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Evaluating the Etiology of Prolonged Unconjugated Hyperbilirubinemia in Term Neonates admitted to Neonatal Wards: A Randomized Controlled Trial

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ABSTRACT

Background: The Jaundice, also known as hyperbilirubinemia, is a potentially fatal condition that affects neonates. Several different factors contribute to this complex illness. **Objective:** The objective of this study was to compare the mean duration of phototherapy in neonates with indirect hyperbilirubinemia treated with ursodeoxycholic acid plus phototherapy versus phototherapy alone. **Study Design:** Randomized Controlled Trial (RCT) study design. **Settings:** This study was carried at Department of Pediatrics Shahida Islam Medical College, Lodhran Pakistan. **Duration:** Over 1 year from March 2020 to March 2021. **Methods:** Seventy full-term babies of both sexes were randomly split into two groups. Indirect hyperbilirubinemia was the diagnosis for all the infants, and phototherapy was being used to treat the condition. The patients in Group-A also received Ursodeoxycholic acid in addition to the phototherapy, while those in Group-B received only the phototherapy. **Results:** The average age of the newborns was 4.77 ± 3.05 days. There were a total of 50 newborns, 49 boys (or 70%) and 21 girls (or 30%). The indirect bilirubin levels of the newborns varied between 8.3 and 13.6 mg/dl, with a mean of 10.731.61 mg/dl. The survival rate of newborns treated with ursodeoxycholic acid and phototherapy was significantly higher than that of neonates treated with phototherapy alone (20.60 ± 4.24 vs. 43.34 ± 4.56 hours; p0.001). **Conclusion:** Due to its low cost, ease of administration, and better safety profile, the addition of ursodeoxycholic acid significantly decreased the mean duration of phototherapy in neonates presenting with jaundice, which supports the preferred use of this novel agent in the management of such neonates in future practice.

Keywords: *Phototherapy, Ursodeoxycholic acid, Neonatal jaundice.*

INTRODUCTION

Overproduction of bilirubin in the blood is a relatively prevalent clinical disease known as hyperbilirubinemia. Most neonates exhibit unconjugated hyperbilirubinemia as a natural part of their physiology.[1] About two-thirds of babies will have clinical jaundice. Unconjugated bilirubin builds up and causes a yellowish tint to the skin and eyes. If neglected, it can cause severe neonatal jaundice. Brain damage, such as deafness and spasticity, can be avoided in many cases by preventing severe NH. Severe neonatal jaundice can induce any of the following consequences jaundice-related mortality or kernicterus and acute bilirubin encephalopathy.[2,3]

The causes of newborn hyperbilirubinemia are complex, however most of the factors are related to either decreased bilirubin clearance or an increased bilirubin load. While the latter may be the consequence of a lack of maturity in the conjugative capacity and/or excretion or defective hepatic absorption, the former may be the result of conditions that enhance the hepatic circulation and the formation of bilirubin.[4]

It has been discovered that an imbalance between conjugation and bilirubin generation plays a significant role in newborn bilirubinemia. Although both genetic and environmental variables have been implicated in the

development of newborn hyperbilirubinemia, genetic factors have received far more attention.[5,6]

Pathologic newborn hyperbilirubinemia is associated with substantial morbidity and mortality. Accumulation of bilirubin in the nuclei of the brain stem and the basal ganglia has been linked to the development of kernicterus.[7] Hypotonia, opisthotonus, lethargy, and poor nutrition can all contribute to the development of chronic encephalopathy, even if an intact animal makes it through the acute phase. Sensorineural hearing impairment, developmental delay, dental dysplasia, cerebral palsy, and facial paralysis in the upward direction are all symptoms of this disorder.[8]

Indirect hyperbilirubinemia has been treated with a wide variety of medications over the years, including activated charcoal, clofibrate, D-penicillamine, metalloporphyrin and phenobarbital. Researchers have found that phenobarbital is beneficial at lowering indirect hyperbilirubinemia and shortening the time needed for phototherapy.[9,10] However, it does have a few drawbacks, such as causing you to feel sleepier than usual, less able to breastfeed, and dehydrated. Accordingly, it appears necessary to conduct research on medications with fewer side effects.[11]

As to the best of the candidate's knowledge, no local study has been published on this topic, this is the rationale for my study. A combination of ursodeoxycholic acid and phototherapy has been shown to have a synergistic impact on indirect hyperbilirubinemia. Also, the medicine shortened the duration of necessary phototherapy, and the patient's time spent in the hospital. This study found that the average period of phototherapy for normalizing indirect hyperbilirubinemia was considerably shorter in the ursodeoxycholic acid + phototherapy group compared to the phototherapy alone group.

METHODS

This research was carried out at the Department of Pediatrics Shahida Islam Medical College, Lodhran over 1 year from March 2020 to March 2021. All patients who presented with direct hyperbilirubinemia with onset in the first three months of life were included in the study after obtaining parental written consent. we gathered age, sex, family history, and consanguinity information. After taking permission from hospital ethical committee these neonates were divided in to two groups randomly by using lottery methods. Group-A was (Ursodeoxycholic acid plus Phototherapy) & Group-B was (Phototherapy alone).

By using aseptic technique 3ml of blood was drawn and was sent to the lab for the measurement of the total, direct and indirect bilirubin levels. Neonates in group-A were treated with phototherapy and 10 mg/kg/day in of Ursodeoxycholic acid in two divided doses, and the time of start of the treatment was noted. The neonates in group-B were treated with phototherapy alone.

All of the patients were subjected to continuous newborn blue light phototherapy, which consisted of blue light fluorescent bulb single surface phototherapy. A phototherapy lamp was placed at a distance of 30 cm from the infant. The eyes were covered with eye patches, and a little nappy was used to conceal the genitalia, all of which were necessary for this treatment to proceed. Only during feedings and diaper changes does phototherapy have to be paused.

Standard treatment was given and proper hydration and bowel care was done according to the ward protocol. Serum total and indirect bilirubin were measured 12 hours apart until bilirubin level reaches out of phototherapy range according to guidelines for phototherapy (American academy of pediatrics subcommittee on hyperbilirubinemia). The rate of decline of serum indirect hyperbilirubinemia and duration of normalizing the indirect bilirubin level in the neonates was noted as per operational definition. All the data along with the demographical details was noted and recorded in to the attached proforma.

SPSS version 22.0 was used for data compilation and statistical analysis. Mean and standard deviation were used to show the continuous quantitative values (or median and range as appropriate). Frequency and percentages for nominal and ordinal categorical variables were shown in a tabulated form. The chi-square test was performed to determine statistical significance, and a p-value of less than 0.05 was considered significant.

RESULTS

The neonates ranged in age from one day to fourteen days, with a mean of 4.77 ± 3.05 days. The majority of the neonates (n=59, 84.3%) were in their first week of life. There were 49 neonates (70%) and 21 (30%). According to Table 1, the newborns' indirect bilirubin levels upon presentation varied from 8.3 mg/dl to 13.6 mg/dl, with a mean of 10.731.61 mg/dl. As demonstrated in Table 3, neonates treated with ursodeoxycholic acid in addition to phototherapy had substantially lower mean phototherapy duration than neonates treated with phototherapy alone (20.60 ± 4.24 vs. 43.34 ± 4.56 hours; p-value0.001). As indicated in Table 4, similar statistically significant differences were seen between the groups in a number of subgroups depending on age, gender, and admission indirect bilirubin levels.

Table 1: Baseline Characteristics of the enrolled neonates

Variables	Characteristics	Participants n=70
Age	Mean ± SD	4.77 ± 3.05
	≤7 days	59 (84.3%)
	>7 days	11 (15.7%)
Gender	Male	49 (70.0%)
	Female	21 (30.0%)
Indirect Bilirubin (mg/dl)	Mean ± SD	10.73 ± 1.61
	<10 mg/dl	27 (38.6%)
	≥10 mg/dl	43 (61.4%)

Table 2: Comparison of Baseline Characteristics of the enrolled neonates

Variables	Characteristics	UDCA + Phototherapy n=35	Phototherapy Alone n=35
Age		4.80 ± 2.96	4.74 ± 3.18
	≤7 days	30 (85.7%)	29 (82.9%)
	>7 days	5 (14.3%)	6 (17.1%)
Gender	Male	24 (68.6%)	25 (71.4%)
	Female	11 (31.4%)	10 (28.6%)
Indirect Bilirubin (mg/dl)		10.69 ± 1.57	10.76 ± 1.67
	<10 mg/dl	14 (40.0%)	13 (37.1%)
	≥10 mg/dl	21 (60.0%)	22 (62.9%)

Table 3: Comparison of Mean Duration of Phototherapy (hours) between the Study Groups

Outcome variable	UDCA + Phototherapy n=35	Phototherapy Alone n=35	P value
Mean Duration of Phototherapy (hours)	20.60 ± 4.24	43.34 ± 4.56	<0.001*

Independent sample t-test, indicating that the difference that was noticed was statistically significant

Table 4: Comparison of the Study Groups' Mean Phototherapy Duration (Hours)

Variables	Subgroups	UDCA + Phototherapy n=35	Phototherapy Alone n=35	P value
Age	≤7 days	20.83 ± 4.43	43.45 ± 4.85	Sign*
	>7 days	19.20 ± 2.78	42.83 ± 3.06	Sign*
Gender	Male	20.13 ± 3.95	43.08 ± 4.76	Sign*
	Female	21.64 ± 4.86	44.00 ± 4.16	Sign*
Indirect Bilirubin	<10 mg/dl	19.64 ± 3.39	41.54 ± 5.13	Sign*
	≥10 mg/dl	21.24 ± 4.70	44.41 ± 3.92	Sign*

Independent sample t-test, indicating that the difference that was noticed was statistically significant

DISCUSSION

There is a high incidence of newborn hyperbilirubinemia in the first week of life, making it a common neonatal clinical issue. Newborns with high bilirubin levels are at risk for neurotoxicity and kernicterus, which can lead to developmental delays in behaviour and the nervous system.[12] Phototherapy is conventional treatment option among such neonates but causes fluid-electrolyte imbalance, retinal changes and temperature dysregulation. It also badly affects the development of bond between mother and the neonate therefore; steps that can shorten the time required for phototherapy and early handover of baby to the mother are encouraged.[13,14] The yellowing of a newborn's skin and eyes, known as jaundice, is caused by bilirubin. This can lead the doctor to worry and the parents to feel anxious.[15]

The mean age of the newborns in the current research who had jaundice was 4.77 ± 3.05 days. A similar mean age of 4.5 ± 2.3 days was reported by Rasul at el. (2009) in Bangladesh among neonates with hyperbilirubinemia.[16] Irshad et al. (2011) observed the mean age to be 3.56 ± 2.56 days in newborns presenting to Lady Reading Hospital in Peshawar, Pakistan.[17] Hassan et al. (2015)[18] reported an equivalent mean age of 5.4 ± 1.4 days in Iraq, whereas Honar et al. (2016) found an equivalent mean age of 3.71 days among Iranian similar infants.[19]

Compared to neonates treated with just phototherapy, those given ursodeoxycholic acid also required significantly less time under the light source (20.604.24 vs. 43.344.56 hours; p0.001). Subgroup analyses by age, gender, and pre-admission indirect bilirubin concentration all revealed a statistically significant difference between the groups. Thus, we observed UDCA to improve the efficacy of phototherapy regardless of neonatal age, gender and bilirubin level.

Our findings are consistent with those of Hassan et al. (2015)[18], who found that neonates treated with UCDA and phototherapy required significantly less treatment time than those treated with phototherapy alone (23.2 ± 5.6 vs. 41.1 ± 7.2 hours: p0.001). In a similar study, Honar et al. (2016) also reported similar significant reduction of mean duration of phototherapy with ursodeoxycholic acid (15.5 ± 6 vs. 44.6 ± 13.3 hours; p-value<0.001).[19,20]

Though there has been some previous research on the topic, the present study is the first of its sort to focus on a local population. In the present study, we observed that addition of ursodeoxycholic acid significantly reduced the mean duration of phototherapy in neonates presenting with jaundice which owing to low-cost, ease of administration and better safety profile advocate the preferred use of this novel agent in the management of such neonates in future practice.

CONCLUSION

According to this study, phototherapy alone is less effective than UDCA as an adjuvant in treating infants with indirect hyperbilirubinemia.

LIMITATIONS

A very strong limitation to the present study was limited sample size of 70 cases. Moreover, we didn't consider various side effects of this bile salts therapy which are very important to consider in pediatric population.

SUGGESTIONS / RECOMMENDATIONS

There is need for a follow-up study with larger sample size considering side effects of UDCA therapy in neonatal jaundice. A study like this is strongly encouraged for use in future studies.

CONFLICT OF INTEREST / DISCLOSURE

None

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