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Original Research Article

An Analytical Prospective Evaluation of Thyroid Profile in Full-Term Neonates Presented with Septic Shock

Chandan Kumar Mishra

Senior Resident, Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India.

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Corresponding author: Dr. Chandan Kumar Mishra
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Abstract

Aim: 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.

Material & Methods: This analytical prospective study was carried out in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India over a period of one year. A total of 220 neonates were selected in the 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.

Results: A total of 220 cases were enrolled, out of which, 62.73% were males and 37.27% were females. 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 ($p>0.05$)**.** Only T3 was found to be significantly co-related with VIS in septic shock in all the groups ($p<0.001$).

Conclusion: 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

Introduction

Thyroid hormones are required for proper brain development throughout pregnancy and after birth. After birth, serum thyroxin (T4) and triiodothyronine (T3) levels rise dramatically, and these hormones are critical for the newborn's growth [1]. Thyroid hormone levels were observed to be abnormal in many individuals without thyroid illness. Euthyroid sick syndrome (ESS) refers to hormonal alterations in the pituitary-thyroid axis in people without thyroid disease [2, 3]. Adults after major surgery or with cardiovascular pathology or and shock have been found to have ESS [4].

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 [5-7].

Since the majority of the previous studies related to septic shock deal with T3 or T4 hormone assay only and was conducted on a small sample size [8-9], 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.

Material & methods:

This analytical prospective study was carried out in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Darbhanga Medical College and Hospital, Darbhanga, Bihar, India over a period of one year.

Methodology

A total of 220 neonates were selected in the 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/mm3 and >24,000/mm3, absolute neutrophil count (ANC) <1800/mm3, 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 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). 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 nonsurvivors 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. The approval was obtained from the institutional ethical committee. 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 220 cases were enrolled, out of which, 62.73% were males and 37.27% were females. The maximum of the neonates (34.55%) were between 7-10 days of age and 64.55% had birth weights between 1.5-2.5 kg.

Out of total cases, 40% were on exclusive breastfeed (EBF). The age of most mothers (53.64%) was between 20-25 years and the percentages of neonates born with institutional delivery and home delivery were 70% and 30%, respectively. The demographic variables of the neonates and their mothers are shown in table 1.

The thyroid profile was performed in all 220 subjects. The mean value of TSH, T3, T4, fT3, and fT4 among neonates with septic shock were 6.55 µg/ml, 61.28 µg/dl, 6.21 µg/dl, 1.55 pg/ml, and

1.27µg/dl and in septic neonates without shock were 5.77 µg/ml, 148.92 ng/dl, 8.62 µg/dl,

2.51 pg/ml, and 1.51 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 6.71 µg/ml, 83.7 ng/dl, 6.71 µg/dl, 7.61 pg/ml, 1.48 µg/dl and 1.61 µg/ml, 39.01 ng/dl, 4.71 µg/dl, 0.92 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 1: Demographic variables of the neonates and their mothers (n=220)

		Total	%
Age	3-7 Days	49	22.27
	7-10 Days	76	34.55

	10-15 Days	35	15.91
	> 15 Days	60	27.27
Gender	Males	138	62.73
	Females	82	37.27
Birth weight	Less than 1.5 kgs	6	2.727
	1.5-2.5 Kgs	142	64.55
	More than 2.5 Kgs	71	32.27
Type of feeding	Exclusive Breast Feed	70	31.82
	Mixed Feed	91	41.36
	Top Feed	59	26.82
Maternal age	<20 Years	70	31.82
	20-25 Years	118	53.64
	>25 Years	22	10
Mode of delivery	Institutional Delivery	154	70
	Home delivery	66	30
Presenting complaints	Abdominal Distension	36	16.36
	Convulsion	39	17.73

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

Thyroid profile	**Septic Shock**			**Septic without Shock**			**Unpaired ttest**
	Mean	Range	SD	Mean	Range	SD	P-value
TSH(µg/ml)	6.55	5.4-7.9	0.80	5.77	0.4-8.9	2.78	P>0.05
T3(ng/dl)	61.28	5.2 – 6.4	29.6	148.92	92.73 – 142.87	21.84	P<0.0001
T4(µg/dl)	6.21	2.4-9.0	1.82	8.62	6.8 – 13.7	1.70	P<0.0001
fT3(pg/ml)	1.55	0.7-2.7	0.48	2.51	1.7-6.2	0.86	P<0.0001
fT4(µg/dl)	1.27	0.5-2.9	0.68	1.51	1.8-2.9	0.38	P<0.0001

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

Thyroid profile	**Septic Shock survivors**	**Septic shock non survivors**	**Unpaired t-test**

	Mean	Range	SD	Mean	Range	SD	P-value
TSH(µg/ml)	6.71	5.7-7.9	0.89	2.91	0.7-8.2	1.71	P<0.0001
T3(ng/dl)	83.7	60.2-89.0	15.7	39.01	5.3-78.91	12.81	P<0.0001
T4(µg/dl)	7.61	5.2-9.6	0.78	4.71	2.8-8.7	1.27	P<0.0001
fT3(pg/ml)	1.48	0.7-3.6	0.41	0.92	0.7-2.1	0.42	P<0.0001
fT4(µg/dl)	1.61	0.8-3.9	0.30	0.84	0.5-1.8	0.39	P<0.0001

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

Vasoactive Vasoactive Inotrope Score	**Thyroid Profile**	**Mean**	**Range**	**SD**	**Unpaired student's t test P- Value**
< 20	TS H(µ g/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(p g/ml)	1.67	1.67-0.42	0.42	p>0.999
	fT4(µ g/dl)	1.31	1.31-0.23	0.23	p>0.999
20 -50	TS H(µ g/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(p g/ml)	1.22	1.22-0.33	0.33	p>0.999
	fT4(µ g/dl)	1.15	1.15-0.38	0.38	p>0.999
> 50	TS H(µ g/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(p g/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:

Sepsis or serious infection within the first four weeks of life kills greater than 1 million newborns globally every year [10]. The attack rate for neonatal sepsis is variable (from <1% to>35% of live births) based on gestational age and time of onset (early[<72 hours after birth] or late[>72 hours after birth]) [12-14]. Neonates with sepsis may present in or progress to septic shock, exemplified initially by cardiovascular dysfunction requiring fluid resuscitation or inotropic support [15].

Regarding the thyroid hormone profile, we found that the diseased neonates had significantly lower TT3 and TT4 levels compared with controls. On the other hand, there was no significant difference between the groups in terms of TSH. Goldsmit *et al.* [16] showed a highly significant difference

between cases and controls in both TT3 and TT4 ($p < 0.01$).

Paul *et al.* investigated 20 full-term neonates who required mechanical ventilation or nasal continuous positive airway pressure. The study showed that thyroid hormones and TSH were significantly decreased in those neonates and correlated inversely with the SNAP score [17]. As regards TSH level, other studies found different results; some neonates with critical illness had transient elevations in serum TSH concentrations (up to 20 mU/l) during recovery from nonthyroidal illness syndrome (NTIS) compared with healthy neonates [18-19]. This was explained by Hemmati and Pishva [19] and Larson *et al.* [20], who stated that the spectrum of thyroid function abnormalities in critically ill neonates includes many pictures; one of them was transient primary hypothyroidism with a late rise of TSH. This pattern can be confusing if the elevated TSH level is associated with the still reduced concentration of FT4.

A study conducted by Angelousi AG et al. [21]. 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 [22]. 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 nonsurvivors. 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. [23]. demonstrated no association between thyroid functions and outcomes in critically ill children. [24]

Conclusion:

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.

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