

# Electrocardiographic Parameters in Neonates with Hyperbilirubinemia in Northeast Iran

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## ABSTRACT

**Background:** Hyperbilirubinemia, a common illness in neonates, imposes a risk of arrhythmia and sudden death, particularly during blood transfusions. The present study aimed to evaluate the electrocardiographic parameters in term newborns with hyperbilirubinemia in Gorgan, northeast Iran.

**Methods:** This cohort study was conducted on 101 term neonates admitted to our academic hospital with hyperbilirubinemia (direct bilirubin > 20 mg/dL). Those with sepsis, TORCH[(T)oxoplasmosis, (O)ther Agents, (R)ubella (also known as German Measles), (C)ytomegalovirus, and (H)erpes Simplex], congenital heart disease, polycythemia, and asphyxia were excluded. An electrocardiogram (ECG) was taken before the initiation of phototherapy, and heart rate, PR interval, QRS duration, QTc interval, and ST-T changes were recorded after every 8 h during the phototherapy.

**Results:** In this population of neonates with a mean age of  $6.09 \pm 3.57$  days, the results demonstrated that after 32 h of phototherapy, bilirubin decreased to less than 20 mg/dL. Following that, intensive phototherapy was replaced with the conventional method. Changes in ECG parameters were not significantly related to changes in bilirubin levels ( $P > 0.05$ ).

**Conclusion:** As evidenced by the results of this study, there was no significant relationship between ECG parameters and serum level of bilirubin; nonetheless, changes in cardiovascular parameters along with bilirubin levels were remarkable.

**Keywords:** Long QTc interval, Neonatal hyperbilirubinemia, Tachycardia

## Introduction

Hyperbilirubinemia is universal capricious morbidity in newborns and a leading cause of hospitalization in the first week of life. Timely and effective phototherapy, as well as exchange transfusion, are well-proven treatments for severe neonatal hyperbilirubinemia. Nonetheless, inappropriate or ineffective treatments still prevail in many poorly resourced countries accounting for a disproportionately high burden of bilirubin-induced mortality and long-term morbidity. Severe forms require transfusion exchange or intensive phototherapy(1).

Total mortality and death rates of 8.2% and 18.2% have been reported in neonatal jaundice

cases, respectively, (2). Whether bilirubin can increase QT or other electrocardiogram (ECG) parameters, including PR distance, QRS duration, changes in ST-T, or arrhythmia, is still open for further research (3, 4). Some studies reported that serum bilirubin levels were not correlated with cardiomyopathy and a prolonged QT interval(5). Irregular heart rhythm and hypercholesterolemia have been significantly associated with diabetes in some reports and bilirubin in other studies(6).

In neonatal hyperbilirubinemia, a significant decrease has been observed in heart parameters (7). In a recent survey, increased heart rate and decreased cardiac output have been observed in

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Please cite this paper as:

Radgoudarzi M, Alaei E, Besharat M, Porreza N. Electrocardiographic Parameters in Neonates with Hyperbilirubinemia in Northeast Iran. Iranian Journal of Neonatology. 2022 Apr; 13(2). DOI: 10.22038/IJN.2022.59816.2141

neonates with hyperbilirubinemia who are treated with phototherapy(8). Nonetheless, no relationship has been reported between cardiac changes and bilirubin levels(9). In light of the aforementioned issues, the present study aimed to measure electrocardiographic parameters in neonatal hyperbilirubinemia in our academic pediatric hospital, in northeast Iran.

## Methods

This single-center, prospective, cohort study was conducted on 155 newborn full-term neonates in 2017. The study population comprised all live-born neonates delivered full-term with jaundice and hospitalized in northeast Iran (Hospital, Golestan province) during the study period in 2017. We selected patients via convenience sampling for this cohort from the population of newborns delivered within the study period.

### Ethical consideration

The study protocol has been approved by the Local Ethics Committee of the Golestan University of Medical Sciences. Informed consent was obtained from all parents before the commencement of any procedure.

### The study population

The exclusion criteria entailed having sepsis, TORCH [(T)toxoplasmosis, (O)ther Agents, (R)ubella (also known as German Measles), (C)ytomegalovirus, and (H)erpes Simplex], congenital heart disease, polycythemia vera, asphyxia, and electrolyte abnormalities. On the other hand, those with pregnancy complications were excluded from the study. Out of 155 neonates admitted due to hyperbilirubinemia, 54 cases were excluded due to sepsis (n=5), a need for blood transfusion (n=21), and insufficient data (n=28), leaving 101 neonates who were included in the study population.

The electrocardiogram (ECG) was recorded at three stages: before starting the phototherapy, every 8 h during phototherapy, and after the completion of phototherapy. All recordings were taken when the neonate was awake. Moreover, parameters, such as heart rate (HR), PR interval, QRS duration, QTc interval, ST-T changes, and arrhythmias, were recorded. These parameters were compared against at least four ranges of bilirubin: when bilirubin was above 20 mg/dL, between 15 and 20 mg/dL, between 10 and 15 mg/dL, and finally, between 5 and 10mg/dL(time to discharge).

QTc interval was calculated manually or with a special measure ruler. In the manual method, when the T wave extreme was clear, the QT interval was calculated by the following equation when the previous PR interval was the least:

Corrected QT interval according to the heart rate:  $\frac{QT}{\sqrt{PR}}$ .

The SPSS statistical software (version 20) was used to analyze data obtained using the t-test, Pearson correlation, and multivariate regression test.

## Results

The mean age score of the studied neonates was  $6.09 \pm 3.57$  days (age range of 2 and 22 days). The mean time of jaundice onset was  $3.01 \pm 1.95$  days, and the majority of them (58.4%) were male. Moreover, 9 (8.9%) neonates were formula-fed, and the remaining 91.1% were breastfed. None of them had been previously treated by phototherapy. The mother's history included hypothyroidism (1 case), premature rupture of membrane (2 cases), vaginitis (2 cases), anemia (1 case), gestational diabetes (4 cases), high blood pressure (7 cases), and upper urinary tract infection (14 cases).

The mean hemoglobin level of the studied neonates was  $15.09 \pm 2.39$  mg/dL. The cause of hyperbilirubinemia was mostly unknown (38%), and ABO incompatibility was then the most common one (22%). Inadequate breastfeeding jaundice, Glucose-6-phosphate dehydrogenase (G6PD) deficiency, and Rh incompatibility were found in 20%, 12%, and 3% of neonates, respectively. Mean total bilirubin levels at admission and 8 h after hospitalization are displayed in Figure 1. All infants were admitted with bilirubin above 20 mg/dL. After the initiation of phototherapy following hospitalization, the level of bilirubin decreased gradually. After 8 h of admission, only two neonates still had bilirubin levels higher than 20 mg/dL, and 40 h after admission, bilirubin levels in all newborns fell to less than 20 mg/dL.

After starting phototherapy following admission, a reduction in heart rate parameters happened, along with a reduction in bilirubin level (Figure 2). Nevertheless, with the continuation of phototherapy, these parameters increased gradually despite a reduction in bilirubin levels. This trend continued until 32 h after hospitalization; thereafter, a considerable decline was recorded. None of the mentioned changes were statistically significant ( $P \geq 0.05$ ).

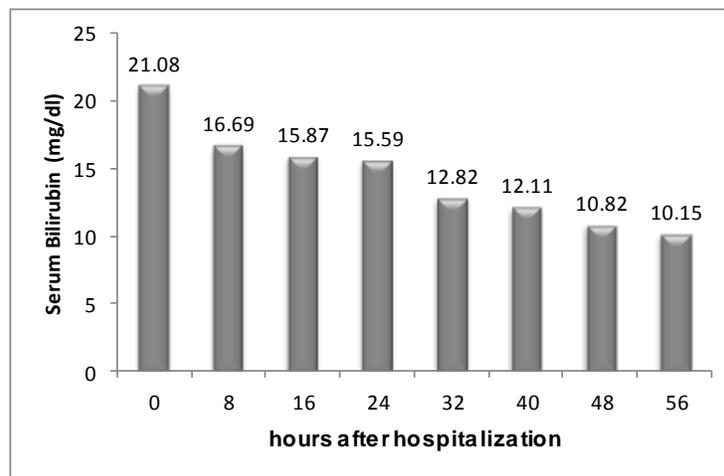


Figure1. Mean levels of bilirubin in the studied neonates at different hours after hospitalization

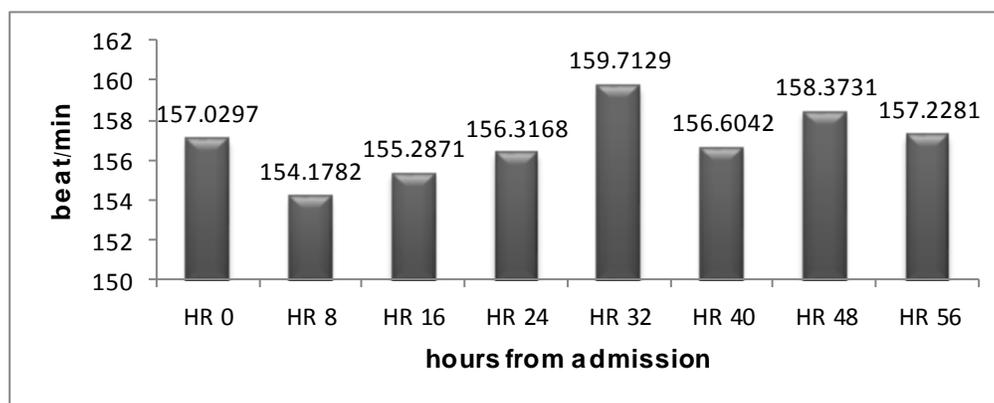


Figure2. Mean heart rate of cases during admission

No arrhythmia or ST-segment changes were recorded in this study. Neonates with G6PD deficiency disease had the highest mean QTC and PR (0.43 and 0.12 sec, respectively), and cases with ABO incompatibility had the highest mean QRS and HR (0.046 and 159 sec,

respectively); nonetheless, no significant difference was observed ( $P > 0.05$ ). Changes in ECG parameters were not found to be significantly related to changes in bilirubin level ( $P > 0.05$ ). The features of ECG are illustrated in figures 3-5.

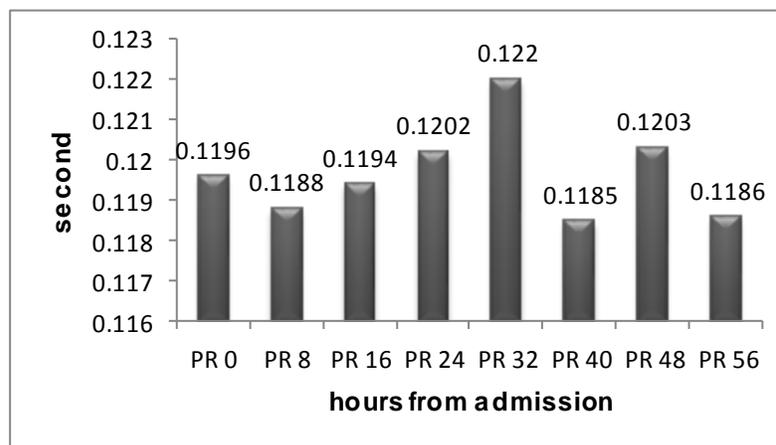


Figure3. PR interval of cases during admission

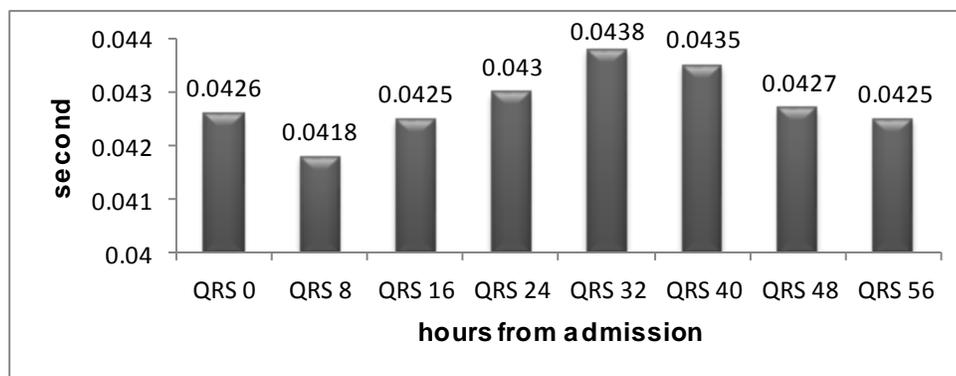


Figure 4. QRS duration of cases during admission

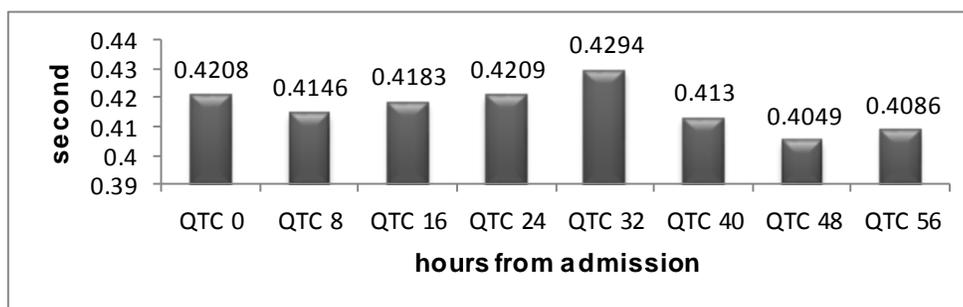


Figure 5. QTc interval of cases during admission

## Discussion

The results of the present study on term neonates admitted with bilirubin higher than 20 mg/dL demonstrated that an increased level of bilirubin is associated with increased heart rate, QTC, and PR, as well as decreased QRS. However, after the initiation of phototherapy following admission, a reduction in cardiac parameters happened, along with a reduction in bilirubin level. Nonetheless, with the continuation of phototherapy, these parameters increased gradually despite a reduction in bilirubin levels. This trend continued until 32 h after hospitalization; subsequently, a considerable decline was recorded (although not significant).

In a study by Kaczala et al. (8), heart rate increased and cardiac output decreased in newborns with hyperbilirubinemia who were treated with phototherapy. In another study by Weissman et al. (7), a significant diminution in heart rate variability was reported during phototherapy in 30 full-term jaundiced neonates. However, Martin et al. (9) recorded no relationship between ECG changes and bilirubin levels in 20 newborns with hyperbilirubinemia. In the same context, Gao et al. (5) demonstrated no significant relationship between cardiac damage or

cardiomyopathy and hyperbilirubinemia in 178 term neonates. These results are somehow in concordance with those obtained in the present study regarding to the role of phototherapy in reducing the level of bilirubin and changes in cardiac parameters.

According to Rahmi et al. (10), severe unconjugated hyperbilirubinemia (UHB) may cause cardiac autonomic dysfunction in favor of parasympathetic predominance in jaundiced neonates. In their study, low frequency-to-high frequency (LF/HF) ratio, which serves as an indicator of sympathovagal balance, was significantly lower in the study group, as evaluated by 24-h Holter ECG recording.

In a study by Specq et al. on preterm lambs, they suggested that sustained and moderate hyperbilirubinemia can induce alterations in cardiorespiratory function with an increased heart rate in response to acute hypoxia. These changes were associated with the activation of Alzheimer's type II astrocytes throughout the brain. While most reflexes returned to normal levels after 72 h of normalization of bilirubin level, increased microglial and astrocyte reactivity was still observed within the nucleus tractus solitarius (11).

Contrary to the above-mentioned issues about the risk of bilirubin, in a study by Cüre et al, increased bilirubin levels were associated with a decrease in HR and arrhythmia risk markers, such as P-wave dispersion (Pd) and QT dispersion (QTd), which consequently, might decrease the incidence of cardiac arrhythmias and coronary artery disease(12). Further studies are needed to establish the protective role of bilirubin in the risk of arrhythmias in these patients.

## Conclusion

Considering the potentially dangerous effect of high-level unconjugated bilirubin on the hearts of neonates, especially heart rate and appropriate heart function, it is suggested to record and closely monitor cardiac parameters in neonates with hyperbilirubinemia, especially during phototherapy.

## Acknowledgments

Authors tend to thank Golestan University of Medical Sciences' research department for the financial support. The study protocol has been approved by the local ethics committee of the Golestan University of Medical Sciences (IR.GOUMS.REC.1394 6).

## Conflicts of interest

There is no Conflict of interest.

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