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Original article

Evaluation of cardiac function in neonates with unconjugated hyperbilirubinemia

Amar M. Taksande, Divya Pujari

Department of Paediatrics, JNMC, DMIMS, Sawangi Meghe, Wardha, Maharashtra, India

Abstract

Background: Unconjugated hyperbilirubinemia (UHB) is an important problem encountered during the neonatal period. It may lead to severe cardiac autonomic dysfunction like heart rate variability and myocardial damage. The aim of this study was to evaluate cardiac function in neonates with UHB by echocardiography.

Methods: This single-center, prospective, case-control study was conducted on 100 full-term neonates with severe UHB requiring phototherapy and 100 healthy infants as controls. Cardiac function was assessed by echocardiography, tissue Doppler imaging (TDI) and serum cardiac troponin measurements.

Results: There was an increase in heart rate, respiratory rate and blood pressure in cases compared to controls, although the difference was not statistically significant. In addition, there was no statistically significant difference in the left ventricular systolic and diastolic function on echocardiography and TDI. Cardiac troponin level was normal in all the cases.

Conclusion: This study shows that UHB did not affect the cardiac functions of the left ventricle.

Keywords

Hyperbilirubinemia, newborn, cardiac functions, echocardiography.

Corresponding author

Amar M. Taksande, Department of Paediatrics, JNMC, DMIMS, Sawangi Meghe, Wardha, Maharashtra, India; email: amar.taksande@gmail.com.

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Introduction

Hyperbilirubinemia is a commonly encountered issue in neonates, occurring in approximately 8% to 11% of babies [1]. Although unconjugated hyperbilirubinemia (UHB) is a frequently benign condition, excessively raised serum bilirubin has potentially harmful side effects. The neurotoxic effects of unconjugated bilirubin are widely known and studied. It has been found that neonatal hyperbilirubinemia also has an effect on cardiovascular functions. The entire spectrum of cardiovascular effects in jaundiced babies is yet to be studied. Nevertheless, few effects have been seen. Increased bilirubin levels increase parasympathetic tone and cause heart rate variability [2]. Evaluation of levels of myocardial enzymes and cardiac troponin I (cTnI) has shown a marked rise during the hyperbilirubinemia period but rapid fall during recovery suggestive that hyperbilirubinemia might cause transient myocardial damage [3]. An *in-vitro* study on hyperbilirubinemia demonstrated decreased myocardial contractility [4]. The degree of myocardial damage was also found to be dependent on the degree and duration of hyperbilirubinemia [5, 6]. The pathology may be attributed to oxidative stress caused by bilirubin [7]. Alternatively, due to autonomic dysfunction, which is in turn caused by neurological toxicity. Although many *in-vivo* studies have been conducted to see the effects of hyperbilirubinemia, neonatal studies leave much to be desired. This study aims to fill a few gaps by assessing the cardiac functions via transthoracic M-mode and Doppler echocardiographies in neonates with UHB.

Material and methods

An observational case-control study was conducted in the Neonatology Department of a tertiary level hospital (AVBRH Hospital, Sawangi, Wardha, Maharashtra, India) from January 2018 to May 2019. Two hundred inborn newborns were included in the study (100 cases and 100 controls). All neonates delivered in our hospital were monitored twice daily through physical assessment and with a transcutaneous bilirubinometer (TcB) for the presence of hyperbilirubinemia.

Cases: full-term, appropriate for gestational age (AGA) neonates whose serum bilirubin levels were in the range of phototherapy according to the recommendations of the American Academy of Pediatrics (AAP) [8, 9].

Controls: full-term, AGA neonates who did not have TcB value in the range of phototherapy were taken as controls in a 1:1 age- and sex-matched ratio.

We excluded neonates with structural congenital heart diseases, history of familial arrhythmia, respiratory and circulatory problems (neonatal sepsis, respiratory distress syndrome, asphyxia, acidosis, and hypothermia), acid-base and electrolyte imbalance, inborn errors of metabolism, bilirubin encephalopathy, systemic drug therapy with arrhythmogenic and chromosome abnormalities.

Perinatal history (including maternal illness, mode of delivery, Apgar score, history of cyanosis or convulsions) and clinical examination (with special emphasis on vital signs, anthropometric measures, presence of cephalhematoma and neurological examination) were recorded in all study cases. Serum bilirubin levels (total, direct and indirect) were determined through direct spectrophotometry. Serum calcium and cardiac troponin levels were also measured.

Echocardiography was performed by using a GE Vivid™ Echocardiography according to the American Society of Echocardiography Guidelines [10, 11]. M-mode and two-dimensional echocardiography was done to measure the left ventricle (LV) internal dimensions, including left ventricular internal dimension in diastole (LVIDd), left ventricular internal dimension in systole (LVIDs), left ventricular interventricular septal in diastole (LVIVSd) thickness, left ventricular posterior wall in diastole (LVPWd) thickness. The diameter of the left atrium and aorta was measured. The fractional shortening (FS) and ejection fraction (EF) was estimated using M-mode and Simpson in the parasternal long- and short-axis views as well as in the apical four-chamber view. The apical view was used to record LV inflow velocities in which the velocities of the LV inflow in early diastole (E) and late diastole with atrial contraction (A) were measured, and the E/A ratio was calculated.

Tissue Doppler imaging (TDI): a 2-mm pulse-wave (PW) sample volume was placed at the

lateral border of mitral valve annulus (LV) and measured the peak systolic and diastolic velocities with TDI in cases and controls. The following parameters were recorded: systolic velocity (S'), early diastolic velocity (E'), late diastolic velocity (A') and time intervals; isovolumetric contraction time (IVCT), isovolumetric relaxation time (IVRT) and ejection time (ET) at each site. The formula used to calculate the Tei index is as follows: (IVCT + IVRT) / ET [11]. Written consent was obtained from each participant's parents, and the Medical Ethics Committee of DMIMS University of Medical Science approved the study.

Statistical analysis was performed by STATA® software. Continuous variables are presented as means ± SDs, and categorical variables are given as frequencies with percentages. To compare continuous variables, the student's t-test was applied. All p-values < 0.05 were considered statistically significant.

Results

A total of 200 neonates, 100 cases and 100 controls, were recruited into the study. The male and female ratio was the same in both groups since they were sex-matched (males: 54% and females: 46%). The mean gestational age was 38.4 ± 1.15 weeks for the cases, and that of controls was 38.05 ± 1.92 weeks. Demographics did not show any statistically significant difference between the cases and controls (**Tab. 1**). In the study cases, 42 (50.85%) babies had hyperbilirubinemia at < 48 hours of life, 32 (27.12%) babies had hyperbilirubinemia at 48-72 hours, 15 (12.71%) babies had hyperbilirubinemia at 72-96 hours, and 11 (9.32%) babies had hyperbilirubinemia after 96 hours of life (**Tab. 2**). There was no statistically significant difference in the heart rate, respiratory rate, oxygen saturation and blood pressure (**Tab. 3**). M-mode echocardiography measures are shown in **Tab. 4**. In terms of left ventricular systolic function, there was no significant difference in the LVIVSd, LVIVSs, LVIDd, LVIDs, LVPWd, LVPWs, EF and FS (p > 0.05). We could not find any significant difference in terms of left ventricular systolic function between cases and control. In terms of the diastolic function of the LV (**Tab. 5**), there was no significant difference in the E wave, A wave and E/A ratio, in both cases and controls (p > 0.05). In terms of myocardial velocity and time interval for the assessment of LV systolic and diastolic function (**Tab. 6**), there was no significant difference in terms of mitral E' wave, A' wave, S' wave, IVRT, IVCT, ET and Tei index, in cases and controls (p > 0.05). Cardiac troponin values were normal in all the cases. There was no statistically significant difference between serum calcium level in cases (9.3 mg/dL) and controls (9.18 mg/dL).

Table 1. Demographic distribution of cases and controls.

Demographic parameters	Controls	Cases	p-value
Age, days (mean ± SD)	4.23 ± 1.14	4.23 ± 1.14	-
Gestational age, weeks (mean ± SD)	38.05 ± 1.92	38.4 ± 1.15	0.11
Sex (male/female)	54/46	54/46	-
Mode of delivery (NVD/LSCS)	63/37	48/52	-
Weight, kg (mean ± SD)	2.70 ± 0.40	2.68 ± 0.40	0.70
Length, cm (mean ± SD)	49.66 ± 1.98	48.64 ± 1.86	0.96
Head circumference, cm (mean ± SD)	32.79 ± 1.04	33.04 ± 1.42	0.28

NVD: normal vaginal delivery; LSCS: lower segment cesarean section.

Table 2. Number of hours of life and bilirubin values in cases.

Hours of life	Neonates with hyperbilirubinemia	Mean serum bilirubin (mg/dL) in cases
< 48 hours	42 (50.85%)	17.17 ± 1.23
48-72 hours	32 (27.12%)	17.98 ± 2.12
72-96 hours	15 (12.71%)	18.67 ± 2.32
> 96 hours	11 (9.32%)	19.45 ± 1.46

Table 3. Distribution of vital parameters of cases and controls.

Vital parameters	Controls (mean ± SD)	Cases (mean ± SD)	p-value
Heart rate (beats/min)	132.35 ± 6.58	133.55 ± 5.84	0.174
Respiratory rate (cycles/min)	43.84 ± 5.63	45.02 ± 5.14	0.123
SpO_2 (%)	98.32 ± 0.74	98.13 ± 0.92	0.109
Systolic blood pressure (mmHg)	64.92 ± 4.82	65.12 ± 3.82	0.745
Diastolic blood pressure (mmHg)	38.11 ± 4.36	38.43 ± 4.48	0.546

Table 4. Assessment of the left ventricular systolic function in cases and controls.

Systolic parameter of LV	Controls (mean ± SD)	Cases (mean ± SD)	p-value
LVIVSd	4.50 ± 0.76	4.55 ± 0.83	0.112
LVIVSs	5.49 ± 0.76	5.52 ± 0.71	0.131
LVIDd	13.37 ± 1.21	13.41 ± 1.22	0.319
LVIDs	8.08 ± 0.88	8.12 ± 0.89	0.139
LVPWd	4.56 ± 0.79	4.53 ± 0.81	0.089
LVPWs	4.96 ± 0.82	4.98 ± 0.81	0.338
EF	66.30 ± 4.39	66.39 ± 4.34	0.402
FS	33.39 ± 2.17	33.33 ± 2.29	0.416
Left atrium	9.47 ± 1.34	9.52 ± 1.41	0.131
Aorta	7.72 ± 1.01	7.74 ± 0.96	0.458
LA/Ao	1.23 ± 0.175	1.24 ± 0.189	0.691

LV: left ventricle; LVIVSd: left ventricular interventricular septal in diastole thickness; LVIVSs: left ventricular interventricular septal in systole thickness; LVIDd: left ventricular internal dimension in diastole; LVIDs: left ventricular internal dimension in systole; LVPWd: left ventricular posterior wall in diastole thickness; LVPWs: left ventricular posterior wall in systole thickness; EF: ejection fraction; FS: fractional shortening; LA/Ao: left atrial to aortic root diameter ratio.

Table 5. Assessment of diastolic function of LV (mitral valve) between cases and control.

Diastolic parameter of LV	Controls (mean ± SD)	Cases (mean ± SD)	p-value
E wave	43.66 ± 9.16	43.74 ± 9.12	0.762
A wave	55.71 ± 10.63	55.63 ± 12.68	0.923
E/A	0.81 ± 0.25	0.83 ± 0.30	0.102

LV: left ventricle; E: early diastole; A: late diastole with atrial contraction.

Table 6. Assessement of myocardial velocity and time interval at mitral valve by TDI.

TDI parameter of LV		Controls (mean ± SD)	Cases (mean ± SD)	p-value
Mitral valve	E' wave	5.67 ± 1.01	5.60 ± 1.02	0.136
	A' wave	7.18 ± 1.41	7.19 ± 1.36	0.689
	S' wave	5.81 ± 0.97	5.90 ± 1.24	0.199
	IVCT	27.13 ± 6.77	26.80 ± 6.65	0.621
	IVRT	25.01 ± 4.11	24.38 ± 4.08	0.157
	ET	219.88 ± 35.97	218.45 ± 33.33	0.196
	Tei index (LV)	0.24 ± 0.05	0.23 ± 0.04	0.367

TDI: Tissue Doppler imaging; LV: left ventricle; E': early diastolic velocity; A': late diastolic velocity; S': systolic velocity; IVCT: isovolumetric contraction time; IVRT: isovolumetric relaxation time; ET: ejection time.

Discussion

Hyperbilirubinemia is common in neonates and caused by an exaggeration of physiological mechanisms or by pathologic conditions that increase bilirubin production, decrease bilirubin clearance, or increase the enterohepatic circulation. It can represent a benign physiologic process or serious illness with associated severe neurotoxicity [6]. Several studies demonstrate that bilirubin exhibits an antioxidant effect at low levels, causes oxidative stress at high levels and damage on cells and organs, and also affects the autonomic nervous system [12-14]. In a study done by Uhrikova et al. [2], they found a relationship between cardiac autonomic control and heart rate variability in neonates with hyperbilirubinemia. In addition, Basu et al. [13] reported that total serum bilirubin decreased the antioxidant defence effect over 16 mg/dL and led to lipid peroxidation with values above 20 mg/dL, resulting in DNA damage of all levels of bilirubin levels. He also found the association of moderate-to-severe UHB with higher oxidative stress and lower antioxidant defense. Researchers [14] also found a decrease in breathing rate and increased apnea frequency in preterm lambs with hyperbilirubinemia compared to healthy preterm lambs. They also pointed out that the inhibition of laryngeal and pulmonary chemoreflexes and bradycardia were more common in the preterm lambs with hyperbilirubinemia. Ostrow et al. [15] showed that elevated UHB levels are caused by astrocyte and neuronal apoptosis caused by mitochondrial and plasma membrane damage. In another study, researcher [16] reported that in full-term newborn infants with severe UHB, the mean minimum heart rate, rMSDD, low frequency, and low frequency to high frequency (LF/HF) ratio were significantly lower due to autonomic dysfunction caused by parasympathetic dominance. There was no statistically significant difference in heart rate, respiratory rate, oxygen saturation and blood pressure among cases and controls in our study.

Another study showed that [4] in an *in-vitro* study on hyperbilirubinemia, myocardial contractility was reduced, whereas, in an *in-vivo* analysis with rats, the left ventricular contractile parameters and ejection (FS and EF) were the same as in the control group. Li et al. [5], in their study, mentioned that the myocardial enzymes and isoenzymes activities, especially creatine kinase (CK) and MB isoenzymes of creatine kinase (CK-MB), were elevated in neonates with UHB. He also found that pathological hyperbilirubinemia in a neonate may induce

myocardial function impairment, which can be correlated with the degree and duration of jaundice. In addition, Gao et al. [17] evaluated CK, CK-MB, cTnI, ECG, for corrected QT intervals (QTc) and QTc dispersion (QTcd), and ECHO, for left ventricular EF, the ratio of the peak velocity of early stage and advanced stage of diastolic phase at the mitral orifice (E/A) in neonates and mentioned that there was inadequate evidence to support the hypothesis that myocardial damage may be seen in jaundiced babies. Furthermore, Karabulut and Şimşek [12] demonstrated no significant differences in EF, FS, left ventricular end-diastolic dimension (LVEDd), and left ventricular end-systolic dimension (LVEDs) between the cases and controls. They also found no significant differences in terms of mitral, tricuspid, septal E', A', and S' between groups. The same result was found in our study also. However, the study done by Yan et al. [18] mentioned that hyperbilirubinemia causes a temporary myocardial injury. They also advised that cTnI and CK-MB can help monitor myocardial injury in jaundiced babies. In addition, Xu and Wang [19] too suggested that pathological jaundice might result in myocardial damage. In the present study, we could not find a significant difference in the systolic and diastolic function of the LV in cases and control.

Conclusions

We report that neonatal hyperbilirubinemia does not impair the left ventricular systolic and diastolic function in neonates.

Declaration of interest

The Authors declare that there is no conflict of interest.

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