Case Report

The effect of blood gas and Apgar score on cord blood cardiac Troponin I

Gülcan Türker, Kadir Babaoğlu, Can Duman, Ayşe S Gökalp, Emine Zengin and Ayşe Engin Arısoy
From the Department of Pediatrics and Biochemistry, Faculty of Medicine Kocaeli University, Kocaeli, Turkey

Objectives: The aims of this study were to (a) establish a reference range for cardiac troponin I (cTnI) in the cord blood of healthy infants, and (b) investigate the effect of Apgar score, cord blood gas, gestational age, and creatine kinase (CK) and creatine kinase MB (CK-MB) fraction levels on cord blood cTnI levels.

Methods: 112 perinatal hypoxic and 84 control newborns without perinatal hypoxia were enrolled in this study. Cord blood samples were collected from the babies for arterial blood gas analysis, cTnI, CK and CK-MB measurements. Gestational age, birth weight, sex, Apgar score and history of fetal distress were recorded. Hypoxic ischemic encephalopathy (HIE) group, hypoxic but without HIE group and control groups were identified according to clinical observations during the first 72 h in the newborn unit.

Results: HIE and perinatal hypoxic without HIE groups had a significantly higher cord blood cTnI level according to the control group (1.8 ng/mL (0–13), 0 ng/ml (0–1.1) and 0 ng/ml (0–0.3) respectively). Cord blood cTnI level did not have a correlation with birth weight and gestational age (r = 0.02, p > 0.05 and r = 0.08, p > 0.05 respectively). Cord blood cTnI level also had a negative correlation with pH, bicarbonate, base deficit, and Apgar score (r = 0.40, p < 0.001; r = 0.39 p < 0.001; r = 0.45 p < 0.001; r = 0.41, p < 0.001) respectively). Cord blood cTnI level showed a positive correlation with CK and CK-MB levels (r = 0.45, p < 0.001 and r = 0.37, p < 0.001 respectively). Receiver operator curve analysis revealed that the most sensitive factor for prediction of perinatal hypoxia is cord cTnI value [area under curve = 0.929]. The optimal cut-off value of cord cTnI was 0.35 ng/ml for hypoxia.

Conclusion: cTnI levels in the cord blood are not affected by gestational age and birth weight. cTnI together with CK and CK-MB has been found to be elevated in hypoxic infants compared to normal infants. Therefore cTnI may be an indicator for perinatal hypoxia in neonates.

Key words: CORD BLOOD; CREATINE KINASE MB; GESTATIONAL AGE; BIRTH WEIGHT; TROPONIN I; PERINATAL HYPOXIA

INTRODUCTION

Cardiac troponin I (cTnI) has emerged as a biochemical marker for the detection of myocardial cell damage in acute coronary syndromes, largely replacing creatine kinase (CK) and creatine kinase MB (CK-MB). Poor correlation of cTnI and CK-MB was noted during the first year of life. Quivers et al. showed that preterm infants had a significantly higher cTnI level than term infants. This differs from the results of Hirsch et al. who found that a significant elevation in cTnI in a pediatric intensive-care setting may be an indicator of poor outcome.

The purpose of this study is to offer an explanation for this discrepancy and to investigate the relation between elevated cTnI levels and cord pH, Apgar score and CK and CK-MB. The aims of this study were to (a) establish a reference range for cTnI in the cord blood of healthy infants, and (b) investigate levels of cord cTnI in hypoxic infants.

Correspondence: G. Türker. Department of Pediatrics, Faculty of Medicine, Kocaeli University, 41900 Kocaeli, Turkey
METHODS

This prospective study was performed between September 2000–December 2002 and was approved by the Ethical Committee of the Medical Faculty. Written informed consent from the parents was obtained.

Perinatal hypoxia group

One hundred and twelve newborns were enrolled in the perinatal hypoxia group. Newborns having at least three of the following criteria were included in the perinatal hypoxia group: (1) fetal bradycardia with a heart rate of less than 100 beats per min, (2) late decelerations (3) an absence of heart-rate variability (4) thick meconium-stained amniotic fluid (5) Apgar score of 7 or less at 5 min (6) arterial blood pH value of 7.20 or less. Thirty-nine of the 112 newborns fulfilling three of the above criteria but without symptoms and signs of Hypoxic ischemic encephalopathy (HIE) were defined as hypoxic but not HIE group. Seventy-three of the 112 newborns were included in HIE group according to Sarnat and Sarnat clinical classification5.

Control group

Eighty-four newborns that were followed in the neonatal unit with transient minor problems and who fulfilled all the following criteria were enrolled in the control group: no maternal illness, cord arterial blood pH ≥ 7.2, 5 min Apgar score of ≥ 7 and an uneventful course during the first 3 days of life. Cord blood samples (2 ml) were collected from the umbilical artery of all newborns for blood gas analysis, cTn I, CK and CK-MB measurement. Data about gestation, birth weight, sex, Apgar score and history of fetal distress were recorded. Hypoxic and control groups were identified according to the clinical observations during the first 72 h in the newborn unit.

Predefined exclusion criteria for both groups were congenital abnormalities, tumors, maternal drug addiction, infections and congenital metabolic disorders. Specimens that were visibly icteric, lipemic, or hemolyzed were excluded from the study. Physical examinations were performed by the same pediatrician at postnatal 2nd, 6th, 12th, 24th, 48th, 72nd hours.

Table 1  Characteristics of 112 infants with hypoxia and 84 control infants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control Infants with perinatal hypoxia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 84)</td>
<td>No HIE (n = 39)</td>
</tr>
<tr>
<td>Preterm/term (n)</td>
<td>44/40</td>
<td>20/19</td>
</tr>
<tr>
<td>Birth weight (gr)</td>
<td>(2800–4550)</td>
<td>(2550)</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>Apgar Score</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>44/40</td>
<td>18/21</td>
</tr>
<tr>
<td>Mode of delivery (V/C)</td>
<td>(40–1676)</td>
<td>(89–1610)</td>
</tr>
<tr>
<td>Cord CK (U/L)</td>
<td>298</td>
<td>274</td>
</tr>
<tr>
<td>Cord CK-MB (U/L)</td>
<td>67</td>
<td>69</td>
</tr>
<tr>
<td>Cord cTnI (ng/ml)</td>
<td>0.00</td>
<td>0.6</td>
</tr>
<tr>
<td>Base deficit</td>
<td>2.05</td>
<td>5.8</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>21.1</td>
<td>20</td>
</tr>
<tr>
<td>pH</td>
<td>7.29</td>
<td>7.21</td>
</tr>
</tbody>
</table>

All values are given as median (min-max). Kruskal-Wallis Varyans test was used
Abbreviations: No HIE: perinatal hypoxic infants without HIE; HIE: Hypoxic ischemic encephalopathy; F/M: female and male; V/ C&S: vaginal and cesarean section
Analysis of CK-MB, CK, Troponin I

Creatine kinase was measured on the Biotrol CK Monoreactiv using manufacturer’s reagents, by colorimetric and coupled enzyme methods. CK-MB (Menarini Diagnostics) was measured on the Opera auto analyzer. cTnI concentrations were measured with AxSYM System (Abbott Lab, Abbott Park, IL, USA). The assay’s limit of detection is 0.3 ng/ml and its coefficient of variation is 0.3–47.5 ng/ml \((N=29)\). Cross reactivity of cTnI is minimal with cardiac troponin C (0.01 %), cardiac troponin T (0.34 %) and skeletal troponin I (0.04 %) at a concentration of 1000 ng/ml. A measured cTnI value of \(\geq 2\) ng/ml was considered indicative of myocardial injury in adult in accordance with the manufacturer’s insult. But there was no cut-off value in children and newborns. Less than 1 ml of excess blood was required for the cTnI assay.

Data analysis

The SPSS 11 for Windows was used. Median values of cTnI, CK and CK-MB in neonates with HIE (mild, moderate, and severe), hypoxic but without HIE and control groups were compared by using Kruskal-Wallis Varyans test after Shapiro-Wilk test of normality. Correlation analyses were performed with Spearman’s Rho correlation analysis. Probability values \(\leq 0.05\) were considered to be significant. Receiver operator curve analysis revealed the most sensitive factor for prediction of perinatal hypoxia. The coordinate points were analysed and an optimal cut-off value that provides for the highest sensitivity and specificity.

RESULTS

Characteristics of the perinatal hypoxic and control groups are given in Table 1. Birth weight, gender and mode of delivery were similar in the hypoxia and in the control group. Gestational age was lower in the hypoxic group in comparison to the control group, because the severe HIE group included more term infants (Table 1). HIE and perinatal hypoxic without HIE groups had a significantly higher cord blood cTnI level in comparison to the control group (Table 1, Figure 1). Cord blood cTnI levels were similar for mode of delivery and gender \((p > 0.05\) Mann Whitney U test). Cord blood cTnI level did not have a correlation with birth weight and gestational age. Cord blood cTnI level showed a negative correlation with pH, bicarbonate, base deficit, and Apgar score (Table 2). The cord blood cTnI level had a positive correlation with creatine kinase and creatine kinase MB levels \((r = 0.45, p < 0.001\) and \(r = 0.37, p < 0.001\) respectively) (Table 2).

Figure 1 Cord cTnI levels of control, perinatal hypoxia and hypoxic without HIE groups. Abbreviations: No HIE, perinatal hypoxic without HIE. HIE: Hypoxic ischemic encephalopathy

Figure 2 ROC curves for cord cTnI, CK and CK-MB values (A) and pH, Apgar score values (B) for detecting hypoxia. The optimal cut-off value of cord cTnI had a highest sensitivity and specificity.
Receiver operator curve analysis revealed that the most sensitive factor for prediction of perinatal hypoxia was cord cTnI value (area under curve (AUC) = 0.929) (Table 3 and Figure 2). The optimal cut-off value of cord cTnI with a 0.35 ng/ml had the highest positive and negative predictive value (Table 3).

**DISCUSSION**

This study demonstrated significantly high cTnI levels in the newborns with perinatal hypoxia. Also there was a correlation between elevated cTnI cord blood pH, bicarbonate, base deficit and Apgar score. Quivers et al. and Soldin et al. showed that preterm infants had a significantly higher cTnI level than term infants in the first year. We did not find such a correlation with cTnI between gestational age and birth weight. Also they did not study Apgar score, cord blood pH and the history of perinatal hypoxia. They suggested that the results of their study may indicate that apoptosis could occur during postnatal maturation of the heart and to a greater degree in the preterm infants. Apoptosis of the heart contributes to the adaptive changes required during postnatal maturation of the heart. The rate of apoptotic myocardial cell death in the right ventricle is two- to fourfold higher than in the left ventricle of the postnatal rat, allowing the faster growth of the left ventricle such that a twofold higher muscle mass and myocardial cell count result. But we are not in agreement, because we found a correlation between high cTnI levels and perinatal hypoxia. Neither preterm nor term infants without hypoxia had high cTnI. But only hypoxic preterm and term infants had significantly high cTnI levels. Therefore it may be speculated that elevated cTnI levels may indicate programmed cell death due to perinatal hypoxia instead of adaptive myocardial apoptosis in the preterm infants during postnatal maturation of the heart. Further investigation is required to better understand this phenomenon. Also Shelton found a significantly higher prevalence of respiratory distress syndrome in a small number of neonates with elevated cardiac troponin T levels. Engin et al. found high cTnI levels in fetuses of pregnant women with hypertensive disorder. All of these reports may reflect the relation of elevated cTnI perinatal hypoxia.

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Receiver operator curve analysis revealed that the most sensitive factor for prediction of perinatal hypoxia was cord cTnI value compared to CK, CK-MB and pH values. Cord cTnI is the marker with highest, specificity, sensitivity, negative predictive value, positive predictive value and AUC for hypoxia. Elevated CK and CK-MB cannot be used to diagnose perinatal hypoxia because it has a correlation with mode of delivery, gestational age and birth weight. The optimal cut-off value of 0.35 ng/ml for cTnI was predictive for early diagnosis in hypoxic infants. It is important to diagnose early and to initiate supportive treatment after birth asphyxia. We did not study maternal cTnI values. There was no difference in cTnI concentrations between term patients with intrapartum magnesium sulfate therapy and controls who did not receive magne-
sium sulfate but maternal cTnI levels have not been studied previously\textsuperscript{10}.

**CONCLUSION**

cTnI levels in the cord blood are unaffected by gestation, birth weight, gender and mode of delivery. cTnI is elevated parallel CK and CK-MB in only hypoxia but not in normal preterm and term newborns. Therefore we suggest that elevated cord cTnI levels can be used as a new early diagnostic marker for perinatal hypoxia with cord blood pH, cord blood base deficit and Apgar score in both preterm and term newborns.

**REFERENCES**
