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Comparison of the Effect of Phenobarbital and Phototherapy to Phototherapy in the Treatment of Non-Hemolytic Hyperbilirubinemia in Neonates Admitted to the NICU of Mashhad Hospitals: A Clinical Trial

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ABSTRACT

Introduction: Neonatal jaundice is a significant problem that occurs in 80% of premature infants and 30-60% of term infants in the first week of life. About 6-10% of these cases develop severe hyperbilirubinemia in need of treatment (bilirubin level above 90% of age per hour), and 5-36% of healthy full-term neonates who are discharged from the hospital are readmitted due to moderate to severe hyperbilirubin. Treatments for jaundice include phototherapy and blood exchange transfusions. Percutaneous phototherapy by photoisomerization reduces blood bilirubin. However, it is expensive, and due to the necessity of hospitalization and the eyes being covered, it disrupts the relationship between the mother and the child. Furthermore, the power of phototherapy to reduce bilirubin levels above 20 is not so high.

Methods: The infants at the neonatal intensive care units (NICUs) of Imam Reza (AS) and Samen Al-Aimeh hospitals, Mashhad, Iran, were selected for this study after receiving approval from the Research Council of Mashhad University of Medical Sciences, informing the infants' parents, and obtaining their informed consent. Phenobarbital complications were explained to the parents of infants weighing more than 2.5 kg before admission, and adjustments were made based on gestational age. Infants were randomly assigned to either the phenobarbital (case) or the placebo (control) group. Routine laboratory tests for jaundice were performed for all infants. After that, phototherapy and medications were administered. Bilirubin levels were checked every 6, 12, 24, and 48 h after medication, and at discharge. The collected data were analyzed using SPSS software (version 16). The results are considered with 80% power, a 95% confidence interval, and a 5% significance level.

Results: This study was performed on 80 jaundiced infants who were referred to Imam Reza (AS) and Samen Al-Aimeh hospitals, Mashhad, Iran, for treatment and were transferred to the NICU. According to the results, 45% of infants in the study group and 52.2% of the total number of them were male, but the difference was not significantly significant (P>0.05). There was also no significant difference in infants' gestational age, weight, or the age of hospitalization. The mean and standard deviation of bilirubin levels before and after the intervention were not significantly different between the two groups after 6, 12, 24, and 48 h and at discharge time. Despite the significant difference, the length of hospital stay could not be studied due to the absence of exact hospitalization and discharge hours, as well as measurement errors.

Conclusion: This double-blind clinical trial study aimed to determine the effect of a single dose of 20 mg/kg of phenobarbital on healthy full-term infants who were breastfed and had symptomatic bilirubin levels in need of phototherapy. Overall, 80 full-term neonates with nonhemolytic hyperbilirubinemia were studied in two groups. The treatment in the case group included phototherapy and phenobarbital, while the control group only received phototherapy. The inclusion and exclusion criteria were considered for each infant, and the study was started after parents' informed consent was obtained. Phototherapy with 20 mg/kg phenobarbital was prescribed for the case group, while phototherapy alone was performed for the control group. After that, the bilirubin levels of both groups were checked every 6, 12, 24, and 48 h, and at the time of discharge. Decreased bilirubin was observed every 6, 12, 24, and 48 h, as well as at the time of discharge in the case group. In neonates with jaundice, phototherapy with a single dose of phenobarbital (20 mg) did not reduce bilirubin levels or the length of hospital stay.

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Introduction

Jaundice is one of the most common problems in the neonatal period, which, if severe, can cause serious damage to the nervous system, even in term infants. Between 30-60% of full-term infants and up to 80% of preterm ones have clinical symptoms in the first seven days, and about 6-10% show hyperbilirubinemia (1-4).

The cause of jaundice in infants is complex. Neonatal jaundice can be divided into two types: physiological and pathological. Pathological jaundice can lead to severe bilirubin encephalopathy. This type of jaundice can have neurological consequences in some children, including cerebral palsy, hearing loss, and dizziness (5), and it can cause type 1 diabetes in others (6). The yellow color of these infants is due to the accumulation of unconjugated pigment and fat-soluble bilirubin in the skin. This pigment is derived from hemoglobin by the enzymes hemoxygenase and bilirubin reductase. The complications of elevated bilirubin manifest as kernicterus. Considering the prevalence of jaundice and its dangerous side effects, several treatments are needed (7), including phototherapy and blood transfusions. Percutaneous phototherapy by isomerization reduces blood bilirubin, but despite being the common method of treating jaundice (8), it is expensive and disrupts the mother-child relationship due to the need for hospitalization and covering the eyes to prevent any complications. Furthermore, at bilirubin levels above 20, phototherapy can reduce bilirubin only by 10-17%. Percutaneous phototherapy with photoisomerization can reduce jaundice (9). Therefore, a combination of these two methods may be a more effective treatment. However, this case has not yet been fully investigated. Therefore, comparing the therapeutic effect of phenobarbital and phototherapy to that of phototherapy alone on the treatment of non-hemolytic hyperbilirubinemia in hospitalized infants can be of great help in considering the best method for the treatment of jaundice.

Materials and Method

Based on similar studies and considering a 95% confidence interval and a 5% accuracy, the sample size of the study was determined to be 40 infants in each group.

This double-blind clinical trial study was performed from August 2017 to March 2018 on 80 infants admitted to the NICU of Imam Reza and Samen Al-Aimeh hospitals, Mashhad, Iran. After this study was approved by the Research Council and the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran, it was registered in the International Center for Registration of Clinical Trials in Iran with code 31031.

Infants who did not have symptoms of hemolysis, extensive internal bleeding, G6PD deficiency, sepsis, severe respiratory disease requiring mechanical ventilation, or congenital anomalies were included in this study. On the other hand, those who were unresponsive to phototherapy or those whose parents did not continue the study were excluded from the analysis. After completely informing the parents and obtaining their informed consent, the study was performed on infants who met the inclusion criteria.

Patients were block-randomized and divided into the phenobarbital group (case) and the sterile distilled water group (control). Routine laboratory tests for hyperbilirubinemia were performed for all infants. Regular phototherapy was then continued, and a single dose of phenobarbital (20 mg/kg) was prescribed. Bilirubin levels were checked every 6, 12, 24, and 48 hours after drug administration, as well as at discharge. After recovery, the babies were kept under observation for one day in the hospital for rebound hyperbilirubinemia.

Statistical Analysis

All the collected data were entered into the computer and statistically analyzed using SPSS software (version 16). Descriptive findings were reported in the form of tables using appropriate dispersion and centrality indices. Mean and standard deviation were used to describe quantitative data with a normal distribution, and median and quartile range were used for data with a nonnormal distribution. Frequency (percentage) was used to describe qualitative data. In order to compare qualitative variables, the Chi-squared test or Fisher's exact test was used. If necessary, an unpaired t-test or its non-parametric equivalent (Mann-Whitney U) was used to compare quantitative variables. A significance level of less than 0.05 was considered in all calculations.

Results

Overall, 45% (18 patients) of infants in the case group and 55% in the control group were male, meaning that in the two groups, 55% and 45% were female, respectively. However, the difference was not significant. The results can be seen in Table 1.

The results showed that the duration of phototherapy in the control group and the case group was 16.2 and 17.41 h, but the difference was not significant (P=0.23). In addition, the length of hospital stay was 55 and 72 h in the two groups, respectively; however, this difference

Table 1. Demographic characteristics of patients

		Case	Control	P-value
Gender, N (%)	Male	18 (45%)	22 (55%)	>0.05
	Female	22 (55%)	18 (45%)	
Gestational age (weeks), mean (SD)		36.4 (2.39)	36.9 (2.169)	0.33
Birth weight (grams), mean (SD)		2808 (539.12)	2861 (651.91)	0.62
Age of hospitalization (days), mean (SD)		3.9 (1.66)	4.1 (1.93)	0.62

*T-test analysis

was not significant either (P>0.05). The P-values for bilirubin levels in the two groups on arrival, 6, 12, and 24 h later were 0.33, 1, 1, and 0.23, respectively, and the differences were not significant (P>0.05). However, bilirubin levels at discharge were significantly different between the two groups (P=0.001). The findings can be seen in Table 2.

Discussion

This clinical trial examined and compared the effect of phenobarbital and phototherapy to that of phototherapy alone on the treatment of non-hemolytic hyperbilirubinemia in neonates. It was performed on 80 jaundiced infants, with 45% in the study group and 55% in the control group being male. There was no significant difference between the two groups in terms of infants' gestational age, weight, and the age of hospitalization. There was also no significant difference between the two groups in the mean and standard deviation of bilirubin levels before the intervention, at 6, 12, 24, and 48 hours after the intervention, or at the time of discharge. Due to the absence of exact hospitalization and discharge hours, as well as measurement errors, the length of stay in the hospital could not be assessed.

In one study, the efficacy of oral phenobarbital, compared to placebo, was evaluated in 37 high-risk infants with hyperbilirubinemia. There was no significant difference in the results between the phenobarbital and placebo groups, and no significant side effects were observed with phenobarbital (10). In another study investigating the effect of phenobarbital on bilirubin metabolism, phenobarbital did not reduce serum bilirubin levels significantly (11). In a child with type 2 Crigler-Najjar syndrome, jaundice and bilirubin were reduced by 50% after phenobarbital administration. Phenobarbital can also improve bilirubin liver uptake in infants. Premature infants are prone to the toxic effects of hyperbilirubinemia. It is true that phenobarbital can potentially cause severe sedation in infants, but in Greece, the risk of kernicterus is reduced by giving phenobarbital to pregnant women in the last trimester of pregnancy. Similar positive effects were observed in healthy full-term infants in Korea. On the other hand, another study showed that the combination of phenobarbital and phototherapy does not have a more beneficial effect than phototherapy alone (12). Contrary to the findings of our study, the results of a previous study showed that the combination of phenobarbital and phototherapy in neonates with non-immune hemolytic disease leads to a decrease in bilirubin levels and the need for blood transfusions, compared to phototherapy alone (13).

In one study, a 10 mg/kg dose of oral phenobarbital was administered at the beginning of treatment and then a 5 mg dose every 6 h by injection for five days in infants weighing 1499-1000 g, which reduced the need for blood transfusions and the duration of phototherapy. This dose further reduced the duration of phototherapy compared to the 5 mg dose in five

Table 2. Duration of phototherapy and length of hospital stay in the two groups

		Groups		P-value
		Case	Control	
Duration of phototherapy (hours), mean (SD)		17.41±39.7	16.02±43.55	0.23
Hospitalization (hours), mean (SD)		72±1.66	55±1.88	0.12
Bilirubin levels (Mg/dl)	Bilirubin at the beginning of the study	17.52±1.54	17.84±1.41	0.33
	Bilirubin after 6 hours	15.73±1.40	15.73±1.45	1
	Bilirubin after 12 hours	13.79±1.51	13.96±1.42	1
	Bilirubin after 24 hours	12.69±0.97	12.38±1.28	0.23
	Bilirubin discharge	11.53±0.77	10.80±1.09	0.001

days (14). Although phenobarbital is known to clear bilirubin from the blood in term and preterm infants (16) and reduce the duration of phototherapy (17), in another study, it had no direct effects on lowering bilirubin (15). A previous study also found that phenobarbital had no clear effects on the reduction of jaundice due to erythrocyte iso-immunization hemolytic hyperbilirubinemia (18), which was similar to our study.

Regarding the effect of phenobarbital on the treatment of indirect jaundice in preterm infants, in three studies, the maximum serum bilirubin and the duration of phototherapy were significantly lower in the phenobarbital group, and the need for phototherapy and blood transfusion was also reduced in this group (19).

In a study that examined the effects of phenobarbital and clofibrate, the results showed that phenobarbital had a faster effect on reducing serum bilirubin and the length of hospital stay compared to clofibrate (20). On the other hand, in another study that only looked at the effect of phenobarbital on neonatal jaundice, taking 2.5 mg of phenobarbital four times a day for three days, which started 8 h after birth, had no significant effects on lowering plasma bilirubin (21). Regarding the time of hospitalization, in another study, phenobarbital reduced the duration of phototherapy and the need for blood transfusions, but it had no effects on the duration of hospitalization (22). In our study, there was no significant difference between the study and control groups in the duration of hospitalization or the duration of phototherapy. However, bilirubin levels decreased significantly at the time of discharge.

The limitation of this study was that we did not measure the level of phenobarbital in the blood, and we did not put the infants on a maintenance dose.

Conclusion

Phenobarbital is effective only in reducing bilirubin, but it has no role in reducing the duration of phototherapy or the length of hospital stay. We suggest that future studies use a larger sample size and measure the level of phenobarbital in the blood.

Conflict of interest

The authors declare that there is not conflict of interest.

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