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Finding a biomarker to predict patent ductus arteriosus in preterm babies

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Abstract

Background: Few studies have evaluated the relationship between the presence of PDA and cardiac troponin T (cTnT) levels; however, the results are conflicting. The present study aimed to compare blood cTnT levels among preterm neonates with and without PDA.

Methods: A case-control study was conducted at Iranian Hospital in 2021. For all included neonates, echocardiography examination was performed on admission time. According to the clinical presentation and echocardiography findings, preterm neonates were divided into the case (with PDA) and control (without PDA) groups. A blood test was also performed for all participants to detect levels of plasma cTnT. Finally, the levels of plasma cTnI (ng/ml) were compared between the case and control groups.

Results: Totally 36 neonates (12 with PDA and 24without PDA) aged 1.972±0.696 days entered the study. The mean neonatal Troponin T level was 116.352±83.470 ng/ml. The results have shown no significant difference between the groups regarding the means of Troponin level (124.506±113.138 and 112.275±66.546; P=0.476). The results have indicated that there were significant and inverse correlations between the cTnT level with the 1st (Correlation Coefficient= -0.450; P=0.006) and 5th (Correlation Coefficient=-0.532; P=0.001) minutes Apgar Scores. This relationship was also observed between the mean of TnT level and maternal gravidity (Correlation Coefficient= -0.356; P=0.033).

Conclusion: The results of the present study delineate no correlation between the presence of PDA and increased blood cTnT levels in preterm neonates. While low Apgar scores at 1 and 5 minutes as well as maternal gravidity could significantly change the levels of cardiac troponin T levels.

Keywords: Troponin T; Ductus Arteriosus; Patent; Premature Birth; Newborn

1. Introduction

Patent ductus arteriosus (PDA) as a frequent complication in preterm neonates is responsible for severe morbidities like persistent left-to-right shunting, congestive heart failure, bronchopulmonary dysplasia, increased ventilator dependence, pulmonary hemorrhage, necrotizing enterocolitis, and so on [1, 2]. The incidence of PDA among preterm neonates is 5-fold higher than term infants (with an incidence of 0.1-0.2%) because of a reduction in the probability of

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spontaneous closure of ductus arteriosus [3, 4]. This incidence drastically increases to about 50% in preterm neonates with gestational age below 28 weeks [5].

Besides clinical presentation, an echocardiographic examination is a gold standard for the diagnosis of PDA. While recently several studies have focused on proposing a PDA biomarker with better accessibility, lower cost, and fewer drawbacks compared to this diagnostic modality. Biomarkers like Pro-B-type natriuretic peptide, plasma superoxide dismutase, ischemia modified albumin, platelet distribution width and absolute nucleated red blood cell (aNRBC), cardiac troponin T (cTnT), and Troponin I have been proposed determining preterm neonates with risk of PDA [4-7].

Previous studies have shown that post-cardiac ischemic injuries, Troponin T (a component of cardiac muscle myofibril) releases and remains high for about 2 weeks [8]. It has also shown that PDA by potential myocardial damage may alter cardiac troponin T level [9]. Another study demonstrated that the increase of High-sensitivity TnT in PDA cases were secondary to the increased oxygen demand of the stretched myocyte due to left to right shunting [10]. Furthermore, it was indicated that PDA neonates with higher blood cTnT levels had poorer neurodevelopmental outcomes after 2 years in comparison with those with lower values [11]. These findings have proposed cTnT as a biomarker that may show the presence of PDA, its responses to treatment, and closure [9]. On the other hand, other studies demonstrated that the level of cTnT in preterm neonates was correlated to the presence of PDA or the size of PDA diameter [12, 13].

Despite these few studies from other countries with such conflicting results, we found that no investigation has been conducted in our country (Iran) to examine the relationship between cardiac troponin T levels and neonatal PDA. Therefore, in the present study, we aimed to investigate the relationship between this biomarker and PDA among preterm neonates. The results may confirm the hypothesis regarding the diagnostic and prognostic values of troponin T resulting in earlier PDA diagnosis and timely treatment.

2. Material and methods

A case-control study was conducted at Yas Hospital (affiliated with Tehran University of Medical Sciences, Tehran-Iran) in 2021. Inclusion criteria were singleton pregnancy, preterm birth (gestational age <37 weeks), NICU hospitalization, presence and absence of PDA. For all included neonates, echocardiography examination was performed on admission time.

According to the clinical presentation and echocardiography findings, preterm neonates were divided into the case (with arterial diameter>1.5 mm) [12] and control (without PDA) groups. All eligible subjects entered the study until the number of participants reached the proposed sample size for each group. Subjects with other structural, chromosomal, or congenital heart diseases were excluded from the study.

A blood test was also performed for all participants. One ml of venous blood was collected, placed in a heparinized tube, centrifuged, labeled, stored at -20^{o} C, and sent to the laboratory. By a colleague who was completely blind regarding the groups, levels of plasma cTnT were determined using the Elisa Kit (Elecsys, 08469814190; TnT hs STAT; Immuno Enzymometric Assay; China) and Cobas e411 Analyzer machine.

The study was explained to the neonate's mother before the admission of the participant. Then she was asked to sign written informed consent. Maternal and neonatal demographic characteristics such as mother's age, obstetric history, type of delivery, neonate's birth weight, height, head circumference, first and fifth minutes Apgar scores, history of intubation, or death were recorded.

Finally, the levels of plasma cTnT (ng/ml) were compared between the case and control groups as the primary outcome. Moreover, the relationships between some maternal/neonatal factors and the levels of plasma TnT were assessed as the secondary outcome.

2.1. Sample size

Based on another investigation by Asrani et al. [10], the mean±SD of TnT in the case and control groups were18181.02 and 3149.23 (pg/ml). Using the following formula, 10 subjects in each group entered the study. To have at least 12 subjects in the case group (2 numbers more than sample size), a total of 36 participants were included. With this proposed sample size, the study had a power of 90% and an alpha error of 0.05.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

Alfa=	0/05	Z1-a/2=	1/96
Beta=	0/10	Z1-B=	1/25
µ1=	18181.02		
µ2=	3149.23		
SD1=	7842.87		
SD2=	826.8	n=	10

2.2. Data Analysis

All statistical analyses were conducted using SPSS 22. Quantitative and qualitative variables were presented as mean±standard deviation and number (%), respectively. Independent samples t and Chi-square tests (or Fisher Exact) were used for analyzing the relationships between variables with a normal distribution. As Kolmogorovab Smirnov Test showed non-normal distribution in quantitative variables, Mann-Whitney analysis was also used. The Correlation Coefficient was also determined by using Spearman's Correlation test to show the levels of significance between variables. P-Value less than 0.05 was considered statistically significant.

3. Result

Totally 36 neonates (12 with PDA and 24 without PDA) aged 1.972±0.696 days (Min; 1, Max; 3 days) entered the study. Of all, 51.4% were male. The mean age of neonates' mothers and the mean of gestational age were 30.914±6.532 years and 32.658±1.554 weeks. All neonates in both groups were born by cesarean section. Two cases with PDA died after birth and no cases had Intraventricular hemorrhage. The mean neonatal Troponin T level was 116.352±83.470 ng/ml.

Table 1 Comparison of demographic characteristics between the case and control groups

Variables	**Case group n=12**	**Control group n=24**	**P value**
Maternal age (Mean ±SD)	31.818±6.615	30.500±6.593	0.605
Gestational age (Mean± SD)	32.991±1.180	32.491±1.709	0.503
Gravidity (Mean ±SD)	1.666±0.651	2.125±1.075	0.227
Parity (Mean± SD)	1.0000±0.632	0.761±0.768	0.431
Maternal disease (n %) Diabetes Hypertensive disorders Thyroid disorders Other none	 2(16.7) 4(33.3) 1(8.3) 0 5(41.7)	 4(16.7) 2(8.3) 6(25.0) 1(4.2) 11(45.8)	0.322
Gender (n %) Male Female	 4(36.4) 7(63.6%)	 14(58.3) 10(41.7)	0.289
Birth Weight (Mean±SD)	1624.583±545.883	1748.333±296.826	0.347
Birth height (Mean±SD)	43.083±4.981	43.847±2.842	0.807

Birth Head Circumference (Mean±SD)	29.5000±2.34521	29.9565±1.637	0.391
First minute Apgar Score (Mean±SD)	7.0833±1.62135	8.2500±0.794	0.026
Median	7.000	8.000	
5th minute Apgar Score (Mean±SD)	8.9167±1.08362	9.3750±.57578	0.245
Median	9.0000	9.0000	
Intubation (n %) Yes No	 7(58.3) 5(41.7)	 12(50.0) 12(50.0)	0.732
Death (n %)	2(16.7)	0	0.105
Troponin T levels (Mean± SD)	124.506±113.138	112.275±66.546	0.476

Comparison of variables between the case and control groups showed that both groups were matched and there were no significant differences in maternal age (P=0.605), gestational age (P=0.503), neonates' gender (P=0.289), history of the maternal disease (P=0.322), numbers of gravidity (P=0.227), and parity (P=0.431), as well as anthropometric parameters (P>0.005) (Table 1).

Table 2 Assessing the relationships between qualitative variables and Troponin T levels

Variables	**Troponin T levels (Mean± SD)**	**P value**
Gender Male Female	 85.333±34.789 151.034±107.393	0.057
Intubation Yes No	 140.1474±101.314 89.7582±83.470	0.156
Death Yes No	 179.950±61.447 112.6115±83.758	0.178

As data are shown in Table 1; the mean± SD and median values related to the first minute Apgar score in the case group were significantly lower than in the control group (7.083±1.621 & 7.000 vs. 8.250±0.794 & 8.000; P=0.026). While this significant difference in Apgar score was not observed after 5 minutes between the groups (P=0.245). The mean of gestational age in the case and control groups was not also significant (0.503). Although mechanical ventilation was more frequently performed in the case group compared to the control group, the difference was not significant (58.3% vs. 50.0; P= 0.732). Anthropometric measures in the case group were significantly lower than the control group; however, the differences were not significant (P>0.05). Moreover, the results have shown no significant difference between the groups regarding the means of Troponin level (124.506±113.138 and 112.275±66.546; P=0.476).

Regarding the relationships between qualitative variables and TnT levels, the results showed that TnT levels in female subjects were higher than males but the difference was not significant (P=0.057). Moreover, the relationships between intubation or death of neonates with TnT levels were not significant (P=0.156 & P=0.178) (Table 2).

Further analysis was also used to determine the influence of each quantitative variable on Troponin levels. The results have indicated that there were significant and inverse correlations between TnT level with the first (Correlation Coefficient= -0.450; P=0.006) and fifth (Correlation Coefficient=-0.532; P=0.001) minutes Apgar Scores. This relationship was also observed between the mean of TnT level and maternal gravidity (Correlation Coefficient=-0.356;

P=0.033). On the other hand, maternal age, parity, gestational age, or neonatal anthropometric measures were not significant influencing factors on Troponin T level (P>0.05) (Table 3).

Table 3 Assessing the correlations between each quantitative variable with Troponin T levels

Variables	Pearson Correlation Coefficient	P value
Mother's age	-0.214	0.218
Gestational age	-0.275	0.105
First minute Apgar score	-0.450	0.006
Fifth minute Apgar score	-0.532	0.001
Gravidity	-0.356	0.033
Parity	-0.321	0.102
Birth weight	-0.140	0.415
Birth height	-0.206	0.234
Birth head Circumference	-0.227	0.190
Neonate's age	-0.103	0.549

4. Discussion

To our knowledge, very few studies have assessed the alterations of troponin T in neonates with PDA to show that this clinical complication may lead to an increase of cTnT [9, 10]. The results of our study could not confirm such a significant correlation between the presence of PDA and increased cTnT levels among preterm neonates. In accordance with our finding, Cruzet al. have shown that the levels of cTnT were not significantly different between neonates with and without PDA [13]. Another study by Perugu et al. also demonstrated that there were no significant differences in TnT levels between neonates with large, small, and intermediate sizes of PDA. The authors also declared that receiving dopamine was a significant factor for the increase of cTnT in preterm infants regardless of the presence of PDA [12]. In contrast to our findings, Asrani et al. demonstrated higher High-sensitivity TnT levels in neonates with a hemodynamically significant PDA in comparison with neonates without this complication [10]. El-Khuffash et al. have also shown the significant relationship between PDA and cTnT among preterm newborns. The authors indicated that after 48 hours, the mean of cTnT level in infants with PDA was significantly higher than this value in the cases with spontaneous PDA closure or with successful treatment. It was reported that ductal diameter, left atrial-to-aortic diameter ratio, and descending aortic end-diastolic velocity were significant influencing factors on cTnT alterations [9].

According to the results, the mean of the first minute Apgar score in the neonates with PDA was significantly lower when compared to the controls. Moreover, the results showed that there were significant and inverse correlations between the cTnT level with the 1st and 5th minutes Apgar scores. The correlations between hypoxia and low Apgar scores with the risk of PDA have been shown [14, 15]. Consistent with our findings, Ognean et al. showed a significantly lower 1st minute Apgar score in NICU hospitalized preterm neonates with PDA when compared to their counterparts without PDA (6.3±2.0 vs. 6.7±1.8; P=0.022) [16]. Furthermore, in line with our findings related to the relationship between the first minute Apgar score and cTnT levels among preterm neonates with PDA, Cruz et al. have indicated significantly higher serum cTnT levels in neonates with lower Apgar scores compared to those with higher Apgar scores. (r=−0.39, P= 0.04). This significant correlation was also found regarding 5th minute Apgar scores <4 and cTnT levels (P≤ 0.001) [13].

Our results showed that the number of maternal gravidity was the other significant affecting factor on the cTnT level. This relationship may indirectly relate to perinatal, placental, umbilical factors or type of conception (normal or conception with assisted reproductive technology) that may adversely influence the number of pregnancies; however, we did not consider these factors in the present study. We also could not find other studies to compare our results and it seems further studies are needed to clarify this possible relationship.

Finally, we could not find any correlations between Troponin T levels with maternal age, parity, neonatal gestational age, sex, or anthropometric measures that these findings were confirmed by previous studies [17-19].

Limitation

Our study had several limitations. A small sample size was one of them. The correlations between blood cTnT concentrations and other possibly involving factors like blood pressure, O_2 saturation, and echocardiographic measures were not assessed. We did not evaluate cTnT concentration after PDA spontaneous closure or treatment. The data of prenatal corticosteroid prophylaxis was not also considered; however, that may influence the risk for PDA. Future studies with larger sample sizes and more variables can provide further data.

5. Conclusion

The results of the present study delineate no correlation between the presence of PDA and increased blood cTnT levels in preterm neonates. While low Apgar scores at 1 and 5 minutes as well as maternal gravidity could significantly change the levels of cardiac Troponin T levels.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

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Authors' contributions

Dr. MRZ, Dr. KK., and Dr. M Kh carried out the design and coordinated the study, participated in most of the experiments. Dr. MV, Dr. MK, and Dr. MS coordinated and carried out all the experiments, analysis of data, and participated in manuscript preparation. All authors have read and approved the content of the manuscript.

Availability of data and materials

The datasets related to our study are available from the corresponding author on reasonable request.

Statement of ethical approval

Ethics approval was obtained from the institutional review board of Tehran University of Medical Sciences according to the Helsinki declaration (IR.TUMS.REC.1399.123).

Statement of informed consent

Informed consent was also obtained from parents of all participants.

References

[1] Jansen EJ, Hundscheid T, Onland W, Kooi EM, Andriessen P, de Boode WP. Factors Associated With Benefit of Treatment of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis. Frontiers in pediatrics. 2021;9:45.

[2] Atasay B ,Erdeve Ö, Sallmon H, Singh Y. Management of Patent Ductus Arteriosus in Preterm Infants. Frontiers in Pediatrics. 2021;9:306.

[3] Anderson JE, Morray BH, Puia-Dumitrescu M, Rothstein DH, editors. Patent Ductus Arteriosus: From Pharmacology to Surgery. Seminars in Pediatric Surgery; 2021: Elsevier.

[4] Guo X, Ji Y, Wang R, Pan J. Identification of the hemodynamic significant patent ductus arteriosus in preterm infants.

[5] Potsiurko S, Dobryanskyy D, Sekretar L. Patent ductus arteriosus, systemic NT-proBNP concentrations and development of bronchopulmonary dysplasia in very preterm infants: retrospective data analysis from a randomized controlled trial. BMC pediatrics. 2021;21(1):1-10.

[6] Clerico A, Aimo A, Cantinotti M. High-sensitivity cardiac troponins inpediatric population. Clinical Chemistry and Laboratory Medicine (CCLM). 2021.

[7] Sallmon H, Timme N, Atasay B, Erdeve Ö, Hansmann G, Singh Y, et al. Current Controversy on Platelets and Patent Ductus Arteriosus Closure in Preterm Infants. Frontiers in Pediatrics. 2021;9:112.

[8] Maynard S, Menown I, Adgey A. Troponin T or troponin I as cardiac markers in ischaemic heart disease. BMJ Publishing Group Ltd; 2000.

[9] El-Khuffash AF, Molloy EJ. Influence of a patent ductus arteriosus on cardiac troponin T levels in preterm infants. The Journal of pediatrics. 2008;153(3):350-3. e2.

[10] Asrani P, Aly AM, Jiwani AK, Niebuhr BR, Christenson RH, Jain SK. High-sensitivity troponin T in preterm infants with a hemodynamically significant patent ductus arteriosus. Journal of Perinatology. 2018;38(11):1483-9.

[11] El-Khuffash AF, Slevin M, McNamara PJ, Molloy EJ. Troponin T, N-terminal pro natriuretic peptide and a patent ductus arteriosus scoring system predict death before discharge or neurodevelopmental outcome at 2 years in preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2011;96(2):F133-F7.

[12] Perugu S, Rehan V, Chow S, Baylen B. Plasma biomarkers and echocardiographic indices of left ventricular function in very low birth weight infants. Journal of neonatal-perinatal medicine. 2014;7(3):213-22.

[13] Cruz M, Bremmer Y, Porter B, Gullquist S, Watterberg K, Rozycki H. Cardiac troponin T and cardiac dysfunction in extremely low-birth-weight infants. Pediatric cardiology. 2006;27(4):396-401.

[14] Nizarali Z, Marques T, Costa C, Barroso R, Cunha M. Patent ductus arteriosus: perinatal risk factors. Journal of Neonatal Biology. 2012.

[15] Tsai M-L, Lien R, Chiang M-C, Hsu J-F, Fu R-H, Chu S-M, et al. Prevalence and morbidity of late preterm infants: current status in a medical center of Northern Taiwan. Pediatrics & Neonatology. 2012;53(3):171-7.

[16] Ognean ML, Boantă O, Kovacs S, Zgârcea C, Dumitra R, Olariu E, et al. Persistent ductus arteriosus in critically ill preterm infants. The Journal ofCritical Care Medicine. 2016;2(4):175.

[17] Clark S, Newland P, Yoxall C, Subhedar N. Cardiac troponin T in cord blood. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2001;84(1):F34-F7.

[18] Tarkowska A, Furmaga-Jabłońska W. The Evaluation ofCardiac Troponin T in Newborns. Biomedicine hub. 2017;2(3):1-7.

[19] Shelton SD, Fouse BL, Holleman CM, Sedor FA, Herbert WN. Cardiac troponin T levels in umbilical cord blood. American journal of obstetrics and gynecology. 1999;181(5):1259-62.