



## The relationship between thyroid hormones and procalcitonin with neonatal sepsis: a case-control study in Iran in 2017

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### Abstract

**Background and Objective:** Neonatal sepsis (NS) is a major cause of mortality and morbidity in neonates. Correct and early diagnosis of NS can prevent its complications. The aim of this study was to investigate the relationship between the levels of thyroid hormones and procalcitonin (PCT) with NS.

**Materials and Methods:** In this case-control study, 40 term neonates with proven NS diagnosis and 40 term neonates whose NS were rejected due to negative paraclinical findings were compared in terms of thyroid hormone levels, PCT and C reactive protein (CRP). Data were analyzed using SPSS v.17.

**Results:** The most common clinical finding was fever in both groups, while there was no significant difference between the two groups ( $P = 0.1$ ). The results of laboratory tests showed that the CRP levels in the NS group were significantly higher than the control group ( $P = 0.03$ ). In terms of thyroid hormones, although TSH and T4 were higher in the NS group, this difference was not statistically significant ( $P = 0.94$  and  $P = 0.22$ , respectively). In addition, PCT measurements and comparisons showed that this parameter was significantly higher in the NS group ( $P = 0.01$ ).

**Conclusion:** The results of this study demonstrated that CRP and PCT levels in NS neonates were significantly higher than non-NS neonates, while there was no significant difference in the level of thyroid hormones in the two groups. Further studies are recommended in this area.

**Keywords:** Neonatal sepsis, Thyroid hormones, Procalcitonin, C-Reactive protein, Diagnosis

### 1. Introduction

Bacterial infections are a common and important cause of mortality and disability in the neonatal period. Sepsis is bacteremia associated with systemic symptoms that can lead to organ dysfunction and death. Neonatal sepsis (NS) occurs following a bacterial infection in the first month of life, which is a major cause of death and morbidity (1). About 40% of neonatal deaths are due to NS (2). In advanced countries, the prevalence of NS is 1 to 4 per 1,000 live births. But in developing countries, it is reported almost 10 times of that proportion (3,4). Clinical symptoms of NS are very diverse. In studies

in Iran, respiratory distress, poor feeding, fever, lethargy, hyporeflexia, jaundice, tachypnea, and cyanosis are the most common clinical findings of NS (5,6). A wide range of non-specific symptoms may cause the diagnosis to be difficult. The definitive diagnosis of NS is based on positive blood culture in the presence of clinical symptoms (7). Non-specific symptoms of NS in neonates and delayed onset of treatment are associated with high mortality, therefore empiric antibiotic therapy should be undertaken (8). The selection of appropriate antibiotics depends on the epidemiology of common organisms in each region. Inappropriate selection of antibiotics, in addition to

lack of proper response, may cause antibiotic resistance (9,10). Total leukocyte count, absolute neutrophil count and immature-to-total neutrophil ratio can help to diagnose NS (11). Some sources emphasize the use of C-reactive protein (CRP) in addition to other tests, such as absolute neutrophil counts for the definitive diagnosis of sepsis (12). But CRP would become positive about 10 to 12 hours after infection, and CRP is also increased in many other situations, which is a defect in this biomarker (13). Procalcitonin (PCT) is the prohormone of calcitonin and an acute phase reactant produced by the C cells of thyroid gland. PCT does not have hormonal activity and in healthy people it is less than the extent to which it can be measured. High concentrations of PCT are also produced by monocytes and hepatocytes 2 to 4 hours after exposure to a bacterial pathogen during the acute phase of sepsis (11). PCT levels get peak after 6 to 8 hours and remain high for 24 hours. Also, the results of studies indicate that the initiation of antibiotic therapy does not reduce the value of PCT test for NS diagnosis (14), so PCT may be more valuable than CRP for the early diagnosis of acute sepsis (15). Thyroid hormones play a controlling role in stress and severe conditions such as trauma or sepsis in the body. The results of studies indicate that in the acute conditions, TSH, T4 and T3 levels decrease (16). It has recently been stated that immune system cells can affect the activity of thyroid hormones and it seems that TSH receptors are affected by the activity of various types of immune cells (17, 18). It has also been reported that in non-thyroid origin, low levels of thyroid hormones are associated with poor prognosis and high mortality (19). Therefore, it is hypothesized that thyroid hormones may change in conditions like NS. Considering the limited researches done especially in Iran, the aim of this study was to evaluate the levels of thyroid hormones and PCT in neonates suspected to NS.

## 2. Materials and Methods

### 2.1. Study design

The current case-control study was conducted on term neonates (gestational age >37 weeks) weighing >2500 g (20) hospitalized due to primary diagnosis of NS at Khatam-al-Anbia hospital in Tehran (Iran) from January to June 2016 with their parents' consent. The subjects with congenital and genetic defects and those of mothers with thyroid disorders and mothers receiving magnesium sulfate or oxytocin before delivery were excluded from the study. Infants who had clinical symptoms associated with sepsis such as fever, tachypnea, poor feeding, hyporeflexia with at least one paraclinical finding indicating sepsis such as chest radiography with pneumonia symptoms, positive blood culture, positive lumbar puncture or positive urine culture were selected as the case group. Other

neonates who had symptoms of NS, but paraclinical findings of sepsis were negative, were considered as case group.

### 2.2. Ethical consideration

The researchers were committed to the ethical guidelines of the Declaration of Helsinki. Ethical approval for the study was obtained from the Institutional Review Board at Shahed University. Signed consent forms were also obtained from all parents of neonates.

### 2.3. Study outcomes

Prior to the administration of empirical antibiotic, 4 ml of venous blood sample was taken from each neonates. Latex agglutination technique with specific measuring kit (Ziest Chem Diagnostics, Tehran, Iran) was used to measure the quantitative amount of CRP. PCT was also measured using ELISA kit. In addition, the levels of thyroid hormones were measured through the immunochemiluminescent method.

### 2.4. Statistical analysis

Data were analyzed by SPSS software version 17 (SPSS Inc., Chicago, IL, USA). First, the normal distribution of data was determined by Kolmogorov-Smirnov test, and then the central and descriptive indicators were calculated and expressed. In addition, independent t-test or Mann-Whitney test were used depending on the distribution of samples. Significant value for all analyses were appointed at  $P < 0.05$ .

## 3. Results

In this study, 40 neonates with proven NS according to positive paraclinical findings and 40 neonates whose NS were rejected in them due to negative paraclinical findings, were compared in terms of demographic characteristics and thyroid hormone tests, PCT and CRP. The most common clinical finding was fever in both groups, while there was no significant difference between the two groups ( $P = 0.1$ ) (Table 1).

**Table 1.** Clinical findings in NS and control groups

	NS Group (n=40)	Control Group (n=40)	P value
Fever	14 (35%)	12 (30%)	0.1
Respiratory distress	12 (30%)	13 (32.5%)	
Hypotonia	5 (12.5%)	4 (10%)	
Poor feeding	4 (10%)	6 (15%)	
Jaundice	4 (10%)	5 (12.5%)	
Bradycardia	1 (2.5%)	0 (0%)	

The case group consisted of 17 boys (42.5%) and 23 girls (57.5%) and control group consisted of 19 boys (47.5%) and 21 girls (52.5%) ( $P < 0.05$ ). The mean age

of neonates in the case group was  $3.12 \pm 1.68$  days and in the control group was  $3.27 \pm 1.69$  days, which was not statistically significant in two groups ( $P=0.69$ ). The mean birth weight in the case and control groups was  $3229.75 \pm 236.86$  and  $3260 \pm 232$  grams, respectively. There was no significant difference between the birth weight of neonates in both groups ( $P=0.54$ ). Also, the gestational age in the case group was  $37.85 \pm 0.76$  and in the control group was  $38 \pm 0.78$ . This parameter was not significantly different between the two groups ( $P = 0.39$ ) (Table 2).

The results of laboratory tests showed that the CRP levels in the case group were significantly higher than the control group ( $P=0.03$ ). In terms of thyroid hormones, although TSH and T4 were higher in the case group, this difference was not statistically significant ( $P=0.94$  and  $P=0.22$ , respectively). In addition, PCT measurements and comparisons showed that this parameter was significantly higher in the case group ( $P = 0.01$ ) (Table 2).

**Table 2.** Basic characteristics and laboratory findings in NS and control groups

	NS Group (n=40)	Control Group (n=40)	P value
Age (day)	$3.1 \pm 1.26$	$3.1 \pm 2.76$	0.69
Birth Weight (gram)	$3229.23 \pm 75.8$	$3260.01 \pm 23.2$	0.54
Gestational Age (week)	$37 \pm 8.57$	$38.78 \pm 9.21$	0.39
CRP	$2.32 \pm 1.17$	$1.64 \pm 0.98$	0.03
PCT	$2.09 \pm 2.79$	$1.35 \pm 1.94$	0.01
TSH	$4.62 \pm 3.82$	$3.79 \pm 2.09$	0.94
T4	$9.16 \pm 2.47$	$8.41 \pm 2.95$	0.22

#### 4. Discussion

The aim of this study was to compare PCT levels and thyroid hormones in NS and non-NS neonates. The results of this study showed that the most common clinical finding in both case and control groups was fever, followed by respiratory distress and other clinical findings including hypotonia, poor feeding, jaundice and bradycardia, while difference between the two groups was not statistically significant. Of course, as mentioned, the NS symptoms are very diverse and non-specific. In other studies, in addition to the symptoms of patients in this study, tachycardia, tachypnea, lethargy, and cyanosis in neonates with NS have been reported that the variety of clinical findings and non-specificity in this study were consistent with the results of other studies (5,6). Therefore, diagnosis should not be limited to clinical symptoms, and more evaluation in suspected NS is important. Therefore, due to the variety of nonspecific clinical symptoms, laboratory tests can be helpful before starting empirical antibiotics. The results of the laboratory tests in this study showed that CRP levels in the NS group were significantly higher than the non-NS group. The results of a study

conducted by Pravin Charles et al in 2018 (11) on 75 suspected NS neonates showed that CRP levels were significantly higher in neonates with proven NS, which is similar to the results of this study. Also, the results of a study by Adib et al (21) in Iran were consistent to the results of the present study. In addition, Mohsen et al (22) in 2015 reported that CRP levels were significantly higher in neonates with proven NS. Also, Park et al (23) concluded that CRP levels were significantly associated with the incidence of NS. The results of these studies are consistent with the results of present study. However, as previously mentioned, CRP levels may increase by about 10 to 12 hours after infection, or in conditions other than NS, which may cause the diagnosis to be difficult (13). Therefore, in this study, another marker of NS was investigated. Measurement and comparison of PCT in both groups showed that this parameter was significantly higher in the NS group.

Memar et al. (24) in Iran also described PCT as a predictive factor for NS. Similar to the results of this study, Mohsen et al. (22) also found a significant positive correlation between incidence of NS and PCT levels and reported that PCT showed a higher sensitivity when compared to CRP. In addition, Yu et al (25) reported that PCT's accuracy in detecting NS is higher than CRP. In the present study, the significance level regarding PCT was lower than CRP, which is consistent with the results of two mentioned studies. Similar results were also found in the Charles et al (11) study, although they concluded that PCT may not be adequately used as a single marker of NS compared to CRP. Similar to the results of present study, the PCT level was associated with the incidence of NS in Park et al. study (23). Although despite to the results of present study, they reported that PCT is a highly effective early diagnostic marker of neonatal infection, however, it may not be as reliable as CRP. Although the results of these two tests are different in definitive diagnosis of NS, overall, the results of the recent studies indicate that PCT has high sensitivity and specificity in the detection of NS (12), especially when measured with CRP (26,27). In addition, the results of meta-analyses in this regard recently showed 85% and 54% of sensitivity and specificity of the PCT test respectively (28), while in another study, sensitivity of PCT was higher than CRP (85% vs. 71%) (29), which is partly consistent with the results of this study. Regarding thyroid hormones, the results of this study showed no significant difference between the two groups in terms of TSH and T4. Similar to the results of the present study, Sharma et al (30) showed no significant difference in terms of TSH, but despite to the results of this study, T4 levels were significantly lower in neonates with NS, while paradoxically, T4 was even higher in neonates who died due to NS. In addition, the results of study conducted by Kurt et al (31) on 292 neonates with NS showed that T4 and TSH levels in neonates with proven NS were higher

than non-NS neonates. Differences in the results of the present study may be due to a lower sample size. Also, in the study of Yildizdas et al (32), T4 levels were lower in neonates with septic shock and NS, but no significant difference was observed in terms of TSH, which is consistent with the results of this study. Considering the differences in the results of the present study and the other studies in this regard, it seems that the value of thyroid hormones level in determining the NS remains uncertain, so it is recommended that systematic review and meta-analysis or more studies with a larger sample size be done.

## Conclusion

The results of this study demonstrated that CRP and PCT levels in NS neonates were significantly higher than non-NS neonates, while there was no significant difference in the level of thyroid hormones in the two groups. Further studies are recommended in this area.

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## Conflict of interest

The authors declared no conflict of interest.

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