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Original Article

Triiodothyronine levels and mortality in children with sepsis and septic shock

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Abstract

Background Sepsis is the most common cause of death in infants and children. It can cause hormonal imbalances, such as euthyroid sick syndrome (ESS), which may increase the risk of death.

Objective To evaluate a possible correlation between the level of triiodothyronine (T3) and mortality in children with sepsis and septic shock.

Methods An observational cohort study was conducted on 80 children with sepsis and septic shock from October 2015 until January 2016 in Haji Adam Malik General Hospital, Medan, North Sumatera. Subjects underwent PELOD score and T3 examination on the first day admitted in Haji Adam Malik General Hospital. Chi-square test was used to analyze for a correlation between the T3 values and mortality.

Results Of the 80 consecutive subjects, 39 (48.75%) had low T3 level on the first day. Of these 39 children, 36 (92.3%) died. Subjects with low T3 level had a 6.31 times higher risk of mortality (PR 6.31; 95%CI 2.99 to 13.28; P<0.001). Of the 31 subjects with high PELOD score, 23 (74.2%) had decreased T3 (PR=2.27; 95%CI 1.45 to 3.57; P<0.001).

Conclusion Low T3 levels have significant relationship with mortality in children with sepsis and septic shock. **[Paediatr Indones. 2018;58:20-4 ; doi: http://dx.doi.org/10.14238/pi58.1.2018.20-4]**.

Keywords: *triiodothyronine; mortality; sepsis; septic shock; children*

Sepsis is the body's response to various systems of systemic inflammatory response syndrome (SIRS) with evidence of infection or suspected infection.[1-3] Sepsis is a common cause of death in infants and children. The incidence of severe sepsis and septic shock has risen in the past 30 to 40 years.[4] *The World Health Organization* (WHO) reported that 70% of the 8 million deaths of children under 5 years in developing countries was due to infectious diseases that mostly ended with sepsis. The incidence of sepsis worldwide reached 0.56 per 1,000 children and 5.6 per 1,000 babies with the presentation of deaths by 10.6 %.[5] *The 2007 Basic Health Research Report* showed that 20.5% of infant deaths was caused by sepsis.[6] In 2009, the Division of Pediatric Emergency, Department of Child Health, Cipto Mangunkusumo Hospital (RSCM), Jakarta, reported a sepsis incidence of 19.3% of 502 pediatric

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patients admitted to the pediatric intensive care unit (PICU), with a mortality rate of 10%.[7] Mortality due to neonatal sepsis in Haji Adam Malik General Hospital, Medan, from 2008 to 2010 was 32.9%.[8]

Hemodynamic disturbances occur in sepsis, such as cardiovascular and hormonal balance disorders. Hormonal changes that frequently occur in sepsis are often from the thyroid, in the form of euthyroid sick syndrome (ESS) or non-thyroidal illness syndrome (NTIS).[9] These syndromes are characterized by decreased levels of thyroid hormones, but without the impaired function of the thyroid hormone that occurs in non-thyroidal severe systemic disease. Changes in thyroid hormone eventually lead to impaired oxygen consumption and hematopoesis, as well as cardiovascular, sympathetic nervous, respiratory, and digestive system problems, which ultimately lead to organ system failure and death.[10] A Jakarta study in 2012 showed that thyroid hormone levels were low in a substantial group of patients before surgery. This abnormal thyroid hormone levels in this study group can be defined as euthyroid sick syndrome (ESS).[11]

Critical illness is characterized by the existence of complex and multiple changes in thyroid pathways. As the patient condition worsens, not only does triiodothyronine (T3) decrease, but thyroxine (T4) and thyroid stimulating hormone (TSH) also do. Decreased levels of T4 and TSH are an indication of worsening disease and poor prognosis, about 80% of subjects, especially in patients with T4 <3μg/dL. Decreased levels of thyroid hormones are still a matter of controversy to this day. Studies in Greece and the United States reported that decreased T4 and TSH levels affect mortality in sepsis and septic shock.[12,13] Study in the Netherlands reported that the decrease in T4 levels affects mortality, but studies in Belgium found that decreased levels of T3 affected mortality. Decreased T3 causes changes in thyroid hormone metabolism.[13-16] This study was aimed to evaluate a possible correlation between the level of triiodothyronine (T3) and mortality in children with sepsis and septic shock.

Methods

This cohort study was conducted in Haji Adam Malik General Hospital, Medan, North Sumatera, from October 2015 until January 2016. Eighty children with sepsis and septic shock aged 1 month to 18 years were evaluated. According to *Surviving Sepsis Campaigne*, sepsis was a systemic inflammatory response syndrome (SIRS) caused by infection, both proven by blood cultures and suspected clinical infection and septic shock was a condition due to severe sepsis resulting in disruption of several organs in the body accompanied by circulatory disorders. Normal level of T3 was 1.4 to 4 nmol/L, and PELOD score with high mortality was > 20 and low mortality was < 20.

Subjects were collected by consecutive sampling. The study was done by conducting interviews the parents to obtain the history of preceding illness. We assessed the degree of disease severity by *Pediatric Logistic Organ Dysfunction* (PELOD) score. Subjects underwent weight, body length, and laboratory parameter measurements (complete blood count/CBC, thyroid hormone, qualitative C-reactive protein/CRP, procalcitonin, and blood cultures). Examination of thyroid hormones on the first day and the fourth day admitted in Haji Adam Malik Hospital Medan was conducted. Patient monitoring was done within 7 days. Exclusion criteria were patients with hypothyroid and hyperthyroid disease. This study was approved by the Medical Ethics Committee of the University of Sumatra Utara Medical School.

The collected data were processed, analyzed, and presented by *SPSS software*. The significance level was P<0.05. Bivariate analysis (Chi-square test) was performed to assess for a correlation between thyroid hormone values and death. The correlation between thyroid hormone level and PELOD was analyzed by Mann-Whitney test.

Results

Eighty patients with sepsis (40 subjects) and septic shock (40 subjects) were included (**Table 1**). Of the 39 subjects that showed decreased T3, 36 (93.2%) did not survive (PR=6.31; 95%CI 2.99 to 13.28; P<0.001). The prevalence ration (PR) indicated that subjects with decreased T3 level had a 6.31 times higher chance of mortality (**Table 2**). Of the 31 subjects with high PELOD score, 23 (74.2%) had decreased T3 (PR=2.27; 95%CI 1.45 to 3.57; P<0.001). Statistical analysis indicated that subjects

with high PELOD scores had a 2.27 times higher chance of low T3 level.

Table 1. Demographic characteristics of subjects

Variables	Septic shock (n=40)	Sepsis (n=40)
Sex, n(%)		
Male	23 (57.5)	23 (57.5)
Female	17 (42.5)	17 (42.5)
Mean age (SD), years	8.15 (5.81)	7.6 (5.33)
Length of stay, n(%)		
< 7 days	19 (47.5)	18 (45)
> 7 days	21 (52.2)	22 (55)

Table 2. Relationship between decreased T3 level with mortality

PELOD score, n(%)	Decreased T3		PR (95%CI)	P value
	Yes (n=39)	No (n =41)		
High	23	8 (25.8)	2.27	< 0.001[a]
Low	16	33 (67.3)	(1.45 to 3.57)	

[a]Chi-square test

Table 3. Relationship between PELOD score and decrease in T3 level

PELOD score, n(%)	Decreased T3		PR (95%CI)	P value
	Yes (n=39)	No (n =41)		
High	23	8 (25.8)	2.27	< 0.001[a]
Low	16	33 (67.3)	(1.45 to 3.57)	

[a]Chi-square test

Discussion

At the beginning, a decrease in T3 occurs due to a defect of enzyme 5'-deiodinase that converts T4 to T3, a decrease in the number of thyroid receptors that are mediated by interleukin 1β and their thyroid binding protein inhibitor, as well as an increase in TNF-α during the critical illness.[17] This T3 decrease early in infection (36-72 hours) is followed by a TSH increase due to peripheral thyroid hormone. This feedback mechanism is called the restoration of metabolic activity, and it is responsible for returning T3 levels to normal.[18] These T3 fluctuations are consistent with a study in the Netherlands which found that 44 children in PICU with low T3.[12] Similarly, we found decreases in T3 and T4 levels, followed by an increase in TSH thyroid axis, called euthyroid sick syndrome.

A Turkish study in 2004 showed a decrease in T3 and T4 in sepsis patients.[19] Another study in Jakarta in 2014 showed that thyroid hormone declined in patients with sepsis, especially T3 values.[20] In our study, 80 children with sepsis and septic shock had their T3 levels measured on the first day and the fourth day of hospitalization. We found decreased T3 in the sepsis and septic shock groups at both days.

In adult patients with serious illness, euthyroid sick syndrome can be used to predict the severity of disease; however, in the pediatric population, there is a lack of data on changes in thyroid hormones, as a predictor of disease severity. Some studies have shown that major changes in thyroid hormone levels indicate severity of illness and rates of survival.[24]

Changes in thyroid hormone will always appear in patients with serious illness as a favorable adaptation response and without intervention. In the acute phase (within 24 hours after infection), enzyme dysfunction D2 and D3 which causes the increased in activity of T3 is not formed; in this condition, more T4 is converted to inactive T3. In a chronic or severe acute condition, central dysfunction of the hypothalamus occurs. This situation is temporary, generally lasting 36-72 hours, and normalizing again after 72 hours, along with recovery from illness.[25] In our study, we found that the decrease in T3 levels of patients with sepsis can occur within a few hours during the acute phase.

T3 hormone plays a role in DNA replication and binds to the D3 enzyme to forestall cell apoptosis. The reduction in T3 leads to increased levels of D3 free-enzyme and apotosis of cells. Poor outcomes may result from this aggravating of the disease condition.[26]

A Dutch study showed that low thyroid hormone in critically ill patients can cause death.[27] Also, a study in Turkey reported that the levels of T3, T4, FT3 and FT4 were lower in children with septic shock, compared to sepsis-related mortality of patients with sepsis.[18] In addition, a European study in 2011 showed that the decrease in thyroid hormones was related to patient prognosis in those with sepsis or septic shock, although not always consistent.[28] A Semarang study showed no significant difference in the levels of thyroid hormone in sepsis patients with mortality.[29] However, a 2014 Jakarta study showed that thyroid hormone

declines in septic patients, especially the value of T3. High PELOD value can be used as a prognosticator in PICU cases of sepsis, despite the lack of a relationship between PELOD and decreased thyroid hormone levels.20 In our study, there was significant correlation of T3 impairment with death. Of the 39 subjects with decreased T3 levels, 36 (92.3%) of them died (PR= 6.31; 95%CI 2.99 to 13.28; P<0.001), which indicated that children with decreased T3 level had a 6.31 times higher chance of mortality.

In patients with severe sepsis and septic shock, FT4 and TSH levels decline because the decrease in plasma thyroxine-binding globulin (TBG) eventually decreases thyroid binding plasma capacity.[13] In our study, all subjects sepsis levels were ignored and the ratio of rT3/T3 and the inotropic agents were not considered. Dopamine has a suppressive effect on pituitary TSH secretion, by directly inhibiting pituitary function through dopamine inhibitor receptors, which causes the decrease in TSH secretion.[30]

Prognostic accuracy of death in critically ill patients treated in the ICU has several advantages. *The Acute Physiology and Chronic Health Evaluation* (APACHE) II has generally been used as a method of prognostic outcome in ICU patients. This measurement does not assess the hormonal response to the underlying disease, especially cortisol and thyroid hormone concentration, which have been significantly associated with mortality in critically ill patients. Mortality in ICU patients is best predicted by a combination of T3 and TSH levels, and APACHE II scores determined at the time patients are sent to the ICU.31 However, we used PELOD score to predict mortality: 31 subjects had high PELOD scores and 23 of them (74.2%) had decreased T3 levels compared to 51.25% in those with low PELOD scores (PR=2.27; 95%CI 1.45 to 3.57; P<0.001). These results indicated that children with high PELOD scores had a 2.27 times higher chance decreased T3, compared to those who had low PELOD scores.

The limitations of our study were not distinguishing the degrees of sepsis, not counting the rT3/T3 ratio, and not taking into account the use of inotropes.

In conclusion, low T3 levels have significant relationship with mortality in children with sepsis and septic shock.

Conflict of Interest

None declared.

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