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Study on Effectiveness of Adding Phenobarbitone to Conventional Therapy in Preterm Neonates with Unconjugated Hyperbiliurubinemia in Comparison with Conventional Therapy

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Authors' contributions

Authors are contributed in this study as well as the direction of corresponding author and with the support of the department of pediatrics.

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ABSTRACT

Aim: To assess the effectiveness of adding prophylactic phenobarbitone to conventional therapy in preterm neonatal jaundice in reducing the incidence, peak serum bilirubin levels, duration and need of Phototherapy in the treatment and time taken for complete clearance of jaundice.
Background: Neonatal unconjugated hyperbilirubinemia is a life threatening. The conventional therapy is a long time process & some of neonate cannot tolerate for long-term phototherapy. Adding of phenobarbitone to the conventional therapy gives better results.
Study Design: A prospective observational study in comparison with retrospective data & it was conducted in the 6 months period i.e., from February 2015 to July 2015 at GGH guntur.

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Methodology: In our study a 50 patients of both sex under prospective group to whom oral phenobarbitone was given 3 mg/kg/day and 50 patient case sheets data was analyzed under retrospective group. Preterm neonates admitted in neonatal intensive care unit with body weight >1 kg were included in the study and neonates who are on ventilator and birth weight <1kg were excluded from the study. Effectiveness of phenobarbitone was assessed by comparing prospective group with retrospective group using paired t-test in SPSS software.
Results and Discussion: Peak total serum bilirubine values, Duration of phototherapy, Duration of hospital stay were less in prospective group as compare with retrospective group were statistically significant. Peak TSB value was observed earlier in prospective group than in retrospective group and there was no requirement of exchange transfusion in prospective group. There was no requirement of phototherapy in 18 out of 50 neonates in prospective group.
Conclusion: We conclude that prophylactic oral phenobarbitone dose of 3 mg/kg/day ± phototherapy is effective in healthy preterm neonates in the treatment of unconjugated hyperbilirubinemia and the beneficial affect was more in Low birth weight neonates than in very low birth weight neonates as compare with phototherapy alone.

Keywords: Phenobarbitone; phototherapy; serum bilirubin; preterm neonates with low birth weight; very low birth weight.

1. INTRODUCTION

Jaundice is the most common morbidity in the first week of life, occurring in 60% of term and 80% of preterm newborn. Jaundice is the most common cause of readmission after discharge from birth hospitalization. Approximately 5-10% of them have clinically significant jaundice that requires treatment to lower serum bilirubin levels in order to prevent neurotoxicity.

1.1 Therapeutic Options

There are many treatment options, but the phototherapy (PTx) remains the mainstay of treating hyperbilirubinemia in neonates. PTx is highly effective and carries an excellent safety track record of over 50 years. It acts by converting insoluble bilirubin (unconjugated) into soluble isomers that can be excreted in urine and feces. Many review articles [1] have provided detailed discussion on phototherapy related issues [2-3]. The bilirubin molecule isomerizes to harmless forms under blue-green light (460 to 490 nm); and the light sources having high irradiance in this particular wavelength range are more effective than the others. While exposing body to phototherapy, monitor temperature of the baby every 2 to 4 hr & measure TSB level every 12 to 24 hours. Discontinue PTx once two TSB values 12 hr apart fall below current age specific cut offs. The infant should be monitored clinically for rebound bilirubin rise within 24 hours after stopping phototherapy for babies with hemolytic disorders. However there are some complicated risks like photosensitivity, erythropoietic porphyria, intestinal hypermotility, diarrhea [4] are common with phototherapy and exchange transfusion are difficult and costly to maintain, hence a form of prophylactic phenobarbotone therapy [5], which would prevent the rise of TSB to dangerous levels, would be a better option in VLBW and LBW babies.

Exchange transfusion- Double volume exchange transfusion (DVET) should be performed if the TSB levels reach to age specific cut-off for exchange transfusion or the infant shows signs of bilirubin encephalopathy irrespective of TSB levels.

Intravenous Immunoglobulins (Ivig)-IVIG reduces hemolysis and production of jaundice in isoimmune hemolytic anemia (Rh isoimmunisation and ABO incompatibility) and thereby reduces the need for phototherapy and exchange transfusion. **I**V Hydration can also be considered with 0.9% NS [6].

1.1.1 Pharmacological agents

1.1.1.1 Phenobarbitone

Phenobarbitone, by inducing the activity of uridine-di-phosphate glucuronyl transferase enzyme, can blunt the bilirubin rise seen in neonatal period. By decreasing the peak serum bilirubin or duration of hyperbilirubinemia, phenobarbitone may decrease the need of exchange transfusion and duration of phototherapy [7]. The dose of phenobarbitone in prophylaxis for neonatal jaundice was 3-8 mg/kg.

1.1.1.2 Clofibrate

Glucuronyl transferase activity can be increased with administration of clofibrate [8].

1.1.1.3 Metalloporphyrins

There is now evidence that hyperbilirubinemia can be effectively prevented or treated with tin-mesoporphyrin, a drug that inhibits the production of heme oxygenase [9-12].

1.1.1.4 Ursodeoxycholic acid

UDCA may improve bile flow and lower bilirubin concentrations [13-14].

2. METHODOLOGY

2.1 Study Design

It was a prospective observational study, comparison with retrospective data.

2.2 Study Period

The study was ethically approved & conducted at GGH Guntur. The duration of study was 6 months i.e., from February 2015 to July 2015.

2.3 Study Population

Fifty Patients of either sex under prospective group & 50 patient case sheets data was analysed under retrospective group.

2.4 Inclusion Criteria

Preterm neonates admitted in neonatal intensive care unit from February 2015 to July 2015 & preterm Neonates whose Body weight is >1 kg.

2.5 Exclusion Criteria

Very sick newborns & are on ventilator. Preterm neonates born with Extremely Low Body Weight (Elbw:<1 kg), because phenobarbitone can cause severe respiratory distress in ELBW patients

2.6 Administration of Phenobarbitone

Phenobarbitone was given within first 12 hrs of life. It was given at a dose of 3 mg/kg/day. Syrup formulation was used i.e, GARDINAL manufactured by Nicholas Piramal India limited (NPIL).

Each 5 ml of syrup contains 20 mg of phenobarbitone.NG-tube / Ryle's tube was used for oral administration. It was administered from day1-day 5 of life.

2.7 Measurement of TSB (Total Serum Bilirubin)

TSB was measured daily (24hrly) using bilirubinometer. i.e Bilichek-A noninvasive bilirubin analyzer

2.8 Statistical Analysis

Paired t-test using SPSS.

3. RESULTS AND DISCUSSION

In our study the baseline characteristics like birth weight, gestational age, and weight wise distribution, male to female ratio were similar except for a higher number of male babies in prospective group. Mean peak TSB (Total serum bilirubin) value in retrospective VLBW (Very low birth weight) babies was 16.80(±1.89) and in prospective VLBW babies was 10.73(±2.19). Mean peak TSB value in retrospective LBW (Low birth weight) babies was 17.32(±1.34) and in prospective LBW babies was 10.86(±2.40) (Table no 1). This shows that prophylactic phenobarbitone was effective in decreasing peak TSB in preterm neonates. It was found that phenobarbitone was more effective in LBW than in VLBW babies in decreasing peak TSB value. But in both LBW and VLBW babies the difference in prospective and retrospective groups was statistically significant ($P<0.05$). F. Carswell et al. [15] carried out similar study using phenobarbitone in a dose of 8 mg/kg per day and reported that there was a significantly lower peak bilirubin level found in the treated group. Anwar M et al. [16] evaluated the effect of phenobarbitone 20 mg/kg followed by 5 mg/kg for one week in 57 infants (28 cases, 29 controls) with birth weight below 1500 g. Peak TSB was 7.9(±1.8) mg/dl in treated group and 8.6(±2.2) mg/dl in the control group.

We observed that the decreased phototherapy requirements in phenobarbitone treated babies that are in the prospective group. Phototherapy was required in 32(64%) and 50(100%) babies in prospective and retrospective group respectively. Rajesh kumar et al. [5] conducted a study in which infants are divided in to 3 groups with 50 in each group. They reported that number of babies requiring phototherapy were 35(70%), 32(64%), 43(86%) respectively in 10 mg/kg followed by 5

mg/kg for 4 days; 5 mg/kg for 5 days; control group.

Mean duration of phototherapy (in hours) in retrospective VLBW babies was 47.72(±11.44) and in prospective VLBW babies was 27.64(±8.31) and that in retrospective LBW babies was 50(±15.05) and in prospective LBW babies was 24.66(±10.6) (Table no 2 & Fig. no 1). There was no requirement of phototherapy in 36% of prospective babies of which 5(0.28%) and 13(72.23%) were VLBW and LBW babies respectively. This shows that prophylactic phenobarbitone was effective in decreasing the duration of phototherapy in preterm neonates. It was found that phenobarbitone was more effective in LBW than in VLBW babies in decreasing phototherapy duration. But in both LBW and VLBW babies the difference in prospective and retrospective groups was statistically significant.

Table 1. Baseline characteristics

Characteristic	Prospective (no:50)		Retrospective (no:50)	
Gender-no & %				
Male	26 (52%)		25 (50%)	
Female	24 (48%)		25 (50%)	
Weight category- no & %				
Average Birth weight (Kgs)	1.55±0.34		1.57±0.35	
ELBW (Extremely low birth weight) <1 kg	00 (0%)		00 (0%)	
VLBW (very low birth weight)1.1 kg to1.49 kg	22 (44%)		22 (44%)	
LBW (Low birth weight)1.5 kg to 2.49 kg	28 (56%)		28 (56%)	
NBW (Normal birth weight) >2.5 kg	00 (0%)		00 (0%)	
Gestational age category-no & %				
Average Gestational age(weeks)	30.78±2.69		30.78±2.69	
Weight category	**VLBW (n=22)**	**LBW (n=28)**	**VLBW (n=22)**	**LBW (n=28)**
Extra preterm (<28 weeks)	3 (13.63%)	1 (3.57%)	2 (9.09%)	2 (7.14%)
Very preterm (28 to < 32 weeks)	16 (72.72%)	18 (64.28%)	13 (59.09%)	21 (75%)
Late preterm (32 to < 37 weeks)	3 (13.63%)	9 (32.14%)	7 (31.81)	5 (17.85)

Table 2. Efficacy characteristics

Characteristic	Prospective (no:50)	Retrospective (no:50)
Peak TSB values (mg/dl)		
VLBW	10.73±2.19	16.80±1.89
LBW	10.86±2.40	17.32±1.34
Requirement of phototherapy-no & %		
Phototherapy required subjects	32 (64%)	50 (100%)
Not required subjects (VLBW-5 & LBW-13= Total 18)	18 (36%)	00 (0%)
Duration of Phototherapy (hrs)	22 (44%)	22 (44%)
VLBW	27.64±8.31	47.72±11.44
LBW	24.66±10.60	50.00±15.05
Duration of hospital stay (days)		
VLBW	14.40±4.81	17.00±4.17
LBW	11.07±3.60	14.2±4.02
Exchange transfusion required-no & %		
Transfusion required subjects	00 (0%)	Vlbw-2 & Lbw-1 =3 (6%)
Transfusion not required subjects	50 (100%)	47 (96%)

Mean duration of hospital stay (in days) in retrospective VLBW babies was 17.0(±4.17) and in prospective VLBW babies was 14.4(±4.81) and that in retrospective LBW babies was 14.2(±4.02) and in prospective LBW babies was 11.07(±3.6). This shows that prophylactic phenobarbitone was effective in decreasing mean duration of hospital stay but the difference between prospective and retrospective groups failed to reach statistical significance. Day on which peak TSB observed in retrospective VLBW babies was day 5(±0.81) and in prospective VLBW babies was day 4.8(±1.14) and that in retrospective LBW babies was day 4.9(±0.78) and in prospective LBW babies was day 4.5(±1.42) (Table no 3). It was observed that peak was observed earlier in phenobarbitone treated group. But the difference failed to reach statistical significance.

In our study there was no requirement of exchange transfusion in prospective group where as 3 babies (6%) in retrospective group required exchange transfusion. M. Vest. E. Signer et al. [17] evaluated the effectiveness of phenobarbitone by giving dose varied between 1 mg and 5 mg according to weight. They observed that 1 exchange transfusion had to be performed in the treated and 11 in the control group. D. Sinniah et al. [18] reported that in their study exchange transfusions were required in 6 of the 32 control cases and in none of the 28 treated cases.

Table 3. Comparison of TSB values (day 1 to day 5)

Day	Prospective TSB (mg/dl)	Retrospectives TSB (mg/dl)
Day1	5.9	7.2
Day2	8.2	11.3
Day3	9.5	14.6
Day4	9.3	12.1
Day5	7.4	10.2

Out of all phenobarbitone treated cases we found an ADR (adverse drug reaction) of immediate vomiting after administration of drug in one case. No significant adverse effects of phenobarbitone were noted which is consistant with other studies conducted by Ved Bhushan Arya et al. [19] and Anneliese dortmann et al. [20]

In a nutshell, the oral phaenobarbitone 3 mg/kg/day with or without phototherapy was effectively reduces the hyper bilirubinemia in neonatal jaundice and the adopted method i.e oral oral phaenobarbitone 3 mg/kg/day / 5 days very low as compare with other literatures.

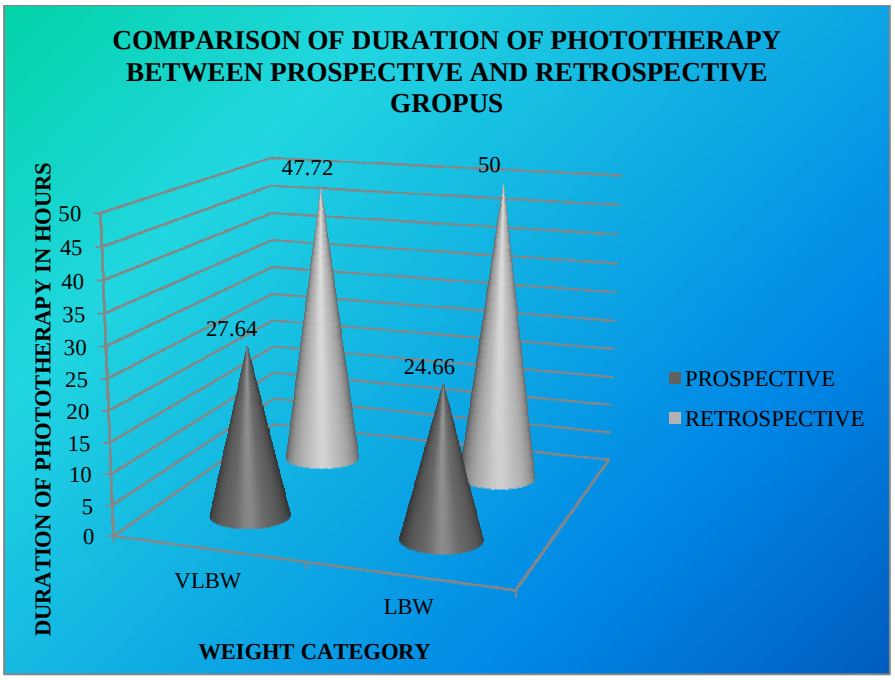

Fig. 1. Comparison of duration of phototherapy between prospective and retrospective groups

4. CONCLUSION

By observing this study we conclude that oral phenobarbitone 3 mg/kg/day for 5 days were effectively reduced the peak serum bilirubin levels & also decreased the duration of Phototherapy in preterm babies with VLBW and LBW neonates. No need of exchange transfusion in phenobarbitone treated group. The duration of hospital stay was also decreased. Hence prophylactic phenobarbitone seems to be a cheap alternative. More knowledge of the effects seems to be desirable before phenobarbitone therapy of hyperbilirubinemia in premature babies can be recommended.

5. STUDY LIMITATIONS

Long term follow up studies of 5-7 years have to monitor & establish to evaluate the safety of its short term use in the neonatal period.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Patient data collection form

Mother name:

Gestational Age at birth of preterm:

Gender: Body weight:

IP number Date of admission:

Date of discharge: Duration of hospital stay:

Day on which hyperbilirubinemia is evident:

Peak serum bilirubun level noted during the hospital stay:

Time taken for complete clearance of jaundice:

Duration of phototherapy required during treatment (in hours):

Investigations:

On admission	During treatment	At discharge

Treatment regimen: Treatment related problems (If any):

Phenobarbitone given:

Yes/no

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