

Is There Any Relationship between Hyperbilirubinemia and Pelvicaliceal Dilatation in Newborn Babies?

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Abstract

Objective: A recent study reported association of high bilirubin concentrations with decrease in basal vesical tonicity and relaxation of pre-contracted ureteral and vesical smooth muscles in vitro, and authors discussed that recovery of antenatal hydronephrosis might partly be associated with decreased bladder resistance to the urine flow due to hyperbilirubinemia. We aimed to investigate whether any relationship between serum bilirubin levels and antero-posterior renal pelvic diameters or pelvicaliceal dilatations exist during newborn period.

Methods: Neonates with hyperbilirubinemia (group 1) and healthy neonates (group 2) were randomly selected to the study. Capillary blood samples were used to measure micro-bilirubin. Urinary system ultrasound (US) was performed in both groups by an experienced radiologist.

Findings: Group 1 (31 neonates, 16 males, 15 females) and group 2 (22 neonates, 11 males, 11 females) were identical by means of postnatal age, gender and weight ($P>0.05$). Mean serum bilirubin levels were 11.1 ± 3.1 mg/dl and 1.4 ± 0.2 mg/dl in group 1 and 2, respectively. Renal length and renal pelvis antero-posterior (AP) diameters were not different between study groups. Pelvis AP diameters of right kidney were 2.1 ± 0.7 mm in group 1 and 1.9 ± 0.7 mm in group 2, and of left kidney were 2.4 ± 0.8 mm in group 1 and 2.3 ± 0.6 mm in group 2. There was no correlation between bilirubin levels and renal length and renal pelvis AP diameters ($P>0.05$).

Conclusion: In this study we were not able to demonstrate any relationship between serum bilirubin levels and renal pelvic diameters and pelvicaliceal dilatation in hyperbilirubinemic neonates. So, it is thought that hyperbilirubinemia might not have a direct effect on outcome of the pelvicaliceal dilatation.

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Introduction

Hyperbilirubinemia, during neonatal period, is considerably frequent, and generally a benign problem. During the first week of life,

approximately 60% of term babies have jaundice. Thus most neonates are exposed to higher than normal levels of bilirubin in the first two weeks of life. The level of indirect bilirubin in the umbilical cord is 1-3 mg/dl normally. Indirect bilirubin level

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increases to 5-6 mg/dl between 2nd and 4th day and decreases to less than 2 mg/dl on 5th-7th day. It reaches adult levels approximately 10-14th day of life in full-term babies^[1].

Antenatal ultrasound usage significantly increased from the early 1980s. Related to this, antenatally detected urinary tract abnormalities increased significantly. Antenatal hydronephrosis is the most common urinary tract anomaly detected by prenatal ultrasound screening studies^[2,3]. Antenatal hydronephrosis is caused by several physiologic and pathologic conditions. Most neonates with antenatal hydronephrosis have a good prognosis with only 15-25% of patients requiring surgery during 4 years of follow-up^[4]. Mallik and Watson reported 350 infants with various antenatally detected urinary tract abnormalities between 1989 and 2003, of which 48.6% (170/350) was non-specific renal pelvic dilatation. The most common final diagnosis of these patients is either transient or physiological hydronephrosis, secondary to large non-obstructive renal pelvis^[5]. Etiology of transient hydronephrosis is uncertain but it may occur due to insufficient maturation of the pelviureteric junction muscles; changes in ureteral and bladder muscle activity may also play a role especially in non-obstructive pelvis dilatation. It is becoming apparent that many of the antenatal hydronephroses spontaneously improve or resolve without any surgical treatment^[4,6].

In a recent study, it was demonstrated that high bilirubin concentrations cause decrease in basal vesical tonicity and relaxation in both pre-contracted ureteral and vesical smooth muscles in vitro. The authors thought that hyperbilirubinemia may have probably contributed to spontaneous improvement of pelvic dilatation^[6]. So, we aimed to investigate whether there was any relationship between serum bilirubin levels and AP renal pelvic diameters or pelvicaliceal dilatation in newborn babies.

Subjects and Methods

Thirty three jaundiced neonates (group 1) and 22 healthy neonates (group 2) were randomly selected. The study was done in Dr. Ekrem Hayri

Üstündağ Women's Diseases and Maternity Hospital in Turkey, between May-December 2007. Our study has followed principles in the Declaration of Helsinki, and written consent was obtained from the patients' parents.

Healthy term babies with (group 1) and without (group 2) jaundice were taken in the study. Babies with onset of hyperbilirubinemia after 24 hours of birth were included in the study. Preterm infants, infants with small for gestational age, with urinary tract infection (UTI), direct hyperbilirubinemia, those known to have antenatal hydronephrosis or another systemic health problem were not included.

Capillary blood samples were used to measure micro-bilirubin. Total bilirubin and direct bilirubin values were checked if hyperbilirubinemia was detected.

Urinary system ultrasound (US) was done in both study groups by an experienced radiologist simultaneously with micro-bilirubin measurement. Dilatation of ureter and/or pelvicaliceal system, renal length, renal pelvis AP diameter and in co-existence of hydronephrosis, its grading according to The Society of Fetal Urology, were recorded.

Data was presented as mean±standard deviations. The statistical analysis was performed in SPSS 13.0 (Chicago, IL) in Windows. Student-t and Chi-Square tests were used to compare the difference between groups. Relationship between bilirubin levels and ultrasonographic kidney measurements was tested using Spearman's rho test. Results were considered significant if $P < 0.05$.

Findings

Physical examination of the babies in group 1 was unremarkable except for jaundice. Group 1 and group 2 were identical regarding postnatal age, gender and weight ($P > 0.05$) (Table 1).

Ultrasonographic findings

Neither hydronephrosis nor hydroureter was detected in the study groups. Left renal agenesis was found in an infant of group 1. Renal length and renal pelvis AP diameters were not found to be

Table 1: Demographic properties of the study groups

Parameter	Group 1 n=31	Group 2 n=22
Gender (Male/Female)	16/15	11/11
Birth weight (gr) [Mean (SD)]	3271.0 (470.9)	3455.5 (562.7)
Age (Day) [Mean (SD)]	9.0 (3.4)	10.9 (4.5)
Weight (gr) [Mean (SD)]	3546.8 (511.5)	3761.4 (516.8)
Serum bilirubin (mg/dl) [Mean (SD)]	11.1 (3.1)*	1.4 (0.2)

* $P < 0.01$ / SD: Standard Deviation

different between the study groups (Table 2). There was no correlation between bilirubin levels and renal length and renal pelvis AP diameters ($P > 0.05$).

Discussion

Bilirubin has well recognized antioxidant properties in renal and other various cell types^[7]. Several studies pointed out that bilirubin has relaxant effect on smooth muscles such as arterial vessels and gastric fundus^[8-10]. In a recent study, Pflueger et al reported that pressor and prooxidant effects of angiotensin II were attenuated in the hyperbilirubinemic Gunn rats which did not have uridine diphosphate glucuronosyl transferase enzyme. They speculated that these effects may have arisen from the quenching of oxidative stress by bilirubin^[8].

In normal renal physiology, urine accumulates in the renal pelvis up to a certain volume and pressure, and then ureteropelvic junction (UPJ) opens. UPJ opening upon renal pelvic distension

postulates a reflex called “pelviureteral inhibitory reflex.” This reflex is believed to regulate the passage of urine from the renal pelvis to the ureter. In addition ureteric distension closes the UPJ; this reflex action is called the “ureteropelvic excitatory reflex” as it seems to prevent reflux of urine through the UPJ and thus protects the kidney. The concept that the UPJ acts as a physiologic sphincter has been put forward^[11]. In normal physiologic conditions, opening of the ureterovesical junction occurs synchronously with the UPJ. The urine is delivered from the renal pelvis to the relaxed bladder. This reflex is called “renal pelvivesical reflex^[12].”

In a recent study, Murat et al focused on effect of bilirubin to the ureteral and bladder smooth muscles^[6]. They investigated whether long-term exposure to higher bilirubin levels might have a role in dilatation of ureteral and vesical smooth muscles that may cause recovery of transient pelvicaliceal dilatation. They investigated the effects of normal and high bilirubin concentrations on both basal and pre-contracted ureteral and bladder muscles in vitro. They reported that normal and high bilirubin levels caused no change in the basal ureteral tension, normal bilirubin

Table 2: Renal lengths and renal pelvis antero-posterior diameters in study groups

Parameter	Group1 Mean (SD)	Group2 Mean (SD)	P value
Right renal length (mm)	43.6 (3.5)	43.6 (3.1)	>0.05
Right renal parenchyma thickness (mm)	8.6 (1.0)	8.1 (0.9)	>0.05
Right renal pelvis antero-posterior diameter (mm)	2.1 (0.7)	1.9 (0.7)	>0.05
Left renal length (mm)	43.7 (3.5)	44.2 (3.1)	>0.05
Left renal parenchyma thickness (mm)	8.9 (0.9)	8.5 (0.8)	>0.05
Left renal pelvis antero-posterior diameter (mm)	2.4 (0.8)	2.3 (0.6)	>0.05

SD: Standard Deviation

levels caused no difference in basal bladder tension but high bilirubin concentrations caused a decrease in bladder tension. After potassium chloride (KCl) application to tissues for contraction of ureteral and bladder muscles, normal bilirubin caused $86.4 \pm 7.2\%$ relaxation, high bilirubin caused $133.9 \pm 17.4\%$ relaxation, which was statistically significant. In pre-contracted bladder muscles, normal and high bilirubin concentrations caused $35.3 \pm 2.2\%$ and $53.5 \pm 3.5\%$ relaxation, respectively, which was significantly higher in high bilirubin concentrations. As a result, they did not find any effect of hyperbilirubinemia on basal ureteral tension. But, on contrary hyperbilirubinemia may also worsen the outcome of pelvicaliceal dilatation rather than improve it, because it causes relaxation of pre-contracted ureteral tension, namely ureteral peristalsis. On the other hand, they found that hyperbilirubinemia caused decreased bladder muscle activity, in a dose dependent manner. They speculated that neonates with hyperbilirubinemia might have a more relaxed bladder which might result in lower resistance for the renal pelvis and might contribute to the improvement of hydronephrosis. They discussed that recovery of antenatal hydronephrosis might be, not directly, but partly associated with decreased bladder resistance to the urine flow^[6].

We therefore planned this study to investigate whether relationship between serum bilirubin levels and pelvicaliceal dilatations in the newborn babies exists. However, in our study renal length, renal parenchymal thickness and renal pelvis AP diameter of both kidneys were not different between hyperbilirubinemic and normobilirubinemic newborns. So, it is thought that hyperbilirubinemia might not have a direct effect in outcome of the pelvicaliceal dilatation.

On the other hand, more relaxed bladder and decreased ureteral peristalsis in hyperbilirubinemic neonates may result in urinary stasis. Urinary stasis is one of the most important reasons for UTI^[13,14]. Besides, the relationship between UTI and hyperbilirubinemia has not been clearly determined. A lot of study pointed out that UTI was relatively frequent in neonates with hyperbilirubinemia^[15-19]. Bacteriuria in asymptomatic neonates is approximately 0.7-

1.4%, however the prevalence of UTI is between 5% and 11% in hyper-bilirubinemic neonates^[15]. UTI in hyperbilirubinemic neonates shows co-existence with anatomical abnormalities of the urinary tract infection such as vesicoureteral reflux, hydronephrosis and pelvicaliectasis^[17,18]. Interestingly, in a recent study, Xsinias et al reported that increased bilirubin level was related to renal damage in DMSA scintigraphy. Renal damage was observed in 46.7% in their 30 neonates with jaundice and UTI. Besides these different observations, the relationship between UTI and hyperbilirubinemia has not been clearly determined^[19]. In our study, there was no UTI, neither in hyperbilirubinemic nor in healthy neonates.

Conclusion

We were not able to demonstrate any relationship between serum bilirubin levels and renal pelvic diameters and pelvicaliceal dilatations in hyperbilirubinemic neonates. So, it is thought that hyperbilirubinemia might not have a direct effect on outcome of the pelvicaliceal dilatations. Although we were not able to show association between hyperbilirubinemia and pelvic diameters, as a limitation of our study, our study sample was small and we did not have follow-up data of the included babies. Further studies with larger sample size are required to draw more precise conclusions regarding this subject.

Conflict of Interest: None

References

1. Piazza AJ, Stool BJ. Jaundice and hyperbilirubinemia in the newborn. In: Kliegman RE; Behrman RE, Jenson HB, Stanton BF (eds). Nelson Textbook of Pediatrics. 18th ed. Philadelphia: Saunders. 2007; Pp:756-66.
2. Sever L. Antenatal Hidronefroz: Tanı, Tedavi Ve İzlem Türkiye Klinikleri. *J Pediatr Sci* 2008;1:49-58. (In Turkish)

3. Woodward M, Frank D. Postnatal management of antenatal hydronephrosis. *BJU International* 2002;89(2):149-56.
4. Koff SA. Postnatal management of antenatal hydronephrosis using an observational approach. *Urology* 2000;55(5):609-11.
5. Mallik M, Watson AR. Antenatally detected urinary tract abnormalities: more detection but less action. *Pediatr Nephrol* 2008;23(6):897-904.
6. Murat N, Kasap B, Kavukcu S, et al. In vitro analysis of the effect of hyperbilirubinemia on rabbit ureter and bladder. *Pediatr Nephrol* 2006; 21(3):328-32.
7. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. *Science* 1987;235 (4792):1043-6.
8. Pflueger A, Croatt AJ, Peterson TE, et al. The hyperbilirubinemic Gunn rat is resistant to the pressor effects of angiotensin II. *Am J Physiol Renal Physiol* 2005;288(3):F552-8.
9. Colpaert EE, Timmermans JP, Lefebvre RA. Investigation of the potential modulatory effect of biliverdin, carbon monoxide and bilirubin on nitrenergic neurotransmission in the pig gastric fundus. *Eur J Pharmacol* 2002;457(2-3):177-86.
10. Mayer M. Association of serum bilirubin concentration with risk of coronary artery disease. *Clin Chem* 2000;46(11):1723-7.
11. Shafik A. Pelviureteral inhibitory reflex and ureteropelvic excitatory reflex: role of the two reflexes in the regulation of urine flow from the renal pelvis to the ureter. *Neurol Urolog* 1997;16(4):315-24.
12. Shafik A. Effect of renal pelvic distension on the ureteropelvic and ureterovesical junctions and the urinary bladder: the renal pelvovesical reflex. *World J Urol* 1998;16(3):219-23.
13. Lidfelt KJ, Erasme U, Bollgren I. Residual urine in children with acute cystitis and in healthy children: assessment by sonography. *J Urol* 1989;141(4):916-7.
14. Leonardo CR, Filgueiras MF, Vasconcelos MM, et al. Risk factors for renal scarring in children and adolescents with lower urinary tract dysfunction. *Pediatr Nephrol* 2007;22(11):1891-6.
15. Edelmann CM, Ogwo JE, Fine BP, Martinez AB. The prevalence of bacteriuria in full-term and premature newborn infants. *J Pediatr* 1973; 82(1):125-32.
16. Pashapour N, Nikibakhsh AA, Golmohammadlou S. Urinary tract infection in term neonates with prolonged jaundice. *Urol J* 2007;4(2):91-4.
17. Bilgen H, Ozek E, Unver T, et al. Urinary tract infection and hyperbilirubinemia. *Turk J Pediatr* 2006;48(1):51-5.
18. Ghaemi S, Fesharaki RJ, Kelishadi R. Late onset jaundice and urinary tract infection in neonates. *Indian J Pediatr* 2007;74(2):139-41.
19. Xinias I, Demertzidou V, Mavrousi A, et al. Bilirubin levels predict renal cortical changes in jaundiced neonates with urinary tract infection. *World J Pediatr* 2009;5(1):42-5.