IJN
Iranian Journal of Neonatology
http://ijn.mums.ac.ir

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Original Article

Incidence of Hyperbilirubinemia and Urinary Tract Infection (UTI) in Asymptomatic Term Neonates Under Two Weeks of Age

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ABSTRACT

***Background*:** Hyperbilirubinemia is a common cause of referral to neonatal care units. According to several studies, jaundice is among the primary symptoms of urinary tract infection (UTI) in neonates. This study aimed to determine the prevalence of UTI in asymptomatic term neonates diagnosed with indirect hyperbilirubinemia within the first two weeks of birth.

***Methods*:** This prospective study was conducted on 314 term neonates under 14 days of age, presented with unexplained indirect hyperbilirubinemia for UTI (total bilirubin level: 15 mg/dl). Subjects were referred to 17-Shahrivar Children's Hospital in Rasht during 16 months, and neonates diagnosed with UTI were further investigated.

***Results*:** Out of 314 neonates, 12 patients (3.8%) were diagnosed with UTI, and E. coli was the most prevalent pathogen in these patients. No significant differences were observed between neonates with and without UTI in terms of gender, birth weight, age, bilirubin level on admission and mode of delivery (P>0.05). Additionally, pyuria and bacteriuria were significantly more prevalent among UTI patients compared to other neonates (P<0.0001).

***Conclusion*:** According to the results of this study, appropriate urine tests could rule out the possibility of coincidental UTI in icteric term neonates under two weeks, who are diagnosed with unexplained indirect hyperbilirubinemia.

Keywords: Hyperbilirubinemia, Neonate, Urinary Tract Infection

Introduction

Hyperbilirubinemia is a common disorder among neonates. Jaundice is detected in approximately 60% of term neonates within the first week of birth (1). Incidence rate of neonatal urinary tract infection (UTI) ranges between 0.1-1% in all newborns, while the symptoms referable to the genitourinary system rarely appear in this condition (2). Neonatal jaundice could be considered as one of the initial symptoms associated with UTI (3, 4).

UTI presenting as jaundice has been widely recognized since 80 years ago (5); nevertheless, the American Academy of Pediatrics (AAP) and National Institute for Health and Care Excellence (NICE) do not recommend any specific measures for evaluation of UTI in neonates diagnosed with indirect hyperbilirubinemia within the first two weeks of birth (6, 7).

This study aimed to determine the prevalence of UTI in hospitalized term neonates diagnosed with asymptomatic unexplained unconjugated hyperbilirubinemia within the first two weeks of birth.

Method

This prospective, cross-sectional study was conducted on term infants presented with jaundice (age: <14 days), who were otherwise known to be clinically well. Total serum bilirubin and direct bilirubin levels of the subjects were estimated at >15 mg/dl and <1.5 mg/dl, respectively. All the patients were referred to the neonatal ward of 17-Shahrivar Children's Hospital in Rasht, affiliated to Guilan University of Medical Sciences, Iran. The study was performed during 16 months, from June 2010 to October 2011.

Demographic data of the neonates, including age, gender, serum bilirubin level, mode of delivery and birth weight, were recorded, and the exclusion criteria of the study were as follows: 1) diagnosis of jaundice within the first 24 hours of birth; 2) presence of hemolysis (ABO or Rh incompatibility), or glucose-6-phosphate dehydrogenase (G6PD) deficiency; 3) presence of fever or symptoms of sepsis, and 4) history of antibiotic consumption.

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Direct Coombs test and blood smear were performed on all the subjects, and different variables including the blood type of infant and mother, complete blood count, G6PD activity and reticulocyte count were recorded for each infant.

Moreover, urine cultures were obtained from the subjects using urine drainage bags, and cultures positive for any types of bacteria were repeated via bladder catheterization or suprapubic bladder aspiration. If a single pathogen with more than 103 colony-forming unit/ml was detected via bladder catheterization, or bacteria were observed through suprapubic bladder aspiration, the neonate would be diagnosed with UTI (2).

In the laboratory, urine specimens were centrifuged at 2000 rpm for 5 minutes, and microscopic examinations were performed using a high-power field (HPF) in order to detect pyuria and bacteriuria in the patients; pyuria was identified in the presence of more than 5 white blood cells (WBC)/HPF in the microscopic examinations (3). In addition, renal sonography, sepsis work-up and renal function tests were conducted on all the neonates diagnosed with UTI.

Data analysis was performed in SPSS V.16, using Fisher's exact test and Chi-square for the comparison of study groups, and $P<0.05$ was considered as significant.

Results

During the study period, 314 asymptomatic icteric term neonates were referred to our health care center, 181 of whom (57.6%) were male. Mean of age and birth weight of the subjects was 6.56±2.87 days and 3318.98±254.79 g, respectively. In addition, mean of the total bilirubin level on admission was 18.12±3.52 mg/dl, and the mean duration of phototherapy was estimated at 2.91±1.12 and 3.21±1.25 days in patients with and without UTI, respectively ($P>0.05$).

With regard to the mode of delivery, 212 neonates (67.5%) were born via vaginal delivery, and all the male infants were uncircumcised. Out of 314 infants enrolled in this study, 12 cases (3.8%) were diagnosed with UTI, and the majority of the cases were male (10/12, 83.3%). The youngest patient was 3 days old, and one single organism was isolated in all the neonates; E. coli (10/12, 83.3%) and Enterobacter (2/12, 16.7%) were the major isolated organisms.

In this study, all the infants diagnosed with UTI had bacteriuria, and 9 cases (75%) had pyuria. Furthermore, none of the UTI patients had positive blood cultures, and renal function tests of all the studied neonates were within the normal range. However, renal ultrasound was indicative of hydronephrosis in one neonate diagnosed with UTI (1/12, 8.3%).

A voiding cystourethrogram was performed on only one patient with UTI, and the results were normal. Demographic features of the studied infants with and without UTI are presented in Table 1.

In general, no statistically significant difference was observed between the study groups in terms of age, gender, birth weight, mode of delivery and initial bilirubin level ($P>0.05$).

Discussion

In the present study, 3.8% of the neonates with unexplained indirect hyperbilirubinemia were diagnosed with coincidental UTI. Although several

Table 1. Demographic Characteristics of Patients with UTI (Group 1) and Without UTI (Group 2)

Characteristics	Group 1 (N=12)	Group 2 (N=312)	P-value
Male/Female	10/2	171/131	0.079
Age on Admission (Days)			
2-4	3	74	
5-7	6	135	0.905
7-14	3	93	
Mean	6.08	6.57	0.558
SD	2.15	2.89	
Birth weight (g)			
< 2500	1	35	0.728
≥2500	11	267	
Mean	3256.66	3321.46	0.08
SD	389.43	259.86	
Mode of Delivery (N)			
Vaginal/Cesarean Section	6/6	96/206	0.214
Initial Bilirubin Level (mg/dl)			
15-20	10	258	
20-25	1	33	0.690
>25	1	11	
Mean	18.47	18.16	0.757
SD	2.96	3.43	
Urine Microscopy, WBC/HPF(n)			
≤5	3	301	0.0001
>5	9	1	
Bacteriuria (n)			
Positive	12	32	0.0001
Negative	0	270	

studies have reported icter as the primary sign of UTI in neonates (3, 8), it is more frequently screened in cases with prolonged jaundice (7, 9).

In one study, Garcia et al. (10) detected UTI in 7.5% of their study population (N=160), consisting of asymptomatic, afebrile, jaundiced neonates under 8 weeks of age. Among their subjects, there were older infants, as well as some cases with direct hyperbilirubinemia.

In another study, Shahian et al. (8) estimated the incidence rate of UTI at 12.5% among a study population consisting of asymptomatic jaundiced neonates less than four weeks of age. Similarly, Chen et al. (11) reported the prevalence of UTI to be 5.5% among 217 icteric infants under eight weeks. The aforementioned studies investigated both term and preterm neonates, including cases presented with direct bilirubin level of >1.5 mg/dl.

In another research, Omar et al. (12) detected UTI in 21.1% of 152 icteric infants, using samples collected by urine bags from male neonates. Differences in the reported frequency of UTI might be due to variations in the study groups, as well as the applied methods of investigation.

According to the findings of Murat et al., high concentrations of bilirubin could result in mild relaxation of basal ureteral and bladder tensions in rabbits. Such alternations in the bladder, as well as the concomitant reduction of ureteral peristalsis, may cause problems in the urinary tract and lead to urine stasis (13).

On the other hand, production of hepatotoxins from specific gram-negative bacilli, especially E. coli, might increase the fragility of red blood cells and cause hemolysis. This is considered as another significant pathogenesis of coincidental hyperbilirubinemia and UTI among neonates (11).

In a study conducted by Bilgen et al., Enterobacter aerogenes was reported as the predominant organism (38%) responsible for the occurrence of UTI in their icteric neonates; other contributing organisms were Enterococcus faecalis (25%), Klebsiella pneumonia (25%) and E. coli (12%). In addition, they evaluated the incidence of UTI with unknown etiology among icteric neonates under 14 days with total bilirubin level of >15 mg/dl, who were otherwise reported to be clinically well (3).

In another report, Klebsiella pneumonia was cultured in 40% of patients diagnosed with UTI, and other cultured bacteria included E. coli (27%), Enterobacter (27%) and Serratia (7%). All the subjects were presented with unexplained unconjugated hyperbilirubinemia (8). In the current study, E. coli was observed to be the predominant cause of UTI among the neonates (83.3%).

According to the findings of the present study, 9 neonates diagnosed with UTI (9/12, 75%) had pyuria, which was found to have a higher prevalence among UTI cases compared to other subjects (P<0.0001). In other reports, prevalence of pyuria ranged between 27.4-58.3% (11, 14). Moreover, bacteriuria was detected in 100% of UTI patients in our study, with a significantly higher prevalence among the neonates diagnosed with UTI (P< 0.0001). According to the results obtained by Bilgen et al. (3), bacteriuria was detected in 88% of UTI cases. In comparison to pyuria, bacteriuria was considered as a more reliable parameter in the diagnosis of UTI (2).

In the present study, approximately 11.8% of UTI patients had bacteriuria, which could be due to the use of unsterile methods for urine sample collection (i.e., urine bags). Accordingly, it could be concluded that urinalysis may fail to predict the incidence or absence of UTI accurately. Therefore, other proper methods should be applied for the collection of urine cultures from icteric infants.

The main limitation of the current study was the absence of circumcised infants in the study groups, which did not allow the researchers to investigate the effects of this parameter on the incidence of UTI among neonates.

Conclusion

Hyperbilirubinemia could be the most significant clinical finding in term neonates presented with UTI within the first two weeks of birth. Therefore, it is recommended that urine cultures be obtained from asymptomatic term infants with jaundice of unknown etiology in order to rule out the possibility of UTI during the first week of birth, especially in neonates with bacteriuria.

Acknowledgements

Hereby, we extend our gratitude to the physicians and nurses of 17-Shahrivar Children's Hospital of Rasht for their assistance and meticulous care of the neonates enrolled in this research project.

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