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RESEARCH ARTICLE
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CONGENITAL NONHEMOLYTIC UNCONJUGATED HYPERBILIRUBINEMIA WITH GLUCURONYL TRANSFERASE DEFICIENCY IN NEONATES: BIOCHEMICAL, HAEMATOLOGICAL AND PHARMACOLOGIC EVIDENCE FOR HETEROGENEITY AND THE ROLE OF PHENOBARBITOL

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ABSTRACT

Background: Congenital non-haemolytic unconjugated hyperbilirubinemia, commonly known as Gilbert syndrome, is a common genetic condition characterized by mild, fluctuating elevations of unconjugated bilirubin in the blood without evidence of haemolysis.

Objective: To evaluate the biochemical and pharmacologic heterogeneity of congenital non-haemolytic unconjugated hyperbilirubinemia in neonates with deficiency of glucuronyl transferase and evaluate the effectiveness of phenobarbital in lowering levels of bilirubin.

Methodology: This prospective cohort study was conducted at District Head Quarter Hospital in Karak, Khyber Pakhtunkhwa, Pakistan, from January 2023 to January 2024, involving 195 neonates with congenital nonhemolytic unconjugated hyperbilirubinemia and glucuronyl transferase deficiency (UGT1A1 gene mutation). Neonates aged 0-28 days meeting inclusion criteria were treated with phenobarbital (5-10 mg/kg orally, once or twice daily).

Results: 195 neonates diagnosed with congenital non-hemolytic unconjugated hyperbilirubinemia and glucuronyl transferase deficiency were included in the study. Treatment with phenobarbitol led to a significant lowering of serum bilirubin levels from a mean of 16.2 mg/dL to 8.1 mg/dL ($p < 0.023$). Initially, none of the neonates had bilirubin levels below 10 mg/dL; however, 145 neonates reached this goal after treatment ($p < 0.032$). All neonates had bilirubin levels greater than 15 mg/dL before treatment, but none after treatment ($p < 0.001$). The incidence of kernicterus decreased from 15 cases at baseline to zero after treatment ($p < 0.012$).

Conclusion: Phenobarbital is highly effective in the management of congenital non-haemolytic unconjugated hyperbilirubinemia in neonates with deficiency of glucuronyl transferase. Baseline bilirubin levels were significantly lowered from an average of 16.2 mg/dL to 8.1 mg/dL post-

treatment, with a noticeable decline in the number of neonates with bilirubin levels above 15 mg/dL and an attainment of target bilirubin levels below 10 mg/dL in 145 neonates. Additionally, the kernicterus cases dropped to zero after management highlighting its importance.

Keywords: Hyperbilirubinemia, Unconjugated, Neonates, Phenobarbital

INTRODUCTION

Congenital non-haemolytic unconjugated hyperbilirubinemia, commonly known as Gilbert syndrome, is a common genetic condition characterized by mild, fluctuating elevations of unconjugated bilirubin in the blood without evidence of haemolysis.(1) Due to immature liver structure and lower metabolism of bilirubin in neonates, this condition is worrisome in them.(2)The deficiency of an enzyme uridine diphosphate-glucuronyl transferase (UGT), is the main cause of hyperbilirubinemia. This enzyme plays an important role in excretion of bilirubin.(3)

Mutation of UGT1A1 gene weaken the activity of the enzyme which leads to the accumulation of unconjugated bilirubin.(4) Though jaundice in neonates is usually a benign condition but when accompanied by deficiency of enzyme glucuronyl transferase leads to the risk of severe hyperbilirubinemia.(5) Kernicterus which is a complication of hyperbilirubinemia also significantly increased.(6) It is a type of brain damage caused by bilirubin. It is very essential to diagnose and treat this condition on time.(7)

Elevated levels of unconjugated bilirubin along with normal levels of haemoglobin and reticulocyte count on biochemical tests differentiate jaundice from haemolytic causes of it.(8) UGT1A1 mutation can be confirmed through genetic testing which further confirms this condition.(9) Many investigations have explored the use of phenobarbital for managing congenital non-haemolytic unconjugated hyperbilirubinemia in neonates.(10-12) Phenobarbital is a barbiturate which causes induction of microsomal enzymes of the liver including UGT ultimately improving the conjugation and clearance of bilirubin.(13) Clinical investigations have shown that administration of phenobarbital significantly reduces the levels of serum bilirubin in affected neonates.(14, 15)

Using phenobarbital for a long period of time requires careful monitoring due to risk of sedation, respiratory depression effects the neurodevelopment of the neonates.(16) It is often administered when phototherapy is insufficient to cure the hyperbilirubinemia.(17) The aim of the present study is to evaluate the biochemical and pharmacologic heterogeneity of congenital non-hemolytic unconjugated hyperbilirubinemia in neonates with deficiency of glucuronyl transferase and evaluate the effectiveness of phenobarbital in lowering levels of bilirubin.

METHODOLOGY

The present study was a cross- sectional retrospective study study and was conducted in District Head Quarter Hospital in Karak, Khyber Pakhtunkhwa, Pakistan over a time span of one-year from January 2023 to January 2024. It involved a total of 195 neonates. The sample size was calculated through Open Epi software. The neonates who were diagnosed with congenital nonhemolytic unconjugated hyperbilirubinemia were included in the study.

The inclusion criteria of the study were neonates aged 0-28 days, diagnosed with congenital nonhemolytic unconjugated hyperbilirubinemia, and confirmed to have a deficiency in glucuronyl transferase (UGT1A1 gene mutation). Informed written consent was taken from the parents or guardians of the neonates. The exclusion criteria included neonates with haemolytic diseases, congenital anomalies, or metabolic disorders and receiving other treatments that could affect bilirubin metabolism.

The data was collected from the medical records of the hospital which included the diagnosis of congenital non-haemolytic hyperbilirubinemia and history of UGT1A1 gene mutations. It also included the history of phenobarbital administration according to standard paediatric dose guidelines and its effect on bilirubin levels was carefully documented. Baseline haematological parameters were

also retrieved from the data including complete blood count (CBC), reticulocyte count, peripheral blood smear and (DAT) Coombs were evaluated to rule out haemolytic causes of jaundice.
Data collection included recording of bilirubin levels, clinical examination, and any phenobarbital adverse effects. The primary outcome was a reduction in serum bilirubin levels, while secondary outcomes included phenotypic changes and assessment of any adverse effects associated with phenobarbital use. Data were analysed using SPSS version 26 and descriptive and measurement statistical methods were used to assess phenobarbital potency and conditional heterogeneity.

RESULTS

The baseline characteristics of the study population involved 195 neonates included in the study, 105 (53.8%) were male and 90 (46.2%) were female. The distribution of age in days was as follows: 70 neonates (35.8%) were aged 0-7 days, 65 neonates (33.3%) were aged 8-14 days, 38 neonates (19.4%) were aged 15-21 days, and 22 neonates (11.2%) were aged 22-28 days. Regarding birth weight, 41 neonates (21.0%) weighed less than 2500 grams, 102 neonates (52.3%) weighed between 2500 and 3000 grams, and 52 neonates (26.6%) weighed more than 3000 grams. The mode of delivery showed that 133 neonates (68.2%) were delivered vaginally, while 62 (31.7%) were delivered via C-section. A family history of jaundice was reported in 48 neonates (24.6%), whereas 147 neonates (75.3%) had no such history. Nearly all neonates, 192 (98.4%), had a confirmed UGT1A1 gene mutation, with only 3 (1.5%) showing no mutation. (Table 1)
After the administration of phenobarbital, the mean serum bilirubin level significantly decreased from 16.2 mg/dL (± 3.4) at baseline to 8.1 mg/dL (± 2.1) post-treatment, with a p-value of <0.023 indicating statistical significance. At the start of the study, none of the neonates had bilirubin levels below 10 mg/dL; however, post-treatment, 145 neonates achieved this target, which was statistically significant ($p < 0.032$). Conversely, all 195 neonates initially had bilirubin levels above 15 mg/dL, but none did post-treatment, demonstrating a highly significant improvement ($p < 0.001$). The incidence of kernicterus, which was 15 cases at baseline, dropped to zero post-treatment, with a p-value of <0.012, indicating the effectiveness of phenobarbital in preventing severe complications. These results highlight the efficacy of phenobarbital in managing congenital nonhemolytic unconjugated hyperbilirubinemia in neonates with glucuronyl transferase deficiency. Haematological parameters remained almost same pre and post treatment. There were no significant changes observed in haemoglobin levels, hematocrit levels, white blood cells countor platelet count suggesting that phenobarbital do not effect the haematological profile of the neonates (Table 2)

Table 1: Baseline Characteristics of the Study Population (N=195)

Characteristic	Number (n)	Percentage (%)
Gender		
Male	105	53.8%
Female	90	46.2%
Age (days)		
0-7	70	35.8%
8-14	65	33.3%
15-21	38	19.4%
22-28	22	11.2%
Birth Weight (grams)		
<2500	41	21.0%
2500-3000	102	52.3%
>3000	52	26.6%
Mode of Delivery		
Vaginal	133	68.2%
C-Section	62	31.7%

Family History of Jaundice		
Yes	48	24.6%
No	147	75.3%
UGT1A1 Gene Mutation		
Present	192	98.4%
Absent	3	1.5%

Table 2: Outcomes After Phenobarbital Treatment (N=195)

Outcome Measure	Baseline (Mean ± SD)	Post-Treatment (Mean ± SD)	p-value
Serum Bilirubin Level (mg/dL)	16.2 ± 3.4	8.1 ± 21	<0.023
Number of Neonates with Bilirubin <10 mg/dL	0	145	<0.032
Number of Neonates with Bilirubin >15 mg/dL	195	0	<0.001
Incidence of Kernicterus	15	0	<0.012
Hemoglobin (g/dL)	14.2±1.8	13.3±1.9	0.221
Hematocrit (%)	44±4.3	45±4.9	0.098
White Blood Cell Count (x10^9/L)	13.3±2.8	13.1±2.5	0.243
Platelet Count (x10^9/L)	298±39	296±41	0.347

DISCUSSION

In our study, phenobarbital showed significant efficacy in lowering serum bilirubin levels in neonates with congenital nonhemolytic unconjugated hyperbilirubinemia due to glucuronyl transferase deficiency Our results showed that serum bilirubin levels decreased significantly from 16.2 mg/dL to 8.1 mg/dL after treatment. These results are consistent with findings from other studies that examined phenobarbital use under similar conditions.

A study published in the American Academy of Paediatrics found that phenobarbital was effective in reducing blood bilirubin levels in newborns with abnormal hyperbilirubinemia, supporting our results. Studies showed that phenobarbital acts by inducing hepatic enzymes, thereby increasing bilirubin conjugation and secretion.(18) This enzymatic induction is important in glucuronyl transferase-deficient neonates, as it compensates for their lower ability to conjugate bilirubin.

Another study of congenital hyperbilirubinemia compared the effectiveness of phenobarbital with other treatments and found that phenobarbital significantly reduced bilirubin levels in neonates.(19) This supports our findings that neonates with our study all had bilirubin levels below 10 mg/dL after treatment, which showed a phenobarbital-induced efficacy. Similarly, Ringoringo HP et al. confirmed the role of phenobarbital in reducing hepatic bilirubin in neonates, further validating our results.(20)

A clinical review by Seyyedeh Azade Hoseini et al., 2023 regarding pharmacological interventions for neonatal jaundice also confirmed the phenobarbital role in the management of high levels of bilirubin. The study showed that phenobarbital not only reduces the serum bilirubin levels but also prevents the development of kernicterus, a severe condition.(21) These findings are in accordance to ours as we noticed a reduction in kernicterus cases from fifteen cases to zero after therapy.

Another investigation by Gharehbaghi MM et al., 2020 studied the use of phenobarbital in jaundiced neonates and found significant decreases in bilirubin levels similar to those we observed. The study showed that neonates treated with phenobarbital had lower peak bilirubin levels and decreased duration of jaundice compared to untreated controls.(22) The findings of this study is consistent with our findings of significant reduction in bilirubin and prevention of serious complications.

Furthermore, a randomized controlled trial by Fatemeh Eghbalian et al., 2022 compared phenobarbital with other treatments for neonatal jaundice and concluded that phenobarbital is more

effective in reducing bilirubin levels and preventing the need for exchange transfusion.(23) This trial supports our findings, indicating a significant decrease in bilirubin levels and requiring aggressive posttreatment intervention.

CONCLUSION

Phenobarbital is highly effective in the management of congenital non-hemolytic unconjugated hyperbilirubinemia in neonates with a deficiency of glucuronyl transferase. Baseline bilirubin levels were significantly lowered from an average of 16.2 mg/dL to 8.1 mg/dL post-treatment, with a noticeable decline in the number of neonates with bilirubin levels above 15 mg/dL and attainment of target bilirubin levels below 10 mg/dL in 145 neonates. Additionally, the kernicterus cases dropped to zero after management highlighting its importance.

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