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Research Article

Role of phenobarbitone in prophylaxis of neonatal jaundice in babies with birth weight 1250-2400 grams

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ABSTRACT

Background: This study was performed to study the role of prophylactic phenobarbitone in preventing neonatal jaundice in babies with birth weight 1250 to 2400 gm and to study the incidence of neonatal jaundice, need for phototherapy and exchange transfusion in babies inspite of giving prophylactic phenobarbitone.
Methods: The babies were randomized into 2 groups. Group I babies were given 10 mg/Kg loading dose of phenobarbitone within 6 hrs of life followed by maintenance dose of 5 mg/Kg/day intravenous from day 2 to day 5. Group II babies were taken as controls, ensuring that both the group babies weighed between 1250gms to 2400gms. 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. Depending on Serum bilirubin levels, according to birth weight, Phototherapy, Exchange Transfusion was opted.
Results: Among group I, out of 51 babies, 8 babies (15.68%) required phototherapy,5 babies (62.5%) required for 2 days and 3 babies (37.5%) required for 3 days,, whereas among group II, out of 53 babies, 24 babies (45.28%) required phototherapy, 13 babies (54.16%%) required for 2 days and 11 babies (45.83%) required for 3 days. Among group I, none of the babies (0%) required Exchange Transfusion whereas among group II, 4 babies (7.54%) required Exchange transfusion.
Conclusions: Incidence of jaundice was 100% among both the groups, No of babies who developed significant jaundice were low in Group I, day of appearance of significant level of jaundice was delayed in Group I, mean age of onset of significant level of jaundice was delayed in preterm babies compared to term babies, need for phototherapy and exchange transfusion were low in Group I.

Keywords: Jaundice, Serum bilirubin level, Phototherapy, Exchange transfusion, Low birth weight

INTRODUCTION

The incidence of neonatal hyperbilirubinemia (>15 mg/dl); NNF India national neonatal perinatal database network 2002-03 report was 3.3% for intramural deliveries and 22.1% for outborns.[1]

In very low birth weight (VLBW) neonates, the incidence of significant jaundice (requiring phototherapy and or exchange transfusion) was 76.6%, with 37.3% requiring an exchange transfusion.[2]

Neonatal hyperbilirubinemia is the most common reason for readmission after early hospital discharge. Concerns regarding jaundice have increased after reports of bilirubin induced brain damage occurring in healthy infants even without hemolysis.

The aim and objectives of the study was to study the role of prophylactic phenobarbitone in preventing neonatal jaundice in babies with birth weight 1250 gm to 2400 gm and to study the incidence of neonatal jaundice, need for phototherapy and exchange transfusion in babies inspite of giving prophylactic phenobarbitone.

METHODS

This study was done on babies born at Dr. PSIMS & RF hospital Chinnautapalli with birth weight between 1250 gms to 2400 gms. The babies were randomized into 2 groups. Group I babies were given 10 mg/Kg loading dose of 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, ensuring that both the group babies weighed between 1250 gms to 2400 gms. Phenobarbitone was given as Intravenous injection not exceeding at a rate of 1 mg/Kg/min to the study group. Total no of babies included was Group I=53 Group II = 53. Informed consent was taken from mother/father/blood relative in local language (Telugu). Babies were 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. 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.

Inclusion criteria

1. Babies with Birth weight less than 2400 gms and greater than 1250 gms.
2. Those Babies not having Jaundice at Birth, Septicaemia and Hydrops Foetalis.
3. Babies who have not received phenobarbitone at birth within 6 hrs. for Seizures.
4. Babies of mothers who were not given any dose of phenobarbitone antenatally.

Exclusion criteria

1. Babies with birth weight less than 1250 Gms and greater than 2400 Gms.
2. Babies having jaundice at birth, septicaemia and Hydrops Foetalis, Asphyxia etc.
3. Babies who have received phenobarbitone at birth within 6 hrs for seizures.
4. Babies of mothers who have received phenobarbitone dose antenatally.
5. Any genetic or metabolic disorder that interferes with phenobarbitone or bilirubin metabolism.

Facilities of equipment available /used in the department

a) Radiant warmer
b) Double surface Phototherapy unit
c) Investigation methods used: Blood grouping, Rh typing, diazo test.

Diazo method of Pearlman and Lee[4]:

Principle

Bilirubin reacts with diazotized sulphanilic acid in acidic medium to form pink coloured azobilirubin with absorbance directly proportional to bilirubin concentration. Direct bilirubin, being water soluble directly reacts in acidic medium however indirect or unconjugated Bilirubin is solubilised using a surfactant and then it reacts similar to direct Bilirubin.

Reagent composition

The following laboratory information were collected and analysed:

Reagent 1 composition:

Surfactant: 100%
HCl: 100 mmol /l
Sulphanilic acid: 5 mmol/l

Reagent 2 composition:

Sulphanilic acid: 10 mmol/l
HCl: 100 mmol/l

Reagent 3 composition:

Sodium nitrite: 144 mmol/l

Sample

Unhemolysed serum or plasma .Avoid haemolysis as it causes falsely low results. Samples should protect from bright light as bilirubin is photo labile. Sample may be stored refrigerated for 3 days or frozen for 1 month.

Factors

Various factors are determined according to wavelength for the calculation of bilirubin levels.

Mix well; incubate for 5 minutes at 37 degree Celsius for Total bilirubin and direct bilirubin. Read absorbance at 546/630 nm against reagent blank.

Assay parameter

Parameter	Bilirubin total	Bilirubin direct
Factor 546/630	23	17

Assay procedure

Total bilirubin/direct bilirubin

Pipette into test tubes marked	Blank	Standard	Test
Working reagent	500 micro liters	500 micro liters	500 micro liters
Distilled water	25 micro liters	-	-
Standard /caliber	-	25 micro liters	-
Test	-	-	25 micro liters

Calculation with factors

Total bilirubin =Absorbance of test x Factor (refer assay parameter) (mg/dl)
Direct bilirubin =Absorbance of test x Factor (refer assay Parameter) (mg/dl)

Linearity

The assay is linear up to 20 mg/dl for higher values it is recommended to dilute the sample with normal saline and repeat the assay. Multiply the result with dilution factor**.**

Notes

Gross haemolysis may cause falsely low results

The colour developed for Total bilirubin is stable for 1 hour when protected from bright light. Reading for Direct Bilirubin should be taken immediately after the incubation is over

The regent and the sample volumes can be altered proportionally to accommodate various autoanalyzer requirements

Does not mouth pipette, if split wash thoroughly with water. The working Total and Direct reagent may be stored at 2-8 degree celsius away from strong light and used for 21 days after preparation for testing patient's sample.

Normal values

Bilirubin total
Adults: 0.1 mg/dl
Infants: 1.2 to 12 mg/dl
Bilirubin direct
Adults and infants: 0 -0.3 mg/dl

Indirect bilirubin was calculated by subtracting direct bilirubin from total bilirubin.

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

During the study period, 53 babies each were enrolled in to two groups. Since one baby expired on 3 rd. day of life due to Aspiration pneumonia and one baby was taken away by her mother from the hospital before the completion of the course of phenobarbitone, among the Group I, only 51 babies were taken into count in Group I.

Total no. of Neonates in Group I – 51
Total no. of Neonates in Group II- 53

Table 1: Sex distribution of neonates.

	Group I	Group II
Boy Babies	20	17
Girl Babies	31	36

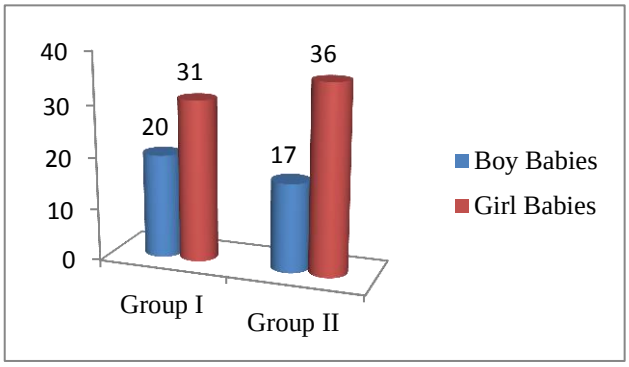

Figure 1: Sex distribution of neonates.

Out of 51 babies in Group I, 20 were boy babies accounting to 39.25%, 31 were girl babies accounting to 60.78%.

Out of 53 babies in Group II, 17 were boy babies (32.07%), 36 were girl babies (67.92%).

Table 2: Distribution according to birth weight.

	Group I	Group II
1250-2000 gms	6	15
2000-2400 gms	45	38

Out of 51 babies in Group I, 6 of them weighed between 1250 to 2000 gms accounting to 11.76%, 45 of them weighed between 2000 to 2400gms accounting to 88.23%.

Out of 53 babies in Group II, 15 of them weighed between 1250 to 2000 gms accounting to 28.23%, 38 of them weighed between 2000 to 2400gms accounting to 71.69%.

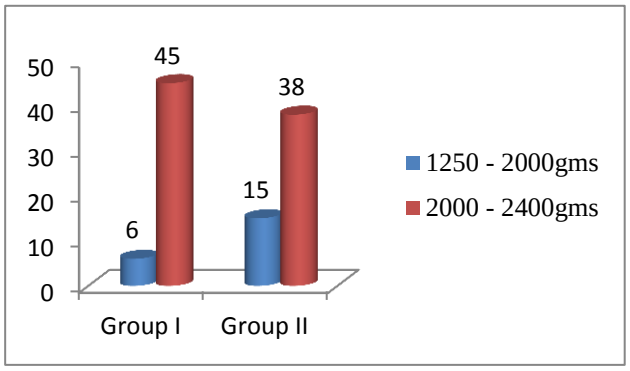

Figure 2: Distribution according to birth weight.

Out of 51 babies in Group I, 14 babies were Preterm accounting to 27.45%, 37 babies were Term IUGR babies accounting to 72.54%.

Out of 53 babies in Group II, 21 babies were Preterm accounting to39.62%, 32 babies were Term IUGR babies accounting to 60.37%.

Hence Term IUGR babies were more in both the groups compared to Preterm babies.

Table 3: Distribution according to gestational age.

	Group I	Group II
Preterm	14	21
Term (IUGR)	37	32

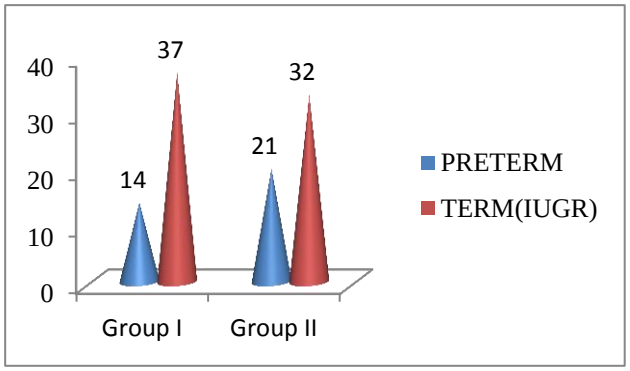

Figure 3: Distribution according to gestational age.

All the babies in both groups developed jaundice. Hence the incidence was 100%.

Out of 51 babies in Group I, 47 babies (92.15%) developed significant level of jaundice. Out of 53 babies in Group II, 52 babies (98.11%) developed significant level of jaundice.

Table 4: Incidence of jaundice.

	Group I	Group II
No. of babies who developed jaundice	51	53
No. of babies who did not develop jaundice	0	0

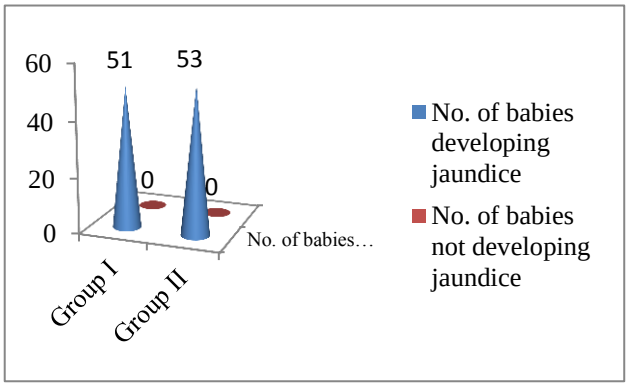

Figure 3: Incidence of jaundice.

Table 5: Total no. of neonates who developed significant level of jaundice.

	Group I	Group II
No. of babies who developed significant level of jaundice	47	52
No. of babies who did not develop significant level of jaundice	4	1

P-Value: 0.9 as per t-test

Out of 47 babies in Group I, significant level of jaundice was noticed in 9 cases (19.14%) on day 2 , 23 babies (48.93%) on day 3, 14 babies (29.78%) on day 4 ,1 baby (2.127%) on day 5 where as In group II ,out of 52 babies, significant level of jaundice was seen in 12 cases (23.07 %) on day 2 , 39 cases (75%) on day 3, 1 case (1.92%) on day 4.

There was no onset of significant level of jaundice on day 1 among either of the groups.

Mean age of onset of significant level of jaundice among Group I babies was 3.19 days, whereas among group II it was 2.79 days.

The mean total serum bilirubin levels on the day of appearance of significant level of jaundice and after 24

hrs. was 9.02 mg/dl and 9.27 mg/dl in Group I whereas 10.30 mg/dl and 10.73 mg/dl in Group II.

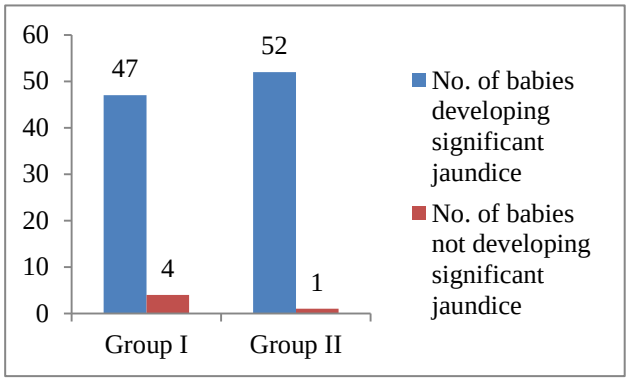

Figure 5: Total no. Of neonates who developed significant level of jaundice.

Table 6: Day of appearance of significant level of jaundice.

	Group I	Group II
Day 1	0	0
Day 2	9	12
Day 3	23	39
Day 4	14	1
Day 5	1	0

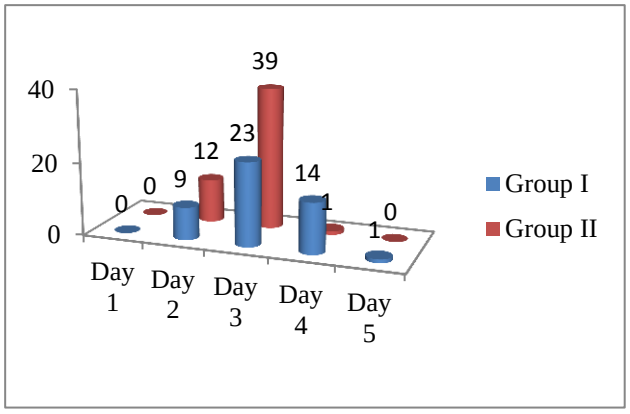

Figure 6: Day of appearance of significant level of jaundice.

Table 7: Mean age of onset of significant level of jaundice.

Group I	Group II
3.19 days	2.79 days

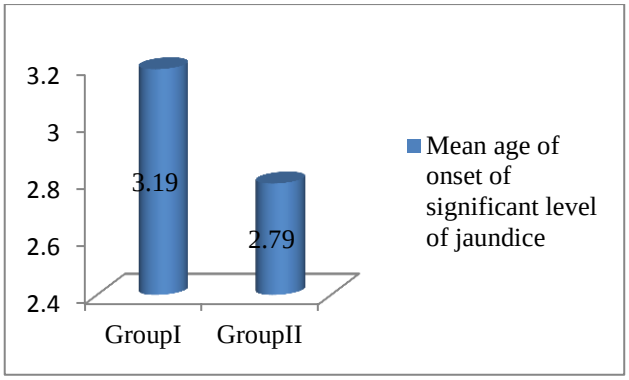

Figure 7: Mean age of onset of significant level of jaundice.

Table 8: Mean serum bilirubin levels.

	Group I	Group II
On the day of onset of Significant level of jaundice (in mg/dl)	9.02	10.30
24 hours later (in mg/dl)	9.27	10.73

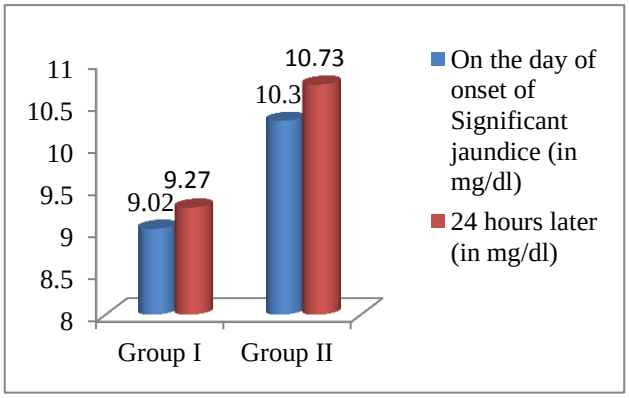

Figure 8: Mean serum bilirubin levels.

Among group I, out of 51 babies, 8 babies (15.68%) required phototherapy, whereas among group II, out of 53 babies, 24 babies (45.28%) required phototherapy.

Table 9: Number of babies requiring phototherapy.

	Group I	Group II
No. of babies requiring phototherapy	8	24
No. of babies not requiring phototherapy	43	29

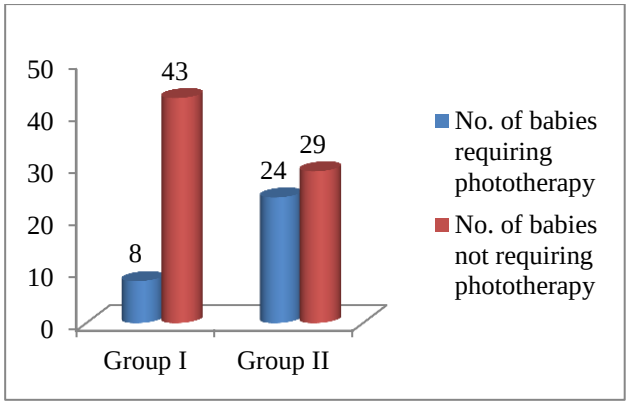

Figure 9: Number of babies requiring phototherapy.

Among group I, out of 8 babies who required phototherapy, 5 babies (62.5%) required for 2 days and 3 babies (37.5%) required for 3 days, whereas among group II, out of 24 babies who required phototherapy, 13 babies (54.16%) required for 2 days and 11 babies (45.83%) required for 3 days.

Table 10: Duration of phototherapy.

	Group I (cases)	Group II (cases)
1 day	0	0
2 days	5	13
3 days	3	11
4 days	0	0
5 days	0	0

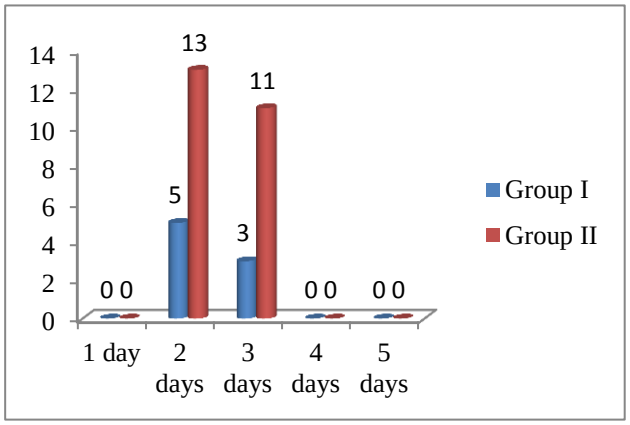

Figure 10: Duration of phototherapy.

Table 11: Mean duration of phototherapy.

Group I	Group II
2.39	2.485

The mean duration of phototherapy requirement was 2.375 days among group I, whereas 2.458 days among group II.

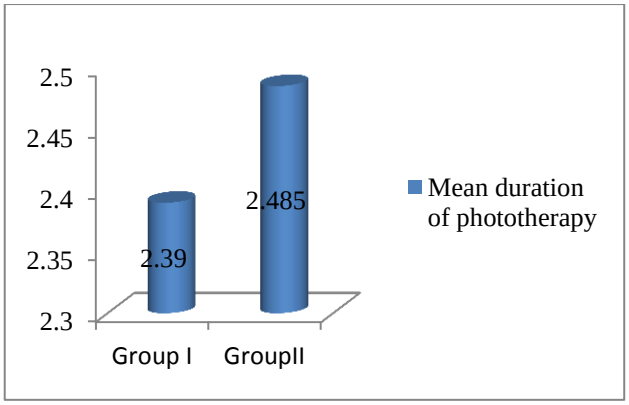

Figure 11: Mean duration of phototherapy.

Among group I, none of the babies (0%) required Exchange Transfusion whereas among group II, 4 babies (7.54%) required Exchange transfusion.

Table 12: Number Of babies requiring exchange transfusion.

	Group I	Group II
No. of babies who required Exchange transfusion	0	4
No. of babies who did not require Exchange transfusion	51	49

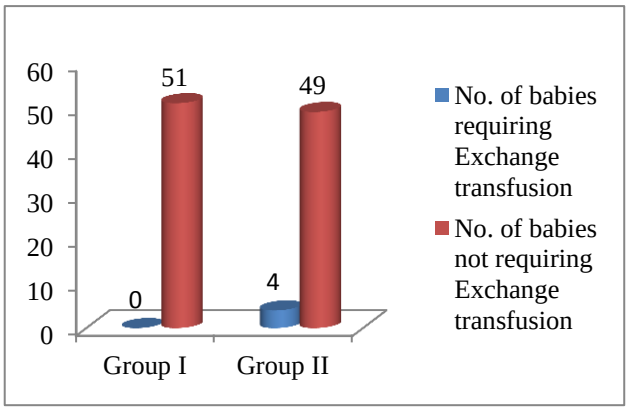

Figure 12: Number Of babies requiring exchange transfusion.

DISCUSSION

During our study period, 53 babies each were enrolled into 2 groups, Group I- (who received Phenobarbitone), Group II-(who did not receive phenobarbitone). Since 1 baby expired on day 3 of life and 1 baby was taken by her mother before the completion of course of phenobarbitone, only 51 babies were taken into account into Group I against Group II which were 53. Babies

were taken randomly into Group I and Group II ensuring that the birth weight was between 1250 to 2400 g.

Table 13: Effect of phenobarbitone on need for phototherapy and exchange transfusion.

	Group I	Group II	Group I vs. Group II P - value
No. of babies who required phototherapy	8	24	P<0.05
Mean duration of Phototherapy	2.375 days	2.458 days	P>0.05
No. of babies who required Exchange transfusion	0	4	P<0.05

In our study, we found that, the mean serum bilirubin levels were low in babies who were given phenobarbitone compared to Group II babies. The need for phototherapy was lower in the phenobarbitone treated group (only 8 babies (15.68%) out of 51 required phototherapy whereas, among Group II babies, 24 out of 53 babies (45.28%) required phototherapy) with a mean duration requirement of 2.375 days among group I, whereas 2.458 days among group II. Similarly the need for exchange transfusion was also lower in the phenobarbitone treated group (none of them among Group I required Exchange transfusion against 4 babies in Group II). However, incidence of jaundice was 100% (jaundice confined to face) in both the groups with 47 babies (92.15%) developing significant level of jaundice in Group I and 52 babies (98.11%) developing significant level of jaundice in Group II.

Epstein et al evaluated the effect of perinatal phenobarbitone 10 mg/kg followed by 2.5 mg/kg twice daily for 5 days in 280 ventilated babies (128 cases and 118 controls) with birth weight < 1750 g. They found TSB of >10 g/dl in 7% of babies who were treated with phenobarbitone against 13.6% of babies who were not given the drug.[5] Valdivieso et al observed similar results in their study6. Rajesh et al evaluated the effect of postnatal phenobarbitone in 150 babies wherein, they found that phenobarbitone was effective in lowering serum bilirubin levels.[7] Chawla D evaluated the effect of phenobarbitone for prevention and treatment of unconjugated hyperbilirubinemia in preterm infants, it was observed that peak serum bilirubin levels was lower in phenobarbitone group, duration of phototherapy was shorter, need for Exchange transfusion was also reduced in the phenobarbitone group.[8]

In our study, we found similar kind of results suggesting that phenobarbitone can be used as a prophylactic drug in bringing down the serum bilirubin levels among low birth weight babies which would further decrease the need of phototherapy and Exchange transfusion which was statistically significant, although duration of requirement of phototherapy did not vary much with insignificant statistical value.

There were few limitations in our study, the serum bilirubin levels were not repeated as frequently as required due to large blood sample size required for test. Serum bilirubin levels were taken, one on the day of onset of significant level of jaundice (up to trunk and beyond clinically) and the other 24 hrs later. If the babies required phototherapy, then serum bilirubin levels were monitored every 24hrs, till the baby was taken off from phototherapy unit. Most of the babies could not be followed for more than 5 days of age as mother was discharged by 5 days. Hence the study was limited only to first 5 days of life.

CONCLUSION

Among the neonatal age group, jaundice remains one of the main treatable problem 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 Phenobarbitone is used prophylactically with a loading dose of 10mg/kg iv within 6 hrs of life on Day 1 followed by maintenance dose of 5 mg/kg/day OD for the next 4 days of life.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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