

The Differences of Cord Blood Troponin I (TnI) Level between Normal and Asphyxiated Infants and Its Correlation with APGAR Score

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Abstract

Asphyxia could increase infant morbidity and mortality. Ante- and intrapartum cardiotocography (CTG) examination could lead to a false positive diagnosis of asphyxia (fetal distress). Troponin I (TnI) is an important factor to the pathogenesis of asphyxia. Cord blood TnI level is increased in infants with fetal cardiac dysfunction, causing pathological CTG and low APGAR score (<7). In the future, TnI is expected to reduce false positive diagnosis of asphyxia caused by CTG. This research was conducted to examine and analyze the differences of cord blood TnI level between normal and asphyxiated infants and to determine the correlation between TnI level and APGAR score. An observational analytical cross sectional study was conducted to a total of 36 patients with asphyxiated infants (18 patients) and normal infants (18 patients). Subjects were selected according to the inclusion and exclusion criteria. Cardiotocography, TnI level, and APGAR score were examined. Umbilical cord blood samples were taken from each subject for the measurement of TnI level using a highly sensitive indirect sandwich Enzyme Linked Immunosorbent Assay (ELISA). Statistical analysis was performed by Mann-Whitney and Rank Spearman correlation coefficient test. Cord blood TnI level of asphyxia and normal groups were 1615.77 ± 1199.98 pg/mL and 819.88 ± 145.82 pg/mL respectively ($p \le 0.05$). Rank Spearman correlation coefficient between cord blood TnI level and 1' and 5' APGAR score was -0.523 (p = 0.026; p \leq 0.05) and -0.502 respectively (p = 0.034; $p \le 0.05$). There was a statistically significant difference between cord blood TnI level of asphyxia and normal groups; cord blood TnI level of asphyxia group was higher than normal group. Furthermore, negative correlation was observed between cord blood TnI level and APGAR score.

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Keywords

APGAR Score, Asphyxia, Cord Blood Troponin I Level, TnI

1. Introduction

Infant asphyxia is a medical condition that occurs in newborns due to lack of oxygen received by the fetus during labor. Infant asphyxia may cause physical disruption of the heart, lungs, liver, kidneys and brain. Disturbance in the brain due to hypoxia may cause developmental disorders in children, both physically and mentally. Detection of fetal asphyxia should be done early, one of which is intrapartum fetal monitoring [1].

Fetal asphyxia is generally caused by a low oxygenated utero-placental circulation blood or other causes, such as impaired lung and placenta function, which may result in a lack of blood flow to the baby's brain during labor. Infants which are having cyanosis, respiratory distress, unresponsive, and less active in the first 5 minutes of APGAR assessment (Appearance, Pulse, Grimace, Activity, Respiration) were identified as high-risk infants toward acute asphyxia. During 2010, there were 226 cases of fetal distress of the total 2774 deliveries (8.15%) in Hasan Sadikin Hospital Bandung. Currently, cases of fetal distress are diagnosed using intrapartum cardiotocographic (CTG) monitoring.

Cardiotocography is a heart rate monitoring tool that simultaneously monitor uterine contractions, fetal heart rate (FHR), and fetal movement, so as to know the fetal response to contractions and fetal movement. Fetal asphyxia is characterized by the occurrence of changes in FHR, acute metabolic acidosis in fetal cord blood, and low APGAR score (<7). In a CTG monitoring, fetal distress is defined by the occurrence of late, repeated, or prolonged deceleration. Determination of fetal distress diagnosis based on CTG monitoring may lead to false positive result due to several factors, such as fetus hypothermia, maternal drugs (such as propranolol and local anesthetic), and fetal congenital heart disorders. Cardiotocographic reading error is approximately 50%, hence the use of CTG increases the incidence of cesarean section by 1.41 times and enhances the action of artificial vaginal parturition by 1.2 times [2]. Reading error can be corrected by adding other indicators, because it requires a basic alternative diagnosis to diagnose cases of fetal distress.

Troponin I is a specific protein that is only expressed when heart muscle disorder occurs, and its level is not affected by maternal troponin level. Troponin I is not found in skeletal muscle during fetal development and is not detected in the blood of healthy people. This protein is a regulator of contraction found in the thin filaments of skeletal and cardiac muscle. At present, elevated level of cardiac troponin subunit T (cTnT) and I (cTnI), which in turn uses the terms TnT and TnI, are often used as markers in the diagnosis of acute myocardial infarction (AMI), both in adults and fetuses. Troponin I has a higher specificity than TnT. The TnI level increases in the state of heart muscle damage. Several studies have shown that elevated level of TnI may indicate fetal heart muscle disorder [3].

Heart muscle disorder may cause changes in CTG pictures [3]. Therefore, fetal asphyxia which caused cardiac muscle disorder may also result in pathological CTG pictures. Impaired fetal heart muscle is suggested to increase TnI level. Troponin I (TnI, 26 kDa) inhibits the actomyosin ATP-ase activity. As a biochemical marker of IMA, TnI has a sensitivity of 100%. Through TnI examination, the percentage of false positive determination of fetal asphyxia by CTG is expected to decline. Until now, no research has been conducted to compare the TnI level in normal and asphyxiated infants in Indonesia. This research was conducted to examine and analyze the differences of cord blood TnI level between normal and asphyxiated infants and to determine the correlation between TnI level and APGAR score.

2. Subjects and Method

This study was an observational analytical cross sectional study to compare cord blood TnI level between normal and asphyxiated infants and its correlation with the APGAR score. Cardiotocographic monitoring, cord blood TnI level examination, and APGAR assessment were done of the two sample groups.

Research on the relationship between Troponin I (TnI) level and asphyxia in infants was conducted from December 2011 until April 2012. Throughout this period, samples were obtained from 18 pregnant women with normal infants and 18 pregnant women with asphyxiated infants who met the inclusion criteria. Subjects'

characteristics, cord blood TnI levels, and APGAR scores were obtained from the two groups. To be comparable, the two groups' characteristics were matched including age and parity. Data of subjects' characteristics are presented in Table 1.

3. Result

Based on the subjects' characteristics, it was known that the mean age of the mothers in normal infants group was 28.7 years; standard deviation of 7.0 with a range of 20 - 42 years. In the group of asphyxiated infants, mothers were in the age range of 22 - 36 years, had a mean age of 29.6 years and standard deviation of 4.0. The mean gestational age in normal and asphyxiated infants group was 37 and 38 weeks respectively

Based on parity, in normal infants group the number of primigravida (8 subjects) was less than the number of multigravida (10 subjects). Meanwhile, in the asphyxiated infants group, the number of primigravida (10 subjects) was more than the number of multigravida (8 subjects).

The t test and chi square test were used to compare the two groups' characteristics. Table 1 shows the results of statistical analysis with a 95% confidence level which indicates that there are no statistically significant differences in the maternal age (p = 0.635), gestational age (p = 0.069), and parity (p = 0.176) for both study groups. Thus, both study groups were homogeneous and comparable.

Table 2 shows that 5 normal infants (27.78%) were found in the group that was diagnosed as asphyxiated infants. Whereas in the control group, there were 15 infants (83.33%) of 18 infants who were diagnosed as

Table 1. Characteristics of normal and asphysiated infants groups.				
	Groups	of infants		
Characteristics	Normal	Asphyxia	p value [*]	
	(n = 18)	(n = 18)		
1. Age (years)				
- Mean (SD)	28.7 (7.0)	29.6 (4.0)	0.646	
- Range	20 - 42	22 - 36		
2. Gestational age (weeks)				
37	12	6		
38	6	7	0.060	
39	0	4	0.009	
40	0	1		
- Mean (SD)	37.0 (0.5)	38.0 (0.9)		
3. Parity				
1	8 (44.44%)	10 (55.56%)		
2	9 (50%)	7 (38.89%)	0.480	
3	1 (5.56%)	0 (0%)		
4	0 (0%)	1 (5.56%)		

*p value was calculated based on t-test (for age) and chi-square (for gestational age and parity).

Table 2. Normal dan asphyxiated infants' distribution based on CTG examination.			
APGAR score	Normal CTG images (n = 18)	Pathological CTG images (n = 18)	
\geq 7 (normal infants)	15	5	
<7 (asphyxiated infants)	3	13	

normal. This finding suggests that the detection of fetal asphyxia by CTG monitoring was non-specific and having the possibility to be false positive.

Toward all research, subjects both normal and asphyxiated infants, the levels of cord blood TnI and APGAR scores were measured. Through the normality test, it was known that the obtained data were not normally distributed, therefore, the Mann-Whitney test was used to compare the characteristics of the two study groups. Comparison of cord blood TnI levels in normal and asphyxiated infants are presented in **Table 3**.

The results showed that the umbilical cord blood TnI levels in normal infants (control group) ranged from 618.22 to 1080.77 pg/mL, whereas in infants from asphysia group it ranged from 245.61 to 5018.87 pg/mL. The mean of cord blood TnI level in the control group was 819.88 pg/mL, whereas in the asphysia group was 1615.77 pg/mL. It shows that the average level of cord blood TnI in asphysiated infants was higher than normal infants. Based on statistical analysis with a 95% confidence level, it was known that there was a significant difference of TnI level in normal and asphysiated infants (p value = 0.009 < 0.05).

The APGAR assessment was conducted toward all subjects: normal infants (18 subjects) and asphyxiated infants (18 subjects). The APGAR score at the 1st and 5th minute after birth (APGAR 1' and APGAR 5') may indicate the level of infant asphyxia. In this study, it was known that 15 infants (83.33%) was asphyxiated in the 1st minute after birth, whereas 5 infants (27.79%) was asphyxiated in the 5th minute after birth. The correlation between cord blood TnI level and APGAR score was presented in Table 4.

Based on the data presented in **Table 4**, it is known that there was a negative correlation between cord blood TnI level and APGAR score that was taken in the 1st and 5th minute after birth. The correlation coefficients were -0.523 (p = 0.026, p ≤ 0.05) and -0.502 (p = 0.034, p ≤ 0.05) respectively.

4. Discussion

In this study, examination was conducted toward 36 subjects that were consisted of 18 pregnant women with normal infants and 18 pregnant women with asphyxiated infants. Sample classification was done based on diagnosis through CTG examination during labor. The asphyxiated infants group had pathological CTG images. The CTG images showed a variability of fetal heart rate (FHR). Normal FHR variability indicates the normal central nervous system integrity and adequate oxygenation, so that suspicious picture on CTG indicates the reduction of fetal activity in uterus that marks fetal asphyxia condition [1].

Subjects' characteristics in this study were including maternal age and parity. Statistical analysis (t test for age and chi square test for parity) was used to determine the data homogeneity of both study groups. Homogeneity test ought to be done in order to eliminate confounding factors that may degrade the meaning of the results. Based on statistical analysis with a 95% confidence level, it was known that p values for the subjects' characteristics (age, gestational age, and parity) were 0.646, 0.096, and 0.480 respectively. Those values (p > 0.05)

	Study groups		Statistical test	
Cord blood TnI level (pg/mL)	Normal infants (n = 18)	Asphyxiated infants (n = 18)	Z_{M-W}^{*}	p value
Mean (SD)	819.88 ± 145.82	1615.77 ± 1199.98	2.595	0.009
Range	618.22 - 1080.77	245.61 - 5018.87		
Median	823.81	1199.97		

Table 3. The differences of cord blood Thi levels in normal and asp	sphyx	sphy	hyxı	xıate	ted	ınfan	its.
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^{*}Z_{M-W}: Mann-Whitney test.

Table 4. Correlation between cord b	lood TnI level and APGAR score.	
Correlation	Correlation coefficient (r_s^*)	p value
TnI toward APGAR 1'	-0.523	0.026
TnI toward APGAR 5'	-0.502	0.034

 $r_s = Rank$ Spearman correlation coefficient.

show no significant differences in the mean of age and parity for both study groups. Thus, the two study groups were homogeneous and comparable. The distribution of normal and asphyxiated infants based on CTG examinations was shown in Table 2. It was known that not all infants who were diagnosed as asphyxiated had a bad outcome. The APGAR 1' assestment which was done immediately after birth showed that there were 5 normal infants (27.78%) of 18 infants that were diagnosed to experience fetal asphyxia. It was proved that the diagnosis of fetal asphyxia using CTG monitoring may lead to false positive results. False positives in CTG monitoring resulted in the increased number of unnecessary caesarean section rate.

One of the biochemical markers that are considered to be potential as an alternative diagnosis of fetal asphyxia is troponin I (TnI) [3]-[10]. Troponin I is a protein that is only expressed in heart muscle disorder and the level is not affected by maternal troponin level [11]-[15]. The TnI level is influenced by the level of heart muscle disorder itself [16]-[20]. Heart muscle disorder in infants may be caused by asphyxia [7] [8] [18]-[21]. Cord blood Troponin I (TnI) is increased in infants with heart disorders [3] [7] [19] [22]-[26].

Through TnI examination, the percentage of false positive determination of fetal asphyxia by CTG was expected to decline. Until now, no research has been conducted to compare TnI level between normal and asphyxiated infants in Indonesia, therefore this study was conducted to measure and analyze the differences between cord blood TnI level of normal and asphyxiated infants, particularly in Hasan Sadikin Hospital Bandung.

Result of this study showed that the range and mean level of cord blood TnI in normal infants group was 618.22 - 1080.77 pg/mL and 819.88 pg/mL respectively. The mean value was within the range of blood TnI level of normal born babies as shown in a study conducted by Bader, *et al.* (2006), which ranged from 0 to 4300 pg/mL [27]. Study by Turker *et al.* (2005) also showed a similar case, with normal infant blood TnI level ranged from 0 to 1800 pg/mL [4].

Cord blood TnI level of asphyxiated infants group in this study ranged from 245.61 to 5018.87 pg/mL with a mean value of 1080.77 pg/mL. Although the mean level of cord blood TnI in asphyxiated infants group was within the range of normal infants as shown by Turker *et al.* (2005) and Bader, *et al.* (2006), however the range value of TnI level in this study was also equal to those in hypoxic infants as shown by Turker *et al.* (2004) *i.e.* 0 to 1100 pg/mL [28]. This study result showed a visible presence of top outliers above the value of umbilical cord blood TnI level which reached 5018.87 pg/mL. Although this value far exceeded the other mean values, other studies indicated the possibility of achieving TnI level of >5000 pm/mL, as shown by Turker *et al.* (2005), which is equal to 13,000 pg/mL.

In addition to the top outliers, this study result also indicated the presence of botom outliers. There were 2 cases of asphyxiated infants with minimum level of TnI (245.61 and 361.25 pg/mL) that was far from the mean level of TnI itself. This is probably due to the characteristics of CTG examination that is highly sensitive, but not necessarily reflect the accurate conditions of fetal asphyxia. This finding proved the high rate of false positives which often occur in the determination of fetal asphyxia diagnosis that is merely based on CTG examination.

Statistical analysis using the Mann-Whitney test (95% confidence level) gave a significance of 0.009. This value indicates that there was a significant difference in the mean of cord blood TnI level between normal and asphyxiated infants as the subjects of this study.

Similar results were also demonstrated by Turker *et al.* (2005). In their study, cord blood TnI level of critically ill infants like those who suffered acute respiratory distress, cardiac disorders, and pneumonia, was found higher than that of healthy infants [4]. Study by Trevisanuto *et al.* (2006) also indicated the same thing, which showed significant differences between cord blood TnI level in the healthy and asphyxiated infants [24]-[26].

To determine the baby condition, APGAR assessment was carried out immediately after delivery. APGAR scores were determined by evaluating five simple criteria including skin color, heart rate, reflex irritability, muscle tone, and respiration at the 1^{st} , 5^{th} , and 10^{th} minute after birth. Each criteria was assessed on a scale of 0 to 2, so that the APGAR scores were in the range of 0 to 10. Asphyxiated infants were indicated by APGAR score of <7.

APGAR scores of the 1st and 5th minute have been known to be a poor predictor of long-term neurological disorders [9]. Nevertheless, APGAR assessment is still done today because it is the simplest examination that can be conducted to assess infant asphyxia. Low APGAR score suggests that newborns experience asphyxia and require special medical treatment. Nonetheless, the APGAR score assessment is not designed to determine long-term prognosis of the neonates [23]. The APGAR score which remains below 3 in subsequent tests (10, 15, or 30 minutes) indicates that the baby may suffer long-term neurological disorder and the risk of brain damage.

In this study, it was known that 15 infants (83.33%) were asphyxiated in the 1st minute after birth, while only

5 infants (27.79%) were found to be asphyxiated in the 5^{th} minute after birth. The reduced number of asphyxiated infants in the 5^{th} minute was influenced by several factors, such as the increase of infant health condition due to neonatal resuscitation performed by the medical team after the APGAR 1' assestment. This finding has encouraged the use of APGAR 1' as the primary infant outcome assessment in this research to avoid neonatal resuscitation as confounding factor.

To identify the correlation between cord blood TnI level and APGAR score, Spearman correlation test was performed. Spearman Rank correlation coefficient showed the relationship between independent and dependent variables. In this study, the condition of the infants (normal or asphyxiated) was an independent variable, while the umbilical cord blood TnI level was a dependent variable. If the Spearman Rank correlation coefficient is positive, the value of dependent variable will increase along with the increasing value of independent variable. On the contrary, if the value of dependent variable increases along with the decreasing value of independent variable, the Spearman Rank correlation coefficient will likely be negative.

Based on the results of this study, the value of correlation coefficient between cord blood TnI level and APGAR score in the 1st and 5th minute after birth were as follows: rs = -0.523 (p = 0.026, p ≤ 0.05) and rs = -0.502 (p = 0.034; p ≤ 0.05) respectively. It shows that cord blood TnI level was negatively correlated with APGAR score. Increased infant APGAR score would result in decreasing level of cord blood TnI and vice versa. The p value of <0.05 indicates that there was a significant correlation between the two variables [29], *i.e.* umbilical cord blood TnI level and APGAR score.

Based on its value, Spearman Rank correlation coefficient is interpreted as very strong in the range of 0.80 to 1.00; strong in the range of 0.60 to 0.799; moderate in the range of 0.40 to 0.599; weak in the range of 0.20 to 0.399; and very weak in the range of 0.00 to 0.19929. In this study, the Spearman Rank correlation coefficient was interpreted as moderate, both for the 1^{st} and 5^{th} minute APGAR score.

Research conducted by Turker (2004) also showed the same thing. Cord blood TnI level had a correlation of -0.41 (p < 0.001; moderate correlation) toward APGAR score [28]. Lee *et al.* (2006) also conducted their research on the blood TnI level and APGAR score in asphyxiated infants. Although it did not show the correlation coefficient between blood TnI level and APGAR score, asphyxiated infant with or without multiorgan failure (MOF) had a mean APGAR score 1' of 2.10 (±1.66) and 3.12 (±1.59), compared with normal infants who had mean APGAR score of 5.01 (±2.01) [18]. Blood TnI level in that study was 0.036 ng/mL (±0.044), 84 pg/mL (±0.074); and 1287 pg/mL (±2.25) respectively for normal infants, asphyxiated infants without MOF, and asphyxiated infants with MOF. It shows that the increase of blood TnI levels occurs along with the decrease of APGAR score.

Based on the results of this study we concluded that the cord blood TnI level of asphyxiated infants was higher than that of normal infants, and there was a negative correlation between elevated level of cord blood TnI with APGAR score.

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