RESEARCH PAPER

Relation of Thyroid Hormone Levels with Fluid-Resistant Shock among Preterm Septicemic Neonates

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Objective: To compare thyroid hormone levels between septicemic preterm neonates with and without shock. **Methods:** Preterm septicemic infants with shock constituted Group A (*n*=36) and those without shock constituted Group B, with groups matched (1:1) for gestation and postnatal age. Those with maternal thyroid disorders, thyrotropic medication and life expectancy <12 hours were excluded. We compared serum tri-iodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) between the groups by univariate and multivariate (adjusting for SNAPPE-II) analysis. **Results:** Median (IQR) TSH was significantly lower in Group A [1.39 (0.83,3.48)] *vs* Group B [5.1 (2.32,7.19)] mmol/dL *(P*<0.001). Serum T3 and T4 were also lower in Group A (*P*<0.001). On multivariate analysis, none of these measures were independently associated with septic shock. **Conclusions:** Thyroid hormone levels do not independently predict presence of shock among septic preterms.

Keywords: *Hypothyroidism, Prematurity, Septicemia, Thyroid stimulating hormone.*

Changes in thyroid hormone levels in critically sick patients, including neonates, in the absence of primary thyroid pathology has been termed Euthyroid sick syndrome [1]. It is characterized by reduction in tri-iodothyronine (T3) in moderately sick patients, and reduction in thyroxine (T4) in severe disease. Among children with septic shock, non-survivors have lower thyroid hormone levels compared to survivors [2]. In addition, preterm infants are predisposed to transient hypothyroxinemia of prematurity, characterized by low levels of T3 and T4 [3]. Unlike adults who may not have any long-term consequences of transient hypothyroidism, preterm neonates suffer from neurodevelopmental disabilities [4-6]. Thus, septic preterm neonates are under a double jeopardy, both by virtue of sepsis and prematurity.

There is a relationship between thyroid function tests (TFT) and cardiac function. Children who undergo cardiac bypass surgery have deranged TFTs and treatment with T3 improves myocardial function [7,8]. On comparison of children (beyond neonatal period) with septic shock *versus* those with sepsis but no shock, researchers have reported lower thyroid hormone levels among the former [2,9]. Septic shock may just reflect greater severity of sickness, as the above authors did not adjust for the level of sickness to determine whether TFTs have an independent relationship with shock. In view of the proven association of lower levels of thyroid hormones and septic shock in older children, paucity of data in preterm infants, and the uncertainty whether deranged TFTs are associated with hypotension independent of the level of sickness, we planned this study.

METHODS

We conducted a cross-sectional study in a level III Neonatal Intensive Care Unit (NICU) in northern India, after Ethics Committee approval. Written informed consent was obtained from parents.

We recruited inborn premature neonates (30-35 weeks of gestation) diagnosed to have sepsis, based on clinical sepsis associated either with a positive body fluid culture, or C-reactive protein value >10 mg/L, or a chest *X*-ray suggestive of pneumonia. Subjects were excluded if they had maternal thyroid disorder; intake of drugs that could affect TFTs; or anticipated life expectancy <12 hours. We enrolled two groups: those with sepsis and fluid-resistant hypotensive shock (Group A) and those with sepsis but no shock (Group B). Shock was defined as systolic blood pressure (BP) less than the lower bound of the 95% CI by Zubrow's charts after receiving two normal saline boluses of 10 ml/kg each. For those with an arterial cannula, we used the invasive BP and for others we used non-invasive BP records.

In Group B, absence of shock was defined as both systolic and diastolic BP above the lower bound of the 95% CI's; no oliguria (urine output <1 mL/kg/h); no prolongation of capillary refill time (>3 seconds); and no narrowing of pulse pressure (<20 mm Hg) in the preceding 6 hours, data for which was obtained from the patient's records. Subjects in group B were individually matched (1:1) with subjects in group A for gestation (± 1 week) and chronological age. They included the first eligible subject after the corresponding case in group A had been enrolled. We defined subjects in Group A according to BP as this objective measure reflects decompensated shock. Group B was defined to exclude all signs of hypoperfusion and shock so that there was a clear demarcation between groups. We recorded baseline demographics, morbidity profile, and clinical features of hypoperfusion. We assayed serum T3, T4 and TSH in all subjects by immuno-radiometric assays before the administration of inotropes. Hemolyzed and lipemic samples were not assayed. We calculated the SNAPPE-II over a 12-hour period after enrolment.

We followed up all subjects until death or discharge from the NICU. We compared the groups for TSH, T3 and T4 values. We determined the independent predictors of group membership as mentioned below, and determined the independent predictors of the risk of dying.

To detect a difference in mean TSH level of 2.3 mIU/ml assuming a 1:1 ratio of the groups; standard deviation of 3.5 mIU/ml; 5% alpha error and 20% beta error [10], 36 subjects were required per group. Data regarding the standard deviation of the difference in TSH values between matched neonates are not available in the literature, hence we could not calculate sample size for matched groups.

Statistical analysis: Statistical tests for related groups were used as the groups were matched. Categorical variables were compared by McNemar's test. Numerical variables were compared by paired Student's t-test and Wilcoxan signed rank sum test. Since derangement of TFTs is associated with the degree of sickness, we determined whether the TFTs were associated with septic shock after adjusting for level of sickness. We performed univariate followed by multivariate conditional logistic regression analysis to estimate the adjusted odds ratio (OR) of belonging to group A, for the following variables: SNAPPE-II, T3, T4 and TSH values. We also performed multivariate logistic regression to estimate the adjusted OR of dying, for the following covariates: gestational age, baseline mean BP, SNAPPE-II score, and T3, T4 and TSH values.

RESULTS

Of 4794 livebirths, 255 babies in the gestational age group 30-35 weeks developed sepsis. 58 of them developed septic shock of which 10 were missed, 5 refused consent and 7 excluded for other exclusion criteria; leaving 36 cases for enrollment in Group A. An equal number of matched subjects were selected in Group B. All subjects in Group A had at least one abnormal perfusion parameter (urine output <1 mL/kg/h, capillary refill time >3 seconds or pulse pressure <20 mm Hg) in addition to low BP. Twenty-six, 30 and 13 subjects in Group A had oliguria, delayed capillary refill and/or narrow pulse pressure, respectively, with several having >1 abnormal parameter (***Table* I**).

TABLE I COMPARISON OF CLINICAL CHARACTERISTICS BETWEEN SEPTIC PRETERM NEONATES WITH (GROUP A) AND WITHOUT (GROUP B) SHOCK (*N*=72)

Variable	*Group A (n=36)*	*Group B (n=36)*
Gestational age, wks	32 (2*)	32 (2)
Birthweight, grams	1353 (471)	1347 (303)
Male gender (%)	26 (72)	23 (64)
SGA (%)	11 (31)	7 (20)
^Apgar score	8 (5,9)	8 (6.5, 8.75)
Enrolment age, d	3 (1,17)	4 (1, 7)
*SNAPPE-II score	53 (41,76)	16 (16,29.5)
*Mean BP, mmHg	25.5 (22.25, 27.75)	40 (34.25, 43.75)
*Blood pH	7.08 (0.2)	7.3 (0.12)
#Hypoxemia (%)	15 (36)	4 (11)
$Blood glucose, mg/dL	85 (28)	75 (14)
Ionised serum calcium, mEq/L	0.9 (0.2)	0.9 (0.2)
Blood culture positive (%)	7 (19)	13 (36)
‡Pneumonia (*X*-ray)	11 (31)	1 (3)

**P<0.001, #P=0.007, $P=0.04, ‡P=0.002, ^at 10 minute.*

TABLE II COMPARISON OF THYROID FUNCTION TESTS BETWEEN THE TWO GROUPS

Variable	*Group A (n=36), Median (IQR)*	*Group B (n=36) Median (IQR)*
T3	0.83 (0.65, 1.03)	1.57 (1.03, 1.98)
T4	3.1 (1.25, 6.75)	8.1 (6.18, 8.97)
TSH	1.39 (0.83, 3.48)	5.1 (2.32, 7.19)

All P values <0.001; T_3 & T_4 in mg/dL; TSH in µmol/dL. TSH: Thyroid stimulating hormone.

WHAT THIS STUDY ADDS?

- Thyroid hormone levels are not independently associated with the presence of shock in preterm neonates.

The median (1st, 3rd quartile) TSH value was significantly lower in Group A *versus* Group B 1.39 (0.83, 3.48) *vs* 5.1 (2.32, 7.19) mmol/dL; $P<0.001$) **(*Table* II**).

In univariate conditional logistic regression analysis, SNAPPE-II, T3 and T4 levels predicted septic shock (***Table* III**). For each unit increase in SNAPPE-II, the odds of developing septic shock increased by 2.4%. For each ng/dL increase in T3, the odds decreased by 81% and for each ng/dL increase in T4, the odds decreased by 13%. We checked the TFTs for collinearity. Spearman's coefficient of correlation for pairwise comparisons (T3-T4, T4-TSH and T3-TSH) were 0.589, 0.41 and 0.37, respectively. As the coefficients were <0.8, we included all 3 parameters in the multivariate analysis (***Table* III**). The only independent predictor of fluid-resistant septic shock was the SNAPPE-II. All other parameters being similar, each unit increase in SNAPPE-II increase the odds of developing septic shock by 6%. None of the TFTs were independently associated with fluid-resistant septic shock. By 96 hours, 27 (37.5%) subjects had died, all in group A ($P<0.001$). No subject in Group B went on to develop shock during the 96-hour period after enrolment. During hospital stay, 32 (44.4%) subjects died, all in Group A ($P<0.001$). On multivariable logistic regression, none of the TFTs was independently associated with mortality.

DISCUSSION

Our study shows that low levels of T3, T4 and TSH are associated with fluid-resistant hypotensive shock among septic preterm neonates, but, after adjusting for the level of sickness, TFTs are not independently associated with shock or mortality.

TABLE III CONDITIONAL LOGISTIC REGRESSION ANALYSIS OF PREDICTORS OF FLUID RESISTANT SEPTIC SHOCK

Variable	*Univariate analysis Unadjusted OR (95% CI of OR)*	*Multivariate analysis Adjusted OR (95% CI of adjusted OR)*
SNAPPE-II score	1.024 (1.012, 1.036)	1.062 (1.002, 1.124)
T3, ng/dL	0.188 (0.077, 0.456)	0.162 (0.012, 2.154)
T4, ng/dL	0.866 (0.782, 0.960)	0.833 (0.502, 1.384)
TSH, mmol/dL	0.892 (0.791, 1.005)	0.997 (0.732, 1.359)

Our study had certain limitations. The cases of septic shock had a significantly higher proportion with probable sepsis (defined on chest *X*-ray) and disproportionately less definite sepsis (blood culture-positive) compared to subjects with no shock. We cannot exclude the possibility that a larger proportion of subjects in Group A compared to B may have developed shock due to reasons other than sepsis, introducing a selection bias. Subjects in Group A had significantly lower mean pH and were significantly more hypoxic. We cannot exclude the possibility that these factors were associated with deranged TFTs rather than hypotension *per se*. We do not have a comparison group with other types of shock to address this problem. We had measured BP both by invasive and non-invasive methods. Non-invasive BP measurement is less accurate. Since we did not record the mode of measurement used for each subject, we were unable to analyze subgroups based upon mode of BP measurement.

There is a known association of treatment with dopamine and derangement of thyroid hormones [11]. In our study, the blood sample for thyroid hormone profile was drawn before starting inotropes and hence was not affected using inotropes.

In a similar study in older children, Lodha, *et al*. [9] found significantly lower thyroid hormone levels in those with septic shock. They also reported no deaths in the group without septic shock whereas 50% of the children with septic shock died [9]. Yildizdas, *et al*. [2] showed that mean (SD) total T3 levels among children with sepsis alone *vs* those with septic shock were 0.91 (0.22) nmol/L *vs* 0.64 (0.23) nmol/L and total T4 levels were 100.6 (1.93) *vs* 65.8 (19.35), respectively ($P<0.05$). In both the studies, children with septic shock were sicker and had higher mortality. Since these authors did not adjust for sickness level, it is not clear whether the derangement in TFTs was associated with shock independent of its association with the severity of sickness.

The results of our study do not support the hypothesis that hypotension in neonatal sepsis is associated with deranged thyroid hormone levels. Intervention trials of thyroxine in patients with neonatal septic shock are not warranted with the current level of evidence.

Contributors: SD: planned the study, analyzed the data and wrote the manuscript; SS: recruited patients and collected the data; AB: performed the thyroid hormone assays; SV: helped with data collection and data analysis; PK: supervised the study, supervised the data analysis and finalized the manuscript.
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REFERENCES

1. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev.1982;3:164-217.
2. Yildizdas D, Onenli-Mungan N, Yapicioglu H, Topaloglu AK, Sertdemir Y, Yuksel B. Thyroid hormone levels and their relationship to survival in children with bacterial sepsis and septic shock. J Pediatr Endocrinol Metab. 2004;17:1435-42.
3. La Gamma EF, van Wassenaer AG, Golombek SG, Morreale de EG, Kok JH, Quero J, *et al*. Neonatal thyroxine supplementation for transient hypothyroxinemia of prematurity: beneficial or detrimental? Treat Endocrinol. 2006;5:335-46.
4. Den Ouden AL, Kok JH, Verkerk PH, Brand R, Verloove-Vanhorick SP. The relation between neonatal thyroxine levels and neurodevelopmental outcome at age 5 and 9 years in a national cohort of very preterm and/or very low birth weight infants. Pediatr Res.1996;39:142-5.
5. Meijer WJ, Verloove-Vanhorick SP, Brand R, van den Brande JL. Transient hypothyroxinaemia associated with developmental delay in very preterm infants. Arch Dis Child.1992;67:944-7.
6. Reuss ML, Paneth N, Pinto-Martin JA, Lorenz JM, Susser M. The relation of transient hypothyroxinemia in preterm infants to neurologic development at two years of age. N Engl J Med.1996;334:821-7.
7. Bettendorf M, Schmidt KG, Grulich-Henn J, Ulmer HE, Heinrich UE. Tri-iodothyronine treatment in children after cardiac surgery: A double-blind, randomised, placebo-controlled study. Lancet. 2000;356:529-34.
8. Mackie AS, Booth KL, Newburger JW, Gauvreau K, Huang SA, Laussen PC, *et al*. A randomized, double-blind, placebo-controlled pilot trial of triiodothyronine in neonatal heart surgery. J Thorac Cardiovasc Surg. 2005;130:810-6.
9. Lodha R, Vivekanandhan S, Sarthi M, Arun S, Kabra SK. Thyroid function in children with sepsis and septic shock. Acta Paediatr. 2007;96:406-9.
10. Golombek SG. Nonthyroidal illness syndrome and euthyroid sick syndrome in intensive care patients. Semin Perinatol. 2008;32:413-8.
11. Carrascosa A, Ruiz-Cuevas P, Clemente M, Salcedo S, Almar J. Thyroid function in 76 sick preterm infants 30-36 weeks: Results from a longitudinal study. J Pediatr Endocrinol Metab. 2008;21:237-43.