The Role of Oral Phenobarbital Therapy in the Management of Neonates with Prolonged Unconjugated Hyperbilirubinemia

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Abstract

Background: Prolonged jaundice is a type of neonatal jaundice, which occurs in infants with high bilirubin levels (>10 mg/dl) persisting beyond day 14 of life in term neonates, and beyond day 21 in preterm neonates. Prolonged jaundice may be caused by predominantly conjugated or unconjugated hyperbilirubinemia. Distinguishing between these types of jaundice helps to determine the risk for pathological causes of prolonged jaundice.

Phenobarbital has been used to treat neonatal jaundice since the 1960s. Numerous clinical trials have shown that both administration of phenobarbital to pregnant mothers before delivery and phenobarbital administration to neonates after delivery limit the severity of unconjugated hyperbilirubinemia, reduce the peak serum total bilirubin concentrations caused by physiologic jaundice by 50%, and the need for exchange transfusion.

Objective: The aim of this study was to evaluate the role of phenobarbital in reducing the total serum bilirubin(TSB) in neonates with prolonged unconjugated hyperbilirubinemia.

Methods: This is a prospective clinical trial study that was performed in Karbala teaching hospital for children from 18th of December 2017 to the end of December 2018. A total of 101 neonate with prolonged unconjugated hyperbilirubinemia were included in this study. All neonates who included in this study received phenobarbital tablet (5 mg /kg/day) twice a day for 10 days and some of them need phototherapy according to American Academy Of Pediatrics Guidelines for phototherapy,

Results: There was a highly statistically significant decrease in TSB for the patients who were treated with phenobarbital compared to the baseline level, mean baseline TSB 14.57± 2.31 mg/dl versus TSB after phenobarbital 6.79±1.62 mg/dl (P value <0.001). There was a highly statistically significant decrease in TSB for the patients who were treated with phototherapy in addition to phenobarbital compared to the baseline level, mean baseline TSB 19.94±1.36 mg/dl versus TSB after phototherapy and phenobarbital 6.33±1.37 mg/dl (P value <0.001).

Conclusions:

1. Oral phenobarbital supplementation in the neonates with prolonged unconjugated hyperbilirubinemia can significantly accelerate reduction in serum bilirubin levels.
2. Phenobarbital was safe, tolerable and no obvious adverse effects had been reported.
3. No need for cessation of breast feeding in cases of presumed breast milk jaundice.

Keywords: prolonged jaundice, phenobarbital, unconjugated hyperbilirubinemia**.**

Introduction:

Prolonged jaundice is a type of neonatal jaundice, which occurs in infants with high bilirubin levels (>10 mg/dl) persisting beyond day 14 of life in term neonates, and beyond day 21 in preterm neonates.[1] Prolonged jaundice may be caused by

predominantly conjugated or unconjugated hyperbilirubinemia. Distinguishing between these types of jaundice helps to determine the risk for pathological causes of prolonged jaundice.[2]

Phenobarbital has been used to treat neonatal jaundice since the 1960s. Numerous clinical trials have shown that both administration of phenobarbital to pregnant mothers before delivery and phenobarbital administration to neonates after delivery limits the severity of unconjugated hyperbilirubinemia, reduce the peak serum total bilirubin concentrations caused by physiologic jaundice by 50%, and the need for exchange transfusion.[3,4]

Phenobarbital is a constitutive androstane receptor agonist that enhances the hepatic unconjugated bilirubin clearance; uptake and storage in the liver, hepatic conjugation, and hepatic excretion of bilirubin. Net uptake and storage is enhanced via an increased concentration of ligandin, conjugation is enhanced via induction of uridine diphosphate glucuronosyltransferase 1, and biliary secretion is enhanced via induction of multidrug resistance associated protein 2.

Phenobarbital has an oral bioavailability of about 90%. Peak plasma concentrations are reached eight to 12 hours after oral administration. It is one of the longest acting barbiturates

available, it remains in the body for a very long time (half-life of two to seven days) and has very low protein binding (20 to 45%). Phenobarbital is metabolized by the liver, mainly through hydroxylation and glucuronidation, and induces many isozymes of the cytochrome P450 system. It is excreted primarily by the kidneys.[3]

However, the effect of phenobarbital is not rapid and takes time to show. When used for 3-5 days in a dose of 5 mg/kg after birth prophylactically, it has shown to be effective in babies with hemolytic disease, extravasated blood, and in preterm without any significant side effects.[6]

In a variant of severe genetic insufficiency of uridine diphosphoglucuronic acid (UDPGT) ″Crigler-Najjar syndrome type 2″, treatment with phenobarbital may stimulate UDPGT activity sufficiently that brain toxic levels of TSB are avoided.[7]

Aim of the study

The aim of this study was to evaluate the role of phenobarbital in reducing the total serum bilirubin in neonates with prolonged unconjugated hyperbilirubinemia.

Patientsand methods

This is a prospective clinical trial study that was performed in Karbala teaching hospital for children from 18th of December 2017 to the end of December 2018. A total of 101neonate with prolonged unconjugated hyperbilirubinemia (87outpatient, 14 inpatient) were included in this study, they have previous history of phototherapy, oral consents were taken from parents to investigate and treat their babies.

A structured form was used to cover demographic characteristics (including name, age, gender, gestational age, type of feeding, family history of jaundice and consanguinity), and thorough physical examination (including: general condition, body weight, dysmorphic features, organomegaly, cataract, large posterior fontanelle, and umbilical hernia).

The following investigations were done accordingly when needed:

1. Liver function test: TSB, direct bilirubin, indirect bilirubin, Alanine Aminotransferase.
2. Thyroid function test.
3. Complete blood count, blood film and reticulocyte count,G6PD assay.
4. Blood group and Rh typing for neonates and their mothers.

5. Coombs test.
6. General urine examination and urine for reducing substance.
7. Abdominal ultrasound.

Patient's selection:

Inclusion criteria:

1. Term babies age >14 days.
2. Preterm babies age >21 days.
3. TSB>10 mg/dl.
4. Unconjugated hyperbilirubinemia.

Exclusion criteria:

1. Neonates with conjugated hyperbilirubinemia.
2. Neonates with evidence of hemolysis (anemia, organomegaly, history of ABO or Rh incompatibility "positive coomb's test ", family history of hemolytic disease, G6PD deficiency).
3. Neonates with signs of infection, sepsis or inborn errors of metabolism (galactosemia).
4. Critically-ill newborns.

All neonates who were included in this study received phenobarbital tablet (5 mg /kg/day) twice a day for 10 days and some of them need phototherapy according to American Academy Of Pediatric Guidelines for phototherapy ,[8] then follow up TSB done at 5th and 10th day of treatment with phenobarbital.

Statistical analysis:

All data analyzed using Statistical Package of Social Sciences software version 24 computer program. Statistical analysis included descriptive statistics like: frequency tables and graphs, Including: bar diagrams and pie chart. Results are expressed as mean ± SD. Differences of means within groups were examined by paired sample t-test .*P* value less than 0.05 were considered statistically significant.

Results

A total of 101 patients with prolonged neonatal jaundice were enrolled in this study, 67(66.34 %) were male and 34 (33.66%) were female (Figure 1).

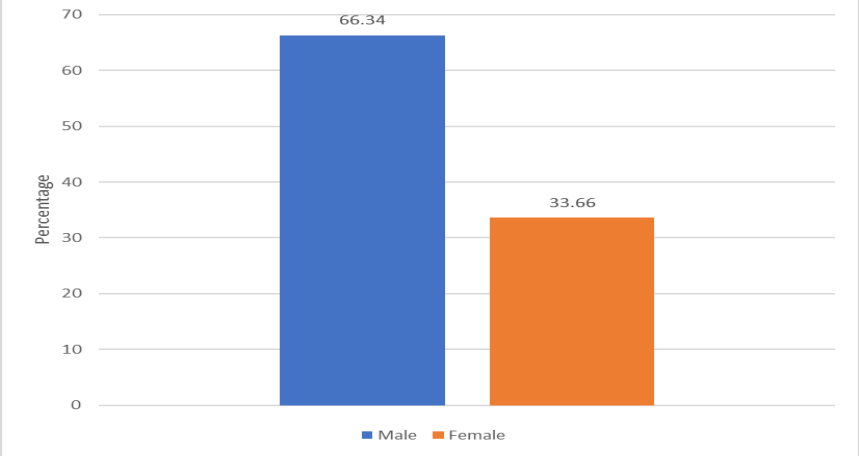

Figure 1. Gender distribution among the cases.

The majority of the neonates were breast fed 86(85.15%) (Figure 2), and regarding the gestational age, 98(97.03%) were full term and 3(2.97%) were preterm (Figure 3).

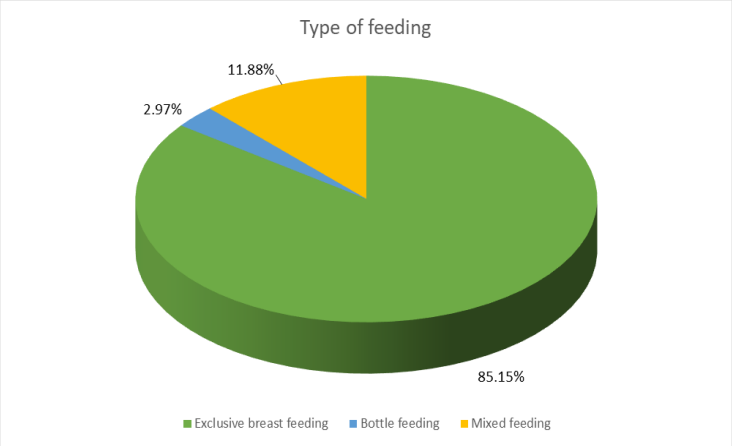

Figure 2. Type of feeding distribution among the cases.

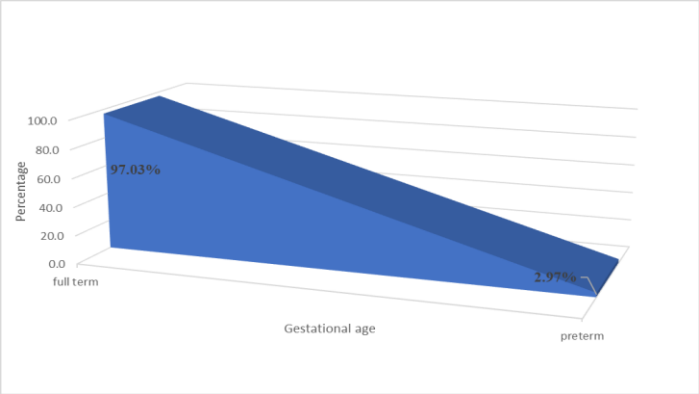

Figure 3. Gestational age distribution among the cases.

Regarding blood group and Rh for the neonates and their mothers, 67(66.3%) were compatible blood group, ABO incompatibility and Rh incompatibility (with no evidence of hemolysis and negative coombs test) were 21(20.8%)and 13(12.9%) respectively. (Figure 4)

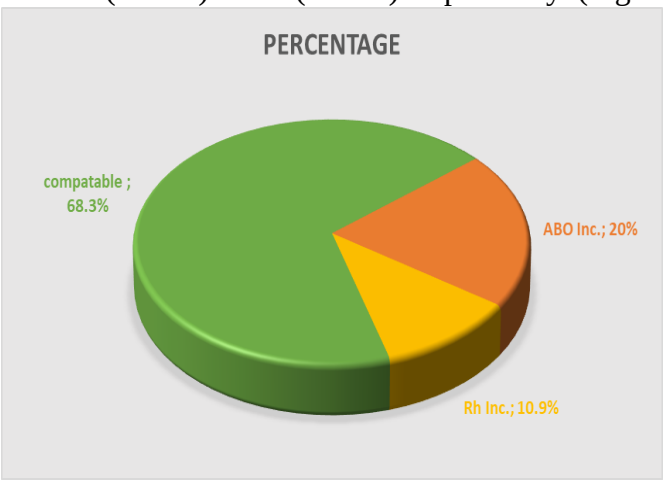

Figure 4. Blood group and Rh distribution among the cases.

The majority of the patients were treated by phenobarbital 87(86.1%), the other 14(13.9%) require phototherapy in addition to the phenobarbital (Figure 5).

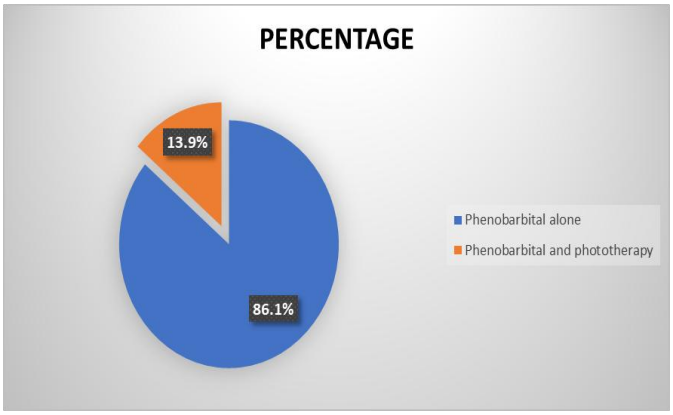

Figure 5. Type of treatment distribution among the cases.

The mean age of the neonates at the presentation was 19.8±3.61 days while minimum and maximum ages were 15 and 27 days respectively, with their distribution shown in figure 6.

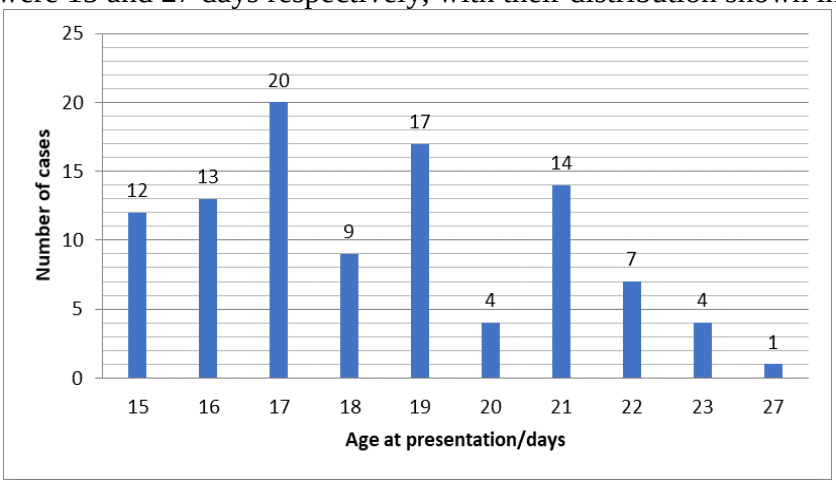

Figure 6. Age at presentation distribution among the cases.

The mean age of the neonates at the onset of jaundice was 4±1.58 days while minimum and maximum ages were 2 and 6 days respectively, with their distribution shown in figure 7.

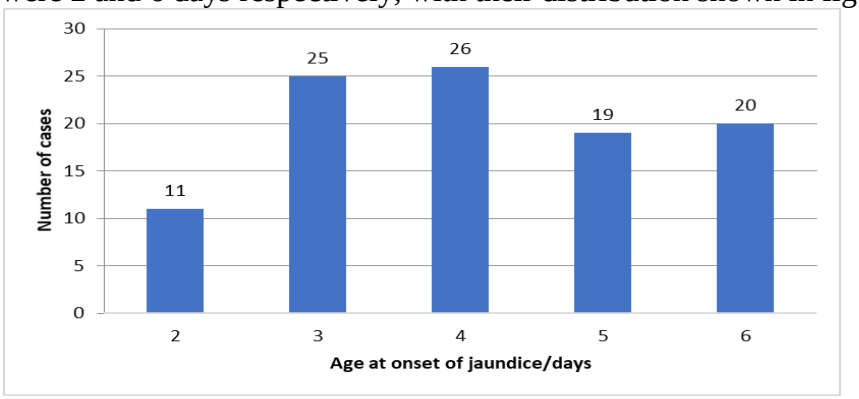

Figure 7. Age at onset of jaundice distribution among the cases.

The mean body weight of the neonates was 3479.650± 567 grams while minimum and maximum weights were 1750 and 4600 grams respectively ,with their distribution shown in figure 8.

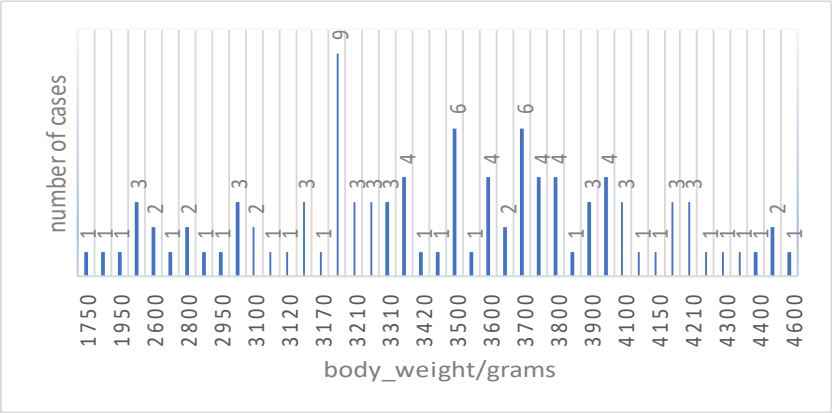

Figure 8. Body weight distribution of cases .

Table 1 shows the TSB level before and after treatment with phenobarbital tablet (5mg/kg/day) in 87 neonates with prolonged neonatal jaundice.

Table 1. Mean ±SD of TSB (mg/dl) levels before and after phenobarbital.

	Baseline TSB (Mean ±SD)	TSB after phenobarbital (Mean ±SD)	P value
Neonates (n=87)	14.57± 2.31	6.79±1.62	<0.001

There was a highly statistically significant decrease in TSB for the patients who were treated with phenobarbital compared to the baseline level ,mean baseline TSB 14.57± 2.31 mg/dl vs TSB after phenobarbital 6.79±1.62 mg/dl (*P* value <0.001).

Table 2 shows the TSB level before and after treatment for neonates whom require phototherapy in addition to the phenobarbital in 14 neonates with prolonged neonatal jaundice.

Table 2. Mean ±SD of TSB(mg/dl) levels before and after phototherapy & phenobarbital .

There was a highly statistically significant decrease in TSB for the patients who were

	Baseline TSB (Mean ±SD)	TSB after phototherapy&phenobarbital (Mean ±SD)	P value
Neonates (n=14)	19.94±1.36	6.33±1.37	<0.001

treated with phototherapy in addition to phenobarbital compared to the baseline level, mean baseline TSB 19.94±1.36 mg/dl vs TSB after phototherapy and phenobarbital 6.33±1.37 mg/dl (*P* value <0.001).

Discussion

Prolonged unconjugated hyperbilirubinemia is a common problem among newborn. Although this condition is normally manageable, it may sometimes be a sign of other serious diseases ,so caution is required when assessing infants with prolonged jaundice.[9]Treatment of jaundice in the newborn infant requires solid knowledge both about the pathophysiology and treatment options in this condition.[10]

Males have a higher incidence as compared to females in this study 67(66.34 %) vs 34(33.66%). These findings are similar to an Indian study by (Agrawal V et al,2017) in which there was a male predominance accounting for 64 (64%) cases.[9]Similarly, Margaret Andre et al, New Zealand,[10] Najati, M.M. Gharebaghi et al, Iran,[11]Khadije Sadat Najib et al, Iran.[12]

While in Yi-Hao Weng et al, Taiwan, the incidence of prolonged unconjugated jaundice was approximately equal between males and females [male 80 (48.8%) female 84 (51.2%)].[13]

In the present study ,86(85.15%)were breast fed, 3(2.97%)bottle fed, and 12(11.88%)mixed feeding, these findings were similar to Margaret Andre et al, New Zealand ,[10]Breast feeding 140(83.8%) ,bottle feeding 2 (1.2%), and Mixed feeding 25 (15%),also in Yi-Hao Weng et al study ,[13]there was breast feeding predominance, breast feeding 113 (68.9%), bottle feeding, 0 (0) and mixed feeding 51 (31.1%).

The majority of neonates in this study were full term 98(97.03%) and the other 3(2.97%)were preterm, comparable to Margaret Andre et al, New Zealand,[10]Agrawal V et al, India,[9] and Yi-Hao Weng et al, Taiwan,[13] incidence of prolonged jaundice in preterm were higher than result of this study [Term 144 (86.2%), Preterm 23 (13.8%) , Term 88(88%), Preterm 12 (12%) and term 135 (82.3%),preterm 29 (17.7%)] respectively.

Preterm neonates are more likely to have hospital admission due to other causes than jaundice e.g, sepsis.

In the present study, mean serum bilirubin level of the neonates who receive oral phenobarbital (n=87) at enrollment was 14.57± 2.31 mg/dl, level was similar to that reported in Agrawal V et al 14.08±2.02 mg/dl.[9] Mohammad Kazem Sabzehei, Behnaz Basiri et al study reported serum bilirubin level in term babies was 17.4±3.6 mg /dl , which was slightly higher than the level of the neonates who receive oral phenobarbital only ,and slightly lower than the level of neonates who require phototherapy according to the guidelines of American Academy of Pediatrics in addition to oral phenobarbital (n=14) 19.94±1.36 mg/dl .[14]

Comparable mean serum bilirubin level at enrollment was reported in study by Gundur NM, Kumar P et al (11.6±3.7mg/dl), which was lower than the mean serum bilirubin level of this study .[15]

The mean body weight of the neonates was 3479±567 g (1750-4600 g) ,approximately similar to Siyah bilgin et al ,Turkey, in which mean body weight was 3150±415 g (2200-4100 g).[16]and slightly higher than Boskabadi H. Goudarzi M. et al study(2900±600 g) .[17]

Regarding blood groups and Rh typing for the neonates and their mothers ,the present study shows ABO Incompatibility 21(20.8%),Rh Incompatibility 11(10.9%) and the remaining 69(68.3%) were Compatible ,these results were approximately similar to the result of Shao-Wen Cheng, Ya-Wen Chiu et al ,Taiwan, ABO incompatibility (21.8%), [13] while

Agrawal V et al. show ABO incompatibility 3(3%) and Rh incompatibility 10 (10%),[9]Mohammad Kazem Sabzehei, Behnaz Basiri et al Iran,ABO incompatibility 5% (5),[14] Gundur NM, Kumar P et al ,ABO incompatibility 5 (8%), Rh incompatibility 2 (3%),[15] Siyah bilgin et al ,Turkey ,blood group incompatibility (2%),[16]Boskabadi H. Goudarzi M. et al ,Iran study blood group (ABO) incompatibility (6.9%),[17] Merih Çetinkaya, Özkan Hilal et al ,Istanbul,blood group incompetency (10%) ,[18] and Mahendra Kumar Banakar et al ,United Kingdom,Hemolytic Jaundice 3 (9%).[19]

The mean age of the study population was 19.8±3.61 days (15-27 days), which was similar to Boskabadi H. Goudarzi M et al study (19.5±4.7 days) ,[17]and the neonates were referred for screening of prolonged jaundice in Parvathamma PA et al study at age 14-73 days.[20]

Phenobarbital proved efficacy on decreasing total serum bilirubin level in this study, there was a highly statistically significant decrease in TSB for the patients who were treated with phenobarbital and those who were treated with phototherapy in addition to phenobarbital compared to the baseline level ,mean baseline TSB 14.57± 2.31 mg/dl vs TSB after phenobarbital 6.79±1.62 mg/dl (*P* value <0.001) and mean baseline TSB 19.94± 1.36 mg/dl vs TSB after phototherapy and phenobarbital 6.33±1.37 mg/dl (*P* value <0.001) respectively.

Numerous clinical trials have shown that both administration of phenobarbital to pregnant mothers before delivery and phenobarbital administration to neonates after delivery limit the severity of unconjugated hyperbilirubinemia, reduce the peak serum total bilirubin concentrations caused by physiologic jaundice, and the need for exchange transfusion. There was no research available about the use of phenobarbital in the management of prolonged unconjugated hyperbilirubinemia. To our knowledge, this study is the first comprehensive survey to use phenobarbital in the management of prolonged unconjugated hyperbilirubinemia.

T. VALAES et al (Greece, 1980) study had demonstrated that prenatal phenobarbital treatment significantly decreases the problem of neonatal jaundice, in which the group of newborns whose mothers received at least 10 (100 mg phenobarbital) tablets, the incidences of marked jaundice and exchange transfusion was reduced.[21]

Kumar et al (2002), an Indian study used two intervention groups Group I in which the preterm neonates were given 10 mg/kg loading dose of phenobarbital on day 1 followed by maintenance 5 mg/kg/day from day 2 to day 5;and Group II — neonates were given phenobarbital in the maintenance dose of 5 mg/kg/day from day 1 to day5. They reported that beneficial effect of phenobarbitone was more pronounced if loading dose was administered at start of phototherapy.[22]

Saipriya et al , an Indian study conclude that oral phenobarbital 3 mg/kg/day for 5 days were effectively reduced the peak serum bilirubin levels & also decreased the duration of phototherapy in preterm babies , no need of exchange transfusion in phenobarbital treated group. The duration of hospital stay was also decreased. Hence prophylactic phenobarbital seems to be a cheap alternative.[23]

Phenobarbital also proved efficacy on decreasing serum bilirubin level in term neonates in different dosage form and route of administrations, Hamidi M et al ,2013 5 mg/kg phenobarbital was used orally.[4]while in Suh HJ, et al Korean study (1996)3 mg/kg phenobarbital was used as intramuscular injection.[24]

Kaabneh et al, 2015 Jordian study evaluate the effect of phenobarbital in combination with phototherapy may help newborn infants

with isoimmune hemolytic disease, they were used oral dose of 2.5 mg/kg phenobarbital every 12 hours for 3 days (this was dispensed in linctus simplex in a concentration of 1 mg/mL) that results in a faster decline in total serum bilirubin, and thus may decrease the need for blood exchange transfusion than phototherapy alone.[25]

Conclusions

1. Oral phenobarbital supplementation in the neonates with prolonged unconjugated hyperbilirubinemia can significantly accelerate reduction in serum bilirubin levels.
2. Phenobarbital was safe, tolerable and no obvious adverse effects had been reported.
3. No need for cessation of breast feeding in cases of presumed breast milk jaundice.

Recommendations

1. It is advisable to use oral phenobarbital (5 mg/kg/day) in treatment of prolonged neonatal unconjugated hyperbilirubinemia.
2. Continue exclusive breast feeding and no need for interruption of breast feeding for treatment of presumably breast milk jaundice. A cessation of breast feeding, even two days, can threaten the infant's ability to return to exclusive breast feeding.

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