RESEARCH PAPER

Phenobarbitone for Prevention and Treatment of Unconjugated Hyperbilirubinemia in Preterm Neonates: *A Systematic Review and Meta-analysis*

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Objective: To evaluate the role of phenobarbitone in the management of unconjugated hyperbilirubinemia during first two weeks of life in preterm neonates.

Design: Meta-analysis.

Methods: A study was eligible for inclusion in the meta-analysis if it randomized preterm neonates into control and treatment groups. Standard search strategy of the Cochrane Neonatal Review Group was used. For categorical and continuous data the odds ratio (OR) and weighted mean difference (WMD) were calculated, respectively. 95% confidence intervals were used and a fixed effects model was assumed for the meta-analysis.

Main outcome measures: Peak serum bilirubin, duration of phototherapy, need of phototherapy and exchange transfusion, neurodevelopmental outcome and adverse effects.

Results: A total of 19 potentially relevant studies were identified. Of these, 3 studies (497 neonates) were included in the meta-analysis. Peak serum bilirubin was significantly lower in phenobarbitone group (mean difference: –1.78 mg/dL, 95% CI: –2.29 to –1.27). Duration of phototherapy was shorter (mean difference: –14.75 h, 95% CI: –26.67 to –2.83). Need of phototherapy (OR: 0.33, 95% CI: 0.13 to 0.81) and exchange transfusion (OR: 0.30, 95% CI: 0.14 to 0.64) were also reduced in phenobarbitone group.

Conclusion: Phenobarbitone reduces peak serum bilirubin, duration and need of phototherapy and need of exchange transfusion in preterm very low birthweight neonates. Further studies are warranted to evaluate adverse effects and neurodevelopmental outcome.

Keywords: *Neonate, Jaundice, Phenobarbitone, Preterm, Prevention.*

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High incidence of neonatal jaundice requiring therapeutic intervention in preterm neonates has been well documented. Among seven hospitals of National Institute of Child Health and Human Development (NICHD) Neonatal Intensive Care Network, 77% of very low birthweight (VLBW) babies received phototherapy and 4% required exchange transfusion for neonatal hyperbilirubinemia(1). Hyperbilirubi-nemia was found to be the most common morbidity (65%) among 137 extremely low birthweight neonates born over a period of 7 years in a tertiary care unit of India(2). In an analysis of 551 cases of neonatal jaundice, 162 (65.6%) of 247 VLBW babies developed significant jaundice(3). Other Indian studies have also found similar high rates of jaundice in VLBW neonates(4). Preterm babies are also probably at higher risk of bilirubin-induced brain damage because of lower serum albumin concentration with weaker bilirubin binding sites and more permeable blood-brain barrier(5).

Accompanying Editorial: Pages 396-397.

Management of hyperbilirubinemia in preterm

neonates with phototherapy causes increased insensible water loss, increased incidence of patent ductus arteriosus and temperature instability(6,7). Exchange transfusion also has significant morbidity and mortality risk, apart from risks associated with exposure to blood products. Therefore, use of a preventive strategy which can decrease the incidence of 'pathological' hyperbilirubinemia in preterm neonates is desirable.

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. We conducted this meta-analysis to assess the effect of phenobarbitone on unconjugated hyperbilirubinemia during first two weeks of life in preterm neonates.

METHODS

The systematic review was carried out as per methodology recommended by Cochrane Neonatal Review Group(8) and is being reported in accordance with the QUOROM statement(9). We planned to include all randomized studies investigating efficacy of phenobarbitone administration on clinical course of neonatal unconjugated hyperbilirubinemia during first two weeks of life. A study was eligible for inclusion if it enroled preterm neonates (born at less than 37 weeks of gestation) and randomized the study subjects into control (placebo or no treatment) and treatment groups (phenobarbitone by oral and/or parenteral route with or without a loading dose; initiated before or after appearance of jaundice). Trials were not excluded based on severity of illness or clinical outcome of enroled subjects.

The standard search strategy of the Neonatal Review Group, as outlined in the Cochrane Library, was used(8). The following sources were searched for eligible reports: Cochrane Controlled Trials Register (online search) and MEDLINE electronic searches using the terms: "jaundice, jaundice/ neonatal, preterm neonate, randomized controlled trial, phenobarbitone", and the text words "phenobarbitone, jaundice" (up to May 2008). In addition, the following sources were hand-searched: reference lists from the articles retrieved in electronic search and from review articles and abstracts from proceedings of annual meetings of The European Society for Paediatric Research and The Society for Pediatric Research (up to 2008). Details of search strategy and its results are depicted in ***Fig.* 1**.

Main outcomes sought in the studies were duration of phototherapy (hours), need of exchange transfusion (proportion of study subjects who underwent one or more exchange transfusion) and survival without major disability at 18-24 months of life. Secondary out-comes were peak serum bilirubin, need of photo-therapy, number of exchange transfusions, apneic episodes needing methylxanthine therapy or venti-latory support, duration of ventilation, duration of neonatal intensive care unit stay, duration of hospital stay, incidence of intraventricular hemo-rrhage, death before discharge from hospital and major and minor disabilities during follow-up. Subgroup analysis was planned for following categories: (*i*) Trials with and without loading dose of phenobarbitone; (*ii*) Trials starting phenobarbitone before and after appearance of clinical jaundice; and (*iii*) Trials investigating phenobarbitone role in VLBW infants.

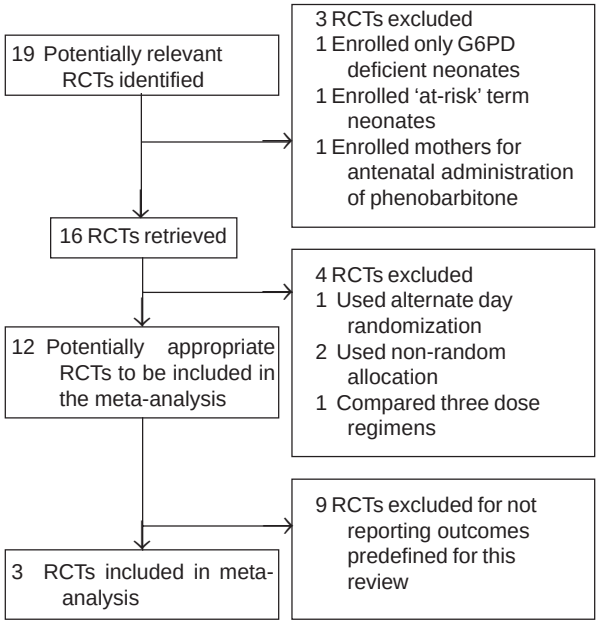

FIG. 1 *Progress through stages of search for eligible studies.*

Potentially relevant studies were assessed for inclusion independently by both the authors. The methodological quality of each trial was assessed by both the authors, with second author blinded to trial author and institution. Having decided which trials to include, authors independently extracted the data and compared results. Disagreements were resolved by consensus. For categorical and continuous data the odds ratio (OR) and weighted mean difference (WMD) were calculated, respectively. 95% confidence intervals were used and a fixed effects model was assumed for the meta-analysis. Review Manager 5 (The Cochrane Collaboration) was used for writing review and carrying out statistical procedures.

RESULTS

Search strategy resulted in retrieval of six studies; five published in peer-review journals and one in a conference proceeding(10-15). Three clinical trials were included in the meta-analysis(10,11,15) and another three(12-14) were excluded as the method of treatment allocation was not by randomization.

Characteristics of participants, intervention, outcomes assessed and quality assessment of included studies are depicted in ***Table* I**. Epstein, *et al*.(15) and Ruth, *et al*.(10) reported secondary analysis of the trial conducted to evaluate efficacy of phenobarbitone in preventing intraventricular hemorrhage. Kumar, *et al*.(11) conducted a randomized controlled trial in neonates with birthweight 1000-1499 g. Subjects fulfilling the eligibility criteria were randomized into 3 groups: Group I – babies were given 10 mg/kg loading dose of phenobarbitone on day 1 followed by maintenance 5 mg/kg/day from day 2 to day 5; Group II – neonates were given phenobarbitone in the maintenance dose of 5 mg/kg/day from day 1 to day

TABLE I CHARACTERISTICS AND POTENTIAL OF BIAS OF INCLUDED STUDIES

	Epstein, *et al*.(15)	Ruth, *et al*.(10)	Kumar, *et al*.(11)
Methods	Randomized controlled trial	Randomized controlled trial	Randomized controlled trial
Participants	Neonates with birth weight <1750 g needing intubation and mechanical ventilation within 12 hr of birth	Neonates with gestation ≥25 weeks, birthweight ≤1500 g, no major congenital malformation, no history of maternal barbiturate treatment and age <4 h	Neonates with birthweight 1000-1499 g
Interventions	Placebo or intravenous phenobarbitone 10 mg/kg at 12 hr of age and 2.5 mg/kg every 12 hr	Intravenous glucose infusion (control group); or intravenous phenobarbitone (treatment group) given as loading dose of 30 mg/kg (in two aliquots of 15 mg/kg each 4 hours apart) followed by maintenance dose of 5 mg/kg/d for 5 days	10mg/kg loading dose of phenobarbitone on day 1 followed by maintenance 5mg/kg/day from day 2 to day 5 OR phenobarbitone in the maintenance dose of 5mg/kg/day from day 1 today 5 OR no treatment (no placebo)
Outcomes	Incidence of hyperbilirubinemia (STB> 10 mg/dL), duration of phototherapy, need of exchange transfusion	Peak serum bilirubin (PSB)	PSB, Age at PSB, peak bilirubin-birth weight index, duration of phototherapy, need of exchange transfusion
Allocation concealment	Yes	Unclear	Unclear
Blinding	Yes	No	No
Incomplete outcome data	No	No	No

5; and Group III babies acted as controls (no placebo given). For the purpose of meta-analysis, Group I and Group II in the study by Kumar, *et al*.(11) were combined and compared with placebo or no treatment.

Peak serum bilirubin (PSB) was reported in all three trials. PSB was significantly lower in phenobarbitone group (*n*=497*;* mean difference: –1.78 mg/dL, 95% confidence interval: –2.29 to –1.27) (***Fig.* 2**). Duration of phototherapy and need of exchange transfusion were reported in two trials (*n*=396). Duration of phototherapy was also shorter in the phenobarbitone group (mean difference: –14.75 h, 95% confidence interval: –26.67 to –2.83). There was 70% reduction in need of exchange transfusion in the phenobarbitone group (relative risk: 0.30, 95% CI: 0.14 – 0.64). Need of phototherapy was reported in one study and it showed significant reduction in the phenobarbitone group (relative risk: 0.33, 95% CI: 0.13 – 0.81). No studied reported on other pre-specified outcomes and possible adverse effects including survival without major disability at 18-24 months of life, apneic episodes needing methylxanthine therapy or ventilatory support, duration of ventilation, duration of NICU stay, duration of hospital stay, death before discharge from hospital and major and minor disabilities during follow-up.

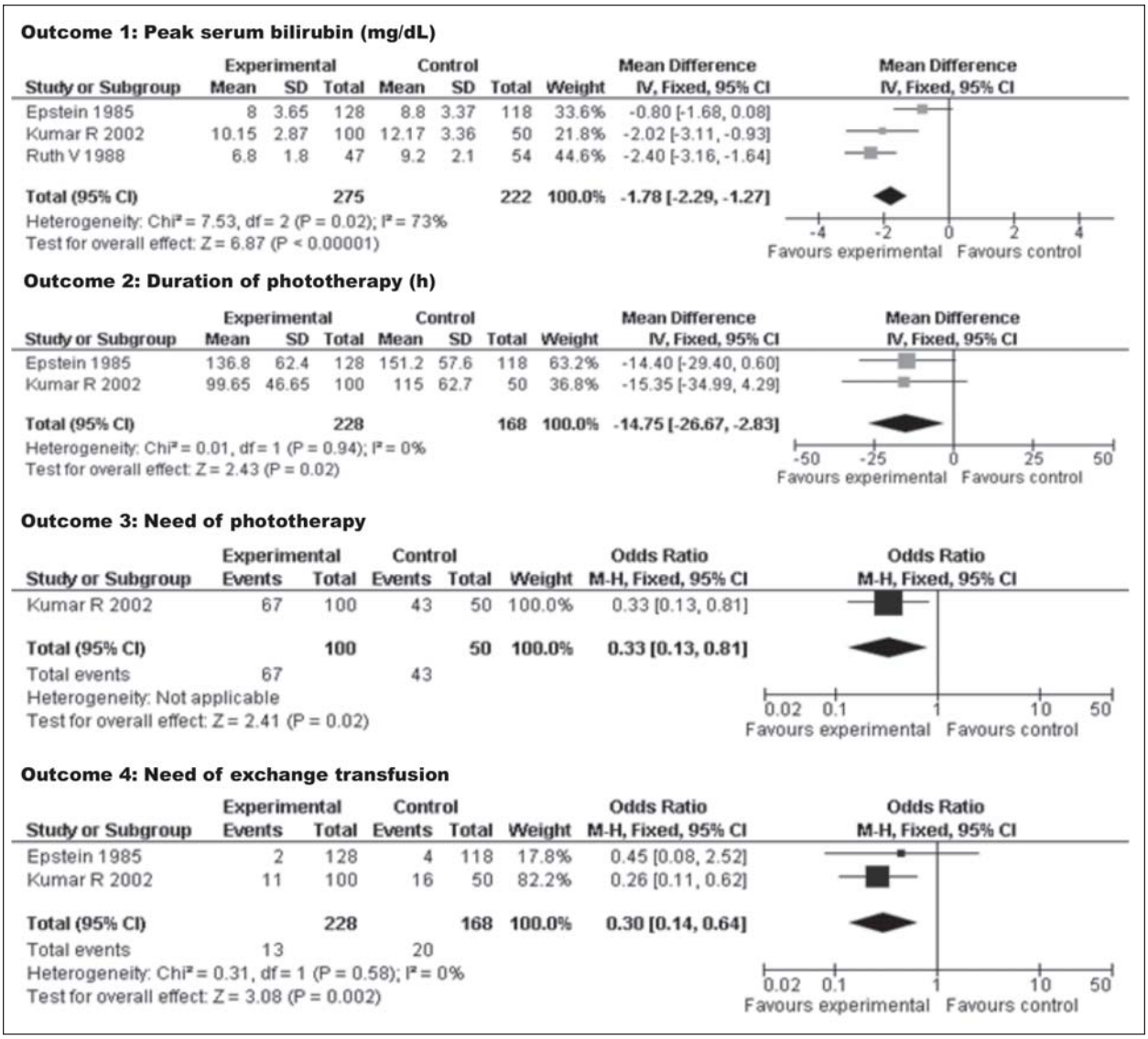

FIG. 2 *Meta-analysis of phenobarbitone use in jaundice in preterm neoataes.*

WHAT IS ALREADY KNOWN?

- Hyperbilirubinemia and its treatment cause significant morbidity in preterm neonates.

WHAT THIS STUDY ADDS?

- Phenobarbitone reduces peak serum bilirubin, duration and need of phototherapy and need of exchange transfusion in preterm very low birth weight neonates.

DISCUSSION

We carried out this meta-analysis to evaluate the efficacy of phenobarbitone in management of hyperbilirubinemia in preterm neonates. Three studies qualified for inclusion in the meta-analysis. A significant reduction was observed in peak serum bilirubin, duration of phototherapy, need of phototherapy and exchange transfusion with phenobarbitone use.

Several reports on use of phenobarbitone in decreasing the incidence and/or severity of jaundice in low birthweight or other 'at-risk' neonates were published in late 1960s and 1970s, when use of phototherapy was not common and incidence of kernicterus was high in small babies(12,16-19). These trials suggested that phenobarbitone therapy may reduce peak serum bilirubin if started early after birth. But with improved intensive care and more aggressive use of phototherapy machines, kernicterus almost disappeared in preterm VLBW neonates and interest in use of phenobarbitone declined. Although, phenobarbitone was later extensively evaluated for prophylaxis of intra-ventricular hemorrhage, its effect on course of hyperbilirubinemia was rarely reported. Two of the studies included in this review have reported hyperbilirubinemia-related outcomes as secondary outcomes with intraventricular hemorrhage being the major outcome(10,15).

Two of the three included studies have used loading dose of phenobarbitone(10,15). Kumar, *et al*.(11) used two intervention groups with one group receiving loading dose of 10 mg/kg.They reported that beneficial effect of phenobarbitone was more pronounced if loading dose was administered at start of phototherapy. Pharmacokinetic evaluation of phenobarbitone given without loading dose has shown increment in plasma drug level throughout the period of administration and non-achievement of steady state even after 7 days of therapy(20). Therefore, administration of loading dose and its amount may be important in achieving the clinical benefit.

Due to non-availability of data or limited data, we could not conduct analysis of adverse effects or pre-specified sub-group analysis. Data on neurodevelopmental outcome at 27 months of age was reported by Ruth, *et al*.(10) and no significant difference was observed in treatment and control groups. A major limitation of this meta-analysis is clinical and statistical heterogeneity observed in participants of the included studies. Although, subjects enrolled in the studies were similar, use of different strategies and loading doses of phenobarbitone resulted in clinical heterogeneity. Although significant statistical heterogeneity was observed for one of the outcomes (peak serum bilirubin), the observed benefit did not disappear with use of alternate analysis strategies (fixed *versus* random effect analysis) and we have reported only fixed-effect meta-analysis. There is also a possibility of studies without clinically significant effect remaining unpublished. We have not looked for the publication bias. We did not conduct sensitivity analysis as number of eligible trials was small.

Beneficial effect of phenobarbitone in reducing hyperbilirubinemia, need of treatment and treatment related morbidities may be of special relevance to a resource-restricted setting where availability of working phototherapy units and adequately trained manpower to perform exchange transfusion is limited.

In summary, phenobarbitone used in preterm very low birthweight neonates reduces peak serum

bilirubin, duration of phototherapy, need of phototherapy and exchange transfusion. A loading dose of 10 mg/kg at start of therapy may enhance the therapeutic benefit without causing respiratory depression seen with higher doses. Due to paucity of data, further studies are warranted to evaluate adverse effects and neurodevelopmental outcome of this therapeutic strategy.

Contributors: DC conceptualized and designed the study. Retrieval of relevant studies, quality assessment, pooling of results and manuscript writing was done by DC and VP. DC will be guarantor of the study.

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