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Original Article

Thyroid hormone profile and PELOD score in children with sepsis

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Abstract

Background Thyroid hormonal dysfunction, also known as euthyroid sick syndrome or nonthyroidal illness, can be seen in sepsis. There have been few studies on thyroid hormone dysfunction in septic children, as well as on a relationship between their thyroid hormone profiles and pediatric logistic organ dysfunction (PELOD) scores. Procalcitonin (PCT) is one of the sepsis biomarker.

Objective To evaluate the thyroid hormone profile in children with sepsis as well as to assess for a correlation between the thyroid levels and PELOD scores, PCT levels, and patient outcomes.

Methods This cross-sectional study included children aged 1-18 years admitted to the pediatric intensive care unit (PICU) with a primary diagnosis of sepsis. PELOD scores and thyroid hormonal levels were assessed once during the first 24 hours after PICU admission.

Results Thirty subjects were included in the study. The median values of T3, free T4, and TSH were 45 (range 17-133) ng/dL, 0.81 (range 0.3-1.57) ng/dL, and 1.36 (range 0.05-7.78) μIU/L, respectively. The T3, free T4, and TSH levels were decreased in 97%, 50% and 40% of the subjects. There were no significant differences between low and normal to high TSH with regards to the PELOD score (P=0.218), PCT level (P=0.694), or patient outcomes (P=0.55). The risk of death increased by 15 times among the subjects with PELOD score $\geq$20 compared to those with PELOD score <20 (OR 15; 95%CI: 1.535 to 146.545; P=0.012).

Conclusion Thyroid hormones are decreased in septic children with the majority having low T3. A high PELOD score is strongly correlated with mortality and can be used as a prognostic parameter for septic children in the PICU, but there is no correlation with decreased TSH. **[Paediatr Indones. 2014;54:245-50.]**

Keywords: *euthyroid sick syndrome, nonthyroidal illness, sepsis, procalcitonin, thyroid, PELOD, PICU*

Sepsis remains a major cause of morbidity and mortality among children. Sepsis is a clinical syndrome involving a deleterious host response to an infection.[1] In 1991, Sepsis was defined to comprise of clinical evidence of infection: tachypnea, tachycardia, hypothermia or hyperthermia.[2] In 2002, the *International Pediatric Sepsis Consensus Conference* defined sepsis as a systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection.[3]

Thyroid hormone has an important role in the regulation of metabolic homeostasis. Altered thyroid function in critical illness is known as the sick euthyroid syndrome or nonthyroidal illness. The most common finding is reduced T3 level, while T4 and free T4 levels may also be reduced in more severe illness.[4] The reduction in the levels of T3 and T4 is proportional to the severity of illness and may serve as a predictor of poor outcomes in critically ill adult patients.[5,6,7]

The *2001 Society of Critical Care Medicine*, the *European Society of Intensive Care Medicine*, the *American College of Chest Physicians*, the

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American Thoracic Society, and the *Surgical Infection Society International Sepsis Definition Conference* suggested that PELOD score could be used to measure the severity of organ dysfunction over the course of critical illness in children.[8] PELOD score and delta PELOD (dPELOD) scores are valid outcome measures of the severity of multiple organ dysfunction syndrome in the PICU.[9]

The aims of this study were to evaluate the thyroid profile in septic children admitted to the PICU, as well as to assess for a correlation between thyroid profiles and PELOD scores, procalcitonin (PCT) levels, and patient outcomes (survival). Furthermore, we aimed to assess for a correlation between PELOD score and survival.

Methods

We conducted the study during a 6-month period from June to November 2009 in the PICU at Dr. Cipto Mangunkusimo Hospital (a tertiary teaching hospital). Thirty subjects were included in the study. All subjects were diagnosed with sepsis based on *International Pediatric Sepsis Consensus Conference 2002* criteria and were confirmed by the Pediatric Intensivist. We included patients whose procalcitonin level was $\geq$ 2ng/mL and those with positive blood culture examinations. We excluded patients with neuroendocrine problems (such as thyroid hormone dysfunction, diabetes, or adrenal insufficiency), head trauma, history of thyroid hormonal therapy, or congenital anomalies.

The study protocol was approved by the Ethics Committee of the University of Indonesia Medical School/Dr. Cipto Mangunkusumo Hospital and written informed consent was obtained from the parents.

PELOD scores[9] were obtained along with blood examinations during the first 24 hours after PICU admission. PELOD score is used to evaluate the degree of organ failures. Each organ failure will be scored between 0 to 20 and the total maximum of PELOD score is 70.[10]

The T3, free T4, and TSH levels were measured using an *ADVIA Centaur* T3 assay, FrT4 assay, and TSH-3 assay, a competitive immunoassay using direct chemiluminescent technology. The *ADVIA Centaur* T3 assay measured T3, free T4, and TSH concentrations up to 8 ng/mL (12.3 nmol/L), 12.0 ng/dL (155 pmol/L), and 150 μIU/mL, respectively, with a minimum detectable T3, free T4, and TSH concentration (analytical sensitivity) of 0.1 ng/mL (0.15 nmol/L), 0.1 ng/dL (1.3 nmol/L), and 0.004 μIU/mL, respectively. The reference values of TSH, T3 and fT4 can be seen in **Table 1**.[11]

Table 1. Normal value of thyroid hormones

Thyroid hormones	Normal level
TSH (1 – 18 year)	0.7 – 6.4 µIU/L
T3	
1 – 5 year	100 – 260 ng/dL or 1.54 – 4 nmol/L
5 – 10 year	90 – 240 ng/dL or 1.39 – 3.70 nmol/L
10 – 15 year	80 – 210 ng/dL or 1.23 - 3.23 nmol/L
>15 year	115 – 190 ng/dL or 1.77 – 2.93 nmol/L
Free T4	
Infants	0.9 – 2.6 ng/dL or 12 – 33 pmol/L
Pre-pubertal	0.8 – 2.2 ng/dL or 10 – 28 pmol/L
Pubertal	0.8 – 2.3 ng/dL or 10 – 30 pmol/L

Procalcitonin (PCT) was measured using *VIDAS® BRAHMS PCT*, an automated test for use on the VIDAS instruments to measure human procalcitonin in serum or plasma (lithium heparinate) using an enzyme-linked flourescent assay (ELFA) technique. The *VIDAS® BRAHMS PCT* measurement range was 0.05 – 200 ng/mL with a coefficient of variation (functional detection limit) of 0.09 ng/mL. Blood cultures were examined using *Pediatric BACTEC*. Procalcitonin $\geq$2 ng/mL was considered as sepsis.

The minimum number of required subjects was calculated to be 40, using an estimation of proportion in the population.[12] Statistical analysis was performed using the SPSS version 16 program.

Results

Thirty children were included in the study, with 14 girls and 16 boys. Subjects' mean age was 64.7 (SD 58.216) months. More than half of the subjects were 1 to 4 years of age. Most patients (23/30) stayed in the PICU for at least 7 days. More than half of subjects were on mechanical ventilators and 14/30 died. (**Table 2**).

High PELOD scores ($\geq$20) were observed in 7/30 of the subjects and 20/30 of subjects had high

PCT levels (≥10ng/mL). The median values of T3, free T4 and TSH levels were 45 (range 17-133) ng/dL, 0.81 (range 0.3-1.57) ng/dL, and 1.36 (range 0.05-7.78) μIU/L, respectively. All but one subject had decreased T3 levels. Low free T4 levels were seen in 15/30 of subjects, and low TSH levels were seen in 12/30 subjects. Bacterial growth in blood cultures was found in 9/30 subjects. (**Table 3**).

Seven subjects had only low T3, 10 subjects had low T3 and low free T4, 7 subjects had low T3 and low TSH, 5 subjects had low T3, low free T4, and low TSH, and 1 subject had high TSH. (**Figure 1**).

Pearson Chi square test revealed no significance difference in the PELOD score between the group with decreased TSH levels (low T3 level, low free T4/low TSH levels, and low T3/low TSH levels) and the group with normal TSH levels (low T3 levels, low T3/low free T4 levels) (P=0.218). There were also no significant differences between the two groups with regards to PCT levels (P=0.694) and survival rate (P=0.55). (**Table 4**). The risk of death increased by 15 times among the subjects with PELOD scores ≥20 compared to those with PELOD scores <20 (P=0.012) (**Table 5**).

Table 2. Characteristics of subjects

Characteristic	n=30
Gender	
Male	16
Female	14
Age group	
1 – 4 years	17
5 – 9 years	7
≥10 years	6
PICU length of stay	
1 – 3 days	9
4 – 7 days	13
≥8 days	8
On ventilator	
Yes	17
No	13
Patient outcomes	
Survived	16
Died	14

Table 3. Distribution of thyroid profiles, PCT level, and blood culture

	n=30
PELOD Score	
<20	23
≥20	7
Procalcitonin, ng/mL	
>2 - < 10	10
≥10	20
T3 value, ng/dL	
Low	29
Normal*	1
Free T4 value, ng/dL	
Low	15
Normal	15
TSH value, μIU/L	
Low	12
Normal	17
High	1
Blood Culture	
Positive	9
Sterile	21

T3: triiodothyronine, fT4: free thyroxine, TSH: thyroid stimulating hormone

Table 4. Correlations between the groups of decreased TSH with PELOD score, procalcitonin level and patient outcomes

	Group A n=17	Group B n=12	P value
PELOD score			
<20	14	7	0.218#
≥20	3	5	
Procalcitonin level			
<10 ng/mL	6	3	0.694#
≥10 ng/mL	11	9	
Patient outcomes			
Survived	8	7	0.55*
Died	9	5	

Group A (subjects without decreased TSH: low T3 alone and low T3/low free T4). Group B (subjects with decreased TSH: low T3/low free T4/low TSH and low T3/low TSH). One subject with high TSH was excluded from the statistical analysis.

#Statistical significance between the groups of decreased thyroid hormone with PELOD score and PCT state by Fisher's exact test analysis.

*Statistical significance between the groups of decreased thyroid hormone with outcome state by Pearson Chi-square analysis.

Table 5. Correlation between PELOD score and patient outcomes

	Survived	Died	OR (95% CI)	P value
PELOD Score				
<20	15	7	15 (1.535 to 146.545)	0.012
≥20	1	7		

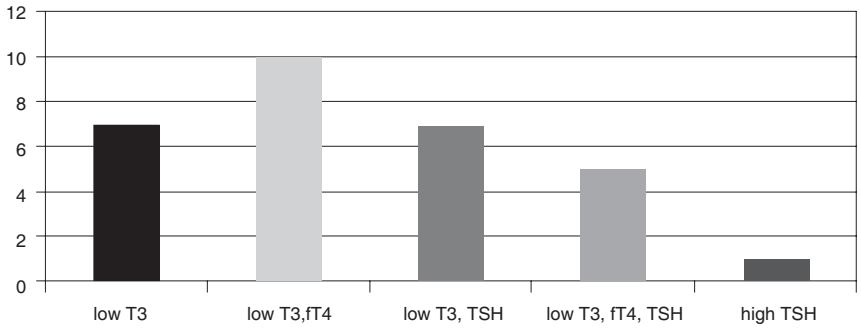

Figure 1. Thyroid hormone dysfunction

Discussion

Euthyroid sick syndrome or nonthyroidal illness is seen in severe illness, sepsis, or septic shock. We found that T3, free T4, and TSH levels were decreased in 97%, 50%, and 40% of our subjects.

A limitation of this study was the small number of subjects. Also, thyroid hormone and PCT levels as well as PELOD scores were examined only once during the study. These values are dynamic and influenced by many factors, such as those relating to the host, infectious agents, and the environment.

Thyroid hormone dysfunction was found in all subjects except one subject with high TSH (**Figure 1**). Our classification differed from that of Chopra who grouped his patients into the following: low T3 syndrome, low T3/low T4 syndrome and high T4 syndrome.[7] A study found that all septic pediatric subjects had decreased T3 when sepsis was caused by meningococcal infection, but none of the subjects had increased TSH.[13] Another study found that 48% of adult patients with sepsis had decreased T3 and T4, but normal TSH was seen in all subjects.[14]

A study found that a PELOD score of 17.6 predicted dysfunction in 3 organs with a 10% risk of mortality. If the PELOD score increased to 24.5, the number of organs with dysfunction increased to 4 and the risk of mortality increased to 19%.[9] Thukral *et al.* found that the mortality rate increased from 6.25% in 1 organ dysfunction to 15.7% in 2 organ dysfunction and to 100% in 6 organ dysfunction.[15] The PELOD score cut off used in our study was 20 with at least ≥2 organ dysfunction and about 15% risk of death. We found no correlation between decreased thyroid hormone and PELOD score. Similarly, Hebbar *et al.* found that PELOD score and Pediatric Risk of Mortality III (PRISMS III) were not correlated with neuroendocrine dysfunction (adrenal insufficiency and low T3 syndrome).[16]

Procalcitonin is a sepsis biomarker. Reported cut off values for procalcitonin in sepsis vary. Ray *et al.* used a cut off of >1.1 ng/mL procalcitonin in sepsis.[17] Arkader *et al.* found that ≥2 ng/mL procalcitonin had a sensitivity of 88% and specificity of 100% with positive predictive value of 100 and negative predictive value of 86 for sepsis. The sensitivity decreased to 41% but the specificity remained 100% if the cut off for sepsis was increased to 5 ng/mL.[18] The cut off for procalcitonin in sepsis and septic shock were 2 ng/mL and 10 ng/mL, respectively, in the study done by Fioretto *et al.*[19] Casado-Flores *et al.* found that ≥10ng/mL procalcitonin (PCT-Q semiquantitative) had 100% sensitivity to predict multiple organ failure and mortality.[20] We used a cut off of ≥10 ng/mL procalcitonin, and found no correlation between the groups with decreased thyroid hormone and procalcitonin (P=0.694).

Thyroid hormones decrease during sepsis. In the beginning of illness, the T3 level decreases. The prognosis is poor if T4 or free T4 also decreases and poorer still if the TSH level decreases.[21,22,23] We found no correlation between the groups of decreased TSH and survival (P=0.55).

PELOD score is a valid measure of the severity of multiple organ dysfunction syndrome in pediatric intensive care units.[9,10] We found that the risk of death increased by 15 times in subjects with PELOD score ≥20 compared to those with PELOD score <20, further validating the use of the PELOD scoring to determine the risk of death in septic children.

In conclusion, thyroid hormones are decreased in septic children with the majority having low T3 levels. There is, however, no correlation between TSH level and PELOD score, procalcitonin level or patient outcomes.

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