THE STUDY OF A NEW METHOD IN TREATMENT OF TERM NEWBORNS WITH NON-HEMOLYTIC HYPERBILIRUBINEMIA

NADER PASHAPOUR*
ALI MACCOEI*
SARIYEH G. IOU**
HOSSEIN AKHONDI*

SUMMARY: The purpose of the study was to determine whether reduction of serum levels of bilirubin is more in full-term newborn with non-hemolytic hyperbilirubinemia that treated with new treatment than in matched control subjects.

Eighty consecutively admitted term healthy neonate with indirect hyperbilirubinemia and indication for phototherapy were randomized into receiving phenobarbital (3 mg/kg/day) plus phototherapy as new treatment method or phototherapy as routine method after obtaining informed consent. The neonate followed up until discharge. The total serum bilirubin levels were measured four times a day. Patient's data regarding variation of bilirubin and hospitalization duration collected and compared from the two groups. Results are presented as the mean, 95% confidence interval, 0.05% significance level and 80% power.

The baseline characteristics were similar in two groups. Mean ages were 5.5 ± 2.81 and 4.80 ± 1.68 days for control and case group respectively. Mean bilirubin levels in admission were 19.48 ± 2.80 mg/dl and 18.51 ± 1.66 for control and case group respectively. There was significant reduction of bilirubin levels in case group compared to control group (10.54 ± 3.00mg/dl versus 8.60 ± 1.99 mg/dl) (P=0.001). No significant difference with respect to duration of hospitalization was observed in two groups' (2.05 ± 0.59 days for control versus, 2.15 ± 0.80 days for case group).

In despite of significant reduction of bilirubin levels in case group compared to control group, combined treatment is not helpful in reducing of hospitalization days of non-hemolytic hyperbilirubinemia in healthy term neonates.

Keywords: Phenobarbital, phototherapy, non-hemolytic hyperbilirubinemia, neonate, icter.

INTRODUCTION

Jaundice is arguably the most common condition requiring investigation and treatment in the newborn period (1). Jaundice in term newborn is clinically evident in over 60% of newborn during the first week after birth (2). Approximately 6-10% of infants have significant hyperbilirubinemia mandating treatment (Serum bilirubin values above 95th percentile for age in hours) (1,3).

Hyperbilirubinemia is the most commonly reported cause for readmission during the early neonatal period, and 0.36-0.5% of healthy term newborn discharged 72 hours of life with no more than mild hyperbilirubinemia may even develop a subsequent moderate to severe hyperbilirubinemia (4,5).

Phototherapy is commonly used to lower elevate serum bilirubin levels in newborns. However, phototherapy is expensive and inhibits parent-child bonding because the newborn is confined to an incubator in hospital and the newborns' eyes are covered. Studies showed that phototherapy had an absolute risk reduction rate of 10% to 17% for prevention of serum bilirubin levels higher than 20 mg/dl in healthy infant with jaundice (6).

* From Department of Pediatrics, Oromieh Medical Science University Faculty of Medicine, Oromieh, Iran.
** From Department of Prenatology, Oromieh Medical Science University Faculty of Medicine, Oromieh, Iran.

Table 1: Adapted AAP Guideline for Management of Hyperbilirubinemia Newborn Based on Age and TSB levels.

Age (Hours)	No Phototherapy	Consider Phototherapy	Recommend Phototherapy
<24	No recommendation	No recommendation	No recommendation
24-48	<12 mg/dl	≥12 mg/dl	≥15 mg/dl
49-72	<15 mg/dl	≥15 mg/dl	≥18 mg/dl
>72	<17 mg/dl	≥17 mg/dl	≥20 mg/dl

There is also sufficient evidence to indicate that phenobarbital is effective in decreasing serum bilirubin levels in newborn infants. Since phototherapy breaks down bilirubin in the skin by photoisomerization, and phenobarbital is known to induce bilirubin conjugating activity in the liver (7), the possibility of an additive effect in combined therapy was expected. Present study evaluated the efficiency of possible oral phenobarbital additive effect in non-hemolytic hyperbilirubinemic of term-hospitalized neonates and its effects in reducing serum bilirubin levels, reduction the hospitalization duration.

MATERIALS AND METHODS

Patients and Methods

The study was carried out from April 2004 to May 2005 at Imam Hospital Oromieh, Iran on all consecutively admitted term healthy neonates, with indirect non-hemolytic hyperbilirubinemia and indication of phototherapy treatments. Ethical Committee of the institute approved the study protocol. Neonates receiving phenobarbital in the preadmission period, those born to mothers receiving phenobarbital in the antenatal period, cases with hemolytic or other known causes of jaundice, non-breastfeeding neonates, inability of mother to attend hospital for breastfeeding, prior phototherapy received newborn and cases that did not complete the study were excluded.

The babies fulfilling the eligibility criteria were randomized into 2 groups according to sequence of admission: Group I-Babies were given 3mg/kg/day phenobarbital dissolved in 10cc of 5%dextrose solution and phototherapy (case group= 40), Group II-Babies were given 5% dextrose solution in same volume with phototherapy (control group= 40) after obtaining informed consent from their parent.

American Academy of Pediatric Guideline for hyperbilirubunemia therapy was used for treatment of enrolled neonates (Table 1) (8). The total serum bilirubin level below 12 mg/dl was selected as cutoff point for discontinuing of treatment. The sufficiency of phototherapy units irradiance were regulary detected by respective technician. Neonates were also monitored for side effect of oral phenobarbital such as excessive sleepiness, decreased feeding, dehydration and neurological dysfunction. The total serum bilirubin (TBS) was measured four times a day by dual wavelength spectrophotometer method using spun capillary tube sample, until patient was discharged. Babies were investigated for cause of jaundice (CBC, Hg, Hct. blood grouping of mother and baby, direct coomb's test, glucose 6 phosphatase dehydrogenase level) and evidence of hemolysis (reticulocyte count>5%).

The number of patients enrolled was collected to be sufficient to detect an assumed difference of 40% with power value of 80% between groups in the reduction of serum bilirubin levels.

Total levels of bilirubin after 48 hours (8th test) of admission and hospitalization duration were considered as outcomes of study.

Statistical analysis

The probability of significant differences between the indexes for independent groups was assessed by t-test. Chi-square and t-test were used to compare the probability of sex and age difference between case and control groups. Results are presented as the mean, 95% confidence interval, 0.05% significance level and 80% power. Statistical tests were performed by using 'SPSS version 11.5'computer software.

RESULTS

The total enrolled patients were 80, forty cases in each group. The number of male and female patients in case and control groups was, 30 versus 10 and 26 versus 14 respectively.

Mean of age in admitting time were, 4.80 ± 1.68 (CI 95% 4.26- 5.33) or case versus 5.55 ± 2.81 (CI 95% 4.64- 6.451) days for control group.

Mean of admission total serum bilirubin levels were 19.48 ± 2.80 (CI 95% 18.56- 20.40) versus 18.51 ± 1.66 (CI 95% 17.98- 19.04) mg/dl for case and control group respectively.

The baseline characteristics of two groups including age, sex, weight, total serum bilirubin levels (TSB) were similar at admission (Table 2).

Average of hospitalization days was 2.15 ± 0.80 (CI 95% 1.89 - 2.40) versus 2.05 ± 0.59 (CI 95% 1.85- 2.24) for case and control groups respectively. There was no significant difference in mean hospitalization days between two groups (p=0.52).

Table 2 : Identification of patients in two groups at admission.

Subjects		No. M/F	Mean	SD	P-Value
Sex of Case	"Phototraphy	30/10	-	-	0.43
	"Phototraphy" +Photobarital"	26/14	-	-	
Age of Case/day	"Phototraphy	40	5.55	2.81	0.15
	"Phototraphy" +Photobarital"	40	4.80	1.68	
Weight /gr	"Phototraphy	40	3131.25	313.51	0.75
	"Phototraphy" +Photobarital"	40	3108.75	321.63	
TSB in Admission mg/dl	"Phototraphy	40	18.51	1.66	0.06
	"Phototraphy" +Photobarital"	40	19.48	2.8	

M= Male , F= Female TSB= Total Serum Bilirubin

Table 3 : Patients data on eighth test and hospitalization duration.

Subjects		No.	Mean	SD	P-Value
TSB mg/dl	"Phototraphy	40	9.90	2.00	0.014
	"Phototraphy" +Photobarital"	40	8.93	1.39	
Reduction of Billirubin /mgdl	"Phototraphy	40	8.60	1.99	0.001
	"Phototraphy" +Photobarital"	40	10.54	3.00	
Hospitalization / Days	"Phototraphy	40	2.05	0.59	0.52
	"Phototraphy" +Photobarital"	40	2.15	0.80	

TSB= Total Serum Bilirubin

Mean of eighth test of total serum bilirubin levels were 8.93 ± 1.39 (CI 95% 9.58 - 11.50) versus 9.90 ± 2.00 (CI 95% 7.96 - 9.24) in case and control groups respectively (p=0.014).

Mean total serum bilirubin reduction levels were 10.54 ± 3.00 (CI 95% 9.58-11.50) versus 8.60 ± 1.99 mg/dl (CI 95% 7.96- 9.24) for case and control groups respectively in time of eighth test (p=0.001). Significant complications of drug were not observed in phenobarbital group.

Patients' data on eighth test and hospitalization duration were presented in Table 3.

DISCUSSION

This study investigated the effects of two different treatments on nonphysiologic hyperbilirubunemia in breast-feeding full-term newborn infants. The important cause of exaggerated physiologic jaundice (non-hemolytic) is deficiency of uridine diphosphate glucuronsyl transferase (UGT) in liver of neonates (9). Phenobarbital induces UGT enzymes as well as subfamilies of cytocrome P450 in the liver. Oral absorption of Phenobarbital is complete but somewhat slow; peak concentrations in plasma occur several hours after a single dose (10). Since phototherapy breaks down bilirubin in the skin by photoisomerization and phenobarbital is known to induce bilirubin conjugating activity in the liver (11), the possibility of an additive effect in combined therapy was expected. In our study, 3mg/ kg oral administration of Phenobarbital to conventional phototherapy treatment result in significant difference on reduction of total serum bilirubin levels on third day of therapy between case and control group (10.54 ± 3.00 (CI 95% 9.58-11.50) versus 8.60 ± 1.99 mg/dl (CI 95% 7.96- 9.24) for case and control groups respectively). This result is compatible with a study conducted by Kumar

R for assessment of Phenobarbital prophylaxis effect in babies' hyperbilirubinemia with birth weight less than 1500 grams. Researcher concluded that Phenobarbital efficacy is dose dependant and in dose of 10mg/kg given within 6 hours of life followed by 5mg/kg/day till day 5 intravenously significantly decreased the need for exchange transfusion and duration of phototherapy better than dose of 5 mg/kg for 5 days (12).

Other study were conducted to assess the efficacy of oral phenobarbital in decreasing neonatal hyperbilirubinemia rates in term "at risk" neonates. Phenobarbital was administrated orally (5mg/kg/day) in at risk infant for hyperbilirubinemia for three days starting within 12 hours of birth. There was no significant reduction in incidence of hyperbilirubinemia in Phenobarbital group (6/37) compared to in placebo group (13/38). The researchers concluded that prophylactic phenobarbitone is not helpful in reducing the incidence of hyperbilirubinemia in ' at risk' term neonates (13).

Although in our study significant reduction of bilirubin were observed between case and control groups but this amount was not enough to reduce hospitalization days.

This result is incompatible with a study concluding that in treatment of hypebilirubinemia combination of the phototherapy and medication seems to be more effective than phototherapy alone because each round of treatment in combination cases require less time and the bilrubin concentration levels off more steadily (14).

Some risk factors especially hemolysis in term infants predispose neonates to exchange transfusion (15). All enrolled subjects were non-hemolytic so good response to phototerapy and lack of exchange transfusion may attribute to this factor.

There are few limitations in our study. We used minimum dose of Phenobarbital, higher dose may shows other results, which were not searched in this study.

CONCLUSION

Combined therapy of phenobarbital plus phototherapy reduced bilirubin levels better than phototherapy alone. However, phototherapy plus 3mg/kg/day oral phenobarbital and phototherapy treatments are equally effective in treatment of non-hemolytic hyperbilirubinemia of neonates regarding duration of hospitalization time. Therefore, according to our findings, it was recommended that only phototherapy protocol to be applied in the indirect non-hemolytic hyperbilirubinemia of the neonates.

REFERENCES

1. Willy T, Tommarello: Effect of Phenobarbital on bilirubin metabolism in rat brain. Biol Neonate, 73:106-111, 1998.

2. Riskin A, Abend-weinger M, Bader D: How accurate are neonatologist in identifying clinical jaundice in newborns. Clinical Pediatrics, 42:153-158, 2003.

3. Bhutani VK, Gourley GR, Adler S et al: Noninvasive measurement of total serum bilirubin in a multiracial predischarge newborn population to assess the risk of severe hyperbilirubinemia. Pediatrics, 106:1-9, 2000.

4. Maisels MJ, Kering E: Lengh of stay, jaundice, and readmission. Pediatrics, 101:995-998, 1998.

5. Sarici S, Yurdakok M, Serdar M et al: An early (six hour) serum bilirubin measurement is useful in predicting the development of significant hyperbilirubinemia and severe ABO hemolytic disease in a selective high-risk population of newborn with ABO incompatibility. Pediatrics, 109:53, 2002.

6. Ip S, Chung M, Kuling J et al: An evidence-based review of important issues concerning neonatal hyperbilirubinemia. Pediatrics, 114: e130, 2004.

7. Stoll BJ, Kliegman RM: Digestive system disorders. In origin of Nelson textbook of pediatric. Volume 1. 17th ed. Edited by RE Behrman, RM Kliegman, HB Jenson. NewYork: Saunders, 588-590, 2004.

8. Aktinson LR, Escobar GJ, Takayama JI: phototherapy use in jaundiced newborns in a large managed care organization: Do the clinician adhere to the guideline. Pediatric, 111: 581-590, 2003.

9. Dennery P, Seidman DS, Stevenson KS: Neonatal hyperbilrubinemia. NEngl J Med, 344:581-590, 2001.

10. McNamara JO: Drug effective in the therapy of the epilepsy. Goodman&gillman: The pharmacologic basis of therapeutics 10th edition, McGraw-hill. London: 531, 2001.

11. Maizels MJ: Jaundice. In origin of Neonatalogy and Pathophsiology Manangment of the newborn. 15th ed. Edited by GB Avery, MA Fletcher, MG MacDonald. Philadelphia: Williams and Wilkins, 808-811, 2000.

12. Kumar R, Narag A, Kumar P et al: Phenobarbitone prophylaxis for neonatal jaundice in babies with birth weight 1000-1499. Indian Pediatrics, 39(Oct): 945-951, 2002.

13. Arya VB, Agrawal R, Paul Vinod K et al: Efficacy of oral phenobarbitone in term "at risk" neonates in decreasing neonatal hyperbilirubinemia: A randomized double blinded placebo controlled trial. Indian Pediatrics, 41(Apr): 327-332, 2004.

14. www.rose-human.edu/mathjournal/2004/vol5/paper5

15. Bertini G, Dani C, Tronchin M et al: Is breast feeding really favoring early neonatal jaundice. Pediatrics, 107: 1-5, 2001.

Correspondence:
Nader Pashapour
Department of Pediatrics,
Faculty of Medicine,
Oromieh Medical Science University,
Oromieh, IRAN.
e-mail: npashapor@yahoo.com