Section: Pediatrics and Neonatology

Original Research Article

UNEXPLAINED NEONATAL JAUNDICE AS A SIGN OF URINARY TRACT INFECTION IN NEWBORNS

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ABSTRACT

Background: Hyperbilirubinemia is one of the presenting signs of bacterial infection in newborns, and the association of neonatal jaundice with urinary tract infection (UTI) has been particularly emphasized. The present study was aimed at determining the prevalence of UTI in jaundiced neonates less than 2 weeks old (> 34 weeks of gestation).
Materials and Methods: Our retrospective study evaluated the incidence of jaundice in neonates with UTI. Patients with UTI were defined as > 50,000 colony-forming units of a single pathogen per millilitre of urine obtained by bladder catheterization. The information, including the age, sex, and feeding type, as well as the results of physical examination, treatment, radiology studies, etc, were recorded. The etiology of jaundice was assessed by laboratory tests. Urine analysis and urine culture were performed for all subjects
Results: 27 of 143 neonates with hyperbilirubinemia were diagnosed with UTI. The mean age had a significant difference (4±1 day with UTI versus 5±2 days without UTI, p <0.0001). Neonates in the UTI group had significantly lower birth weight than those without UTI. The incidence of severe dehydration was higher among those with UTI. Urine culture was positive among 5/27 (55.5%) of them. E. coli (73.3%) was the most predominant organism grown. E. coli strain has maximum sensitivity for Amikacin (>90%). The mean reduction in bilirubin levels was comparatively less among the neonates with UTI.
Conclusion: UTI was found in 18.8% (27/143) of the jaundiced neonates with the onset of unconjugated hyperbilirubinemia in the first week of life. Therefore, we suggest that urine analysis should be considered as a part of the diagnostic evaluation of jaundiced neonates older than 3 days with an unexplained etiology.
Keywords: Hyperbilirubinemia, Neonatal jaundice, Urinary tract infection.

INTRODUCTION

During the first week of life, most of the neonates have apparent jaundice due to the increased levels of unconjugated bilirubin, due to low activity of the glucuronosyltransferase, which is crucial for converting unconjugated bilirubin to conjugated bilirubin that can be easily excreted. Also, the shorter life span of the foetal Red Blood Cells (RBC), and lesser conversion of bilirubin to urobilinogen by the intestinal flora result in relatively high absorption of bilirubin back into the circulation.[1] Hence, hyperbilirubinemia is very common during the neonatal period. About 60% of full-term and 80% of premature neonates develop clinical jaundice in the first week of life.[2,3]

One of the challenging scenarios we face in clinical practice among the neonatal hyperbilirubinemia cases is asymptomatic afebrile hyperbilirubinemia. Though we investigate the neonate for all possible causes, urinary tract infection (UTI) has been rare. The lack of a clear recommendation for screening UTIs in neonates, especially in unexplained hyperbilirubinemia, might be one of the reasons.[4]

However, some studies have reported unexplained hyperbilirubinemia, but they have not well established the positive association.[5,6] As per the few available pieces of evidence, UTI is thought to be the main reason for prolonged jaundice.[7] The clinical manifestations of UTI in neonates are extremely variable, ranging from severe illnesses to nonspecific signs and symptoms such as growth failure or jaundice.[8] UTI is thought to be the main reason for prolonged jaundice, thus urine culture is routinely performed in neonates with jaundice aged more than 3 weeks.[6] This study aimed to determine the prevalence of UTI in neonates with unexplained unconjugated hyperbilirubinemia in the first 2 weeks of life.

MATERIALS AND METHODS

This was a retrospective study that included the data of 143 neonates (> 34 weeks of gestation) diagnosed with jaundice younger than 2 weeks of age and admitted to the newborn unit of Cloudnine Hospital, Jayanagar, Bangalore, from March 2023 to February 2024.

The inclusion criteria we opted for were the patients who presented with jaundice with or without signs of UTI or sepsis, which is explained by the symptoms of documented fever >380C, vomiting, poor feeding, lethargy, etc., were included in the study. Jaundiced in the first 48 h of life were excluded from the study. Demographic data, including gestational age, maternal infections, mode of delivery, and prolonged rupture of the membranes, were recorded. Postnatal events, including neonatal fever, onset of jaundice, and whether the infant was breastfed or formula-fed, were also collected.

Complete blood count, peripheral blood smear, glucose-6-phosphate dehydrogenase (G6PD), direct Coombs' test, blood typing of the neonate and mother, total and direct bilirubin, reticulocyte count, and a catheterized urine sample for routine and culture were done in all neonates admitted to NICU for jaundice.

For microscopic analysis, urine specimens were centrifuged at 2000 revolutions per minute for 5 min, resuspended, stained, and examined microscopically under high power field (HPF) for pyuria, which was defined as 10 white blood cells (WBC)/HPF.[9]

Any urine sample with a leucocyte esterase positive was also taken as positive for UTI. All the urine specimens were sent for standard quantitative culture in our lab. The urine culture obtained by bladder catheterization was considered positive if a single pathogen with more than 50,000 colony-forming units per milliliter (CFU/ml) was isolated.[10] A sepsis evaluation consisting of blood cell counts, C-reactive protein (CRP), and blood culture was also performed in all cases of symptomatic UTI. A renal function test and a renal ultrasound were performed in all the neonates with UTI.

Statistical Method

Data is analysed using SPSS software version 21 and Excel. Categorical variables are given in the form of a frequency table. Continuous variables are given in Mean ± SD/ Median (Min, Max) form. The chi-square test is used to check the association of categorical variables with groups. Normality of the variable is checked by the Shapiro-Wilk test and QQ plot. If data follows normal distribution, parametric tests like an independent t-test are used. Otherwise, non-parametric tests like Mann-Whitney U test will be used. Correlation was analyzed by Spearman's rho test. A p-value less than or equal to 0.05 indicates statistical significance.

RESULTS

The obtained results are expressed as the graphs and tables below.

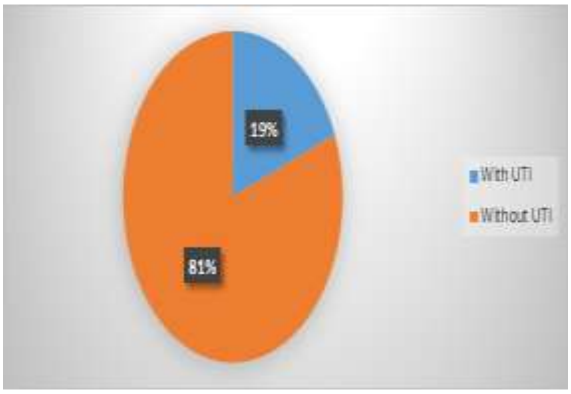

Figure 1: Distribution of study population based on status of UTI

Table 1: Distribution of demographic data

Parameter	N (%) N = 143	With UTI n = 27	Without UTI n = 116	P value
Average age of the neonates	5±3 days	4±1 day	5±2 days	<0.0001
<7 days	26 (18.2%)	7 (25.9%)	17(14.7%)	0.14
7 to 14 days	117 (81.8%)	18 (66.7%)	97(83.6%)	
Male	75(52.4%)	8 (29.6%)	67(57.8%)	0.23
Female	68(47.6%)	19 (70.4%)	49(42.2%)	
<2.5 kg	13(9.1%)	9 (33.3%)	4 (3.4%)	0.097
2.5 to 3.5	111(84.6%)	13 (48.1%)	98 (84.5%)	
>3.5kg	19(6.3%)	5 (18.5%)	14 (12.1%)	
Average birth weight in kg	2.9±1.2	2.4±0.8	2.6±0.5	0.011
<37 weeks	87 (60.8%)	16 (59.3%)	55(47.4%)	0.17
37 to 38 weeks	28 (19.6%)	4 (14.8%)	31(26.7%)	
38 to 39 weeks	23 (16.1%)	5 (18.5%)	30(25.9%)	
39 to 40 weeks	5 (3.5%)	2 (7.4%)	5(4.3%)	
>40 weeks	Nil (0%)	--	--	
PROM	17 (11.9%)	3 (11.1%)	14 (12.1%)	0.88

Vaginal delivery	28 (19.58%)	5 (18.51%)	23 (19.82%)	0.73
LSCS	115 (90.42%)	22 (81.49%)	93 (90.18%)	

From the Table 1, we can analyse that, although there was no significant difference in the distribution of demographic data, the incidence of neonates aged less than 7 days, female babies, and those born at a gestational age of less than 37 weeks had a higher incidence of UTI than the non UTI group. Meanwhile, the average age and birth weight in the neonates with UTI were significantly lower than those without UTI.

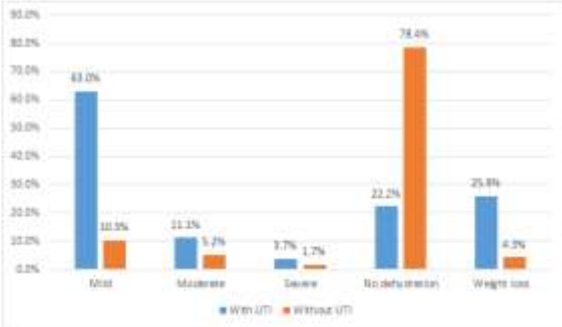

Figure 2: Distribution of Severity of dehydration and incidence of weight loss between the two groups

Table 2: Distribution of Biochemical changes

Parameter	With UTI n = 27	Without UTI n = 116
Urine routine		
Pus cells present	14 (51.85%)	0
RBC casts present	3 (11.11%)	0
Leucocyte esterase positive	8 (29.6%)	0
Nitrite positive	7 (25.9%)	0
Blood investigations		
Mean WBC in blood	13850±2860	11670±2975
Decreased Hb	9 (33.3%)	4 (3.4%)
CRP positive	19 (70.4%)	32 (27.6%)

From Table 2, we can analyse, the urine routine of patients in the without UTI group was completely normal. Whereas among the 27 with UTI, 14 of them had a significant number of pus cells, accounting for 14 (51.85%). Majority of the patients with UTI had leucocyte esterase, nitrate and CRP positive compared to without UTI group.

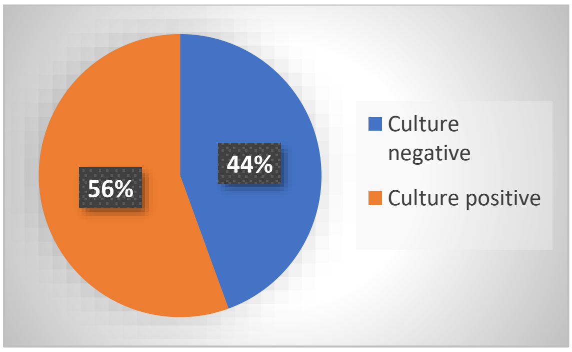

Figure 3: Distribution of culture growth among UTI group

From Figure 3, we can analyse, out of 27 patients with UTI, culture was positive among 15 (55.5%) of them, and 12 (44.5%) had negative culture.
Below is the bar graph explaining the incidence of various organisms grown on the culture.

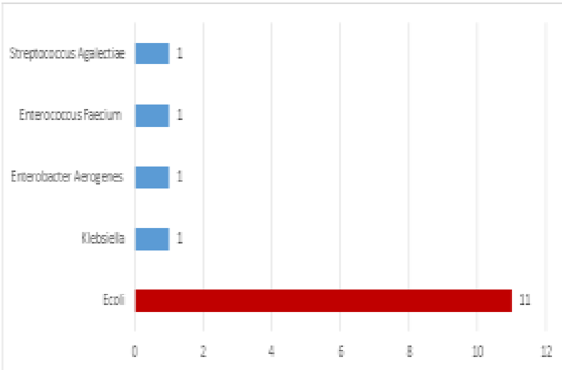

Figure 4: Distribution of the number of the frequency of patients based on the organism grown on urine culture

Table 3: Distribution of antimicrobial sensitivity for Ecoli

Anti-microbials	Sensitive n = 11	In %	Resistant n = 11	In %
Ampicillin	4	36.4%	7	63.6%
Trimethoprim + sulfamethoxazole	2	18.2%	9	81.8%
Nitrofurantoin	7	63.6%	4	36.4%
Gentamicin	6	54.5%	5	45.5%
Amikacin	10	90.9%	1	9.1%
Ceftriaxone	9	81.8%	2	18.2%
Ceftazidime	6	54.5%	5	45.5%
Cefotaxime	8	72.7%	7	63.6%
Ciprofloxacin	9	81.8%	2	18.2%
Norfloxacin	9	81.8%	2	18.2%

From the above table 3, we can observe that the E. coli strain has maximum sensitivity for Amikacin, which accounted for 10 out of 11 (90.9%) E. coli grown, followed by Ceftriaxone with an incidence of 81.8%. Equally sensitive towards fluoroquinolones. Nitrofurantoin has 54.5%

Table 4: Day-wise mean reduction in average total Bilirubin levels after admission

Day	With UTI n = 27	Without UTI n = 116	P value
1	2.71 mg/dL±0.19	2.84 mg/dL±0.1	<0.0001
2	2.9 mg/dL±0.11	2.92 mg/dL±0.4	<0.0001
3	3.05 mg/dL±0.3	2.83 mg/dL±0.19	<0.0001

From the above table 4, we can observe that the day-to-day reduction in average total bilirubin was significantly higher among neonates without UTI than those with UTI. The majority of the neonates had normal bilirubin levels by day 3.

DISCUSSION

In the present study, out of 143 neonates admitted with hyperbilirubinemia, 27 (18.8%) had UTI, and the rest 116 (81.2%), did not have a diagnosis of UTI. On further comparison of each parameter between these two groups, we found that UTIs were significantly higher among infants with lower birth weight and <37 weeks. Whereas in Hasan SM et al.,66 (56.89%) patients with hyperbilirubinemia were male neonates and infants, and 50 cases (43.11%) were females. They have not analysed the gender distribution based on whether or not there are UTI cases.[11] Aygun E et al., and Firinci F et al., in their separate studies, have reported the male predominance among UTI neonates.[12,13] Even in Amiri FB et al., the incidence was significantly higher among male babies and those with lower birth weight.[4] They have substantiated this finding with a probability that anatomical abnormalities, such as phimosis, peri-urethral colonisation, would increase the susceptibility to infections. We did not observe a significant difference between the incidence of PROM and mode of delivery between the two groups. We observed a predominance of females (70.4%) among our study population, but this did not have statistical significance. compared to males (29.6%). Higher rates of UTI were seen in babies <7 days old and those <2.5 kg, although these differences were not statistically significant. A trend towards UTI in preterm infants (<37 weeks) was noted, but did not reach significance. Whereas in Hasan SM et al,18.10% of them were preterm babies.[11]

On analysing the obtained urine culture reports, we found that 55.5% (n=15) had positive cultures, while 44.5% (n=12) were culture-negative. E. coli was the predominant organism, as typically expected in neonatal UTIs. Similarly, in Hasan SM et al., the incidence of culture-positive UTI was 12 of 20 cases. Out of these 12 cases, 8 cases showed culture for Escherichia coli (E. coli), and in the remaining four cases, for Klebsiella pneumoniae.[11] In Shahian M et al., who studied 120 neonates of less than 4 weeks, the incidence of UTI was 12.5%.[14] Ghaemi S et al., reported that 23(5.8%) out of 400 neonates with icterus were diagnosed to have UTI. Even in their study, the most common causative bacteria were Ecoli, accounting for about 74%.[15] In Amiri FB et al, the pooled prevalence of UTI in neonates with unexplained hyperbilirubinemia was 6.81%.[4]

Although the majority of the neonates had normal bilirubin levels by day 3, the day-to-day reduction in mean total bilirubin after admission was greater in the non-UTI group than in the UTI group, implying that the UTI would prolong the recovery from hyperbilirubinemia. This outcome is consistent with observations by Hasan SM et al,[11] Harb et al. found that UTI cases had significantly longer phototherapy compared to non-UTI babies.[16] Similar to our study, Karadağ et al. quantified that the UTI-positive newborns had a52.4%mean decrease in serum bilirubin after 24h phototherapy versus 58.4% in the UTI-negative group ($P < 0.0001$).[17] Meanwhile, Simsek et al interpreted that a relatively inadequate response to the phototherapy should raise the suspicion of UTI.[18] Omar C et al documented increased bilirubin levels as one of the most common and initial symptoms of UTI among neonates, with a prevalence rate of 3 to 21% of UTIs being associated with unexplained hyperbilirubinemia among neonates.[19]

Bahat Ozdogan E et al have suggested that UTI should be one of the differential diagnoses to be considered among the neonates presenting with jaundice to provide timely management.[20] Xinias I et al substantiated this finding by interpreting that the UTI in neonates will have many nonspecific symptoms such as lethargy, fever, vomiting, diarrhea, anorexia, weight loss, changes in urine characteristics, and jaundice.[21] So, the newborns with UTI could present early with jaundice. Interestingly, none of our babies with hyperbilirubinaemia were G6PD deficient in our study.

Though this indirectly indicated that there is a positive association between the bilirubinaemia and UTI, the negative association between the incidence of UTI and time taken for reduction in bilirubin levels, the external validation of this study would be better if we had included a higher sample size.

CONCLUSION

Our study observed a significant association between unexplained neonatal hyperbilirubinemia and urinary tract infections (UTIs), with a UTI prevalence of

18.8%. E. coli was the predominant causative agent. Neonates with UTI showed delayed bilirubin resolution despite phototherapy, supporting the role of infection in altered bilirubin metabolism. These findings reinforce the importance of including UTI screening in the diagnostic workup of jaundiced neonates, especially when no other cause is evident. The fact that none of our babies with hyperbilirubinemia were G6PD deficient suggests that our cohort of G6PD are genetically different than many Chinese populations. Early detection and treatment of UTI can improve outcomes and reduce complications in this vulnerable population

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