Research Article

Comparative study of Phototherapy only and Phototherapy plus Phenobarbitone in treatment of Neonatal Jaundice - An Observational Study

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ABSTRACT

Objectives: The study was intended to compare the effectiveness of phenobarbitone and phototherapy combination over phototherapy alone in treatment of neonatal jaundice.

Materials and methods: A total of 47 neonates were enrolled in this observational study,of which 17 were randomised to Group 1 and were given only phototherapy. Sixteen neonates were placed in Group 2 and were given phototherapy plus phenobarbitone. Fourteen neonates were excluded from the study. Phototherapy was started in neonates with total serum bilirubin ≥13 mg/dl. Phenobarbitone was given in a dose of 5 mg/dl/day in two divided doses. Various parameters were evaluated regarding demographics, maternal data, physical examination, laboratory data and treatment. Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program was used for statistical analysis.

Results: The demographics, maternal data and hematologic data were not statistically different ($p>0.05$) between both the groups. The percentage decrease in total serum bilirubin was 26.06% and 31.06% for Group 1 and Group 2, respectively ($p=0.105$). However, the rate of decrease of bilirubin was 0.09 mg/dl/hr and 0.16 mg/dl/hr in Group 1 and Group 2, respectively ($p=0.004$). The mean total duration of phototherapy was 103.57 hr and 76.41 hr in Group 1 and Group 2, respectively ($p=0.019$). The most prevalent risk factor was low birth weight, followed by ABO incompatibility and infection.

Conclusion: The combination of phototherapy plus phenobarbitone is effective in decreasing the duration of phototherapy, thereby decreasing the adverse effects that may occur due to longer duration of phototherapy. The combination also reduces the hospitalization stay thus decreasing the overall cost.

Keywords: Neonatal Jaundice; Phenobarbitone; Phototherapy

1. INTRODUCTION

Jaundice is one of the most common conditions needing medical attention in newborn babies. Jaundice refers to the yellow color of the skin and whites of the eyes caused by excess bilirubin in the blood. Normally, bilirubin passes through the liver and is excreted as bile through the intestines. Jaundice occurs when bilirubin builds up faster than a newborn's liver can break it down and pass it from the body.[1]

Adults are usually jaundiced when bilirubin levels exceed 2 mg/dl. Neonates appear jaundiced when

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serum total bilirubin levels reach 5-7 mg/dl. Various factors are responsible for development of jaundice and treatment depends on the type and intensity of hyperbilirubinemia.[2]

In the majority of newborns, jaundice is a benign condition. However, an incorrect or delayed diagnosis and delayed treatment may put newborns at risk of developing kernicterus or acute bilirubin encephalopathy[3]. Kernicterus is the chronic form of bilirubin encephalopathy and occurs when the deposition of bilirubin in the brain causes irreversible damage and may lead to neurological toxicity and even death.[4]

Phototherapy has been the most extensively used approach for treatment of neonatal jaundice since its inception in 1952. It gradually decreased the need of exchange transfusion in neonates and the adverse effects of the increased level of bilirubin. Phototherapy alone may take longer duration to bring down bilirubin to normal or safe levels and such long duration may inherently lead to development of side effects.

In recent years, medications have also been used to prevent and treat neonatal jaundice, which comprise of intravenous immunoglobulin, phenobarbitone and clofibrate.[5] High dose intravenous -globulin (IVIG) (0.5 to 1 gm/kg) has been shown to reduce the need for exchange transfusions in Rh and ABO hemolytic disease.[6] Phenobarbitone improves hepatic uptake, conjugation and excretion of bilirubin thus helps in lowering of bilirubin. However its effect takes time. When used prophylactically in a dose of 5 mg/kg for 3-5 days after birth, it has shown to be effective in babies with hemolytic disease, extravasated blood and in preterm without any significant side effects.[7] Clofibrate is an activating factor (Peroxisome Proliferators Activated Receptors, PPARS) that increases conjugation and excretion of bilirubin.[8] It has been used to treat jaundice combined with phototherapy in hospitalized infants.

Phenobarbitone can be used in adjunct to phototherapy for treating neonatal jaundice. The mode and site of action of phototherapy and phenobarbitone are different. Phototherapy acts by generating singlet oxygen which upon collision with the bilirubin in the skin, causes its oxidation,[9] whereas phenobarbitone increases the hepatic bilirubin conjugating capacity by enhancing the maturation of the enzyme glucuronyl transferase.[10] Since the modes of both therapies are different they lead to minimized plasma bilirubin concentration through their synergistic action.[11]

The objective of present study was to evaluate the effectiveness of phenobarbitone and phototherapy combination over phototherapy alone in treatment of neonatal jaundice by measuring the serum bilirubin level and duration of phototherapy. Further, the assessment of factors which may affect the prevalence of jaundice, like age at onset of treatment, birth weight, gestational age, gender, G6PD deficiency, mode of delivery, and ABO incompatibility were also evaluated.

2. MATERIALS AND METHODS

2.1. Study Design

This observational study was carried out in Modi Children's Hospital in India from September 2014 to March 2015. Forty seven neonates with jaundice were admitted to the hospital during this period.Prior approval of the Institutional Ethics Committee was obtained and written informed consent was obtained from the parent or legal guardian before randomization of patients.

2.2. Subject Selection

The included neonates had total serum bilirubin (TSB) ≥13mg/dl and normal vital parameters (heart rate, respiratory rate, body temperature). The exclusion criteria was: neonates who had exchange transfusion during previous 24 h, neonates with any evidence of congenital malformations or other disorders, history of maternal use of phenobarbitone in last month of pregnancy, neonates being treated with phenobarbitone through intravenous or intramuscular routes, neonates whose parents refused to give consent.

Table 1: Baseline demographics

Baseline parameters	Phototherapy only group (n = 17)	Phototherapy + phenobarbitone group (n = 16)	p value
Age at admission (days, mean ±SD)	2.59 ± 2.00	3.81 ± 2.74	0.156
Age at starting phototherapy(days, mean ± SD)	3.88 ± 1.53	4.62 ±2.33	0.293
Gender			
Male, n(%)	12 (70.58%)	8 (50%)	X^2= 1.463,
Female, n(%)	5 (29.42%)	8 (50%)	p = 0.226
Gestational age (wks, mean ± SD)*	34.42 ± 3.03	35.25 ± 2.80	0.480
Mode of delivery			
Normal, n(%)	6 (35.29%)	7 (43.75%)	X^2= 0.247,
Cesarean, n(%)	11 (64.71%)	9 (56.25%)	p = 0.619
Weight at birth (gms, mean ± SD)	2315.00 ± 565.69	2516.56 ± 509.53	0.293
<= 2000.00	6 (35.29%)	4 (25%)	
2001.00 - 2500.00	4 (23.52%)	4 (25%)	X^2 = 1.462
2501.00 - 3000.00	6 (35.29%)	5 (31.25%)	p = 0.691
>3001.00	1(5.88%)	3 (18.75%)	
Weight at admission (gms, mean ± SD)	2296.17 ± 510.24	2320.00 ± 716.47	0.914

*** n= 14 and 12, respectively for phototherapy only and phototherapy + phenobarbitone group**

2.3. Study Procedure

Patients were selected as per eligibility criteria. Randomly the neonate was assigned in one of the two groups. Group 1 constituted of patients who were treated with phototherapy alone. Group 2 consisted of patients to be treated with combination of phototherapy and phenobarbitone. Phototherapy cycle of 1 hour on and 1 hour off round the clock was maintained. Blue florescent light of wavelength 400-490 nm was used. Light source was placed at a distance of 30-45 cm above the cradle and only the eyes and genitals were covered and rest of the body was directly exposed to light. Gardenal® Syrup (Abbott India Limited, India) 60 ml bottle containing 20mg/5ml of phenobarbitone was administered orally twice daily as per body weight in a dose of 5mg/Kg/Day. Duration of phototherapy was based on individual's clinical signs and need. The duration of phenobarbitone dosing was equivalent to that of duration of phototherapy. Case Report Form (CRF) was filled accordingly to collect data. Age at onset of treatment, TSB (mg/dl), indirect Bilirubin (mg/dl), duration of phototherapy, birth weight (gms), gestational age (wks), dehydration(% birth weight loss), CBC, icteric scale, gender, breastfeeding, G6PD deficiency, mode of delivery, socioeconomic status, religion, diet habits of mother were recorded in the CRF. The collected data was then evaluated.

2.4. Statistical Analysis

Continuous variables were presented as mean ± standard deviation and categorical variables as counts and percentages. Independent t-test was applied for continuous variables and Chi-square test was applied for categorical variables. All data were analysed using the Statistical Package for Social Sciences (SPSS; Chicago, IL, USA) program, version 19. P value < 0.05 was considered statistically significant.

3. RESULTS

A total of 47 neonates were screened for presence of jaundice. In all, 33 eligible neonates were randomly assigned to phototherapy only (n=17) or phototherapy + phenobarbitone (n=16) groups. Fourteen neonates were excluded from the study.

Twelve neonates were excluded before randomization: three for lack of consent, two for bilirubin levels less than 13 mg/dl, one for occurrence of congenital heart disease, one for presence of meningitis, and two were being given i.v. phenobarbitone due to convulsions. Two neonates were ex-

cluded after randomization: one for discontinuation of phenobarbitone dose due to respiratory tract feeding and one had been discharged against medical advice.

3.1. Patient Demographics

Baseline demographics of neonates are outlined in Table 1**.** Parameters like, age at starting treatment, gender, gestational age, mode of delivery, birth weight, weight at admission were assessed for neonates in both groups. There was no significant difference between the groups ($p > 0.05$), which depict that the groups were randomly allotted.

3.2. Maternal Data

The details regarding mother's age, blood group, diet habits, etc. in both groups are detailed in Table 2. There was no significant difference ($p < 0.05$) between any of the parameters which denote random distribution.

3.3. Physical Examination

The physical examination was performed by observing the colour of skin and eyes. Majority of patients had yellow coloured skin and eyes. Based on icteric scale, the majority of neonates presented with score of 1(39.40%) and 2(36.37%). There was no significant difference between the icteric scores of two groups ($p = 0.631$). Vital parameters like respiratory rate, SpO_2, pulse rate and body temperature were normal in all the neonates with no significant difference ($p> 0.05$) between the groups (Table 3).

3.4. Laboratory Data

The hematologic data for both groups is outlined in Table 4. The hematologic data were comparable in both the groups with no significant difference between the groups ($p > 0.05$).The level of total serum bilirubin at hospitalization was 15.32 ± 2.25 mg/dl in Group 1 and 15.12 ± 1.12 mg/dl in Group 2. The decrease in total bilirubin and indirect bilirubin levels was observed in both the groups. This decrease was greater in Group2 than in Group 1, but the difference was not statistically significant with p value of 0.105 and 0.071 for percentage decrease in total serum bilirubin and indirect bilirubin, respectively. The decreasing rate of total serum bilirubin was 0.09 ± 0.05 mg/dl/hr in Group 1 and 0.16 ± 0.05 mg/dl/hr in Group 2 (Figure 1). It reveals that bilirubin decreases with a greater slope in Group 2 compared to Group 1. There was a significant difference in both the groups ($p = 0.004$).

3.5. Treatment

The duration of phototherapy was estimated for both the groups in terms of total phototherapy duration and effective phototherapy duration (only 'on' hours). There was a decreased duration of phototherapy in Group 2 as compared to Group 1, which was statistically significant ($p = 0.011$) (Table 5).

On average, the hospitalization time in Group 1 was 4.47 days and 3.19 days in Group 2. There was a significant reduction in hospitalization days ($p = 0.009$) in Group 2. The range of hospitalization in Group 1 was 2 days to 7 days, whereas for Group 2 was 1 day to 5 days.

The dose of phenobarbitone was 5mg/kg/day in two divided doses. The number of doses ranged from 3 to 10 doses, with a mean of 6.06 doses and maximum number of patients were administered 6 doses (31.3%).

3.6. Risk Factors

There are many etiologic factors responsible for the development of jaundice in neonates (Table 6). Among various known factors low birth is found to be the most prevalent factor, followed by ABO incompatibility and infection.

3.7. Side Effects/ Adverse Events

There were no serious adverse events observed during treatment in any of the patient. The side effects observed were skin rashes, dehydration, continuous crying and drowsiness (Table 7).
Dehydration is the most common side effect of phototherapy. The weight loss after treatment was found to be higher in Group 1 (8.47%) than in Group 2 (-4.07%) with a significant difference of 0.021.

Table 2: Maternal data

Parameters	Phototherapy only group (n = 14)	Phototherapy + phenobarbitone group (n= 12)	p value
Mother's age(yrs, mean ± SD)	25.00 ± 4.18	25.25 ± 3.81	0.875
≤ 24 yrs, n(%)	8 (57.14%)	6 (50%)	X^2= 0.478
25 – 29 yrs, n(%)	3 (21.43%)	4 (33.33%)	P = 0.788
≥ 30, n(%)	3 (21.43%)	2 (16.67%)	
Religion			
Hindu, n(%)	10 (71.42%)	10 (83.33%)	X^2= 0.780, p = 0.677
Muslim, n(%)	4 (28.58%)	2 (16.67%)	
Diet habits of mother			
Vegetarian, n(%)	1 (7.14%)	3 (25.00%)	X^2= 1.842, p = 0.398
Non-vegetarian, n(%)	13 (92.86%)	9 (75.00%)	
Mother's blood group			
A +, n(%)	4 (28.57%)	3 (25.00%)	
B +, n(%)	1 (7.14%)	2 (16.67%)	
AB +, n(%)	3 (21.43%)	2 (16.67%)	X^2= 0.901, p = 0.970
O +, n(%)	5 (35.71%)	4 (33.33%)	
AB -, n(%)	1 (7.14%)	1 (8.33%)	
Previous pregnancy, n(%)	6 (42.86%)	5 (41.67%)	0.945
0, n(%)	8 (57.14%)	7 (58.33%)	X^2= 0.113
1,n(%)	3 (21.43%)	2 (16.67%)	P = 0.995
2, n(%)	3 (21.43%)	3 (25.00%)	
Previous Mode Of Delivery			
Normal, n(%)	6 (100.00%)	4 (80.00%)	X^2= 2.015, p = 0.365
Cesarean, n(%)	0 (0.00%)	1 (20.00%)	
Previous sibling jaundice, n(%)	1(16.6%)	0 (0.00%)	X^2= 1.125, p = 0.570
Phototherapy needed in previous sibling, n(%)	1 (16.67%)	0 (0.00%)	X^2= 1.638, p = 0.441
Hemolyticanemia, n(%)	0 (0.00%)	0 (0.00%)	1.00
Diabetes in mother, n(%)	0 (0.00%)	0 (0.00%)	1.00
Sickle cell anemia, n(%)	2 (14.28%)	0 (0.00%)	X^2= 2.114, p = 0.347

Table 3: Vital parameters and feeding

Parameters	Phototherapy only group (n = 17)	Phototherapy + phenobarbitone group (n= 16)	p value
Respiratory rate (per min., mean ± SD)	31.06 ± 5.46	31.00 ± 3.59	0.971
SpO_2 (%, mean ± SD)	97.88 ± 2.02	98.19 ± 0.98	0.584
Pulse rate (per min., mean ± SD)	137.06 ± 10.48	131.56 ± 11.98	0.172
Temperature (^{0}F, mean ± SD)	98.45 ± 0.59	98.56 ± 0.71	0.618
Breast feeding at admission			
Yes, n(%)	7 (41.18%)	13 (81.25%)	X^2= 5.544
No, n(%)	10 (58.82%)	3 (18.75%)	P = 0.019*
Feeding during treatment			
Bottle feed, n(%)	9 (52.94%)	6 (37.50%)	X^2 = 0.847
Breast milk, n(%)	2 (11.76%)	3 (18.75%)	P = 0.655
Both, n(%)	6 (35.30%)	7 (43.75)	

*** Indicates significant difference between the groups (p<0.05)**

Table 4: Hematologic data

Hematologic data	Phototherapy only group (n = 14)	Phototherapy + phenobarbitone group (n = 11)	p value
Hemoglobin (gm/dl, mean ± SD)*	15.82 ± 1.12	15.86 ± 1.29	0.933
Total WBC (per cmm, mean ± SD)	11378.57 ± 2406.14	10345 ± 2119.13	0.266
Band cells (%, mean ± SD)	3.29 ± 0.61	2.82 ± 0.98	0.186
Neutrophils (%, mean ± SD)	51.43 ± 7.81	48.55 ± 7.34	0.354
Eosinophils (%, mean ± SD)	1.00 ± 0.00	1.09 ± 0.30	0.341
Basophils (%, mean ± SD)	0.00 ± 0.00	0.00 ± 0.00	1.000
Leucocytes (%, mean ± SD)	43.00 ± 8.06	44.09 ± 6.96	0.720
Monocytes (%, mean ± SD)	3.57 ± 0.76	3.45 ± 1.03	0.757
RBS (mg/dl, mean ± SD)**	113.22 ± 62.51	141.37 ± 126.15	0.493
Serum calcium (mg/dl, mean ± SD)***	5.23 ± 3.63	3.61 ± 3.78	0.288
G6PD deficiency			
Yes, n(%)	1 (7.14%)	0 (0.00%)	X^2= 1.638
No, n(%)	13 (92.86%)	11 (100.00%)	P = 0.441
C- Reactive protein			
Positive, n(%)	7 (50.00%)	4 (36.36%)	X^2= 1.298
Negative, n(%)	7 (50.00%)	7 (63.64%)	P = 0.525
Blood group			
A +, n(%)	5 (29.41%)	3 (18.75%)	
B +, n(%)	6 (35.29%)	5 (31.25%)	X^2 = 0.873,
AB +, n(%)	2 (11.77%)	3 (18.75%)	P = 0.832
O +, n(%)	4 (23.53%)	5 (31.25%)	
Total serum bilirubin			
Initial (mg/dl, mean ± SD)	15.32 ± 2.25	15.12 ± 1.12	0.743
Final (mg/dl, mean ± SD)	11.22 ± 1.54	10.31 ± 1.29	0.072
Indirect bilirubin			
Initial (mg/dl, mean ± SD)	12.55 ± 3.89	13.58 ± 1.03	0.308
Final (mg/dl, mean ± SD)	9.99 ± 1.60	9.29 ± 1.42	0.186

***n = 17 and 15, respectively for phototherapy only and phototherapy + phenobarbitone groups. ** n = 14 and 12, respectively for phototherapy only and phototherapy + phenobarbitone groups. ***n = 13 and 12, respectively for phototherapy only and phototherapy + phenobarbitone groups. WBC – White Blood Cells; RBS – Random Blood Sugar; G6PD – Glucose 6 Phosphate Dehydrogenase**

Table 5: Duration of phototherapy

Duration of phototherapy	Phototherapy only group (n = 17)	Phototherapy + phenobarbitone group (n = 16)	p value*
Total duration (hrs, mean ± SD)	103.6 ± 36.08	76.41 ± 26.52	0.019
Effective duration (hrs, mean ± SD)	45.71 ± 15.46	32.50 ± 12.29	0.011

*** P value (<0.05) show significant difference between the groups**

4. DISCUSSION

Use of phenobarbitone in management of neonatal jaundice is rarely reported.[12] Phenobarbitone has been previously used in adjunct with phototherapy, but its efficacy was not established due to lack of sufficient data.[11, 13-16] Since, the mode of action of phenobarbitone and phototherapy are different and might lead to synergistic decrease in bilirubin levels, in this study we have compared the effectiveness of phenobarbitone and phototherapy combination over phototherapy alone in treatment of neonatal jaundice by measuring the serum bilirubin level and duration of phototherapy.

In present study, the patients were divided into two groups. Group 1 received only phototherapy (12 hours/day) and Group 2 received phototherapy (12 hours/day) and oral phenobarbitone (5 mg/kg/day in two divided doses).

Table 6: Possible predisposing risk factors in neonates with jaundice

Predisposing factors	Male, n(%)	Female, n(%)
G6PD deficiency + ABO incompatibility + infection	1 (5%)	0 (0%)
Low birth weight alone (≤ 2500 gms)	4 (20%)	3 (23.08%)
ABO incompatibility alone	2 (10%)	1 (7.70%)
ABO incompatibility + low birth weight	2 (10%)	2 (15.38%)
Rhesus incompatibility alone	1 (5%)	0 (0%)
Rhesus incompatibility + low birth weight + infection	1 (5%)	0 (0%)
Infection alone	0 (0%)	1 (7.70%)
Infection + ABO incompatibility	2 (10%)	0 (0%)
Infection + low birth weight	2 (10%)	2 (15.38%)
Infection + ABO incompatibility + low birth weight	0 (0%)	2 (15.38%)
Unknown factors	5 (25%)	2 (15.38%)
Total	**20 (100%)**	**13 (100%)**

G6PD – Glucose 6 phosphate dehydrogenase

Table 7: Adverse events

Adverse events	Phototherapy only (n = 17)	Phototherapy + Phenobarbitone (n = 16)
Serious adverse events, n (%)	00 (0.00%)	00 (0.00%)
Skin rashes, n (%)	01 (5.89%)	02 (12.50%)
Dehydration, n (%)	01 (5.89%)	00 (0.00%)
Hyperactivity and crying, n (%)	01 (5.89%)	01 (6.25%)
Drowsiness, n (%)	00 (0.00%)	01 (6.25%)
Total adverse events, n (%)	**03 (17.65%)**	**04 (25.00%)**

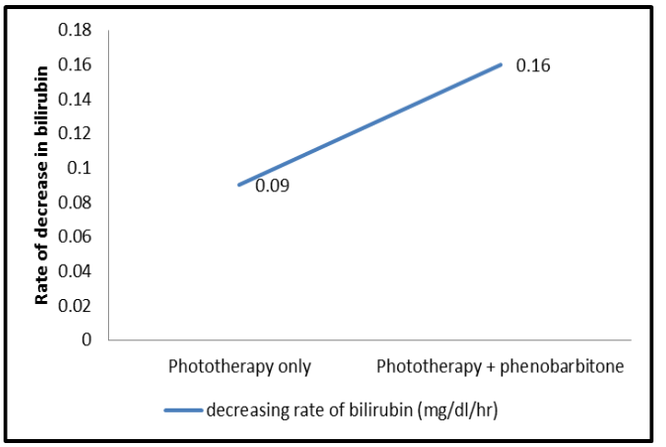

Figure 1: Rate of decrease in bilirubin level (mg/dl/hr).*p = 0.004, indicates significant difference

The baseline demographics were similar in both the groups with no statistical difference (p >0.05). This depicted that baseline demographics would not affect the difference in results between the groups. Similarly, maternal data did not vary significantly between the groups, so they would also not affect the difference in results between the groups.

All the vital parameters were found to be normal in all neonates. There was no significant difference in the icteric scale between two groups. Breastfeeding at admission did not show any effect on the total serum bilirubin (p = 0.347). This is in contrast to previous study by Schneider[17] who stated that serum bilirubin levels were found to be significantly higher in breastfed neonates than in artificially fed neonates.

Mishra *et al, (2008)* [7] have specified that decreased frequency of breastfeeding, not the characteristics of breast milk is associated with the augmented occurrence of jaundice in breast fed neonates.

The hematologic data for both the groups were found to be similar with no significant difference (p >0.05). There was no significant difference (p = 0.743) in the total serum bilirubin levels at hospitalization between the two groups, with a mean of 15.32 ± 2.25 mg/dl and 15.12 ± 1.12 mg/dl in group 1 and group 2, respectively. There was a greater percentage decrease in total bilirubin levels in group 2 (31.06%) than in Group 1 (26.06%), but the difference was not statistically significant (p = 0.105). On contrary, the hourly decrease in total bilirubin level was significantly higher in group 2 than in group 1 (p =0.004) with the mean

rate of decrease in bilirubin of 0.09 mg/dl/hr (1.08 mg/dl in 12 hours) and 0.16 mg/dl/hr (1.92 mg/dl in 12 hours) in Group 1 and Group 2, respectively. The rate of decrease of bilirubin in Group 1 was in accord to a previous study by Lall*et al*, (1982)[15] that stated an expected total bilirubin fall of 0.97 mg/dl in 12 hours on using conventional day-light phototherapy. Nevertheless, the rate of decrease of bilirubin on using combination of phototherapy and phenobarbitone was higher in our study than in study by Lall *et al*, (1982)[15] who stated drop of 1.02 mg/dl 12 hourly on administering similar dose of 5 mg/kg/day. However, the rate of decrease was less in the combination group as compared to a study reported by Ahadi *et al*, (2013) [18] which accounted for an hourly decrease of 0.22 mg/dl at first 24 hours after administration of phenobarbitone on use of phototherapy and phenobarbitone together. The lower decreasing rate of bilirubin in our study might be the probable cause for the insignificant difference between the percentage decrease of total serum bilirubin levels in both the groups.

Wong *et al*, (1973)[16] used intramuscular phenobarbitone in combination with phototherapy and compared it with phototherapy and phenobarbitone as individual regimens. They reported that the decrease in bilirubin levels was greater in combination group than other groups but the difference was not statistically significant. On the other hand, they confined the duration of phototherapy to 60 hours in both the groups and also the number of doses of phenobarbitone (10 doses) were fixed with a higher dose per day (8 mg/kg/day). Whereas, in our study the duration of phototherapy was not constrained to particular time period, instead it was based on individual's clinical signs and need and the number of doses of phenobarbitone varied in adjunct the duration of phototherapy and the dose was lower than the previous study. Thus, titration of doses might lead to better difference in both the regimens.

Sircar *et al*, (1979)[11] reported that phototherapy and phenobarbitone in combination is advantageous in treatment of neonatal jaundice than using phototherapy or phenobarbitone alone. However, the dose of phenobarbitone used was much higher than in this study. They divided the neonates on bases of birth weight into two groups. One group with neonates of weight >2.5 kg were given 5 mg 8 hourly and other group with weight <2.5 kg was given 6 mg/kg. The infant was exposed to blue light 6 hours on and 2 hours off around the clock. Though in our study the dose was low and the phototherapy cycle was different from the previous study, the per hour decrease in bilirubin was significantly higher in Group 2 than in Group 1 and the difference in duration of phototherapy adds icing on the cake. The total duration of phototherapy in Group 1 and 2 was 103.57 hr and 76.41 hr, respectively. This difference was statistically significant ($p = 0.019$) which denotes that the combination of phenobarbitone and phototherapy decreases the duration of phototherapy as compared to use of phototherapy only.

Ahadi *et al*, (2013)[18] reported that 63.3% of patients were confined to phototherapy for 72 hours and 16.7% were confined to phototherapy for 94 hours on using combination of phototherapy and phenobarbitone and the mean stay of hospitalization was 2.9 days. In spite of a greater initial decrease in bilirubin levels (0.22 mg/dl/hr) in their study, the duration of phototherapy and hospital stay are found to be similar to our study. Lall *et al*, (1982)[15] stated that the mean duration of phototherapy for phototherapy only and photobarb therapy was 96 hours and 92 hours, respectively and concluded that there was no significant difference between the two regimens. In present study, the duration of phototherapy for Group 1 was higher than that stated in previous study but the Group 2 underwent lesser duration of phototherapy than the previous study. This difference leads to the significance of combination therapy in decreasing the duration of phototherapy.

The duration of hospitalization stay is one of the indicators of cost of therapy. In the present study, the mean duration of hospitalization stay was significantly reduced in combination group (3.19 days) as compared to phototherapy alone (4.47 days). These results were similar to previous study carried by Ahadi *et al*, (2013).[18] These results

indicate that apart from reducing the duration of phototherapy, combination of phenobarbitone also reduces cost of treatment.

The most common causes of occurrence of jaundice was found to be low birth weight (54.55%) followed by ABO incompatibility (36.37%) and infection (33.3%). On contrary, Narang *et al,* (1997)[19] reported that the most common cause of jaundice was idiopathic followed by sepsis and G6PD deficiency and also stated that preterm neonates are at a greater risk of development of jaundice than the term neonates. Whereas, in present study, the proportion of term neonates (61.54%) was higher than the preterm neonates (38.46%). There is a variability in the prevalent risk factors in various studies, which might be solved on including a greater number of patients in the study. In a study, Maisels *et al,* (1988)[20] mentioned that Male gender is a known risk factor for pathological jaundice. Similarly our study also presented higher number of males with jaundice than females.

There were no serious adverse events in any of the patient. The side effects observed were skin rashes, crying, dehydration and drowsiness. There are a number of studies that have used phenobarbitone in different dosage ranging from 2.5 mg once a day for 3 days to a single dose of 12 mg/kg.[21-23] In present study, a lower dose of phenobarbitone was used which might subside adverse effects associated with the higher doses. In previous studies[18, 24], phenobarbitone is thought to be associated with gastrointestinal side effects like nausea and vomiting and also with respiratory insufficiency but in our study no such side effects were encountered. Many studies establish the presence of drowsiness on use of phenobarbitone.[15, 24, 25] However in present study there was only one case of drowsiness probably due to low dose of phenobarbtone. Due to paucity of data, further studies are warranted to evaluate late adverse effects and neurodevelopmental outcome of this therapeutic strategy.

Thus, the present study demonstrates the effectiveness of combination of phototherapy and phenobarbitone in management of neonatal jaundice as there is a significant difference in the duration of phototherapy and also in hospitalization stay. But there was no statistical significant difference in decreasing the bilirubin levels between the two groups. The possible reason for this is the small number of data collected in the present study. The present study suffers a limitation of smaller number of patients.

5. CONCLUSION

In the present study, we aimed to provide therapy to ensure that serum bilirubin is kept at a safe level and consequences of hyperbilirubinemia are prevented with an objective of comparison of the effectiveness of phenobarbitone and phototherapy combination over phototherapy alone. We found that combination of phototherapy and phenobarbitone is effective in reduction of duration of phototherapy, thereby decreasing the adverse effects that may occur due to longer duration of phototherapy. The combination also reduces the hospitalization stay thus decreasing the overall cost. There was an increased reduction of bilirubin level in the combination group than in phototherapy only group, but the decrease was not statistically significant. The small number of data might be probable cause for such insignificance. There were no serious adverse events in any of the patient during hospital stay, which depicts safety of both the treatments. But the long term follow-up is required to demonstrate the occurrence of any late adverse events and neurodevelopmental outcomes.

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