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Original Research Article

A Prospective Study to Determine the Thyroid Hormone Levels in Neonates Suffering from Sepsis and to Correlate These Levels with the Severity of the Disease

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Abstract

Background: Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low and middle-income countries. Thyroid hormones levels tend to decrease in critical care patients who suffer from severe trauma or sepsis.

Aim: to assess the thyroid hormone levels in neonates with sepsis and correlating these levels with disease severity.

Materials and Methods: This is a type of prospective study which was done in a neonatal intensive care unit of Department of Pediatrics, Patna Medical College and Hospital, Patna, Bihar, India, for the duration of 1 year. A group of septic newborns and a control group of healthy noninfected newborns were evaluated. Blood samples were obtained at onset from septic and healthy newborns and at 10th day of the antibiotic therapy from only septic newborns, and thereafter serum total T3 (TT3), total T4 (TT4), and TSH levels were determined. 67 neonates were admitted in NICU during the duration of study and were identifies as the case group. Other 63 healthy full-term neonates were randomly selected as the control group. Comparison of mean levels of thyroid hormones between cases and controls was done.

Results: At onset, serum TT3 and TT4 levels of all septic newborns were significantly lower with respect to those of healthy controls, while serum TSH levels were not significantly different between these groups. At the 10th day of the antibiotic therapy serum TT3, TT4, and TSH levels of septic newborns were markedly increased, but only the difference between TT4 levels was significant.

Conclusion: levels of thyroid hormones like T3 and T4 are less in septic neonates as compared to healthy neonates before treatment, irrespective of gestational period and birth weight. So, the thyroid abnormalities at admission in septic neonates could be of prognostic value.

Keywords: Thyroid Hormones, Sepsis, Neonates.

Introduction:

Neonates are usually susceptible to sepsis with non-specific clinical manifestations. Neonatal sepsis is an alarming condition resulting in high morbidity and mortality. Thyroid abnormalities are common in neonates with sepsis and non-thyroidal critical illness. Alteration of thyroid function in septic neonates is mediated by various cytokines as a nonspecific response. Alteration of thyroid hormone abnormalities can adversely impact prognosis in children with critical illness [1].

During fetal life, the thyroid gland develops with production of thyroxine (T4) and triiodothyronine (T3) and secretion into the serum from about 12 weeks gestation, the levels of which increase to term. Throughout gestation, maternal T4 crosses the placenta in limited amounts, but in the first trimester, this plays a critical role in central nervous system development.[2] From the second trimester, the continued transfer of T4 from mother to fetus remains important for those babies with primary thyroid abnormalities.[3] From mid-gestation, hypothalamic expression of thyrotrophin releasing hormone (TRH), pituitary production of thyroid stimulating hormone (TSH), and thyroidal production of T4 rise steadily until 36 weeks gestation.[4] T3 and T4 are also inactivated to sulphated analogues by sulpho transferase in fetal liver [5]. In the fetus, levels of T3 are low, and increase only at the end of gestation. when a baby is born preterm, the level of T4 is lower than that of term babies and correlates with gestational age and birth weight [6]. Levels of TSH and T3 are normal to low, free T4 concentrations are also low, and thyroglobulin levels are high. Normally at delivery at term, with the fall in ambient temperature, there is a surge in TSH to about 80 mU/ml within about 30 minutes. This stimulates the thyroid gland to release T4 and T3, which rise to well above normal levels. In term babies, the total and free T4 levels fall over the next four to six weeks, but are still higher than in older children and adults at six months. T3 levels gradually reach infancy levels between 2 and 12 weeks of age.

In the preterm infant, there is a similar TSH, T4, and T3 surge, but the magnitude is attenuated. In babies born at more than 30 weeks gestation, T4 and free T4 levels increase over the next six to eight weeks to levels comparable to those of babies born at term [7,8]. However, in the preterm baby born at less than 30 weeks gestation and with very low birth weight (< 1500 g), the TSH and T4 surges are limited and there is often a fall in T4 in the first one to two weeks after birth, and transient hypothyroxinaemia is common [8,9] The more preterm the baby the more pronounced is this hypothyroxinaemia. Although there is an increase in the incidence of transient primary hypothyroidism in these babies (when the TSH level is also raised) [9], in the majority, the hypothyroxinaemia is associated with a normal TSH level [10].

There is a paucity of data on thyroid function abnormalities as a predictor of outcome in critically ill children and the available results are variable. It is also not known, whether newborns react in the same way as adults in critical illness like sepsis [11]. . The aim of this study is to investigate the changes in thyroid hormones levels during the neonatal sepsis and their relation to the outcome.

Materials and Methods:

This is a type of prospective study which was done in a neonatal intensive care unit (NICU) of Department of Pediatrics, Patna Medical College and Hospital, Patna, Bihar, India, for the duration of 1 year. A group of septic newborns and a control group of healthy non-infected newborns were evaluated. Blood samples were obtained at onset from septic and healthy newborns and at 10th day of the antibiotic

therapy from only septic newborns, and thereafter serum total T3 (TT3), total T4 (TT4), and TSH levels were determined. 67 neonates were admitted in NICU during the duration of study and were identifies as the case group. Other 63 healthy full-term neonates were randomly selected as the control group. The Local Medical Ethics Committee approved the study protocol. Informed consent was obtained from the parents of all children.

Inclusion criteria:

Sepsis is defined as systemic inflammatory response syndrome (SIRS) in the presence of or as a result of suspected or proven infection, inclusion criteria were determined according to International Consensus Conference on Pediatric Sepsis [12]. Evidence of infection includes positive findings on clinical exam, imaging and laboratory tests. Clinically, the Systemic Inflammatory Response Syndrome (SIRS) is the occurrence of at least two of the following criteria: temperature (>38.5°C and <36C), tachycardia(>180 beats/minute) or bradycardia(<100 beats/min), tachypnea(>40 breaths/minute and leucocytosis >19500/mm*3 or leucopoenia <5000/mm*3) and systemic BP(<75mm Hg)

Exclusion criteria:

- Mothers having any disease during pregnancy.
- Mothers using corticosteroids, antihypertensive, thyroid or antithyroid drugs during pregnancy.
- Newborns presenting any congenital malformation and congenital infection diseases associated with the TORCH complex.
- Refusal of parental consent.

Blood samples were obtained at onset from septic and healthy newborns and at the 10th day of antibiotic therapy from only septic newborns, and TT4, TT3, and TSH levels were determined.

Comparison of mean levels of thyroid hormones between cases and controls was done.

Results:

A total of 130 newborns were included in the study; 67 (51.54%) were diagnosed as septic and 63 (48.46%) were healthy. 35 (52.24%) were at term and 32 (47.76%) were preterm out of the septic cases and 31 (49.21%) were at term and 32 (50.79%) preterm out of all the controls. Out of septic cases, 27 (40.30%) were females and 40 (59.70%) were males while out of controls, 26 (41.27%) were females and 37 (58.73%) were males. The mean birth weight and gestational age of septic newborns were 2413.0±1014.5 (1450-4150) g and 35.7±3.6 (32-40) weeks, respectively.

Similarly, the mean birth weight and gestational age of the healthy newborns were 2634.5±943.1 (1600-4500) g and 36.7±3.2 (34-41) weeks, respectively. 2 term and 3 pre-term infants died, the total mortality rate was 7.5 % and the causes of death other than sepsis were prematurity and respiratory distress.

Table 1: Demographic details

Demographic data	**Septic newborn (67)**		**Healthy newborn (63)**	
Number	**Term**	**Pre-term**	**Term**	**Pre-term**
	35(52.24%)	32(47.76%)	31(49.21%)	32(50.79%)
Number of deaths	2	3	0	0
Male/female	40(59.70%) / 27(40.30%)		37(58.73%) / 26(41.27%)	
Gestational age (week)	35.7±3.6 (32-40)		36.7±3.2 (34-41)	
Birth weight (g)	2413.0±1014.5 (1450-4150)		2634.5±943.1 (1600-4500)	

Term and pre-term septic newborns had similar serum TT3, TT4, and TSH levels as showed in Table 2. At onset, serum TT3 and TT4 levels of all septic newborns were significantly lower with respect to those of healthy controls, while serum TSH levels were not significantly different between these groups. At the 10th day of the antibiotic therapy serum TT3, TT4, and TSH levels of septic newborns were markedly increased, but only the difference between TT4 levels was significant.

Septic newborns	**At onset**		**At 10th day**	
	Term	**Pre-term**	**Term**	**Pre-term**
TT3 (ng/dl)	**163.2±60.7**	**160.5±65.7**	**181.8±38.7**	**174.3±27.8**
TT4 (mg/ml)	**6.8±2.7**	**6.3±2.6**	**11.6±3.1**	**11.0±3.1**
TSH (µU/ml)	**4.0±2.4**	**3.8±2.7**	**3.1±2.1**	**4.1±2.9**

Healthy newborns	**At onset**	
	Term	**Pre-term**
TT3 (ng/dl)	182.1±8.9	180.2±46.8
TT4 (mg/ml)	9.9±2.9	11.4±3.5
TSH (µU/ml)	3.7±2.1	4.1±2.4

Discussion

Present study showed significantly low mean levels of T3 and T4 at admission in neonates with sepsis as compared with gestational age matched controls. No significant difference was observed with levels of TSH. Although many theories have been proposed to explain the mechanism and significance of non-thyroid illness, there are still no clear answers. The questions, whether these represent an adaptive stress response or are a manifestation of pituitary-thyroid axis pathology, and whether this condition should be treated with thyroid hormone replacement, still need to be answered. Studies in animal models with sepsis have demonstrated no identifiable benefit from thyroid hormone replacement [13,14].

Schonberger et al. [15] observed transient hypothyroidism in 12% of the neonates admitted to the neonatal intensive care with various problems like sepsis, prematurity, and respiratory distress. On a serial study, Romagnoli et al. [16] observed that preterm newborns affected by respiratory distress syndrome or sepsis showed a significant reduction in mean TT4 concentrations up to 20th day of life. TSH levels were not significantly different. Low serum TT3 and TT4 levels with normal TSH is often described in severely ill, moribund patients with various systemic illnesses [17].

Study conducted on forty-nine neonates by Das BK et al., had similar observation [18]. They evaluated T3, T4 and TSH at diagnosis and at the time of discharge. Improvement in T3 and T4 level were observed with the treatment of sepsis. In contrast, Borkowski J et al., have shown that decreased levels of FT3 and TSH were associated with poor prognosis in patients with septic shock [19]. Low T3, T4 and low baseline TSH was associated with higher mortality in neonates admitted in NICU with sepsis [20]. Slag et al. [21] also reported association of low TT4 with poor prognosis for a wide range of non-thyroidal illness.

Conclusion

From the above study, it can be concluded that levels of thyroid hormones like T3 and T4 are less in septic neonates as compared to healthy neonates before treatment, irrespective of gestational period and birth weight. So the thyroid abnormalities at

admission in septic neonates could be of prognostic value. Hence hypothyroxinemia has considerable prevalence in neonatal intensive care setting and is related with critical illness as neonatal sepsis.

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