity of late preterm infant make them vulnerable to bilirubin induced neurological damage and kernicterus (Bhutani *et al.,* 2006).

Premature babies have much higher incidence of neonatal jaundice requiring therapeutic intervention more commonly than term newborns (Kumar *et al.,* 2001).

A significant proportion of these neonates develop pathological hyperbilirubinemia during the first week of life. Although the outcome for the majority is benign, infants with untreated, severe hyperbilirubinemia can develop signs of acute bilirubin encephalopathy (ABE). If not treated immediately, they might go on to develop kernicterus, a chronic, neurologically devastating condition resulting from the bilirubin toxicity. National neonatal perinatal database network 2002-2003 reported incidence of hyperbilirubinemia in 3.3% for intramural deliveries and 22.1% for outborns in India.

Kaabneh *et al.,* (2015) conducted a study to evaluate in limited resources setting, phenobarbitone in combination with phototherapy may be helpful to new born infants. phototherapy causes increased insensible water loss, increased incidence of PDA and temperature instability especially in small babies.

There are very few studies regarding use of prophylactic phenobarbitione in the late preterm neonates hence we intend to evaluate the efficacy of prophylactic phenobarbitone in reducing the peak serum bilirubin levels, duration and the need of phototherapy in this vulnerable group and thus prevent the complications and enable the early discharge of these neonates.

MATERIALS AND METHODS

Inclusion Criteria*:*

1) All Late preterm neonates born at 34 through 36 weeks gestational age (238-258 days)
2) Cord bilirubin levels > 3 mg/dl

Exclusion Criteria*:*

1) Babies having jaundice at birth, septicaemia and Hydrops Foetalis, Asphyxia etc.
2) Babies receiving any drug in this period and with other neonatal morbidities.
3) Babies of mothers who have received phenobarbitone dose antenatally.

This was a prospective study that was performed in the department of pediatrics of M.V.J. Medical College & Research hospital. 106 Eligible Late-preterm babies born at this hospital during 2 Year period was prospectively enrolled in the study and randomized into two groups. This study was approved by the Research Ethics committee of M.V.J. Medical College and Research Hospital.

The babies fulfilling the eligibility criteria were randomized into 2 groups using table of random numbers. Proposed study has been submitted to institutional ethical committee and clearance has been obtained.

Group I babies were given 10 mg/Kg loading dose of oral phenobarbitone within 6 hrs of life followed by maintenance dose of 5 mg/Kg/day from day 2 to day 5. Group II babies were taken as controls. Phenobarbitone was given orally to the baby along with breast milk , the concentration of the syrup available in our pharmacy was 200mg/5ml. Total no of babies included in Group I was 53 Group II was 53. Informed consent was taken from parents or legal guardian. Babies who were admitted in NICU monitored hourly for their vital signs and records of daily fluid intake, enteral feeding pattern, stool frequency, daily weight was maintained.

For those babies in Group I and Group II, who developed jaundice up to chest wall and beyond clinically (significant level according to birth weight) by observing in day light, serum bilirubin level was measured i.e >10mg/dl.

Serum bilirubin levels was measured by using diazo method, the samples were collected by Intravenous route. Samples were sent to biochemistry and pathology laboratories for investigations.

Depending on serum bilirubin levels, according to birth weight, phototherapy, exchange transfusion was opted. For those babies who required phototherapy, serum bilirubin levels were measured every 24 hours until they were off the Phototherapy unit.

Primary outcome was to study if use of prophylactic phenobarbitone reduced peak serum bilirubin levels and the duration of phototherapy and need for exchange transfusion.

Statistical analysis:

The Chi square test was used to see the effect of phenobarbitone on categorical variables. The difference of mean values for various parameters among the two groups was determined by using T test.

RESULTS

The study was conducted on 106 late preterm neonates admitted at MVJ Medical College& Research Hospital .All late Preterm babies with cord bilirubin over 3 mg/dl were studied. The babies were randomised into two categories by random control numbers *viz*, group 1 consisting of babies receiving prophylactic phenobarbitone and Group 2 who did not receive the same(control group) each having 53 babies. In group 1, two babies were lost to follow up due to discharge before the study period and hence 51 babies were taken into count.

Table 1: Baseline characteristics

GESTATIONAL AGE	Group 1(n)	Group 2(n)	P value=0.39
32-34+6weeks	11	11	
35-35+6weeks	25	20	
36-36 +6weeks	15	22	
GENDER			0.44
Male	31	36	
Female	20	17	
BIRTH WEIGHT			0.99
1.5-2 Kgs	25	26	
2-2.5 Kgs	26	27	
MEAN CORD BILIRUBIN	3.2	3.6	0.60
MODE OF DELIVERY			0.87
NVD	31	33	
LSCS	20	20	

There was no significant difference between the 2 groups with regard to baseline demographic data like birth weight, gestational age , sex, mode of delivery and mean cord bilirubin.

Table 2 :Peak serum bilirubin levels

Peak serum bilirubin levels	Group 1	Group 2	Total
Jaundice a 48 hours	9	22	31
No jaundice at 48 hours	42	31	73
Total	51	53	104

P value=0.008, Significant.

In group1 , only 9 (18%) babies developed jaundice after 48 hours while in group 2 , 22(41%) babies developed jaundice after 48 hrs. which was statistically significant (p value=0.008) and suggests that the incidence of jaundice was higher in the control group when compared to phenobarbitone group.

Table 3:Duration of phototherapy

No of hours	Group 1	Group 2	Pvalue
24 hrs	0	0	0.05
48 hrs	5	13	
72hrs	3	11	
96hrs	0	0	
120 hrs	0	0	
Total	8	24	

Among group1, out of 8 babies who required phototherapy, 5 babies (62%) required phototherapy for 48 hours, and 3 babies (38%) required phototherapy for 72hours whereas among group2 out of 24 babies, 13 babies (54%) required phototherapy for 48 hours and 11 babies (45%) required phototherapy for 72 hours.

Duration of phototherapy was significantly less in phenobarbitone group compared to control group

Table 4: Need for Exchange Transfusion

Exchange transfusion	Group 1	Group2	P value
Required	0	4	0.045
Not required	51	49	
Total	51	53	

Among group I, none of the babies (0%) required Exchange Transfusion whereas among group II, 4 babies (7%) required Exchange transfusion which is statistically significant. P value <0.05.

DISCUSSION

One hundred and six preterm neonates were included in the study.

In the present study, there was no statistical difference in the demographic data between the two groups with regard to gestational age, weight, gender, mode of delivery and cord bilirubin.

In this study, Gender distribution in group 1 showed 40% female neonates and 60% male neonates while in group 2, 68% were males and 36% were females. A study done by Arya *et al.,* (2004) also showed a similar incidence of 54% males in group 1 and 60 % of males in group 2.

Newborns delivered by NVD in phenobarbitone group were 60% while in control group they were 62%. Similarly newborns delivered by LSCS were 40% and 38% in Phenobarbitone and control groups respectively in this study. A study done by Arya *et al.,* (2004) showed that newborns delivered by NVD were 72% and 73% respectively and newborns delivered by LSCS were 28% and 27% in phenobarbitone and control groups respectively

In our study, mean peak serum bilirubin levels were 9.50 mg/dl and 11.04 mg/dl in phenobarbitone and control group respectively (it was statistically significant) .This was comparable to other studies done by Carswell *et al.,* (1972) which showed mean peak serum bilirubin levels of 9.9mg/dl and12.7mg/dl in phenobarbitone and control group respectively which was statistically significant.

In present study, mean duration of phototherapy was 40±12.2hrs. in phenobarbitone group and 86±24.4 hrs in control group (p value was statistically significant) which was similar to study done by Murki *et al.,* (2005) which showed 56.83±20 hrs. in phenobarbitone group and 63.50±37.2 hrs.in control group.

A study done by Epstein *et al.,* (2002) showed that only 1.5% of the babies required exchange transfusion in phenobarbitone group while 3.3% newborns required exchange transfusion in control group which was similar to the present study showing no babies requiring exchange transfusion in phenobarbitone group and 7% of the babies required exchange transfusion in control group. P=0.04 which is statistically significant.

CONCLUSION

Prophylactic use of phenobarbitone in Late preterm neonates is effective in reducing the peak serum bilirubin and duration of phototherapy and need of phototherapy and exchange transfusion with loading dose of 10 mg/kg orally within 6 hours of life on Day 1 followed by maintenance dose of 5 mg/kg/day OD for the next 4 days of life. Hence prophylactic phenobarbitone seems to be reasonable alternative. However due to paucity of data, further studies are warranted to evaluate adverse effects and neurodevelopmental outcome of this therapy.

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