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Study the Role of Phenobarbitone in the treatment Of Neonatal Hyperbilirubinemia in Low Birth Weight Neonates AN Open Labeled Randomised Control Trial

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ABSTRACT

Objective: To study the role of phenobarbitone in the treatment of neonatal hyperbilirubinemia in low birth weight neonate and the adverse effects of phenobarbitone.

Methods: All the low birth weight neonates admitted in NICU over a period of 2yr from November 2010 to November 2012 were enrolled in the study. 80 cases were randomized into 40 cases and 40 controls. Neonates fulfilling inclusion criteria randomized according to computer generated random number table, oral phenobarbitone 10mg/kg loding dose at the start of therapy followed by 5mg/kg/day in two divided doses for subsequent 4days along with phototherapy was given to A Group; only phototherapy for B Group. Serum bilirubin will be done on admission then every 12hrly for 3 days and every 24 hrly for next 2 days.

Results: The baseline characteristics were similar in two groups. There was no significant difference in mean peak serum bilirubin levels and no significant difference in reduction of serum bilirubin levels estimated over 5 days after use of phenobarbitone in these neonates. Phenobarbitone will not decrease the duration of phototherapy required and exchange transfusion requirement in both of these group. The only adverse noted with phenobarbitone is drowsiness.

Conclusions: Phenobarbitone has no role in treatment of neonatal hyperbilirubinemia.

KEYWORDS : Hyperbilirubinemia, Newborn, Phenobarbitone.

INTRODUCTION:

Neonatal Hyperbilirubinemia is one of the most common conditions seen by newborn care providers. This is usually a physiological transitional phenomenon due to a combination of an increased bilirubin load and decreased bilirubin elimination. High bilirubin levels may be toxic to the developing central nervous system and may cause neurological impairment even in term newborns. Conventional treatment for severe unconjugated hyperbilirubinemia consists of phototherapy and exchange transfusion. Phototherapy, however, has several known disadvantages while exchange transfusion is associated with a significant morbidity, and even mortality. These harmful effects indicate the need to develop alternative pharmacological treatment strategies for unconjugated hyperbilirubinemia.Generally, these strategies aim to decrease the plasma concentration of unconjugated bilirubin (UCB) by inhibiting production, stimulating hepatic clearance, or interrupting the enterohepatic circulation of the pigment.To be considered for routine clinical use, an alternative treatment strategy should be less invasive and at least as effective and safe as phototherapy. Several pharmacological therapies such as metalloporhyrins, clofibrate, bile salts, laxatives and bilirubin oxidase may meet these criteria in the future, but none of them have yet been evaluated sufficiently to allow routine application. In India, although the incidence of prematurity is high and their survival is increasing, maintenance of effective phototherapy system iscostly and difficult. Hence phenobarbitone seems a cheap alternative. In our study we used phenobarbitone for treatment of neonatal jaundice.Phenobarbitone, induces 1) liver microsomalenzymes, ligandin(Y acceptar protein) and UDP Glucoronyl Transferase 2) Increases liver cell membrane permeability. The present study was undertaken to study the role of phenobarbitone in the treatment of neonatal hyperbilirubinemia in low birth weight babies andits adverse effects.

MATERIAL AND METHODS:

It is an open labeled randomized control study in Level II NICU department of Pediatrics in government medical college Aurangabad. All the low birth weight neonates admitted over a period 2yr from November 2010 to November 2012 were enrolled in the study. Ethical committee of the institute approved the study protocol.80 cases were randomized into 4O Cases and 40 controls. Low birth weight babies (wt <2.5 Kg),Jaundice requiring phototherapy and Jaundice requiring exchange transfusion are included in study. Babies with weight >2.5Kg, Sick babies ,Babies with major congenital malformation and Babies requiring exchange transfusion within 24 hours of life are excluded from the study .

Clinical evaluation and procedure:

80 cases were randomized into 40 cases and 40 controls. Detailedantenatal, natal and postnatal history was taken. Thorough clinicalexamination of every baby was done and all the necessary investigations forhyper bilirubinemia were carried out.All the details were entered into standeredproforma. Written informed consent was takenfrom the parents. Cases were those who have jaundice in the phototherapy range.Neonates fulfilling inclusion criteria randomized according to computergenerated random number table, all vertical numbers were given oralphenobarbitone 10mg/kg loding dose at the start of therapy followed by5mg/kg/day in two divided doses for subsequent 4days along withphototherapy (A Group); all horizontal numbers were given only phototherapy(B Group). Phototherapy was given baby was kept under lightsource as close to the baby as possible .Baby was kept naked with eye andgenital pads.Serum bilirubin will be done on admission then after every 12hrly for 3days and then every 24 hrly for next 2 days. (American academy guidelineswere used for reference for babies above 35keeks and for preterm babies <35weeks guidelines from Nelson text were used). Each baby was examinedtwice daily until discharge. Serum bilirubin estimation was done using venepuncturesample by Van den Bergh Reaction.

Sample size calculation & randomization:

Assuming 50%reduction, the sample size was 10, for 40% reduction sample size was 15, for20% reduction sample size was 40. Firefox computer software was used forsample calculation. Neonates fulfilling inclusion criteria randomized accordingto computer generated random numbers.

Statistical analysis:

The data was compiled; analyzed and tabulated.The graphical presentation was used wherever necessary.Statistical analysis was carried out using Repeated Measures ANOVA forcomparing quantitative data over period of time in the same group.For comparing quantitative data between the study groups, unpaired't'test was applied.Comparison of

non-parametric (qualitative) data between the studygroups was done using Chi-square test, Chi-square test for trend andFisher Exact test.Statistical analysis was performed with the help of the software 'Graphpad-Prism 5'.Statistical significance is indicated by conventional symbols: *P <0.05:Statistically significant @ 95 % confidence limit.

RESULTS: Complete follow up was present in allneonates. Baseline characteristics in twogroups were similar (*Table I and II*). No baby ineither group had cephalhematoma or subgalealbleed.There was no significant difference in mean peak serum bilirubin levels in both of these groups. And also reduction of serum bilirubin levels estimated over 5 days after use of phenobarbitone in our study (*Table III and Figure 1*). .There was no significant difference innumber of neonates requiring phototherapyand none required exchange transfusion ineither group (*Table IV*). . None of the babies developinghyperbilirubinemia was G6PD deficient. Ahigher proportion of neonates ingroup A were drowsy as compared to group B.

TABLE-1
SHOWING BASELINE VARIABLES

Sr. No	Parameter	**AGroup**(N=40)	**BGroup**(N=40)	**P-value**
1.	**Age**(Days)	3.725±1.702	3.125 ± 1.079	**0.0634***
2.	**Sex :**(Number) (%) **M** **F**	22(55%) 18(45%)	21(52.5%) 19(47.5%)	**1.0000$**
3.	**Gestation:** (week)	35.40 ± 1.297	34.85 ± 1.562	**0.0906***
4.	**Birth Weight**(gems)	1967 ± 337	1815 ± 444	**0.0883***
5.	**SGA** (Number) (%) **AGA** **LGA**	15(37.5%) 25(62.5%) 0	12(30%) 28(70%) 0	**0.4781#**

Value: Mean ±SD (otherwise mentioned)
* Unpaired t test; two tailed p value > 0.05 Not Significant (@95% CL)
$ Fisher's Exact test; p value >0.05 Not Significant (@95% CL)
# Chi Square test for Trend; p value >0.05 Not Significant (@95% CL)

TABLE-2
SHOWING BASELINE VARIABLES AND RISK FACTORS

Sr. No	**Parameter**	**A Group** (N=40)	**B Group** (N=40)	**P-value**
1.	**Oxytocin use**	40(100%)	40(100%)	__
2.	**Resuscitation Required**	1(2.5%)	0(0%)	**1.0000$**
3.	**ABO incompatibilityΨ**	14(35%)	10(25%)	**0.4647$**
4.	**Rh-incompatibilityλ**	1(2.5%)	1(2.5%)	**1.0000$**
5.	**Cephalhematoma**	4(10%)	0(0)	**0.1156$**
6.	**Hemolysis On P.S.**	0(0)	2(5%)	**0.4937$**
7.	**G6PD positive**	0(0)	0(0)	__
8.	**Total Serum bilirubin**(mg/dl) (Mean ± SD)	17.72 ± 5.375	16.14 ± 3.751	**0.1320***
9.	**Fluid Intake Over 7 Days**(ml/kg/day) (Mean + SD)	121.5 ± 5.335	123.3 ± 7.970	**0.2520***
10.	**Average Number Of Stool per Day** (Mean ± SD)	5.600 ± 1.057	5.650 ± 1.167	**0.8414***

Value: number (%) (Otherwise mentioned)
* Unpaired t test, two tailed p value > 0.05 Not Significant (@95% CL)
$ Fisher's Exact test, p value >0.05 Not Significant (@95% CL)

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

λ"Rh negative" blood group mother with "Rhpositive" blood group neonate (with or without evidence of hemolysis)

– Statistical test cannot be applied

TABLE-3
SHOWING CHANGE IN BILIRUBIN LEVELS

Time interval	**A Group** (N=40)			**B Group** (N=40)			**Total bilirubin P value***
	Total bilirubin (mg/dl)	**Rate of fall of bilirubin**	**% Change From Baseline**	**Total bilirubin** (mg/dl)	**Rate of fall of bilirubin**	**% Change From Baseline**	
Baseline	17.72 ± 5.375	–	–	16.14 ± 3.751	–	–	0.1320
12 hrs	15.07 ± 5.169£	2.655±1.652£	15.96%	13.89 ± 3.623£	2.255±1.626£	13.94%	0.2417
24 hrs (day 1)	12.09 ± 4.228£	2.978±2.512£	31.77%	12.01 ± 4.363£	1.883±3.563£	25.59%	0.9318
36 hrs	7.480 ± 3.828£	4.608±3.387£	57.8%	7.773 ± 3.521£	4.233±3.380£	51.8%	0.7230
48hrs (day 2)	5.725 ± 2.754£	1.755±2.147£	67.7%	5.810 ± 2.987£	1.963±1.588£	64.0%	0.8951
72 hrs (day 3)	4.190 ± 2.149£	1.535±2.703£	76.4%	4.193 ± 1.961£	1.618±2.098£	74.0%	0.9957
96 hrs (day 4)	4.190 ± 2.149£	0	76.4%	4.193 ± 1.961£	0	74.0%	0.9957
120 hrs (day 5)	4.190 ± 2.149£	0	76.4%	4.193 ± 1.961£	0	74.0%	0.9957

Value: Mean±SD
* Unpaired t test; two tailed p value > 0.05, Not Significant (@95% CL)
£ Using repeated measures ANOVA; p value < 0.05, Significant (@95% CL)

FIGURE -1

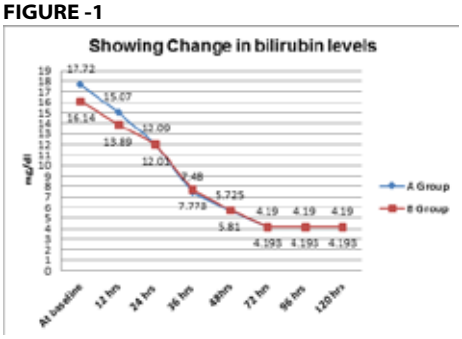

TABLE-4
SHOWING DURATION OF PHOTOTHERAPY AND EXCHANGE TRANSFUSION REQUIRED

	A Group(N=40)	**B Group**(N=40)	P value*
Duration of phototherapy (HRS)	46.30 ± 21.62	44.31 ± 14.86	0.6354
Exchange transfusion required	4(10%)	2(5%)	0.6752

Value: Mean±SD
* Unpaired t test; two tailed p value > 0.05, Not Significant (@95% CL)

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 differentdosage ranging from 2.5 mg once a day for 3 days to a single dose of 12 mg/kg (6-11). Phenobarbitone administration did not demonstrate any reduction in incidence of hyperbilirubinemia. There was no significant difference in mean peak serum bilirubin levels in both of these groups. And also reduction of serum bilirubin levels estimated over 5 days after use of phenobarbitone in our study.

Study by **Y K Wong et al**[36], **J C Lall et al[64], G E Levin et al[32], Sinniah et al[33] and Cunningham *et al.* (1969)[24],** showed that there is no significant difference in 12 hourly fall of serum bilirubin with phenobarbitone and phototherapy

Arya et al [27], Ramboer et al[22], Kumar et al [21], Nader pashapour et al[34], *and* Sumner J. Yaffe et al[42]showed reduction in TSB at 72 ± 12 hours of age.

The dose of phenobarbitone, day of starting phenobarbitone and antenatal use of phenobarbitone will go to affect the fall of serum bilirubin levels.

There was no difference between duration of phototherapy, exchange transfusion requirement in both of the groups.This is similar to findings of **Arya et al[27]**,however**Valdivieso et al[39], Kumar et al [21]** showed decrease in the duration of phototherapy required. This might be because of intravenous use of higher loading dose and use within 6 hour of life. The amount of phenobarbitone given as first dose within 6 hours of life seems to be the crucial factor in the action of phenobarbitone [21]. The sedative effect of phenobarbitone asnoticed by us has been reported by othersalso (11). Study by **Arya et al [27]**showed sedative effect of phenobarbitone.

J C Lall et al[64] and Kumar et al[21]showed no recogaizable complication of phenobarbitone.The dose phenobarbitone in higher dose is having more adverse effects.Apnea and cyanotic spells havealso been reported with higher doses ofphenobarbitone and was more commonly seenin low birth weight infants(6) but these sideeffects were not observed in the present study.

CONCLUSIONS:

Phenobarbitone has no role in treatment of neonatal hyperbilirubinemia.

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