Original Article

Efficacy of Oral Phenobarbitone in Term "At Risk" Neonates in Decreasing Neonatal Hyperbilirubinemia: A Randomized Double-blinded, Placebo Controlled Trial

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*Objective: To evaluate the efficacy of oral phenobarbitone in "at risk " term neonates (with high cord bilirubin) in decreasing hyperbilirubinemia. **Design:** Double blind, placebo-control, randomized trial. **Setting:** Tertiary level neonatal unit. **Outcome:** Primary-hyperbilirubinemia defined as total serum bilirubin (TSB) greater than 13 mg/dL. Secondary–TSB at 72 ± 12 hr, need for phototherapy or exchange transfusion and side effects of phenobarbitone therapy. **Methods:** All consecutively born term healthy neonates with cord bilirubin $\geq$2.5 mg/dL were randomly assigned to receive either phenobarbitone (n = 37) or placebo (n = 38) after obtaining informed consent. Phenobarbitone was administered orally (5 mg/kg/day) for 3 days starting within 12 hours of birth. The neonates were followed up till seven days of life. TSB was estimated in neonates who developed jaundice with clinically assessed level of 8-10 mg/dL and at 72 ± 12 hours of age in 55 neonates. **Results:** The baseline characteristics were similar in two groups. There was no significant reduction in incidence of hyperbilirubinemia in phenobarbitone group compared to in placebo group (6/37 (16.2%) versus 13/38 (34.3%); RR 0.47, 95% confidence interval: 0.20-1.11; risk difference: -18.1%, 95% confidence interval: -39.5 to 3.3%). However TSB at 72 ± 12 hours in phenobarbitone group (mean ± S.D: 10.0 ± 3.7 mg/dL) was significantly lesser than in placebo group (mean ± S.D: 12.3 ± 3.3 mg/dL) (difference of means: –2.3 mg/dL, 95% confidence interval: –3.9 to –0.7 mg/dl, P = 0.018). No significant difference with respect to need for treatment was observed in two groups. No significant adverse effects of phenobarbitone were noted. **Conclusions:** Prophylactic phenobarbitone is not helpful in reducing the incidence of hyper-bilirubinemia in 'at risk' term neonates.*

Keywords: *Hyperbilirubinemia, Newborn, Phenobarbitone.*

HYPERBILIRUBINEMIA is a common problem in early neonatal period(1). It can be associated with neurotoxicity, thus is a cause for anxiety in parents as well as in physicians. Occurrence of hyperbilirubinemia results in the prolonged hospital stay with increased cost(2). With early discharge practice, neonatal hyperbilirubinemia has become an important cause of readmission(3). Cord bilirubin levels have been found to be a good predictor for development of subsequent hyperbilirubinemia(4,5). In a previous study from our center (unpublished information), neonates with cord bilirubin $\geq$2.5 mg/dL were

found to be at a higher risk for subsequent hyperbilirubinemia.

Phenobarbitone is shown to be safe and effective in lowering the serum bilirubin in neonates at varying doses(6-11). However, efficacy of phenobarbitone has not been evaluated in decreasing hyperbilirubinemia in neonates at a greater risk of hyperbili-rubinemia. Present study evaluated the efficacy of prophylactic oral phenobarbitone in term "at risk" neonates (with cord bilirubin >2.5 mg/dL) in reducing the incidence of hyperbilirubinemia.

Subjects and Methods

The study was a prospective, double blinded, placebo controlled, randomized trial conducted at All India Institute of Medical Sciences, New Delhi between October 2000 and November 2001. Ethical Committee of the Institute approved the study protocol. All healthy term neonates (*a*) with cord bilirubin ³ 2.5 mg/dL (*b*) Rh-compatible with their mothers, (*c*) appropriate for dates, and (*d*) having a Apgar score ³ 7/10 at 1 minute were included. Neonates with major malformations or significant illness requiring NICU admission and whose mothers had jaundice during pregnancy were excluded.

Cord bilirubin estimation

Cord bilirubin level was estimated in 898 neonates. The blood sample was collected in microcapillaries free flowing from the cord and centrifuged at 14000 rpm for five minutes. Bilirubin estimation was performed in duplicate by twin beam method (540 and 465 nm wavelengths) using spectrophotometric principle (Ginveri, Italy). The equipment was standardized periodically. Blood grouping and Rh-typing of the neonates of mothers with blood group "O" was also performed from the cord blood sample. Cord TSB ³ 2.5 mg/dL was present in 76 (8.5%) neonates.

Sample size calculation and randomization

Incidence of hyperbilirubinemia was taken as 70% when cord bilirubin is ³ 2.5 mg/dL(6). For a 50% reduction in incidence, with alpha value of 0.05 and beta of 0.2, a sample size of 36 subjects in each group was needed. Stratified randomization was done for neonates with respect to ABO incompatibility with their mothers using computer-generated numbers.

Intervention

Phenobarbitone in a dose of 5 mg/kg/day mixed in glucose powder was orally administered to one group (phenobarbitone group) while glucose powder alone in same quantity was orally administered to other group (placebo group) dissolved in the freshly expressed own mother's milk. The pheno-barbitone or placebo administration was initiated within 12 hours of birth, once a day for a total of three days (total 3 doses). The drug and placebo were similar in color, quantity and taste and were packed in sachets labeled 'A' and 'B'.

Follow up

All enrolled neonates were monitored for the development of clinical jaundice twice a day. At the initiation of study, it was planned to perform the serum bilirubin estimation once baby developed significant jaundice clinically. After enrolling 20 babies, as only a few neonates developed that level of jaundice, it was decided to estimate TSB at 72 ± 12 hours in subsequently enrolled babies. If TSB at 72 ± 12 hours was below 10 mg/dL, the mothers were asked to report on day seven of life for the assessment of jaundice and general well being of the baby. Whereas, the babies with TSB at 72 routinely hours more than 10 mg/dL and whose clinical jaundice had been increasing over last 24 hours were kept in the

hospital. Further assessments were indivi-dualized. Many babies stayed in the hospital for maternal reasons. The babies were weighed again (on the same weighing scale on which the birth weight was recorded) at 72 ± 12 hours of age. Neonates were also monitored for side effects of oral phenobarbitone such as excessive sleepiness, decreased feeding, dehydration and neurological dysfunction.

Once hyperbilirubinemia developed, other relevant investigations such as packed cell volume, reticulocyte count, peripheral blood smear for evidence of hemolysis, direct Coomb's test and glucose-6-phosphate de-hydrogenase (G6PD) assay were performed. Neonates with hyperbilirubinemia were managed as per unit protocol. Exchange transfusion was performed at TSB of ³ 20 mg/dL in hemolytic and at TSB of ³ 25 mg/dL in non-hemolytic setting.

Outcome variable

Primary outcome variable was hyper-bilirubinemia (TSB > 13 mg/dL). Secondary outcome variables were TSB at 72 ± 12 hours, need for phototherapy or exchange trans-fusion, and side effects of phenobarbitone therapy.

Statistical analysis

Data were collected using predesigned and pretested proforma. Chi square test and Fisher exact test were used for categorial and two-tailed student *t*-test for continuous variables. The data was analyzed by statistical software EPI-Info version-6. The statistical signi-ficance was taken at a probability of less than 5%.

Results

Of seventy-six eligible neonates, seventy-five were enrolled. One baby could not be enrolled because of refusal to participate. Complete follow up was present in all neonates. Baseline characteristics in two groups were similar (*Table I*). No baby in either group had cephalhematoma or subgaleal bleed.

Hyperbilirubinemia (TSB >13 mg/dL) occurred in 6/37 (16.2%) subjects in phenobarbitone group compared to 13/38 (34.3%) in placebo group (*Table II*). There was no significant reduction in incidence of hyperbilirubinemia in phenobarbitone group (Relative risk 0.47, 95% confidence interval: 0.20-1.11 risk difference: –18.1%, 95% confidence interval: –39.5 to 3.3%, P = 0.07) (*Table II*). However, TSB at 72 ± 12 hours in phenobarbitone group (Mean ± S.D: 10.0 ± 3.7 mg/dL) was significantly lower than in placebo group (Mean ± S.D: 12.3 ± 3.3 mg/dL) (difference of means: –2.3 mg/dL, 95% confidence interval: –0.7 to –3.9 mg/dL, P = 0.018). There was no significant difference in number of neonates requiring phototherapy and none required exchange transfusion in either group. None of the babies developing hyperbilirubinemia was G6PD deficient. A higher proportion of neonates in pheno-barbitone group was drowsy and passed lesser urine compared to in placebo group. However, weight loss was not significantly different in two groups.

Discussion

Phenobarbitone decreases the jaundice by promoting the excretion of bilirubin by enhancing glucuronidation through induction of hepatic microsomal enzymes and producing more receptor protein for bilirubin uptake(12). There are a number of studies that have used phenobarbitone for this purpose in different dosage ranging from 2.5 mg once a day for 3 days to a single dose of 12 mg/kg(6-11). The present study is different from previous studies in a number of ways. Firstly, a lower dose of phenobarbitone (5 mg/kg orally for

TABLE I–*Baseline Characteristics of the Two Groups*

Baseline characteristics	Phenobarbitone group (n = 37)	Placebo group (n = 38)
Males*	20 (54.1%)	23 (60.5%)
Gestation (weeks)†	38.8 ± 1.1	38.7 ± 1.2
Birth weight (Kg)‡	2.930 ± 0.288	2.841 ± 0.258
ABO setting *‡	5 (13.5%)	4 (10.5%)
Method of delivery*		
Vaginal	27 (72.9%)	28 (73.7%)
Cesarean section	10 (27.1%)	10 (26.3%)
Oxytocin use*	21 (56.7%)	21 (55.3%)
Cord bilirubin (mg/dL)	2.75 ± 0.26	2.76 ± 0.27

* No. (%); † Mean ± S.D. ;

‡ "O" blood group mother with either "A" or "B" blood group neonate (with or without evidence of hemolysis).

TABLE II–*Incidence of hyperbilirubinemia and other study outcomes in two groups*

Outcome	Phenobarbitone group (n = 37)	Placebo group (n = 38)	p
Hyperbilirubinemia* † (TSB>13 mg%)	6 (16.2%)	13(34.3%)	0.07
TSB at 72 ± 12 hr ‡ §	10.0 ± 3.7 mg/dL	12.3 ± 3.3 mg/dL	0.01
Need for phototherapy*	2 (5.4%)	4 (10.5%)	0.69
Cumulative weight loss at 72 hours of age (%)‡	5.5 ± 2.49	4.85 ± 2.86	0.29
Excessive sleepiness*	5 (13.5%)	1 (2.6%)	0.09

* No (%)

† RR: 0.47, 95% confidence interval: 0.2-1.11; risk difference: 18.1%, 95% confidence interval: –39.5% to 3.3%

‡ ± Mean ± SD

§ TSB estimated in 30/38 neonates in phenobarbitone group and 25/37 neonates in placebo group. Difference of means: –2.3 mg/dL, 95% confidence interval: –0.7 to -3.9 mg/dL, p = 0.0l.

3 days) was used because higher dose has been shown to be associated with adverse effects(7). Secondly, phenobarbitone was administered in a select group of neonates at greater risk of hyperbilirubinemia. By this approach, the intervention was required in lesser number of neonates. With availability of prediction tests for subsequent hyper-bilirubinemia in future, this type of selective approach may result in significant cost saving.

Prophylactic administration of pheno-barbitone has shown variable effects in

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Key Message

- A multicentric study is needed to determine the efficacy of oral phenobarbitone prophylaxis in term at risk neonates for reducing hyperbilirubinemia.

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reducing hyperbilirubinemia in different studies(6-11). In a previous trial at our center enrolling 130 subjects, a significant reduction in the mean total and unconjugated bilirubin was noted in neonates receiving pheno-barbitone(8). In a controlled trial, prophylactic phenobarbitone administration showed significant reduction of the incidence of hyper-bilirubinemia and mean TSB(6). Similar effects were shown in preterm babies also(10). In contrast, in a randomized controlled trial, Ramboer et al(11) did not find any significant difference in mean TSB in normal birth weight as well as low birth weight neonates with prophylactic phenobarbitone therapy.

Phenobarbitone administration did not demonstrate any reduction in incidence of hyperbilirubinemia. Hyperbilirubinemia developed in lesser number of babies in the present study than was anticipated at the inception of the study. The present study lacked adequate power to detect a meaningful reduction in incidence of hyperbilirubinemia by phenobarbitone treatment in this setting. However, prophylactic phenobarbitone resulted in reduction in TSB as 72 ± 12 hours of age in present study.

The sedative effect of phenobarbitone as noticed by us has been reported by others also(11). Apnea and cyanotic spells have also been reported with higher doses of phenobarbitone and was more commonly seen in low birth weight infants(6) but these side effects were not observed in the present study.

In conclusion, oral prophylactic pheno-barbitone therapy in term 'at risk' neonates does not decrease the incidence of hyper-bilirubinemia although TSB levels at 72 ± 12 hours were noted to be less. The efficacy of prophylactic phenobarbitone in 'at risk' neonate needs to be tested in a large multicentric trial with adequate power.

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