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Evaluation of Thyroid Hormone Levels in Full-Term Neonates Presented with Septic Shock

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Introduction: The incidence of neonatal sepsis in India is 38 per 1000 live births. Many authors found an association between altered thyroid hormone levels and septic shock in neonates and it may be of prognostic importance in septic shock treatment. This study has been conducted to find the relationship between thyroid profile and septic shock in neonates and also to compare the thyroid profile in survivor and non-survivor groups of septic shock patients. **Methods:** This analytical prospective cohort study was conducted in the NICU of a tertiary care teaching institution in central India. Full-term neonates with late-onset sepsis were included in this study and estimation of thyroid hormones (TSH, T3, T4, fT3, and fT4) was performed. These neonates were divided into those with and without septic shock patients and levels of thyroid hormones were correlated between these patients to find significant relations. The Vasoactive-Inotropic Score (VIS) score was calculated. **Results:** A total of 195 full-term neonates were included in the study. The mean value of TSH, T3, T4, fT3, and fT4 among neonates with septic shock were 5.27 µg/ml, 80.01 ng/dl, 6.36 µg/dl, 1.40 pg/ml, and 1.40 µg/dl, respectively while the values were 5.29 µg/ml, 94.4 ng/dl, 7.25 µg/dl, 1.84 pg/ml, and 1.43 µg/dl, respectively in septic neonates without shock. This difference was statistically significant except for TSH ($p>0.05$). The mean value of TSH, T3, T4, fT3, and fT4 among septic shock survivors were 5.27 µg/ml, 80.01 ng/dl, 6.36 µg/dl, 1.40 pg/ml, and 1.40 µg/dl and in septic shock non-survivors were 2.40 µg/ml, 37.33 ng/dl, 3.86 µg/dl, 0.99 pg/ml, and 0.84 µg/dl, respectively ($p<0.0001$). Only T3 was found to be significantly co-related with VIS in septic shock in all the groups (<0.001). **Conclusion:** Our study suggests that TSH, T3, T4, fT3, and fT4 levels are significantly low in patients suffering from the septic shock which may vary in the case of TSH. Also, there is a significant decrease in thyroid profile among septic shock non-survivors as compared to survivors.

Keywords: Neonate, Thyroid profile, Septic shock, Survivors

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Introduction

Neonatal sepsis is a common disease affecting several tissues through pro- and anti-inflammatory responses in the organism [1]. It is characterized by signs and symptoms of infection with or without accompanying bacteremia in the first month of life. The incidence of neonatal sepsis in the developing world is 10-30% and mortality is around 19% [2]. Neonates with sepsis may present in or progress to septic shock. Initially, it is characterized by cardiovascular dysfunction which eventually requires inotropic support [3]. Septic shock is a clinical syndrome with suspected infection with signs of decreased perfusion including patients with decreased mental status, prolonged capillary refill time >3 sec or flash capillary refill, diminished or bounding peripheral pulses, mottled, cool extremities, and decreased urine output of <1 mL/kg/h) in neonatal age [4-6].

Many neuroendocrine changes take place in our body during critical illness and one of these is the alteration of thyroid hormone activity during sepsis or septic shock. They help in the adaptation of metabolic function to stress and regulation of metabolic homeostasis. It has been hypothesized that the immune system cells can affect systemic thyroid hormone activity. This activity may be attributed to the complex pathophysiological interplay between Thyroid Stimulating Hormone (TSH) and the immune system [7,8]. A few previous literature have found the correlation between thyroid profile and septic shock among neonates [9,10].

Lodha R et al demonstrated that children with septic shock had a lower level of free triiodothyronine (fT3), triiodothyronine (T3), Thyroxine (T4), free Thyroxine (fT4), and TSH compared to those with sepsis [9]. Dutta S. et al. showed that low levels of T3, T4, and TSH are associated with fluid-resistant hypotensive shock among septic preterm neonates [10].

Since the majority of the previous studies related to septic shock deal with T3 or T4 hormone assay only and were conducted on a small sample size [9,10], there is a paucity of studies that have included all of TSH, T3, T4, fT3, and fT4 and correlated them to septic shock. Hence, the present study was conducted to evaluate the relationship between thyroid profile and septic shock in neonates and to compare the thyroid profile in survivor and non-survivor groups of septic shock.

Materials and Methods

This analytical prospective study was carried out in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatric Medicine, Gandhi Medical College, Bhopal, over 12 months from May 2017 to April 2018.

The sample size was calculated using the formula: n = $(z\alpha)^2 p(1-p)/d^2$, where $Z\alpha$ is the confidence level at 95% ($Z\alpha=1.96$ for 95% CI) CI, p is the population proportion (p=13.5, taken from the previous studies), and d is the margin of error (5%). Based on the formula, a sample size of 195 was taken for the present study.

All the full-term neonates (gestational age >37 completed weeks), admitted with features of sepsis between 72 hours to 28 days of life and with positive sepsis screening, were included in the study. The various components of the septic screen were total leukocyte count (TLC) <4,000/mm^3 and >24,000/mm^3, absolute neutrophil count (ANC) <1800/mm^3, immature to the total neutrophil ratio (IT ratio) >0.2, elevated micro-erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) >6mg/dl and/or any of body fluid culture-positive (blood, cerebrospinal fluid, urine, etc). The neonates who did not respond to a fluid challenge of at least 60 mL/kg of isotonic fluids administered in the first hour were diagnosed with septic shock [4,5]. All preterm and post-term neonates, neonates with hypothyroidism, major congenital anomaly, birth asphyxia, and with a history of maternal thyroid hormone dysfunction were excluded.

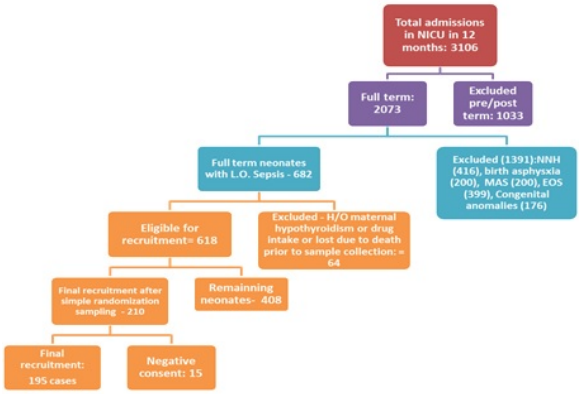
After explaining the nature, procedure, and purpose of the study, written consent was obtained from the parents/ legal guardians of the neonates. The flow chart (Figure 1) describes the protocol followed during the study. The data obtained from the subjects were recorded in a pre-structured proforma. Maternal data including maternal age, religion, socio-economic status, last menstrual period, risk factors, and drug intake were obtained from the mother/legal guardians of the baby, and the medical records of the mother. A detailed natal and postnatal history including age at admission, gestational age, gender, type of feeding, pre-lacteal feeds, and presenting complaints of the neonates were also obtained. A thorough physical examination was done and systemic examination findings were noted for all the recruited neonates.

The gestational age was assessed from the last menstrual period and the New Ballard Score. Neonates were also divided according to the presence of shock and the outcome. The demographic information and data on the use of vasoactive drugs, duration of shock, and blood investigation reports were also collected. Relevant investigations were sent for all the neonates including hemoglobin, TLC, ANC, CRP, blood culture, electrolytes, and random blood sugar. Other investigations like chest X-ray, lumbar puncture, urine routine and microscopy, urine for fungal hyphae, urine culture, and arterial blood gas analysis were done when required. In all the included neonates, the thyroid profile was done.

The blood samples collected in the test tube were centrifuged; serum thus obtained was used to estimate T3, T4, and TSH. They were estimated by the chemiluminescence method (using the Immulite1000 Immunoassay system-Siemens) [11]. Neonates who were found to be hypothyroid were excluded from the study and treated for hypothyroidism. Levels of T3, T4, TSH, fT3, and fT4 were compared in the newborn with septic shock with those without septic shock. They were also grouped and compared as survivors and non-survivors of septic shock. These levels were correlated with the requirement for vasoactive drugs and Vasoactive-Inotropic Score (VIS) was calculated, which is a useful surrogate outcome. We have divided neonatal septic shock cases into three groups based on the VIS. The first group includes<20 VIS, the second group between 20 to 50 VIS, and the third group was >50 VIS. All newborns were managed according to the standard treatment guidelines [1,12,13]. The approval was obtained from the institutional ethical committee of Gandhi Medical College, Bhopal, before the start of the study. After explaining the nature, procedure, and purpose of the study, written consent was obtained from the parents/ legal guardians of the neonates.

Statistical analysis

The data obtained was entered in the MS Excel spreadsheet. The results were expressed in mean ± standard deviation (SD) for continuous variables and as a percent (%) for categorical data. Observations were statistically analyzed using graph pad prism version 7.0. An independent sample t-test was used. The p-value of <0.05 was considered statistically significant. Microsoft Word and Excel were used to generate figures and tables.



Results

A total of 195 cases were enrolled, out of which, 51.2% were males and 48.8% were females. The maximum of the neonates (35.9%) were between 7-10 days of age and 67.7% had birth weights between 1.5-2.5 kg. Out of total cases, 40% were on exclusive breastfeed (EBF). The age of most mothers (50.2%) was between 20-25 years and the percentages of neonates born with institutional delivery and home delivery were 67% and 33%, respectively. The maximum number of the patients included in the study presented with complaints of refusal to feed or poor feeding (32.3%). The demographic variables of the neonates and their mothers are shown in table 1.

Table 1: Demographic variables of the neonates and their mothers (n=195)

		total (n=195)	%
Age	3-7 Days	49	25.1
	7-10 Days	70	35.9
	10-15 Days	18	9.2
	> 15 Days	58	29.8
Gender	Males	100	51.2
	Females	95	48.8
Birth weight	Less than 1.5 kgs	3	1.5
	1.5-2.5 Kgs	132	67.7
	More than 2.5 Kgs	60	30.8
Type of feeding	Exclusive Breast Feed (Ebf)	78	40.00
	Mixed Feed	83	42.56
	Top Feed	34	17.44
Maternal age	<20 Years	75	38.46
	20-25 Years	98	50.26
	>25 Years	22	11.28
Mode of delivery	Institutional Delivery	142	67
	Home delivery	53	33
Presenting complaints	Abdominal Distension	22	11.28
	Convulsion	25	12.82

	Excessive Crying	21	10.77
	Fever	13	6.67
	Not Excepting Feeds	63	32.31
	Dullness	15	7.69
	Respiratory Distress	36	18.46

The thyroid profile was performed in all 195 subjects. The mean value of TSH, T3, T4, fT3, and fT4 among neonates with septic shock were 5.27µg/ml, 59.47ng/dl, 5.16µg/dl, 1.21pg/ml, and 1.13µg/dl and in septic neonates without shock were 5.29 µg/ml, 136.10 ng/dl, 9.74 µg/dl, 2.59pg/ml, and 1.79 µg/dl respectively. A statistically significant (p<0.0001) difference was observed in the thyroid profile of the neonates with septic shock than those without septic shock except for TSH (p>0.05) (Table 2).

The mean value of TSH, T3, T4, fT3, and fT4 among septic shock survivors and non-survivors were 5.27 µg/ml,80.01 ng/dl, 6.36 µg/dl, 1.40 pg/ml, 1.40 µg/dl and 2.40 µg/ml, 37.33 ng/dl, 3.86 µg/dl, 0.99 pg/ml, and 0.84 µg/dl, respectively. We found a significantly low level of TSH, T3, T4, fT3, and fT4 in survivors as compared to non-survivors neonates (P<0.0001) (Table 3). In our study, only T3 was found to be significantly co-related with VIS in septic shock in all the groups (p<0.001). The maximum mean value of T3 was observed with VIS less than 20 while minimum T3 was observed with VIS more than 50 (Table 4).

Table 2: Comparing mean thyroid indices between Septic shock patients and patients with sepsis without shock

Thyroid profile	Septic Shock			Septic without Shock			Unpaired t-test
	Mean	Range	SD	Mean	Range	SD	P-value
TSH(µg/ml)	5.27	4.1-6.7	0.72	5.29	0.4-8.9	2.45	P>0.05
T3(ng/dl)	59.47	4.2-99.2	24.61	136.10	96.5-180.5	19.74	P<0.0001
T4(µg/dl)	5.16	2.1-8.3	1.61	9.74	6.5-12.6	1.28	P<0.0001
fT3(pg/ml)	1.21	0.5-2.3	0.38	2.59	1.5-4.8	0.75	P<0.0001
fT4(µg/dl)	1.13	0.4-2.3	0.38	1.79	1.2-2.3	0.22	P<0.0001

Table 3: Comparing mean thyroid indices between septic shock survivor patients and non-survivors

	Septic Shock Survivors			Septic shock non-survivors			Unpaired t-test (P-value)
	Mean	Range	SD	Mean	Range	SD	
TSH (µg/ml)	5.27	4.1-6.7	0.72	2.40	0.4-6.2	1.54	P<0.0001
T3 (ng/dl)	80.01	52.5-99.2	13.16	37.33	4.2-70.5	10.99	P<0.0001
T4 (µg/dl)	6.36	4.2-8.3	0.98	3.86	2.1-6.2	1.05	P<0.0001
fT3 (pg/ml)	1.40	0.8-2.3	0.30	0.99	0.5-1.8	0.33	P<0.0001
fT4 (µg/dl)	1.40	0.8-2.3	0.27	0.84	0.4-1.4	0.25	P<0.0001

Table 4: Thyroid parameters in patients grouped according to the vasoactive inotrope score (VIS)

Vasoactive Inotrope Score	Thyroid Profile	Mean	Range	SD	Unpaired student's t-test, P- Value
< 20	TSH (µg/ml)	5.39	5.39-0.47	0.47	p>0.999
	T3 (ng/dl)	84.89	84.89-10.16	10.16	p<0.0001
	T4 (µg/dl)	7.10	7.1-0.7	0.70	p>0.999
	fT3 (pg/ml)	1.67	1.67-0.42	0.42	p>0.999
	fT4 (µg/dl)	1.31	1.31-0.23	0.23	p>0.999
20 -50	TSH (µg/ml)	3.97	3.97-1.87	1.87	p>0.999
	T3 (ng/dl)	59.91	59.91-24.32	24.32	p<0.0001
	T4 (µg/dl)	5.15	5.15-1.55	1.55	p>0.999
	fT3 (pg/ml)	1.22	1.22-0.33	0.33	p>0.999
	fT4 (µg/dl)	1.15	1.15-0.38	0.38	p>0.999
> 50	TSH (µg/ml)	1.91	1.91-0.46	0.46	p>0.999
	T3 (ng/dl)	35.33	35.33-8.44	8.44	p<0.0001
	T4 (µg/dl)	3.69	3.69-1.15	1.15	p>0.999
	fT3 (pg/ml)	0.72	0.72-0.22	0.22	p>0.999
	fT4(µg/dl)	0.77	0.77-0.26	0.26	p>0.999

Discussion

The present analytical study was conducted to investigate the relationship between thyroid hormone status and the development of septic shock among 195 full-term neonates and to compare the thyroid levels of septic shock survivors and non-survivors. Thyroid hormones play a vital role in critical illness by up-regulating adrenergic receptors and by increasing the inotropic property of the myocardium [14]. There are two biologically active thyroid hormones: thyroxine (T4) and 3,5,3'-triiodothyronine (T3) [15]. With increasing severity of illness, low total and free T4, and sometimes low TSH, can be observed [14,16].

In normal fetuses, concentrations of TSH, thyroxine-binding globulin (TBG), and thyroid hormones increase progressively during intrauterine life. A surge in the serum TSH is seen at 30 minutes after delivery (up to 60-70 μU/L). Within 1-7 days of the newborn, the concentration of TSH reaches 1-39 μU/ml which dropped to 0.5-6.5 μU/ml between 8-28 days. In the first postnatal week, the T4 serum levels reach concentrations (9-22 μg/dl) that are higher than at any other time of life as between 8-28 days, the concentration dropped to 8.2-17 μg/dl. The levels of T3 are in the range of 36-316 ng/dl within a week of delivery which can rise to 105-346 ng/dl in between 8-28 days. In between 1-7 days of newborn, the concentration of FT3 and FT4 are 1.3-6.1 pg/ml and 2.2-5.3 ng/dL which reaches to 2.2-8 pg/ml and 0.9-2.3 ng/dL at 8-28 days of newborn respectively [11,17-19].

In the present study, a maximum number of cases belonged to the category of low birth babies i.e., 1.5-2.5 Kg (67.69%). The higher prevalence of low birth babies in the study group can be explained as low birth weight is a known risk factor for the development of sepsis and shock. We found an increased number of institutional deliveries (67%) of neonates which can be correlated with the increased awareness and better health transport facilities in the community. The percentages of Institutional deliveries and home deliveries in Madhya Pradesh as per the National Family Health Survey (NFHS-4) were 80.8 and 2.3% respectively [20]. which is almost similar to the findings of our study. Out of total cases, 42.56% were on EBF, while a higher number of cases (57.5%) were either on top feed or mixed feed which are known risk factors for the development of sepsis, whereas, in Madhya Pradesh as per the NFHS-4, 58.2% infants were on EBF [20].

We found that the mean levels of TSH, T3, T4, fT3, and fT4 were lower in septic shock patients than that of without septic shock and the difference was statistically significant except for TSH which is quite similar to the findings of a study done by Yildizdas D et al [21]. where they found that the levels of T3, T4, fT3, fT4 levels of children with septic shock were significantly lower than those of sepsis without shock and control. They also observed low levels of TSH in children with septic shock and children with sepsis without shock, but the difference was not significant [21]. Dutta S et al [10]. compared thyroid hormone levels between septicemic preterm neonates with shock and without shock. They found that the median (IQR) values of T3, T4, and TSH were 0.83, 3.1, and 1.39, respectively among septic shock patients and 1.57, 8.1, and 5.1 respectively among control. The TSH, total T3, and total T4 were significantly lower ($p<0.001$) in septicemic preterm with shock as compared to septicemic preterm without shock but in the present study, we have excluded preterm newborns from the study to keep the age fraction uniform.

A study conducted by Angelousi AG et al. [22]. involving seven neonates and two adults found that six of the nine participants showed that either, free or total, T3 or T4 was lower in the group of patients with sepsis or septic shock who had unfavourable outcomes than in those who had favourable outcomes. Borkowski J et al [23]. their study concluded that low TSH levels could be a significant factor in a patient with septic shock, especially with a low fT3 serum level. In the above-mentioned studies, none of the studies has included all of the five markers (TSH, T3, fT3, T4, and fT4) and correlated them to septic shock; whereas, we have found that there is a significant decrease in the thyroid profile (TSH, T3, fT3, T4, and fT4) among septic shock survivors as compared to non-survivors. Apart from this, the sample size of our study is quite big as compared to the above-mentioned studies. In contrast to the findings of our study and all the above-mentioned studies, Zucker A et al. [24]. demonstrated no association between thyroid functions and outcomes in critically ill children. We found that all the thyroid hormones (T3, T4, fT3, fT4) including TSH have a significant difference between septic shock survivors and non-survivors which is slightly different from the findings of a prospective cohort study conducted by Lodha et al among 20 patients with septic shock. The study group was divided into two subgroups: survivors ($n = 10$) and non-survivors ($n = 10$). They found that there is a statistically significant difference in TSH level ($p=0.04$) but not with the levels of T3, T4, fT3, and fT4 between septic shock survivors and non-survivors [9].

In our study, we divided neonatal septic shock cases into three groups based on the VIS and found that only T3 was found to be significantly co-related with VIS in late-onset sepsis (<0.001), whereas, McIntosh AM et al. did not find any significant correlation of thyroid profile with VIS [7]. The choice of inotropes and the time of the beginning of inotropes are very subjective, which may affect the result.

VIS is independently associated with important clinically relevant outcomes including ICU length of stay, ventilator days, and cardiac arrest /mortality [9,25]. We have tried our best to depict the relationship between thyroid hormone with septic shock among full-term neonates but despite our efforts, several limitations are present in our study. Firstly, we have not investigated the maternal thyroid profile. The maternal thyroid status was assessed based on history and drug intake, so we couldn't assess the exact maternal thyroid status. Lastly, a larger sample size and serial TSH monitoring are required to establish the clear prognostic significance of the thyroid profile.

Conclusion

Our study suggested a significant decrease in TSH, T3, T4, fT3, and fT4 levels in patients with septic shock as that of patients without septic shock. We also found that there is a significant decrease in thyroid profile among septic shock survivors as compared to the non-survivors and only T3 was found to be significantly co-related with VIS in septic shock among all the patients.

What does this study add to existing knowledge?

The findings of this study regarding the association between thyroid hormone abnormalities and the outcome of patients with septic shock indicated that these abnormalities could be of prognostic value.

Author's contribution

SD: Acquisition and interpretation of data, data analysis, drafting the article, and literature review; **SJ:** Concept, interpretation of data and data analysis, drafting the article, and literature review; **AA:** Data analysis, manuscript review, manuscript editing, revising the article critically for important intellectual content; JS will act as guarantor. All the authors approved the final manuscript.

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