

The Relationship between Thyroxine Level and Short Term Clinical Outcome among Sick Newborn Infants

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Abstract- Premature and critically sick infants frequently experience several interventions, including blood transfusions, parenteral nutrition, and prescriptions during hospitalization that could affect the result of thyroid function test. This study aims to investigate the correlation between thyroxine level and clinical short term outcome among the newborn infants in the neonatal intensive care unit (NICU). We assessed serum levels of thyroxine and thyroid stimulating hormone of 99 neonates who were admitted in the NICU from September 1st 2004 to March 30th 2005. Number of patients with low thyroxin level (less than 6.5 µg/dl) was determined and the relation between serum total thyroxine level and birth weight, gestational age, duration of hospitalization, clinical diagnosis, and final outcome was investigated. Short term outcome was considered as duration of hospitalization and discharge alive from hospital. Prevalence of hypothyroxinemia was 26 percent. Later assessment of thyroxine level within 3 weeks revealed normal level of this parameter (8.12 µg/dl ±1.36). Patients with lower gestational age and lower birth weight had lower thyroxine level (7.15 µg/dl ±2.56, and $P=0.03$, 6.72 µg/dl ±3.03, and $P=0.08$). Low thyroxine level was not associated with adverse short-term clinical outcome (mortality rates: 3(11%) and 9(12%), and duration of hospitalization among 17.7±9.8 vs 16.7± 13.0 in patients with hypothyroxinemia and low thyroxine level respectively). Hypothyroxinemia has considerable prevalence in neonatal intensive care setting and is related with lower birth weight and gestational age. Whether thyroxin levels are a marker or mediator of short term clinical outcome remains to be determined by further studies.

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Introduction

The role of thyroid hormones in neurologic development of newborn infants has been elucidated and the absence of adequate thyroid hormones as occurs in congenital hypothyroidism result in adverse neurodevelopmental outcome like mental retardation (1,2). Currently the neonatal screening of congenital hypothyroidism is performed in all developed countries as well as a few developing countries (1). Apart from congenital hypothyroidism it has been noticed that a considerable percent of preterm and sick newborns have low thyroxine levels without an increase in thyroid

stimulating hormone (TSH) level (2-5). This problem mostly resolves within 3 to 8 weeks (4,5).

Some consequences like increased mortality, abnormalities in head ultrasound, cerebral white matter damage, and increased rescue interventions in the ventilated neonates have been reported that can be related with hypothyroxinemia in preterm infants (6-8). However, there are a few studies that have revealed close relation between neonatal hypothyroxinemia and later neurodevelopmental outcomes (9-12).

There are numerous factors that can alter thyroid hormone values among critically ill neonates. These factors include but are not limited to prematurity, low

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birth weight, exposure to some drugs, and presence of certain diseases (2,9,12-14).

In this study we surveyed the thyroid function tests of the newborns at the neonatal intensive care unit of the Children's Medical Center to determine the prevalence of hypothyroxinemia and also to investigate the relationship between thyroxine level and short-term clinical outcome.

Patients and Methods

In a cross-sectional study to explore the association between thyroxine level and clinical short-term outcome, we investigated the results of thyroid function tests of neonates admitted to the NICU at the Children's Medical Center- a referral teaching hospital with tertiary care set up, affiliated with Tehran University of Medical Sciences. The study duration was September 1st 2004 till March 30th 2005. This study was approved by the ethics committee of the university. All of the newborn infants who were admitted to the NICU during this period except those with multiple congenital anomalies were recruited in the study. Newborns were divided by their gestational ages and their birth weights. The gestational age was defined as less than 34, between 34 to 37, and more than 37 weeks of gestation. Birth weight was categorized as: normal (equal or greater than 2500 grams, 1500 to 2500 grams (low birth weight [LBW]), and less than 1500 grams (very low birth weight [VLBW]). Unfortunately, there was no established national screening program of congenital hypothyroidism for Iranian neonates at the time of this study. The Children's Medical Center's NICU routinely measures serum thyroxine and TSH for all admitted neonates on the third day of life or during initial routine paraclinical studies upon their admission. One ml of blood is obtained from venous puncture of each neonate to monitor total thyroxine value of serum and TSH with other blood tests simultaneously. The assessment was performed via immunoradiometric assay (IRMA) (Kavoshyar T4 and TSH IRMA [¹²⁵I] coated tube radiomimmunoassay; manufactured by Kavoshyar Iran Company) method by using gamma-counter reader.

The relation between clinical outcome and serum thyroxine level was analyzed. Various factors such as duration of hospitalization, sepsis (defined as a positive blood culture), patient short term outcome (being expired in hospital or discharged), jaundice (defined by clinical observation and confirmed by laboratory assessment), and the peak level of serum bilirubin (defined by highest level of bilirubin level during

hospital admission) were also taken into account. In addition, different types of medications such as infusion of dopamine, administration of phenobarbital, and Iodine containing antiseptics were considered.

Patients with thyroxine level of less than 6.5 µg/dl were categorized as having hypothyroxinemia (1).

In the cases that TSH level were more than 10 mU/L, the test was repeated again within 1-3 weeks in neonatal period. Thyroxine levels were compared between different gestational age and birth weight groups. We also compared the thyroxine values among the patients who expired during hospitalization and those who were discharged from the hospital.

The thyroxine levels of those with sepsis and jaundice were also compared with those who lacked such illness. In addition, the association between serum thyroxine level and duration of hospitalization, and the peak level of serum bilirubin were investigated.

The level of significance adopted was 0.05. We used student's t-test and Pearson correlation coefficient to compare quantitative variables. Using logistic regression the effect of independent variables on thyroxine level was analysed. In the model we entered only birth weight and gestational age which had significant association with thyroxine level. Statistical analyses were performed using SPSS release 11.5 software.

Results

During the period of this study 103 patients were admitted at NICU. Four patients with multiple congenital anomalies were excluded from this study. The mean of ages of these neonates at time of initial investigation was 11±7.20 days. 26(26%) patients among 99 newborn infants who were included in the study had low thyroxine level (3.62 to 5.57µg/dl). Mean thyroxine level was 8.38 µg/dl ±2.72. Four patients (4%) had TSH level more than 10 mU/L on initial assessment with normal values of thyroxine (6.70 to 7.23 µg/dl). The follow-up of those patients conducted one to three weeks later revealed that their TSH levels were below 7 mU/L. Patients with gestational age less than 34 weeks showed significant lower thyroxine level than others (7.15 µg/dl ±2.56, and $P=0.03$). The infants with less than 1500 grams weight at birth also had lower thyroxine levels compared to others (6.72 µg/dl ±3.03). The p-value was 0.08 that could be considered as a borderline significant value. 55% of VLBW infants (5 of 9) had thyroxine levels less than 6.5 µg/dl compared to 43% of patients (7 out of 16) with gestational age less than 34 weeks.

Table 1. Clinical characteristics of patients with low and normal thyroxine level

Characters	Low thyroxine level*	Normal thyroxine level	Total
	(N=26)	(N=73)	(N=99)
Gestational age<34 weeks; n(%)	7(26)	9(12)	16(16)
Very low birth weight; n(%)	5(19)	4(5)	9(9)
Birth weight(gr)§	2420±896	2740±685	2680±768
Sepsis; n(%)	5(19)	9(12)	14(14)
Jaundice; n(%)	7(26)	25(34)	32(32)
Mortality; n(%)	3(11)	9(12)	12(12)
Duration of hospitalization(days)§	17.7±9.8	16.7± 13.0	16.9±12.3

*Serum total thyroxine level < 6.5µg/dl. §Mean ± SD

Table 2. Comparison of thyroxine level within different clinical subgroups

Groups	Thyroxin level (µg/dl)
	Mean±SD
Neonates with Sepsis	7.85±3.00
Neonates with Jaundice	8.26±2.70
Expired Newborn Infants	8.48±3.31
Very low birth weight infants	6.72±3.03*
Newborn Infants with Gestational age < 34 weeks	7.15±2.56§
Total	8.38±2.72†

*Lower thyroxine level compared to newborns with birth weight more than 2500 gr, $p = 0.08$

§Lower thyroxine level compared to newborns with gestational age more than 34 weeks, $p = 0.03$

†Mean thyroxine level of all patients included in the study

This group had not abnormal TSH values concomitantly. The follow-up thyroxine tests revealed returning to normal values (8.12 µg/dl ±1.36). The neonates with either sepsis or jaundice had lower thyroxine levels compared to others, but these differences were not statistically significant (7.85 µg/dl ±3.00 and 8.26 µg/dl ±2.70). The duration of hospitalization did not show considerable differences among the patients with hypothyroxinemia and those with normal thyroxine levels (17.7±9.8 Vs 16.7± 13.0 days). Comparing the mean thyroxine levels among the

infants who were expired and the others did not demonstrate any significant differences (8.48 µg/dl ±3.31 Vs 8.36 µg/dl ±2.91). There was no correlation between serum thyroxine and bilirubin peak level. These values are demonstrated in tables 1 and 2. However, none of our patients during the time of this study had congenital hypothyroidism based on their thyroid function tests. In the logistic regression model, the effect of birth weight and gestational age on thyroxine level was not significant (Table 3).

Table 3. Relationship between thyroxine, birth weight, and gestational age in infants*

	Coefficient	Standard Error	Significant	Expected (B)
Gestational age§	0.670	0.688	0.330	1.954
Birth weight†	0.764	0.911	0.401	2.147
Constant	-1.352	0.273	0.000	0.259

* Logistic regression analysis

§ Categorized to ≤ 34 weeks and > 34 weeks

† Categorized to ≤ 1500 grams and > 1500 grams

Discussion

26% of the patients had low thyroxine level in this study. Preterm and acutely ill infants in tertiary care settings are often subjected to multiple interventions, including hyperalimentations, transfusions, and medications such as steroids, dopamine, and antibiotics (2,3,12,13). All of these interventions may affect the results of screening (13-15).

As was expected neonates with lower gestational age and lower birth weight had lower thyroxine level. But, we found no association between thyroxine value and presence of sepsis, jaundice, mortality, peak of bilirubin level, and duration of hospitalization. The relation between low thyroxin level and short-term clinical outcomes investigated in some studies, but it will be likely that clinical situations such as illness severity, respiratory distress syndrome, cardiac diseases, and other disorders can alter thyroid function per se, and low thyroxine level is not cause or predisposing for such adverse outcomes (6,8,9).

The importance of thyroxine for brain growth is well known. In infants with congenital hypothyroidism early replacement of thyroid hormones is important for optimizing outcome and development. The mortality rate and the neurological deficit among preterm infants are related to transient hypothyroxinemia (8,11). Preterm infants with hypothyroxinemia have not benefited from thyroid replacement in long-term (11,16,17).

In addition, clinical significant of thyroid function after birth was highlighted by Larson and his colleagues. They demonstrated that very low birth weight and infants with birth weight of more than 2500 grams require intensive care are at risk of transient hypothyroidism identified by delayed elevation of TSH (16,18). They were also able to associate the use of dopamine and iodine with delayed elevation of thyrotropine as declared before by others (13,14,18). Despite the frequent association of low thyroxin levels in preterm infants, hypothyroxinemia in term infants has been investigated less extensively. In addition, several studies showed either infants with perinatal asphyxia or who undergo cardiac surgery have developed reduction in thyroid hormones or euthyroid sick syndrome (19-22).

Lim *et al.* revealed the importance of transient hypothyroxinemia among term infants who required more intensive rescue interventions, including high-frequency ventilation, inhaled nitric oxide, and transfer to an extracorporeal membrane oxygenation center. They

emphasized, whether thyroxin levels are a marker or mediator of clinical outcome remains to be determined and they did not advocate thyroid hormone replacement based on that study (12). While our study revealed that 26% of sick infants had transient hypothyroxinemia, we did not find any differences among those infants regarding duration of hospitalization, and short term outcome. The frequency of hypothyroxinemia among the very low birth infants, and preterm infants were significant compared to the term newborn infants which is consistent with the previous published studies. However its effect was disappeared in multivariate analysis. The reason might be insufficient sample size in our study. In our three weeks follow up, we found that the thyroxine level of the infants has returned to normal ranges the same as findings of former studies (4,5).

In our study we had a few limitations. The first limitation refers to the restricting our measurements to only thyroxine and TSH. We did not measure other important thyroid hormones such as free thyroxine, triiodothyronine, and thyroid hormone binding globulin, because large amount of blood was required from studied infants. The second limitation was that our data only covered single center with consistent clinical management guidelines. Finally, due to the lack of national screening in our country ;at the time of this study; the timing of measurement depended on the age of infants at the time of admission.

In summary, this study shows the likelihood of transient hypothyroxinemia among preterm infants with severe neonatal illness. The study also confirms the necessity of measuring thyroid hormones within the first days of life. The severity of illness should be accounted for interpreting the result of neonatal thyroid function tests within the first weeks of life. Additional investigations, to determine whether thyroxine levels are a mediator or simply a marker of clinical status, are needed. In addition, the importance of national neonatal screening is evident because the early measurement of thyroid hormones will result in better neurodevelopmental outcome.

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