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Original Research Article

Correlation between QoTc and serum as well as ionised calcium in sick neonates

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ABSTRACT

Background: Hypocalcemia is a frequently observed clinical and laboratory abnormality in neonates with risk factors such as prematurity, infant of diabetic mothers and perinatal asphyxia. Hypocalcemia can be asymptomatic or can cause apnoea, seizures, jitteriness, stridor, cardiac abnormalities. Clinically as calcium levels are maintained within narrow ranges. It is therefore imperative to measure and correct any deficit at the earliest. Unfortunately, total serum calcium level correlates poorly with ionized calcium level. Measurement of ionized calcium is both time consuming and expensive and therefore the need for more rapid, inexpensive and non-invasive method for screening at risk-neonates. Serum calcium levels are known to affect the duration of the QoTc interval. Therefore establishing a good correlation between serum/ionized calcium levels and QoTc will validate ECG as a reliable marker of hypocalcemia. Objective was to find correlation between QoTc interval and serum calcium levels in sick neonates.
Methods: Total 730 infants were for serum total calcium and ionized calcium levels. Off these 142 infants with hypocalcemia, 29 infants were excluded based on exclusion criteria. The remaining 113 neonates were subjected to three cycles of ECG measurement before correction of calcium and were taken as cases. QoTc intervals were measured and were correlated with corresponding serum total calcium and ionized calcium levels.
Results: In this study, a moderate negative or downhill correlation was found between total serum calcium QoT ($r = -0.694$ and $p = <0.001$) and QoTc ($r = -0.680$ and $p = <0.001$). The ionized calcium levels were found to have strong negative or downhill correlation with QoT ($r = -0.837$ and $p = <0.001$), QoTc ($r = -0.819$ and $p = <0.001$). All these correlations were found to be statistically significant with $p<0.05$.
Conclusions: QoTc interval can be used as a surrogate marker for blood total or ionized calcium levels.

Keywords: Ionized calcium in neonates, Neonatal hypocalcemia, Neonatal ECG, QT interval in neonates, QoTc interval, Serum calcium in neonates

INTRODUCTION

Hypocalcemia is a common problem in early as well as in late neonatal period. It is more commonly associated with prematurity especially in infants born before 32 weeks of gestational age, infants born to diabetic mothers and those asphyxiated at birth apart from rare genetic and metabolic causes of hypocalcemia.[1,2] Serum calcium is important for maintaining the homeostasis of the body, the functioning of cellular processes, cellular membrane stability, muscle contraction, and nerve conduction. Although early neonatal hypocalcemia is asymptomatic in majority of the neonates, it can manifest as

neuromuscular irritability like jitteriness, tetany, seizures or respiratory instability like apnea and may even cause congestive heart failure and become potentially life threatening. Also, at-risk neonates tend to be sick secondary to multitude of reasons, the signs of hypocalcemia per se maybe obscured. Clinically as calcium levels are maintained within narrow ranges, there is higher risk of physiological dysfunction.[3] It is therefore imperative to measure calcium in all at risk neonates and to correct any deficit at the earliest.

About 45% -50% of total serum calcium is in the ionized form at the normal serum protein concentration and represents the biologically active component of the total serum calcium concentration.[4] About 40% is protein bound, predominantly to albumin, another 8% to 10% is complexed to organic and inorganic acids. Together, the ionized and complexed calcium fractions represent the diffusible portion of circulating calcium.[5]

Unfortunately, total serum calcium level, a more readily available determination, correlates poorly with ionized calcium level which is the active and readily accessible form of calcium.[6] Also serial measurements maybe required in infants during treatment to confirm optimal calcium levels thereby requiring repeated blood sampling increasing the risk of infections apart from requiring significant volume of blood. Measurement of ionized calcium is both time consuming and expensive in developing countries like India and therefore the need for more rapid, inexpensive and noninvasive method for screening at risk neonates.

The interplay between calcium and cardiac repolarisation is very well studied and any derangement such as decreased ionized calcium levels manifests as decreased contractility of the heart by affecting the duration of the Q-Tc/QoTc interval (QT/QoTc interval corrected for heart rate). This study aims to correlate between QoTc and serum as well as ionised calcium levels and its utility in diagnosing neonatal hypocalcemia.

METHODS

The study was conducted in a Neonatal unit of a tertiary care hospital over a period of 18 months. Infants with established risk for hypocalcemia like prematurity, infant of diabetic mothers, birth asphyxia, sepsis, acidosis were routinely screened for hypocalcemia at 12 or 24 hours of life. Neonates with hypothermia or CNS injury were excluded. A detailed maternal history was also obtained in order to exclude neonates with mothers on drugs known to cause QT prolongation, 142 hypocalcemic infants were recruited into the study (Figure 1). Of which, 4 babies were excluded from the study as the mothers were found to be on antidepressants or antipsychotics known to cause QTc prolongation, 5 babies were excluded due to CNS injury such as IVH secondary to prematurity. Parental consent was refused by 1 of the hypocalcemic baby. Of the remaining 132 babies 19 ECGs were deemed as unsatisfactory either to human error or abnormal TU wave morphology leading to unsatisfactory determination of origin of T wave.

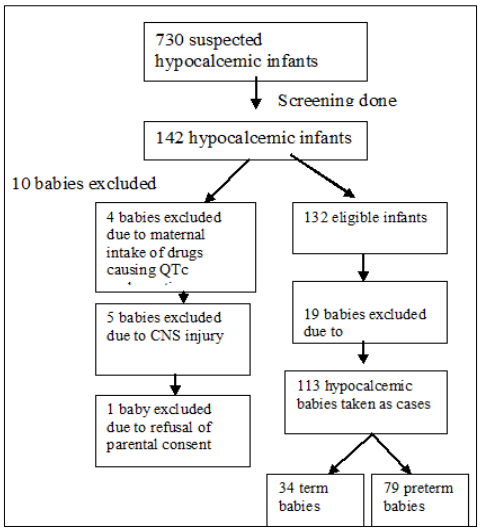

Figure 1: Flow diagram depicting study design.

Under strict aseptic precautions 2ml of venous blood sample was drawn via a needle into a plain tube and processed immediately. Samples not immediately processed were refrigerated between temperature of 0° and 4° Celsius for less than 24 hours. Those babies found to be hypocalcemic were subjected to ECG recording before administering oral or parenteral calcium ideally within 6 hrs of drawing the blood. A 12 lead electrocardiogram was obtained using disposable self adhesive neonatal ECG leads. To obtain readily measurable T waves, babies were kept warm and comfortable, with a pacifier to prevent crying and movement. Three ECG readings of 10 seconds with a speed of 25mm/s were taken from each baby. QoT was measured from origin of Q wave to origin of T wave. QoTc and R-R interval were measured for three consecutive cycles, averaged and corrected for heart rate by Bazett's formula as follows[7]

$$Q\text{-}oTc = Q\text{-}oT/\sqrt{(RR\ interval)}$$

QoT/QoTc >0.22 s or 220 msec was taken as prolonged.

Neonatal Hypocalcemia is defined as total serum calcium of less than 7 mg/dL (1.75 mmol/L) in preterm infants and and less than 8 mg/dl (2 mmol/L) in term infants or ionized calcium less than 4 mg/dL (1 mmol/L) in preterm infants and less than 4.8 mg/dL (<1.2 mmol/L) in term neonates.[8]

Statistical analysis

Data was entered in Microsoft Excel and analysed using EpiData analysis version 2.2.2.186 and Stata 12.0 software. The continuous variables like gestational age, birth weight, serum calcium, ionic calcium QoT and

corrected QoT were entered as mean and standard deviation. The categorical variables such as mode of delivery, gender, birth weight category, risk of hypocalcaemia such as IUGR, infant of diabetic mother, sepsis, history of fever in mother, history of blood transfusion, phototherapy and present of symptoms like seizure, jitteriness and hyperreflexia were summarized as percentage.

The association between the categorical variables and the continuous variables (serum calcium, ionic calcium, QoT and corrected QoT) were assessed using unpaired students t test. The correlation between ECG findings and serum calcium and ionic calcium was assessed using Pearson correlation, p value of <0.05 was considered for statistical significance.

RESULTS

A total of 60(53.1%) samples were collected from male babies and 53 (46.9%) samples from female babies. 56(49.6%) babies were delivered via vaginal delivery and 57(50.4%) were delivered via LSCS. Mean (SD) gestational age of the babies was 34.8 (2.8) weeks. Mean (SD) birth weight was 2307.4(828.5) gms, of which 2 babies were ELBW each measuring 980 gms and 860gms, 21(18.6%) babies were VLBW, 2(1.8%) were large for gestational age babies, remaining 42(37.2%) were normal birth weight babies. Among various risk factors, 20(17.7) babies had birth asphyxia, 24(21.4) babies were born to diabetic mothers, 51(45.1), babies had sepsis, and 10(8.8) babies had intra uterine growth restriction.

Table 1: Patient characteristics and corresponding QoT/QoTc intervals.

Patient characteristics		QoT Mean(SD)	p value	QoTc Mean (SD)	p value
Gender	Male	307.0 (64.9)	0.615	219.8 (48.0)	0.585
	Female	313.2 (65.6)		224.9 (50.4)	
Gestational age	Term	307.1 (63.3)	0.764	220.0 (46.9)	0.001
	Preterm \	311.1 (66.0)		223.2 (50.1)	
Birth weight	ELBW	335.1 (16.1)	<0.001	240 (0.0)	<0.001
	VLBW	368.9 (65.9)		267.1 (49.1)	
	LBW	293.9 (54.1)		210.0 (41.6)	
	Normal weight	295.9 (59.6)		211.7 (44.5)	
	LGA	328.7 (59.6)		235.0 (77.8)	
Risk factors	Birth asphyxia	309.5 (69.3)	0.973	222.5 (52.2)	0.02
	Infant of diabetic mother	309.7(63.2)	0.939	222.1(47.8)	0.005
	Sepsis	292.6(59.2)	0.003	292.6(59.2)	<0.001
	IUGR	327.4(76.7)	0.376	232.0(57.7)	0.510
Clinical features	Symptomatic	308.2(56.5)	0.807	221.7(44.0)	0.919
	Asymptomatic	311.2(71.0)		222.6(52.7)	

QoT and QoTc intervals were correlated across various patient characteristics as shown in table 1. There was no significant variation of QoT and QoTc intervals between male and female babies. We found that QoTc interval showed significant prolongation between in preterm babies with p value of 0.001 as compared to term babies,whereas QoT interval although prolonged showed no significant difference between these groups. Both QoT and QoTc intervals varied significantly across various birth weights with p value <0.001. Various risk factors were also compared between these intervals. Birth asphyxia showed no significance on QoT interval as opposed to QoTc which was found to have a P value of 0.02 which was statistically significant. Infants born to diabetic mothers showed no statistically significant prolongation of QoT interval, whereas there was significant prolongation of QoTc interval. Those babies with sepsis were found to have significant prolongation of both QoT and QoTc intervals. There was no significant prolongation of either of the intervals in babies with IUGR. We also found that there was no significant prolongation of these intervals between symptomatic and asymptomatic babies.

Table 2: Correlation of QoT/QoTc intervals with serum calcium and Ionised calcium.

ECG interval	Calcium level	Correlation values	p value
QoT	Serum calcium	-0.694	<0.001
QoTc	Serum calcium	-0.680	<0.001
QoT	Ionic calcium	-0.837	<0.001
QoTc	Ionic calcium	-0.819	<0.001

We correlated QoT and QoTc intervals with serum and ionised calcium levels (Table 2). There was moderate correlation between serum calcium levels and the ECG intervals with the correlation value of -0.694 for QoT (Figure 2) and -0.680 for QoTc values (Figure 3) which were both statistically significant. However, authors found strong correlation between Ionic calcium and

Qot/QoTc intervals with a correlation value of -0.837 and -0.819 which were statistically significant with a p value of <0.001.

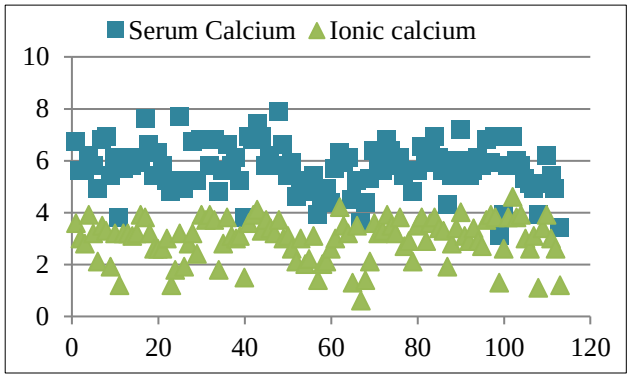

Figure 2: Correlation between serum calcium, ionic calcium and QoT interval.

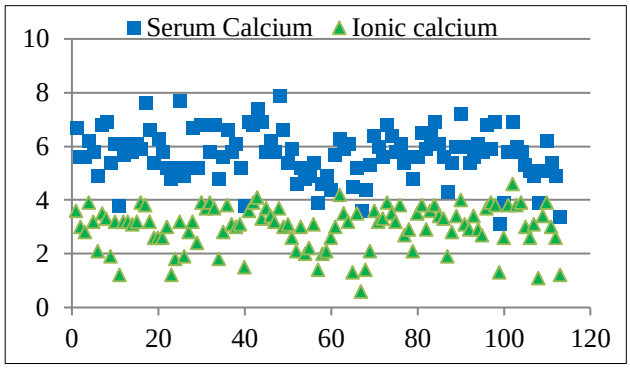

Figure 3: Correlation between serum calcium, ionic calcium and QoTc interval.

DISCUSSION

Hypocalcemia is one of the most common metabolic disturbances known to occur in neonatal period. It can vary from being mild and transient, to severe and persistent requiring emergent management. The physiological variation in total and ionic calcium in the immediate postnatal period plays an important role. Total calcium increases with increasing gestational period, reaches a nadir at 6-12 hr after birth, thereafter increase over the next 1-2 weeks reflecting the large fluctuations that occur in serum albumin levels. Ionized calcium levels fall in the immediate postnatal period by 24hrs after birth thereafter rise over next 12-36 hrs.[9,10]

The Q-T interval in ECG represents time taken for ventricular activation and repolarisation. The various Phases of action potential and corresponding ECG changes are illustrated in Figure 4. The action potential has two important components: the spike and the plateau (phase 1 and phase 2). Ionized calcium is known to exert its most noticeable effect on the duration of the plateau phase, which electrocardiographically corresponds to Origin of T interval (QoT interval) rather than the end of T interval (QT interval).[11] Hence we attempted to find a correlation between ionised calcium and QoT interval.

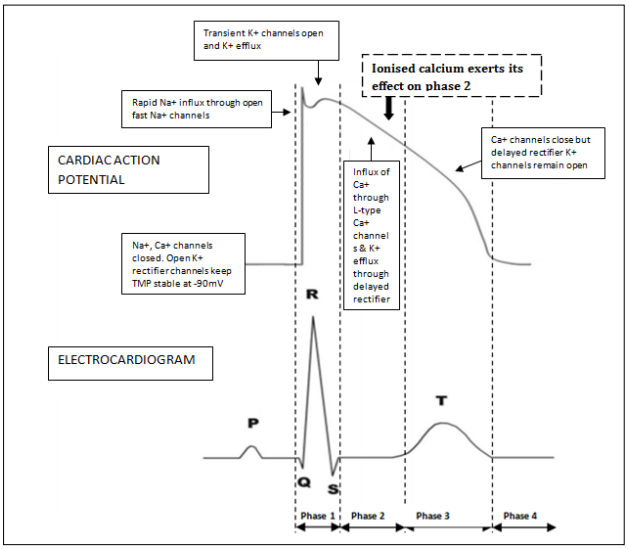

Figure 4: Cardiac action potential superimposed on Electrocardiogram.

The most implicated risk factors for such rise in incidence of neonatal hypocalcemia is found to be its association with perinatal asphyxia and maternal diabetes. Owing to the abrupt cessation of placental calcium supply, prematurity is another important risk factor to neonatal hypocalcemia.[12] In this study it was shown that QoT/QoTc intervals were prolonged in these groups. Further comparison revealed QoTc interval was significantly prolonged among preterm, birth asphyxia, Infants of Diabetic mothers groups as compared to QoT interval. Birth weight and the presence of sepsis played a significant role in prolongation of both QoT and QoTc intervals.

It was found that 42.4% of the hypocalcemic babies were aymptomatic. We also found that aymptomatic and symptomatic babies had equal predisposition to hypocalcemia, which re-emphasises the fact that symptoms in hypocalcemia are non-specific and not sensitive enough to affect any correlation with either presence of hypocalcemia or its severity.

Several studies have evaluated the same and found mixed results. N Nelson et al studied ionized calcium levels and its effect on QTc and QoTc levels in healthy as well as infants receiving exchange transfusion.[13] They found no significant correlation between these variables and suggested that ECG findings lacked practical implications, can only be used a supportive evidence. However, it must be noted that the method used to measure the end of T wave was not standardized and may have possibly lead to wide variations, although the authors claim no difficulty in measuring the end of the T wave. Giacoia et al, studied the correlation of QoTc and blood calcium levels in 27 full term and 77 preterm

infants and found good correlation of QoTc with serum total calcium and ionised calcium in full term as well preterm babies.[11] They found poor correlation of QoTc in sick neonates which may have been due to cardiac sympathetic dysfunction and/or marked variation in circulating catecholamines. Colleti et al, studied utility of QoTc in susceptible infants in 36 full term and 44 preterm infants.[14] They found that QTc was found to significantly correlate well in full term infants but not in preterm infants. However, QoTc was found to be correlating significantly with total as well as ionized calcium in both full term and preterm infants and suggested that QoTc can be used as a rapid and reliable way to detect hypocalcemia.

The major limitation of ECG usage in neonates, as experienced by various investigators lies in the measurement of ECG intervals, which is subject to skill of the person measuring. This limitation can be overcome by standardizing the method of measurement of QT interval and by using an average of multiple measurements as done in this study. It was found that although QoT and QoTc levels both correlated with the serum as well the ionised calcium levels, the correlation was stronger for ionised calcium levels as opposed to serum calcium levels.

CONCLUSION

QoTc interval can be used as a surrogate marker for detection of hypocalcemia in neonatal hypocalcemia, however further studies are necessary to standardize the method of ECG measurement and interpretation.

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