Urinary Tract Infection in Asymptomatic Newborns with Prolonged Unconjugated Hyperbilirubunemia: A Hospital based Observational study from Western Region of Nepal

Malla T,[1] Sathian B,[2] Malla KK,[1] Adhikari S[1]

[1]Department of Pediatrics

[2]Department of Community Medicine

Manipal College of medical science,

Pokhara, Nepal.

Corresponding Author

Tejesh Malla

Department of Pediatrics

Manipal College of Medical Science,

Pokhara, Nepal.

E-mail: tejeshmalla@hotmail.com

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ABSTRACT

Background

Urine culture is usually not a part of work-up for neonatal unconjugated hyperbilirubinemia; hence its prevalence remains unknown.

Objective

This study was done to determine the incidence of urinary tract infection (UTI) in asymptomatic newborns with prolonged unconjugated hyperbilirubinemia and to evaluate which other laboratory parameters are associated with UTIs.

Method

A prospective observational study where jaundiced newborns otherwise clinically well, were evaluated for UTI. The study was carried out in neonatal intensive care unit of Manipal Teaching Hospital, Pokhara from June 2012 -April 2013. The babies were divided in two groups group I- late prolonged jaundice and Group II - early physiological jaundice. Serum bilirubin, Septic screening and suprapubic urine sample analysis was performed for all subjects. Data was analyzed using SPSS version 16 and $p < 0.05$ was considered statistically significant.

Result

Of the 85 neonates, 33(38.8%) were females and 52(61.2%) males; 68(80%) were of term gestation and 17(20%) were preterms. The age at onset of jaundice for group I (n=53) was 13.6±4.88 days and for Group II (n= 32) was 5.0± 1.04 days. 11 /85 (12.9%) were diagnosed to have UTI [10 (90.9%) in group I and 1 in group II (9.01%] (p=0.04). UTI was more prevalent in group I [OR 7.20, 95% CI (0.87, 59.27)], more prevalent in male [OR 8.40, 95% CI (0.59, 74.13) and term babies of group I [OR 4.39, 95% CI (0.48, 39.82) when compared to Group II. Among other lab parameters only total WBC count was statistically significant (p=0.03). *Escherichia coli* was the predominant pathogen (45.45%) isolated. The sensitive antibiotics were *aminoglycosides, fluroquinolones*, *nitrofurantoin* and *vancomycin* and resistant antibiotics were most *cephalosporins* and *penicillins* for the isolated organisms.

Conclusion

The present study highlights significant association between late prolonged unconjugated hyperbilirubinemia and UTI. It is suggested that evaluation for UTI may be considered as a screening test for such cases.

KEY WORDS

Neonatal hyperbilirubinemia, newborn, septic screening, urinary tract infection

INTRODUCTION

Urinary tract infection (UTI) is the most common disease of the urogenital system.[1] Its incidence varies from 0.1 to 1% among neonates.[2,3] Hyperbilirubinemia in newborns may be associated with bacterial infection especially UTI.[4] Hence evaluation of UTI should be a part workup for neonatal hyperbilirubinemia but the current scientific guidelines, that of the American Academy of Pediatrics (AAP) do not recommend any evaluation for UTI among babies with hyperbilirubinemia.[5] Above that the clinical presentation of UTI in neonates are nonspecific hence the diagnosis may be missed. Considering these points this study aimed to determine whether late prolonged unconjugated hyperbilirubinemia in asymptomatic newborns is associated with UTI.

METHODS

A hospital based observational study was undertaken in NICU of Manipal Teaching Hospital, Pokhara for a period of 10 months from June 2012 to April 2013. Ethical approval was taken from the Institutional Review Committee, Manipal Teaching hospital (IRC/MTH). The purpose of the study was explained to the parents and a written consent from parents of the neonates was also obtained before the commencement of the study. Sample size was based in a pilot study done before original study which showed standard deviation of age at onset of late prolonged jaundice to be 4.9 and 1.2 for early physiological jaundice. Sample size required for 95% confidence interval and allowable Error 1.5 and 0.5 were 41 and 23 respectively. But we have taken 53 for late jaundice and 32 for early jaundice. Of the 85/200 (42.5%) who fulfilled the criteria for inclusion were selected for the study. Inclusion criteria was the newborns who presented with jaundice after 24 hours of life and had no clinical symptoms and signs of any disease. The Exclusion criteria were : a) Jaundice on first 24 hours of life, b) those having clinical features of sepsis, c) congenital and chromosomal anomalies ,d) Gestation age ≤ 28 weeks, e) preterm with complications, f) any features of hemolysis, g) Rh and ABO incompatibility and h) suspected metabolic diseases.

The population was divided in two groups: Group I [late prolonged jaundice] – jaundice appearing or prolonged more than 10 days for term and 14 days or later for preterm. Group II [early physiological jaundice] – jaundice on 2-9 days for term and 2-13 days for preterm which is the time for physiological jaundice to appear and then disappear.[6]

Detailed information including gestation age, sex and blood group for baby and mother were recorded. Then all babies were examined and serum bilirubin (direct, indirect), septic screening (complete blood count with peripheral smear, C-reactive protein,blood culture and where required Cerebrospinal fluid culture) and suprapubic urine sample (taken under strict aseptic precaution) was analysed. Centrifuged samples of urine were stained and then studied with High power field; leukocyte count (more than five) and bacterial count (many, moderate, few, none) were reported. All samples were sent for quantitative urine culture - single pathogen, obtained by suprapubic puncture was considered as positive. In cases where the urine culture was positive, ultrasound and renal function tests were performed.

Data was collected, tabulated and analyzed using statistical package SPSS 16.0 version. Microsoft Excel (2003) and SPSS were used for plotting figures. Chi- square test was used to compare the parameters and p <0.05 was considered statistically significant.

RESULTS

Out of total 85 cases of neonatal hyperbilirubunemia there were 52(61.20%) males and 33(38.80%) females, 68(80%) were of term gestation and 17(20%) were preterms. Fifty three had late prolonged (Group I) and 32 had early physiological jaundice (Group II) with mean age at onset of jaundice 13.60±4.88 days and 5.00±1.04 days respectively (Table1).

Table 1. Sample characteristics.

Variables	N	%	Total
Sex :			
Male	52	61.20	
Female	33	38.80	
Gestation age			
Term	68	80	
Preterm	17	20	
Age at onset -jaundice			85
Group I (Late jaundice)	53	62.40	
Group II (Early jaundice)	32	37.60	
UTI			
Yes	11	12.90	
No	74	87.10	
Growth in urine C/S			
Escherichia coli	5	45.45	
Enetrococcus	2	18.18	11
Klebsiella	3	27.27	
Staphylococcus aureus	1	9.09	

**Mean age at onset of jaundice
Group I (late) = 13.60±4.88 days
Group II (Early) = 5.00±1.04 days

Of the 11/85 (12.90%) cases had UTI based on positive urine culture. Ten (90.90%) were in group I and only 1(9.09%) was in group II (p<0.046) [fig1 and table 2]. *Escherichia coli* was the predominant pathogen (45.45%) isolated followed by *Klebsiella* (27.27%), *Enterococcus* (18.18%) and *Staphylococcus aureus* (9.09% %) shown in Table 1.

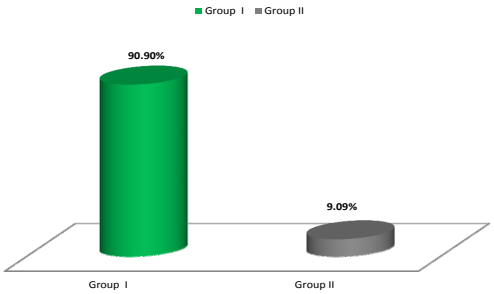

Figure 1. Percentage of UTI in two groups (n=11)

Table 2. Relation of variables in group I and group II with UTI

Variables	UTI		p value	Odds ratio (95% CI)
	Yes	No		
Total (N=85)				
Group I(n=53)	10 18.9%	43 81.1%	0.04	7.21(0.87, 59.27)
Group II (n=32)	1 3.1%	31 96.9%		1
Male (n=52)				
Group I(n=27)	7 25.9%	20 74.1%	0.055	8.40(0.59, 74.13)
Group II(n=25)	1 4%	24 96%		1
Female (n=33)				
Group I (n=26)	3 11.5%	23 88.5%	1	-
Group II(n=7)	0 0%	7 100%		
Term (n=68)				
Group I(n=38)	5 13.2%	33 86.8%	0.218	4.39(0.48, 39.82)
Group II(n=30)	1 3.3%	29 96.7%		1
Preterm (n=17)				
Group I(n=15)	5 33.3%	10 66.7%	1	-
Group II(n=2)	0 0%	2 100%		

Determinants of sociodemographic factors and UTI with two groups by logistic regression.

Logistic regression analysis revealed that UTI was more prevalent in group I [OR 7.209, 95% CI (0.877, 59.278)] when compared to group II. Again UTI was more prevalent in male of group I [OR 8.400 (0.592, 74.138) and Term gestation newborn of group I [OR 4.394 (0.485, 39.823) when compared to Group II.

Other lab parameters

Lab parameters with mean values ± standard deviation (SD) in two groups are shown in table 3 and 4 where

Table 3. Lab parameters of two groups.

Lab parameters	Group		Chi-square test	p value
	I (n=53):	II (n=32)		
Total count				
High	16(30.2%)	2(6.2%)		
Normal	30 (56.6%)	30 93.8%)	13.53	0.001
Low	7(13.2%)	0 (0%)		
Neutrophil count				
High	18(34%)	4(12.5%)	4.72	0.029
Normal	35(66%)	28(87.5%)		
CRP				
Positive	38(71.7%)	15(46.9%)	5.24	0.022
Negative	15(28.3%)	17(53.1%)		
Urine C/S				
No growth	43(81.1%)	31(96.9%)	4.39	0.036
Growth	10 18.9%)	1 (3.1%)		

Table 4. The mean values ± SD of lab parameters in two groups:

Lab parameters	Group	N	Mean ±SD	p value
Total count	Group I	53	10996 ±6844	0.01
	Group II	32	8187±2757	
Neutrophil	Group I	53	64.566±18.49	0.005
	Group II	32	3.750±15.25	
CRP	Group I	53	21.056±18.62	0.001
	Group II	32	8.625 ±12.92	
Total bilirubin	Group I	53	18.611 ±3.05	0.497
	Group II	32	18.196±2.48	
Direct bilirubin	Group I	53	1.196 ±0.52	0.073
	Group II	32	1.450 ±0.67	
Indirect bilirubin	Group I	53	17.226 ±3.11	0.429
	Group II	32	16.747 ±2.39	

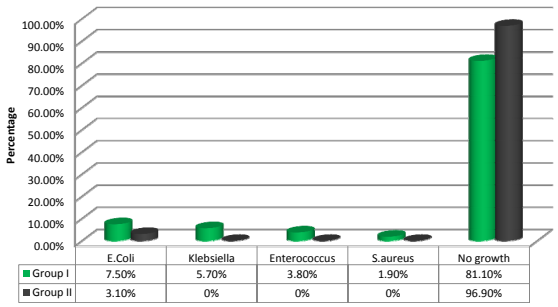

Figure 2. Growth pattern of urine culture in two groups.

total white blood cell (WBC) count, neutrophil count and C-reactive protein (CRP) levels are statistically significant. The growth pattern of urine culture in two groups is highlighted in figure 2. Table 5 shows the antibiogram of isolated organisms.

Table 5. Antimicrobial susceptibility pattern of isolated organisms from urine samples:

Organism	Type of antibiotic	Susceptibility level		
		Sensitive	Resistant	Not done
Escherichia coli =5	*Gentamycin*	4	1	0
	Amikacin/netilmycin	4	0	1
	Nitrofurantoin/ Norflox	3	1	1
	Imipenem	2	0	3
	Ciprofloxacin/cefotaxim	2	1	2
	Ceftriaxone	2	2	1
	Amoxicillin / Piperacillin	1	3	1
	Penicillin/ Cotrimoxazole	1	0	4
	Cefexim	1	1	3
	Ampicillin	0	4	1
	Cefazolin	0	3	2
	Cefalexin	0	2	3
Klebsiella (n=3)	*Imipenem*	3	0	0
	Amikacin/netilmycin	2	0	1
	Gentamicin/Ciprofloxacin/ vancomycin	2	1	0
	Ceftriaxone/cefotaxim/ Piperacillin	1	1	1
	Cefazolin	1	2	0
	Nitrofurantoin	1	0	2
	Cotrimoxazole/Norflox/ Cloxacillin	0	3	0
	Ampi/ Amoxycillin/Cefalexin/ penicillin	0	1	2
Enterococcus (n=2)	*Gentamicin/Nitrofurantoin/ Vancomycin*	2	0	0
	Imipenem/ Ciprofloxacin	1	1	0
	Norflox/ Penicillin	1	0	1
	Cefazolin /cefalexin/ Piperacillin/ cloxacillin / ampicillin	0	1	1
	Ceftriaxone/cefotaxim / Amoxicillin	0	2	0
Staphylococcus aureus (n=1)	*Gentamicin/Nitrofurantoin/Cefazoli/Vancomycin/ Erythromycin*	1	0	0
	Amikacin/Netilmycin/ Cefotaxim /cefalexin/ Amoxicillin/penicillin/ Ciprofloxacin/piperacillin/ampicillin/Cefexim	0	1	0

DISCUSSION

Hyperbilirubinemia is one of the presenting signs of bacterial infection in newborns, and its association with urinary tract infection (UTI) has been reported by several Authors.[8,9] Urinary evaluation is routinely done in seriously ill jaundiced newborns who present with features of sepsis But in cases where newborns are asymptomatic and present with indirect hyperbilirubinemia urine evaluation is not a routine test hence the diagnosis of UTI may possibly be missed in such cases. American Academy of Pediatrics (AAP) has published guidelines where they recommend investigation for urinary tract infection only in direct hyperbilirubinemia.[5] Multiple studies have described patients with proven bacterial infection, who developed jaundice during the course of their illness.[10-12] Other studies, have noted that jaundice may be one of the first signs of bacterial sepsis in neonates in the first few days of life.[13] But none of these studies have mentioned about UTI. According to this study 12.9% cases of asymptomatic babies with indirect hyperbilirubinemia had UTI. This was reported to be 15 and 18% in other studies.[14,15] Ghaemi et al. studies evaluated late and prolonged icterus and found UTI in 5.8%.[4] The reason for lower incidence of UTI in latter study maybe due to the fact that they had evaluated only late and prolonged jaundice and had excluded physiological jaundice whereas other studies including our study had included physiological jaundice. Most of the studies have evaluated late jaundice with UTI where mean age was at range of 5-12.1 days.[3,16] In our study we compared early physiological jaundice with mean age at onset of jaundice 5.0±1.04 days with late prolonged jaundice with mean age 13.60±4.88. To our knowledge, very few studies have compared the incidence of UTI in asymptomatic jaundiced newborns between early physiological and late prolonged jaundice. The incidence of UTI was found to be double in late than early icterus (27.2% Vs 14.2%) in one study.[15] We also had high incidence of UTI in late prolonged jaundice 10/11 (90.9%) Vs 1/11 (10.1%) with p<0.046 and [OR 7.210, 95% CI (0.870, 59.270)]. Another study where mean age at onset of jaundice was 8.9 days the incidence of jaundice was found to be 8.2%.[17] In this study, one case with early physiological jaundice had UTI, however in this case sepsis could have been the cause of jaundice as some asymptomatic babies had high total WBC count and positive CRP. In a study from Turkey Hulya Bilgen et al. emphasized on the importance of urine culture as routine workup in all neonatal jaundice.[9]

Neonatal hyperbilirubunemia was more frequent in males in our study. Similar finding was noted in another study.[4] Again, unlike our study UTI was more prevalent in females, suggesting that there are no sex predominance for UTI in newborns.[18] UTI was noted more in term gestation babies with prolonged jaundice in this study. Supporting our study all culture positive newborns were of term gestation in Chamdine Omar et al. study and other two studies reported that hyperbilirubinemia was the main clinical finding among term newborns with UTI.[19-21]

Although Garcia et al. reported that an elevated conjugated bilirubin fraction was more likely to have UTI; none of our patients had a high direct bilirubin level.[22] The hyperbilirubinemia associated with UTIs can be unconjugated and related to hemolysis caused by *Escherichia coli* and other Gram-negative organisms, or conjugated secondary to cholestasis.[10,23-26] The mechanism by which a UTI causes cholestasis is not clear, but possible

mechanisms include microcirculatory changes in the liver, direct effects from bacterial products, and/or from endotoxin-induced mediators.[27,28] It is postulated that even mild hemolysis can overload the immature liver conjugating mechanism, leading to an increase in serum bilirubin levels.

Supporting the statement, *E. coli* is responsible for the vast majority of UTI in young infants, *E. coli* (45.45%) was the predominant pathogen isolated in this study followed by *Klebsiella* (27.27%), *enterococcus* (18.18%) and *Staph. aureus* (9.09% %). Similar organisms were isolated in other studies but the antibiotic sensitivity pattern differed.[15] Other lab parameters like total WBC count, neutrophil count and CRP was significantly elevated in prolonged jaundice cases so maybe these could also be included as routine screening tool even in asymptomatic hyperbilirubinemic newborns.

CONCLUSION

UTI can occur in asymptomatic, unconjugated neonatal jaundice and was 12.9% in this study. In addition, UTI was significantly high in late prolonged unconjugated hyperbilirubinema. Therefore, based on the result of this study we suggest that urine culture to be considered as part of the diagnostic evaluation for asymptomatic newborns with late prolonged unconjugated hyperbilirubinemia. Since this was just a hospital based study a sufficient large cohort study is essential for better conclusion. This may help identify UTI before signs and symptoms become evident and help in timely treatment.

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