Predictive value of biochemical, echocardiographic and electrocardiographic markers in non-surviving and surviving asphyxiated full-term newborns

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Severe perinatal asphyxia can cause multiple organ dysfunction and early neonatal mortality.

This prospective study was conducted at the Regional University Hospital Neonatology Center in Serbia. The aim of this study was to compare full-term asphyxiated newborn infants (n=55) with (n=13) and without (n=42) mortality outcome and healthy full-term newborns (n=36) regarding biochemical (cardiac troponin I, creatine kinase (total and MB fraction) and C-reactive protein), echocardiographic (ejection fraction, fractional shortening, mitral regurgitation, significant tricuspid regurgitation, and patent ductus arteriosus) and electrocardiographic (ST segment elevation/depression, T wave inversion and corrected QT interval) markers of myocardial damage in order to assess their predictive value in the clinical outcome.

Statistically significant differences in the majority of the tested markers of ischemic myocardial lesion were found between perinatal asphyxia survivors and the control group. However, among the biochemical indicators, only the level of cardiac troponin I was significantly higher in the group of neonates who died compared to the group of asphyxiated neonates who survived (p: 0.000), with an area under the receiver operating characteristic curve of 0.821 and cutoff value for lethal outcome of 0.135 μg/L (sensitivity 0.85; specificity 0.69). In addition, differences in ejection fraction, fractional shortening and significant tricuspid regurgitation (≥2+) were also found between the two subgroups of asphyxiated newborns. Cardiac troponin I is the most sensitive ischemic myocardial lesion biochemical marker in the prediction of early mortality in perinatal asphyxia patients.

Key words: myocardial damage, cardiac troponin I, newborn, asphyxia.

The incidence of perinatal asphyxia (PA) varies between 1% and 5%[1]. PA has a high impact on neonatal mortality and morbidity and may lead to ischemic myocardial damage, as well as poor neurological and gastrointestinal outcomes[1-4]. Ischemia and myocardial necrosis occur in 25-51% of newborn infants with severe PA[2].

A variety of markers have been examined to identify perinatal hypoxia, including electronic fetal heart monitoring, low Apgar scores, cord pH, electroencephalograms, Doppler flow studies, computed tomography, and magnetic resonance imaging scans[1,4]. In adults, biochemical markers are more sensitive and specific than imaging techniques in diagnosing myocardial necrosis[1,2]. There is limited information about cardiac biochemical markers in newborns with PA[5]. Recently, cardiac troponin I (cTnI) has been used as an early marker for the detection of cardiac and respiratory dysfunction, significant patent ductus arteriosus (PDA), and hypoxic-ischemic encephalopathy and in the assessment

of mortality risk in asphyxiated newborn infants[1,5-14]. Our goal was to contribute to this literature by further exploring the predictive value of electrocardiographic, echocardiographic, and biochemical markers in assessing clinical outcomes in asphyxiated newborn infants. Our objectives were to first compare cTnI to other biochemical markers (lactate, C-reactive protein (CRP), total creatine kinase (CK), and MB fraction of creatine kinase (CK-MB)), and second, to determine the value of standard echocardiographic and electrocardiographic markers in predicting death in full-term neonates with PA.

Material and Methods

This prospective study was conducted at the Regional University Hospital Neonatology Center in Serbia from August 2007 to January 2010. The research was approved by the Local Hospital Ethics Committee, and written informed consent was given by the parents.

A power analysis, using the SISA computer program (Uitenbroek, 1997) and a previously conducted pilot study showed that a sample size of 36 participants per group would be needed to detect significant difference in the level of TnI with 80% power and an alpha of 0.05. (http://www.quantitativeskills.com/sisa/distributions/binomial.html).

Patients

Ninety-one term newborn infants, hospitalized in the first 12 hours after birth, were divided into two groups as control (n=36) and asphyxiated group (n=55). The group of asphyxiated neonates was further subdivided into two groups as asphyxiated survivor (n=42) and asphyxiated non-survivor (n=13) groups. Patients who did not survive had critical cardiorespiratory problems or multiorgan dysfunction. Seven patients died within seven days of birth, and six had late mortality.

The clinical definition of PA was based on several clinical criteria: abnormalities in electronic fetal monitoring, meconium-stained amniotic fluid, metabolic acidemia, low Apgar score, and post-asphyctic neurologic and extraneurologic involvement[15]. Inclusion criteria for the study were history of fetal asphyxia and/or obstetric complications; cardiorespiratory and neurological disability defined by Apgar score <4 in the 1st minute and <7 in the 5th minute after delivery; metabolic acidosis (lactate level >3.7 mmol/L in the first 6 hours (h) of life and >2.0 mmol/L in 6-12 h of life)[16]; and post-asphyctic neurologic involvement. Standardized neurological examination was performed at 12, 24, 48, and 72 h of age. Hypoxic-ischemic encephalopathy (HIE) was defined according to Sarnat and Sarnat score with three clinical stages[17]. Additional observed parameters were respiratory distress requiring mechanical ventilation, hypotension and/or oliguria requiring inotropic support and multiorgan failure[18]. During the three-year study, 72 term newborns with PA were analyzed (6.7% of all admitted neonates); 17 subjects were excluded because of proven congenital heart defects (1 hypoplastic left heart syndrome, 1 ventricular septal defect, 1 pulmonary artery stenosis, and 2 atrial septal defects), chromosomal aberrations (1 Edwards and 2 Down syndromes), or connatal sepsis (9 patients with positive blood cultures).

The control group of non-asphyxiated healthy newborn infants (n=36) were randomly selected, and fulfilled the following criteria: absence of signs of fetal distress and maternal illness, 5th minute Apgar score >8, and initial values of postnatal blood lactate levels <2 mmol/L.

Biochemical Markers

The lactate blood level was analyzed within the first 12 h (5.9±3.4) after birth using a gas analyzer (GEM Premier 3000). The serum concentrations of CRP, CK and ischemic myocardial damage biochemical markers (cTnI, CK-MB) were measured in all groups of patients within the first 24-48 h after birth. The measurements of cTnI were carried out using the chemiluminescence immunoassay technique and a mini Vidas analyzer (BioMerieux, Yunycom). Serum CK-MB, CK and CRP levels were measured simultaneously using the SYNCHRON test, Beckman Coulter Olympus diagnostics and immunoassay technique.

Echo- and Electrocardiographic Indicators

Echocardiographic and electrocardiographic examinations were performed within the first 72 h after birth. Echocardiography was used to determine ejection fraction (EF), fractional shortening (FS), and the presence/absence of mitral regurgitation, significant

tricuspid regurgitation (≥ 2+), and PDA. Electrocardiograms were analyzed for signs of myocardial ischemia based on the criteria by Jedeikin et al.[19] Only ST-T changes present in >2 leads (ST segment elevation or depression ≥1 mm or T wave inversion) were deemed significant. Determination of the corrected QT interval was performed as well.

Statistical Analyses

The analytic strategy included one-way ANOVA, the Mann-Whitney test, and the Kruskal-Wallis test for between-group comparisons; Pearson and Spearman coefficients for bivariate correlations; the chi-square test of independence; and the receiver operating characteristic (ROC) curve for determining cutoff values for different markers. The analyses were performed using the Statistical Package for the Social Sciences (SPSS) 14.0 for Windows. Results were considered statistically significant at the 5% level.

Results

There were no statistically significant differences among the examined groups of neonates with respect to gender, gestational age, and body weight at birth (Table I). Hypotension and/or oliguria was found in 23/55 patients who needed inotropic support and in 31/55 who required mechanical ventilation. Mild HIE (23 patients) was diagnosed if hyperexcitability or hypotonia persisted without seizures for >72 h after birth; moderate HIE (21 patients) if the newborn was lethargic and hypotonic, with weak primitive reflexes and seizures <48 h after birth; and severe HIE (11 patients) if the newborn infant had apnea, flaccid weakness, frequent seizures, or coma (Table I). Three patients with severe HIE survived but had severe electrocortical activity depression (revealed by electroencephalography) and diffuse cerebral leukomalacia (DCL) (revealed by brain ultrasonography or magnetic resonance imaging) in the first four weeks of life.

There were statistically significant differences between the control group (n=36) and the asphyxiated-survivor group (n=42) in the majority of tested markers of ischemic myocardial damage (Tables II and III). Analysis of biochemical markers showed statistically significant differences between the asphyxiated survivors and control group in lactate ($p<0.0001$), CRP ($p=0.037$), CK-MB fraction ($p<0.0001$), and cTnI ($p<0.0001$) blood levels (Table II). No difference in CK concentration was noticed ($p=0.996$). A significant difference was found between the two asphyxiated groups (with and without mortality outcome) in lactate and cTnI blood concentrations ($p<0.0001$). However, there was no statistically significant difference between the asphyxiated survivors and the asphyxiated non-survivors groups with respect to the levels of CRP, CK and CK-MB. In the PA group, there were statistically significant differences in cTnI levels in the different clinical stages of HIE ($p<0.001$). Median cTnI level in patients with mild HIE was 0.05 μg/L (interquartile range [IQR] 0.01-0.15 μg/L), while this value was 0.06 μg/L

Table I. General Characteristics of the Three Groups of Patients

	Control group (n: 36)	Asphyxiated survivors (n: 42)	Asphyxiated non-survivors (n: 13)
Male:Female	17:19	24:18	7:6
Gestational week	39.8±1.1	39.7±1.3	39.1±1.4
Birth weight (grams)	3455±352	3404±532	3512±701
Cesarean section	n 0	n 17 (40.5%)	n 2 (15.4%)
Apgar score – 1 min	-	3 (IQR 1-4)	1 (IQR 0.25-2)
Apgar score – 5 min	9 (IQR 9-9)	6 (IQR 4-7)	3 (IQR 1-5)
Resuscitation	n 0	n 30 (71.5%)	n 11 (84.6%)
Mechanical ventilation	n 0	n 18 (42.9%)	n 13 (100%)
Inotropic therapy	n 0	n 11 (26.2%)	n 12 (92.3%)
Mild HIE	n 0	n 23 (54.8%)	n 0 (0%)
Moderate HIE	n 0	n 15 (35.7%)	n 6 (46.2%)
Severe HIE	n 0	n 4 (9.5%)	n 7 (53.8%)

HIE: Hypoxic-ischemic encephalopathy. IQR: Interquartile range.

Table II. Biochemical Markers in Observed Groups of Patients

	Control group (n: 36)	Asphyxiated survivors (n: 42)	Asphyxiated non-survivors (n: 13)	p[a]	p[b]
Lactate (mmol/L)	1.04±0.36	7.54±4.07	12.2±3.74	0.000	0.000
CRP (mg/L)	2.6 (0.8-4.8)	3.9 (1.9-8.5)	6.1 (1.4-16.6)	0.037	0.544
CK (U/L)	1334 (874-2520)	907 (587-4736)	2657 (1214-5225)	0.996	0.218
CK-MB (U/L)	78.9±39.1	223.5±196.8	292.2± 255.2	0.000	0.207
cTnI (μg/L)	0.01 (0.01-0.01)	0.06 (0.01-0.15)	0.23 (0.15-0.53)	0.000	0.000

a: Difference between the control group and asphyxiated survivor group. b: Difference between the asphyxiated survivor and asphyxiated non-survivor groups. CK: Creatine kinase. CK-MB: MB fraction of total creatine kinase. CRP: C-reactive protein. cTnI: Cardiac troponin I.

(IQR 0.02-0.155μg/L) in moderate HIE and 0.23 μg/L (IQR 0.15-0.68 μg/L) in severe HIE.

Echocardiographic marker analysis found differences between the two subgroups of asphyxiated patients in EF, FS and occurrence of significant tricuspid regurgitation (Table III). However, there were no significant distinctions between the two asphyxiated groups with respect to the other echocardiographic (mitral regurgitation and PDA occurrence) or ECG parameters (ST-T changes and corrected QT interval duration).

Cardiac TnI and lactate blood levels were the most important biochemical predictors of death in PA patients (n=55). Calculated area under the ROC curve for lactate level was 0.797 (95% confidence interval [CI] 0.656-0.938; p=0.002) and for cTnI was 0.821 (95% CI 0.690-0.951; p=0.01), suggesting that cTnI is a more sensitive marker for prediction of death in patients with PA. Cutoff value for lethal outcome for lactate concentration (measured at 5.9±3.4 hours after birth) was 8.65 mmol/L (sensitivity 0.83; specificity 0.69) and for cTnI blood level was 0.135 μg/L (sensitivity 0.85; specificity 0.74). When we looked at predictive lactate levels for combined lethal/DCL outcome (n=16/55), serum lactate cutoff concentration did not change (8.65 mmol/L), but had a slightly different sensitivity and specificity (sensitivity 0.80; specificity 0.72) with area under the ROC curve of 0.798 (95% CI 0.651-0.945; p=0.001). Cardiac TnI cutoff level for combined lethal/DCL outcome was 0.135 μg/L (sensitivity 0.81; specificity 0.77) with area under the ROC curve of 0.815 (95% CI 0.696-0.933; p<0.0001).

With respect to biochemical, echocardiographic and electrocardiographic parameters, EF (r=0.505; p=0.001) and FS (r=0.485; p=0.002) best correlated with 5th minute Apgar score. A statistically significant correlation between cTnI concentration and EF (r=0.446; p=0.004) as well as between cTnI concentration and FS (r=-0.445; p=0.004) in patients with PA was noticed as well.

Discussion

Perinatal asphyxia (PA) has a high impact on neonatal mortality and morbidity. However, in milder cases, neonatal myocardial ischemia might be clinically occult. Some cardiac dysfunction is reported in up to 78% of full-term neonates with PA[20]. Consequently, clinical research in the last few years has centered on two major topics: early detection of subclinical cardiac involvement in newborns with diagnosed PA and early detection of the subset of neonates with high risk of poor clinical outcome/death. Addressing the second of these, our study demonstrates that, in full-term newborn infants with severe PA, a combination of standard clinical, biochemical and echocardiographic parameters together with cTnI blood concentration measurement can provide valuable information in the early detection of subsets of patients with a high risk for death. Our findings suggest that the two asphyxiated groups of neonates differed with respect to cTnI blood level, EF, FS, and occurrence of significant tricuspid regurgitation. It is noteworthy that, although ECG changes were present in 76.9% of neonates who died compared to 52.4% of asphyxiated neonates who survived, the difference was not statistically significant. Consequently, in our study, ECG had no predictive value for mortality outcome. This is in contrast to the conclusions of Kanik et al.'s[21] recent paper, but is in agreement with

Table III. Echocardiographic and Electrocardiographic Markers of Ischemic Myocardial Damage in Observed Groups of Patients

	Control group (n: 36)	Asphyxiated survivors (n: 42)	Asphyxiated non-survivors (n: 13)	p[a]	p[b]
EF (%)	82.5±5.6	56.8±14.6	43.9±16.8	0.000	0.006
FS (%)	41.9±3.2	28.8±8.2	21.4±10.3	0.000	0.006
TR (≥2+)	n 0	n 5 (11.9%)	n 10 (76.9%)	0.044	0.000
MR	n 0	n 11 (26.2%)	n 4 (30.1%)	0.001	0.721
PDA	n 0	n 15 (35.7%)	n 5 (38.5%)	0.000	0.916
ST-T changes	n 0	n 22 (52.4%)	n 10 (76.9%)	0.000	0.234
QTc (sec)	0.36±0.02	0.42±0.06	0.45±0.12	0.000	0.244

a: Difference between the control group and asphyxiated survivor group. b: Difference between the asphyxiated survivor and asphyxiated non-survivor groups. EF: Ejection fraction. FS: Fractional shortening. MR: Mitral regurgitation. PDA: Patent ductus arteriosus. QTc: Corrected QT interval. TR: Tricuspid regurgitation.

other reports that failed to demonstrate the predictive value of ECG for mortality outcome [21-24]. Apart from technical limitations related to neonatal ECG recordings, such differences might be explained in part by the fact that, even in clinically severe cases, ECG changes might be mild and remain unrecognized[24].

Contrary to some recent reports, the results of this study demonstrate that standard echocardiographic parameters of myocardial damage, such as FS and EF, do have a statistically significant predictive value for mortality outcome in neonates with PA[20,21]. Moreover, we found that both EF (r=0.505; p=0.001) and FS (r=0.485; p=0.002) best correlated with 5th minute Apgar score, indicating that a combination of standard clinical and echocardiographic parameters can further delineate a subgroup of asphyxiated neonates with increased risk for a poor outcome/death. This is of importance because standard echocardiographic examination is usually routinely performed by a neonatologist at the bedside. Our results are in agreement with Barberi's[24] and Moller's[25] findings, who suggested that reduced EF and FS, as markers of myocardial involvement, are often present in severely asphyxiated newborns[24,25]. In the cases of mild, subclinical cardiac involvement in newborns with PA, standard echocardiographic evaluation is of limited value, and more sophisticated examinations, such as right and left ventricle Tei index and Doppler tissue imaging, performed by a pediatric cardiologist, are more relevant and should be mandatory[20].

Clinically significant tricuspid regurgitation was found in 11.9% of asphyxiated neonates who survived and in 76.9% of asphyxiated neonates who died. Thus, significant tricuspid regurgitation is another marker of myocardial ischemia, which is statistically significant in predicting mortality outcome in neonates with PA. Increased incidence of significant tricuspid regurgitation in neonates with PA was reported previously, but its predictive value with respect to poor outcome/death was not specifically addressed[22-24,26].

Cardiac enzymes have long been used as frontline diagnostic tools in the detection of myocardial injury caused by myocardial ischemia[1,9,10]. However, the most commonly used enzymes, including CK and its myocardial fraction (CK-MB), have a limited role in detecting myocardial injury because of their short diagnostic windows, limited sensitivity, and a lack of specificity[9]. cTnI and cTnT are the most sensitive biochemical markers in the detection of myocardial damage and, at present, are the diagnostic gold standard of cardiac injury in the adult population[1,2,4-14,25,27]. The use of such biochemical markers in newborn infants, especially cTnI, and its relationship to PA and poor neonatal outcomes have not been studied extensively until recently[28-33]. In this study, we prospectively determined the value of cTnI in term newborn infants with clinical signs of PA and an abnormal obstetric history, which may have caused either intrauterine fetal distress or asphyxia during delivery.

Our results confirmed that both cTnI and CK-MB are sensitive and specific biochemical markers of hypoxic myocyte injury[1,2,28-34].

However, comparison of the two groups of asphyxiated newborns demonstrated that, of the examined biochemical markers, only the level of cTnI was statistically significantly different – that is, higher in the group with lethal outcome compared to the group of asphyxiated neonates who survived. The average value of cTnI blood level in the group of asphyxiated neonates who died was 0.23 μg/L (IQR 0.15-0.53 μg/L) compared to 0.06 μg/L (IQR 0.01-0.15 μg/L) in the group of asphyxiated neonates who survived ($p<0.0001$). The cutoff cTnI value for lethal outcome in our study was 0.135 μg/L (sensitivity 0.85; specificity 0.74). This is similar to results published recently by Matter et al.[20], who found a cTnT cutoff of 0.15 μg/L gave a specificity of 100% and a sensitivity of 70% in predicting mortality in asphyxiated neonates. That said, contrary to results published by Matter et al.[20], we found a strong correlation between cTnI concentration and FS, thus confirming the role of cTnI in predicting the outcome of neonates with PA and heart failure/cardiogenic shock.

Unlike cTnI, the levels of CK-MB were not statistically significantly different in the two groups of asphyxiated neonates. This is in agreement with recently published reports, which showed that CK-MB is both less specific and less sensitive in detecting cardiac involvement and in the early prediction of poor outcome/death in neonates with PA[20,23,35]. Everything taken together, we agree with the position that "and extreme caution should be used in the interpretation of increased CK-MB activity in neonates"[20,28]. In conclusion, our results, similar to some other recent reports, confirm that cTnI was the very sensitive single parameter in predicting mortality outcome in full-term newborns with PA[20,23,33].

Our study was limited because hypothermia is not routinely performed as a treatment for birth asphyxia in our country due to technical and financial limitations (as well as in most third world countries). However, the results of this study could help clinicians in the early detection of the high-risk PA neonates. In addition, our results might be very helpful for further studies on the same point, especially in the comparison of cTnI cutoff values and further clarification of the importance of echocardiographic parameters in predicting the clinical outcome of hypothermia-treated PA patients.

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