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Electrocardiographic Corrected QT (QTc) Dispersion Value as a Predictor for Estimation of Neonatal Mortality in Pre-Term Neonates

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ABSTRACT

Introduction: Electrocardiographic (ECG) corrected QT (QTc) interval and dispersion were used as prognostic variables in adult patients and limited studies showed the relationship between QTc prolongation and dispersion with some clinical situations in newborn babies. **Aim:** In the present study, we compared the electrocardiographic (ECG) variables such as QTc interval and dispersion of healthy full-term and pre-term neonates with those who suffered from non-cardiac illnesses. **Methods:** This prospective cohort study involved 127 neonates including four study groups: normal full-term neonates, ill full-term neonates, normal pre-term neonates and ill pre-term neonates. Neonates with fever, apnea, poor feeding, tachypnea, muscle retraction, grunting, reduced neonatal reflexes, positive blood culture or antibiotic therapy > 3 days were considered as ill neonates. QTc interval and dispersion were calculated and compared among the four groups. **Results:** QTc interval was significantly ($p = 0.012$) higher in ill pre-term neonates in comparison with normal pre-term ones (418.74 ± 54.29 ms vs. 386.66 ± 39.26 ms). QTc dispersion was calculated and showed significantly higher mean values in ill pre-term neonates when compared with normal full-term, ill full-term and normal pre-term ones. QT dispersion and QTc dispersion of dead neonates were significantly ($p = 0.0001-0.01$) higher than alive ill pre-term neonates at 3, 7 and 28 days after birth. **Conclusion:** QTc interval and dispersion seem to represent non-invasive, reliable predictors of mortality in pre-term ill neonates, but further investigation is needed to confirm cutoff values for the risk assessment.

Keywords: QTc dispersion, Mortality, Neonate, Pre-term, Full-term.

1. INTRODUCTION

Perinatal and neonatal health and their mortality and morbidity control are among the regional and global priorities of the healthcare systems and World Health Organization (WHO) (1). Early detection of neonatal life-threatening problems such as sepsis is a challenging issue in pediatrics which may lead to abrupt clinical deterioration and death (2).

There are several studies to find precise indices to predict morbidity and mortality and to timely diagnose the potentially catastrophic illnesses in order to improve the final outcome. Clinical signs and symptoms have low sensitivity and specificity in newborn babies. Electrocardiographic (ECG) beat-to-beat interval variability even before significant changes in heart rate was noticed by Hon and Lee in early 1965 (3). Griffin and colleagues hypothesized that

abnormal heart rate characteristics might be related to neonatal sepsis and may add useful information to timely diagnosis (2).

The QT dispersion (QT-d), the difference between the longest and shortest QT intervals in standard ECG, was used as an indicator of heterogeneities of ventricular repolarization and sudden cardiac arrhythmia in adults (4, 5). Neonates are at risk of arrhythmia due to the immaturity of the cardiac conduction system and autonomic nervous system (6).

Few studies have assessed the correlation between QT-d and some clinical situations such as spiramycin (7) or propranolol (8) treatment, hyperthyroidism (9), infantile body position (10), epilepsy (11), breath-holding spells (12), and life-threatening event syndrome (13).

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2. AIM

In the present study, we compared the ECG variables such as QT interval and dispersion of healthy full-term and pre-term neonates with those of who suffered from non-cardiac illnesses.

3. METHODS

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences.

In this study, the newborns suffering from fever, apnea, poor feeding, tachypnea, muscle retraction, grunting, reduced neonatal reflexes, positive blood culture or antibiotic therapy > 3 days were considered as ill neonates.

In a prospective cohort study, 127 neonates including four study groups were evaluated as follows:

- Group 1. Normal full-term neonates who were >37 weeks of gestation.
- Group 2. Full-term neonates who were >37 weeks of gestation and suffering from above-mentioned illnesses or signs & symptoms.
- Group 3. Normal pre-term neonates who were <37 weeks of gestation.
- Group 4. Pre-term neonates who were <37 weeks of gestation and suffering from aforementioned illnesses or signs & symptoms.

Hence, the ill neonates based on their gestational ages were analyzed as Group-2 or Group-4; while, the Group-1 and Group-3 consisted of normal neonates.

Neonates with cardiac arrhythmias or proved congenital cardiac disease were excluded.

After precise study design, written informed consent forms were obtained from the parent(s) and 12-lead ECGs of all 127 neonates were recorded at a paper speed of 50 mm/s. We increased the paper speed to 50 mm/s in order to improve results and reduce computational errors.

We used a magnifying lens to a power of 10-times magnification and scale ruler to assess ECGs. Studied ECG variables were measured and calculated in a blinded fashion by the same physician based on the following formulas:

- QT interval (QT): the average of three consecutive cycles from the onset of QRS complex to the end of the T wave on the isoelectric line or nadir between the T and U waves.
- QT-dispersion (QT-d): the subtraction of longest and shortest QT intervals in one ECG record.
- Corrected QT interval (QTc): the QT intervals were corrected and considered as QTc interval according to the heart rate and based on Bazett's formula: $QTc = QT / \sqrt{R-R}$ (14).
- QTc dispersion (QTc-d): was calculated as the subtraction of longest and shortest QTc intervals.

Neonates were followed at postnatal days 3, 7 and 28 and those who were not available or admitted to another hospital were excluded from the study.

Statistical analyses of student T-test and chi-square were performed using SPSS software (version 12.0 for Windows; SPSS Inc.; Chicago, IL). Statistical significance was taken at $p < 0.05$. All data were presented as the mean $\pm$ SD.

3. RESULTS

One hundred sixteen neonates (62 boys and 54 girls) were initially included in the study; however, 11 of the initial population were excluded due to missed follow-up (9 neonates), confirmed congenital cardiac disease (1 neonate) and admission to another hospital (1 neonate). We compared the birth weight, gestational age, the root of delivery, history of premature rupture of membrane (PROM) and Apgar score at 1 and 5 minutes after birth between the normal (Group-1) and ill (Group-2) full-term neonates. There was no significant difference between these two groups (Table 1). Nevertheless, some of the variables including the birth weight, gestational age and Apgar score at 1 and 5 minutes after birth were significantly different between normal and ill pre-term neonates (Group 3

p value	Ill full-term neonates (n=27)	Normal full-term neonates (n=31)	
	15/12	15/16	Gender (M/F)
0.12	3078.48 $\pm$ 256.9	3306.13 $\pm$ 402.2	Birth weight (g)
0.726	38.48 $\pm$ 0.86	38.56 $\pm$ 0.93	Gestational age (week)
0.67	18 (66.7%)/9 (33.3%)	19 (61.29%)/12 (38.71%)	Root of delivery (NVD/CS)
0.12	5 (18.52%)	0	PROM
0.25	8.3 $\pm$ 1.0	8.81 $\pm$ 0.4	APGAR score (1min)
0.15	9.78 $\pm$ 0.5	9.94 $\pm$ 0.2	APGAR score (5 min)

Table 1. Clinical characteristics of normal and ill full-term neonates (mean $\pm$ SD). NVD: normal vaginal delivery; CS: cesarean section; PROM: premature rupture of membrane. *statistically significant

p value	Ill pre-term neonates (n=33)	Normal pre-term neonates (n=25)	
	21/12	11/14	Gender (M/F)
0.0001*	1811.21 $\pm$ 532.95	2533.2 $\pm$ 264.48	Birth weight (g)
0.0001*	31.48 $\pm$ 2.94	34.92 $\pm$ 1.09	Gestational age (w)
0.85	19 (57.57%)/14 (42.43%)	15 (60.0%)/10 (40.0%)	Root of delivery (NVD/CS)
0.61	7 (21.21%)	4 (16.0%)	PROM
0.0001*	6.94 $\pm$ 1.94	8.76 $\pm$ 0.44	APGAR score (1min)
0.0001*	8.45 $\pm$ 1.68	9.92 $\pm$ 0.28	APGAR score (5 min)

Table 2. Clinical characteristics of normal and ill pre-term neonates (mean $\pm$ SD). NVD: normal vaginal delivery; CS: cesarean section; PROM: premature rupture of membrane. *statistically significant

	Normal full-term neonates (n=31)	Ill full-term neonates (n=27)	p value
QT (ms)	306.87 $\pm$ 32.54	286.30 $\pm$ 38.81	0.035*
QTc (ms)	399.97 $\pm$ 32.91	401.63 $\pm$ 43.92	0.87
QT-d (ms)	81.42 $\pm$ 25.45	77.48 $\pm$ 21.03	0.52
QTc-d (ms)	79.68 $\pm$ 17.13	87.63 $\pm$ 79.78	0.06

Table 3. The electrocardiographic findings of full-term neonates (mean $\pm$ SD). QT: QT interval; QTc: Corrected QT interval; QT-d: QT dispersion; QTc-d: Corrected QT dispersion. *statistically significant

	Normal pre-term neonates (n=25)	Ill pre-term neonates (n=33)	p value
QT (ms)	298.34 ± 53.73	283.38 ± 41.03	0.25
QTc (ms)	386.66 ± 39.26	418.74 ± 54.29	0.012*
QT-d (ms)	65.08 ± 16.01	84.45 ± 33.88	0.006*
QTc-d (ms)	86.04 ± 17.28	121.27 ± 41.41	0.0001*

Table 4. The electrocardiographic findings of pre-term neonates (mean ± SD). QT: QT interval; QTc: Corrected QT interval; QT-d: QT dispersion; QTc-d: Corrected QT dispersion. *statistically significant

		Alive ill pre-term neonates	Dead pre-term neonates	p value
QT-d (ms)	Day 3 (n=25/8)	76.56±33.66	109.13±21.07	0.004*
	Day 7 (n=24/9)	76.58±34.38	105.44±22.59	0.01*
	Day 28 (n=22/11)	73.23±33.11	106.91±23.21	0.002*
QTc-d (ms)	Day 3 (n=25/8)	105.76±33.27	169.75±22.39	0.0001*
	Day 7 (n=24/9)	102.58±29.86	171.11±21.33	0.0001*
	Day 28 (n=22/11)	96.36±20.75	171.09±22.12	0.0001*

Table 5. The comparison between alive ill pre-term and dead neonates (mean ± SD). QT-d: QT dispersion; QTc-d: Corrected QT dispersion. *statistically significant

vs. Group 4) (Table 2).

The QT, QTd, QTc and QTc-d were compared in all four groups.

The normal full-term neonates showed significantly higher values of QT in comparison with ill full-term neonates ($p=0.035$, Table 3). However, there was no significant difference in other ECG variables between normal full-term and ill full-term neonates (Table 3).

The QT of both pre-term groups was similar without significant difference. The QTc interval as an index of ventricular depolarization and repolarization was significantly higher in Group 4 in comparison with Group 3 (418.74 ± 54.29 ms vs. 386.66 ± 39.26 ms). Also, there were significantly higher QT and QTc-d mean values in Group 4 when compared with Group 3 (Table 4).

We followed all neonates at 3, 7 and 28 days after birth. There was no mortality in normal or ill full-term (Group 1 and Group 2) and normal pre-term (Group 3) neonates. However, in ill pre-term (Group 4) neonates, eight died in first 3 days, increasing to 9 and 11 at days 7 and 28, respectively. The QT-d and QTc-d of dead neonates were significantly ($p = 0.0001-0.01$) higher than those of alive ill pre-term neonates in 3, 7 and 28 days after birth (Table 5).

4. DISCUSSION

Our study results showed no significant QTc interval and dispersion values difference between normal and ill full-term neonates; however, ill pre-term neonates showed significant prolongation of QTc interval and dispersion in comparison with normal pre-term babies. QTc interval and dispersion in died pre-term neonates showed significantly higher values than alive ill pre-term ones, as well.

The QT prolongation is one of the potential causes of arrhythmia and QT variability and dispersion can reflect

ventricular repolarization and recovery time (6).

The ECG is a low-cost, non-invasive and feasible tool to assess cardiac conductive system and study of QT interval and dispersion is a reliable indicator to predict susceptibility to cardiac arrhythmia (4). These parameters had been used for years in adult medicine (15).

There are few studies to investigate the value of QTc interval and dispersion (QTc-d) in pediatric patients and particularly in neonates. Pishva et al. studied 96 normal full-term, normal pre-term and sick neonates and showed the significantly higher values of QT-d in sick babies which correlated with increased mortality rate. They suggested calculating QT-d as a prognostic factor of neonatal mortality rate estimation (15). Our results were consistent with their study.

Another study on neonates with cardiac arrhythmia and myocarditis showed significantly longer mean QTc interval and dispersion values in comparison with normal neonates. They concluded that greater value of QT-d in neonates can be regarded as a predisposing factor for arrhythmia (6). There are limited studies which showed prolongation of QTc interval and dispersion in neonates with hyperthyroidism (9), sudden infant death syndrome (10), epilepsy (11), breath-holding spells (12), and life-threatening event syndrome (13).

We did not compare other ECG variables between full-term and pre-term babies but Groote (16) and Vialle (17) showed no significant difference in QTc interval and dispersion with regard to gestational age.

In present study 11 of pre-term ill neonates died in first 28 days after birth. The mean values of QT-d and QTc-d of these neonates were significantly greater than alive ill pre-term ones. Pishva et al. in their study mentioned that 6 out of 7 dead neonates had mean QT-d ≥ 120 ms (15). The mean QT-d and mean QTc-d values in dead neonates in our study were ≥ 105 ms and ≥ 169 ms, respectively.

5. CONCLUSION

It seems that QTc interval and dispersion are useful non-invasive and reliable predictors of mortality in pre-term ill neonates but further investigation is needed to determine their cutoff values to conduct a risk assessment.

- **Author's contribution:** All authors contributed to study conception and design, contributed to data acquisition, data analysis and interpretation, and writing of article. All authors and coauthors contributed to editing, reviewing and final approval of article.
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