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Original Article

Paediatrics Section

Thyroid Hormone Abnormalities in Septic Neonates: A Prospective Study

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ABSTRACT

Introduction: 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. There is paucity of studies regarding thyroid hormone function in neonates with sepsis and relation between thyroid hormone abnormalities and risk of mortality.

Aim: To compare mean serum levels of T3, T4, TSH, Free T3 and Free T4 levels between neonates with sepsis and gestational age matched normal controls and to assess severity of thyroid hormone abnormalities at admission between non-survivors and survivors among septic neonates.

Materials and Methods: The prospective study was done in a level III neonatal intensive care unit. Neonates who were admitted with diagnosis of sepsis beyond day 3 of life were recruited as cases. Normal gestation matched neonates beyond day 3 were enrolled as control. Total 51 cases and 48 controls were enrolled in the study. Thyroid Function Tests (TFTs) were obtained at enrollment. Cases were divided into 'survivors' (86.3%) and 'non-survivors' (13.7%). Analysis was done using statistical software packages SPSS and Microsoft Excel. Comparison of mean levels of thyroid hormones between cases and controls was done by t-test or Mann-Whitney U test.

Results: Serum T3, T4, Free T3 and Free T4 levels were significantly lower among cases as compared to gestational age matched control. {For both groups respectively T3: median (IQR) 69 (55,112) vs. 118 (81.5,142), p=0.002; for T4: 8.3 (5.9,11.7) vs. 12.7 (11.3,16.9) p<0.001; Free T3: 2.1 (1.7,2.6) vs. 3.1 (2.4,3.4) p=0.002; Free T4: 1.18 (0.9,1.48) vs. 1.72 (1.46,2.05), p<0.001}. TSH was not significantly different among the groups. The non-survivors among cases had significantly lesser T3,T4 and Free T4 levels as compared to survivors. {For both groups respectively T3:median (IQR) 38 (34,48) vs. 89 (61.2,112), p<0.001; for T4: 6.2 (5.9,7.5) vs. 9 (6.4,12) p<0.001; Free T4: 1.12 (0.87,1.18) vs. 1.2 (0.95,1.5) p=0.02}. Rest of the TFTs were similar in both the groups.

Conclusion: Neonatal sepsis causes significant decrease of thyroid hormones. Non survivor group of Septic neonates had significant low levels of T3 and T4 at admission. Low T3 and T4 levels at admission may serve as prognostic indicator in neonatal sepsis.

Keywords: Non survivors, Prognosis, Sepsis, Thyroid dysfunction

INTRODUCTION

Neonatal sepsis is a common cause of neonatal mortality accounting for 30-45% deaths [1]. Thyroid hormone abnormalities occur during critical illness. These changes are presumably due to influence of inflammatory cytokines on hypothalamic-pituitary-thyroid axis. Low triiodothyronine (T3) and elevated reverse Triiodothyronine (rT3) levels are common and observed early in Critical iilness. With increasing severity of critical illness the levels of critical thyroxin (TT4), Free Thyroxin (FT4) and Thyroid Stimulating Hormone (TSH) may also decrease [2].

Few studies reported an association of decreased levels of TT3 and TT4 with mortality in critically ill children[3,4]. Baseline thyroid abnormalities at admission in sepsis or septic shock is associated with poor outcome [5]. There are only few studies conducted in critically ill neonates regarding thyroid dysfunction and its relation with mortality [6,7]. It is also unclear whether newborns respond in the same way as adults during the critical illness.

In this study, we aimed at comparing thyroid function in neonates with sepsis and gestational age matched controls and assess the severity of thyroid dysfunction in survivors and sepsis non-survivor groups.

MATERIALS AND METHODS

The present case-control study was conducted in a tertiary care neonatal unit from july 2012-july 2013. Prior approval from the institute ethical committee was obtained. Prior written consent from the parents of all study subject were taken. Total of 51 neonates (age 3 days and above and gestational age >32 wks) who were admitted with the diagnosis of sepsis (poor feeding,decreased activity,respiratory distress, abdominal distension and reduced cry) and positive septic screen during the study period were enrolled as cases and 48 neonates as control, which are gestational age matched.

Neonates with gestational age <32 weeks, major congenital anomalies, asphyxiated babies and meconium aspirated babies were excluded. Baseline information such as the age at the time of admission, gestational age, birth weight, Apgar score, duration of illness, family history of thyroid disease, were recorded in printed proforma.

Methods

Peripheral venous sample was drawn from all the subject. Total T4, Total T3, Free T4 and Free T3 were estimated by Competitive Chemiluminescence Enzyme Immunoassay. TSH was estimated by Ultra sensitive sandwich Chemiluminescence enzyme Immunoassay. Investigations and treatment were done in accordance to the unit protocol. Results of the thyroid hormonal profile were not revealed to the treating team. Outcomes pertaining to mortality and morbidity were recorded.

Outcome Variables

Mean T3, T4, TSH , Free T3 , Free T4 levels of septic neonates were compared with gestational matched controls and assessment of severity of thyroid dysfunction among survivors and non survivor groups of septic neonates.

STATISTICAL ANALYSIS

Descriptive statistics were used to describe baseline variables. Categorical outcome variables were analysed by Chi-square test with continuity correction or Fisher's-exact test, wherever one or more expected cell size was less than 5. Numerical variables were first tested for normality. Variables whose skewness statistic was more than 1.96 times the standard error of skewness were considered to have skewed distributions; whereas the rest were considered to have normal distributions. Normally distributed variables were compared by Student's t test after evaluating equality of variance by Levene's test. Variables with skewed distribution were compared by Mann Whitney U test. The p-value of less than 0.05 was taken as significant. Analysis was done using statistical software packages SPSS and Microsoft Excel. Mean T3, T4, TSH, Free T3, and Free T4 values were compared between cases and controls by t-test or Mann-Whitney U test. The mortality and morbidity data were compared between those with impaired thyroid function and those with normal thyroid function (sub group analysis).

RESULTS

A total of 103 neonates were enrolled in the study. Four neonates were excluded from analysis due to sampling errors. Ninety nine neonates were analysed in the study (51 cases group and 48 control group. Mean gestational age among cases were 35.90±2.73 and control were 36.12±2.09. In the case group 7 (13.7%) neonates died and 44 (86.3%) neonates were discharged [Table/Fig-1].

	Cases (n=51)	Controls (n=48)	p-value
Gestation (wks)	35.90±2.7	36.12±2.0	0.6
Birth Wt (kg in mean mans SD)	2.26±0.6	2.49±0.6	0.08
Sex Male/ Female (in number and %)	27 (52.9%)/24 (47.1%)	27 (56.3%)/21 (43.8%)	0.7
Term/ Preterm (in number and %)	28 (54.9%)23/ (45.1%)	27 (56.3%)/21 (43.8%)	0.9
Outcome as Death/ Discharge (in number and %)	7 (13.7%/44 (86.3%)	048 (100%)/	

[Table/Fig-1]: Comparison of baseline characteristics.

The mean T3, T4, Free T3 and Free T4 values among the cases were 85.09±48.8, 9.69±5.3, 2.41±1.2 and 1.23±0.4. Corresponding values in control group were 112.81±34.8, 13.4±4.4, 8.09±0.8 and 1.77±0.4 respectively. Mean values of T3, T4, Free T3 and Free T4 were significantly lower among cases compared to controls [Table/Fig-2]. No significant difference was seen in mean TSH levels in both the groups.

	Cases (n=51)		Controls (n=48)		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	p-value
T3	85.09±48.8	69 (55,112)	112.81±34.8	118 (81.5,142)	0.002
T4	9.68±5.3	8.3 (5.9,11.7)	13.43±4.4	12.7 (11.3,16.9)	<0.001
TSH	4.36±8.8	1.87 (0.77,5.35)	5.13±4.3	3.55 (2,7.3)	0.585
fT3	2.41±1.2	2.1 (1.71,2.62)	8.09±0.8	3.12 (2.42,3.4)	0.002
fT4	1.23±0.4	1.18 (0.94,1.48)	1.78±0.4	1.72 (1.46,2.05)	<0.001

[Table/Fig-2]: Comparison of thyroid profile among cases and control. fT3: Free T3; fT4: Free T4;

Septic neonates with impaired thyroid function were compared in survivors and non survivors. Impaired thyroid function was labeled if the neonate has <10th centile value of either free T3 or free T4 or TSH value >10th centile. All the survivor had normal thyroid function. The mean T3, T4 and Free T4 values were significantly lower among non survivors compared to discharged neonates. TSH and free T3 levels showed no significant difference among both the groups. Comparison of mortality and morbidity data between neonates with impaired thyroid function and normal thyroid function showed all neonate who died had impaired thyroid function and the difference was statistically significant with p-value 0.001 [Table/Fig-3].

	Death (n=7)		Discharge(n= 44)		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	p-value
T3	40.71±10.4	38 (34,48)	92.15±48.9	71 (61.2,112)	<0.001
T4	6.30±1.3	6.2 (5.9,7.5)	10.23±5.5	9.12 (6.44,12.07)	<0.001
TSH	1.14±1.9	0.47 (0.32,0.58)	4.87±9.4	2.08 (0.96,5.41)	0.3
Free T3	1.63±0.4	1.71 (1.21,2.1)	2.56±1.2	2.19 (1.86,2.97)	0.05
Free T4	1.04±0.2	1.12 (0.87,1.18)	1.27±0.4	1.21 (0.95,1.51)	0.018

[Table/Fig-3]: Comparison of thyroid profile among cases with death and discharge as outcome.

DISCUSSION

Most common and consistent abnormality seen in critically ill patients is reduced serum T3 levels [8]. Low levels of T4 and TSH are not common at admission in critically ill patients. 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. Study conducted on forty nine neonates by Das BK et al., had similar observation [9]. They evaluated T3 ,T4 and TSH at diagnosis and at the time of discharge. Improvement in T3and T4 level were observed with the treatment of sepsis. FT3 and FT4 were found to be significantly low in septic neonates in this study at admission but follow-up levels were not obtained (for the purpose of the study).

Study by Lodha R et al., observed low levels of TT3, TT4, fT3, fT4 and TSH reported in children with septic shock when compared to children with sepsis [10]. TT3 on the first day and TT4 on the third day of admission were found to be helpful in predicting disease outcome in critically ill children [11].

In the present study there was significantly low T4,T3 and FT4 baseline levels in non survivor septic neonates compared to survivor group. The mean TSH and FT3 levels were also low in non- survivors but the difference was not statistically significant. Sharma S et al., in their study showed that non-survivors among septic newborns had statistically significantly lower FT3 and FT4 levels (mean values 1.52±0.86 and 1.47±0.9 respectively) compared to the sepsis survivor group ('p' <0.05). No significant difference was observed in FT3,FT4 and TSH between septic shock survivors and non-survivors [7]. 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 [12]. Low T3, T4 and low baseline TSH was associated with higher mortality in neonates admitted in NICU with sepsis [13].

The physiologic significance of hormonal changes in severe non-thyroidal illness has not yet been clearly defined. Baseline thyroid profile in septic neonates may reflect the severity and duration of illness and correlate with survival [14].

LIMITATION

Major limitation of this study is small sample size and lack of follow-up. Secondly, evaluation of thyroid dysfunction in septic neonates with shock and those without septic shock could not be done as only few neonates presented with shock.

CONCLUSION

To conclude, it was found decrease in thyroid hormone values among neonates with sepsis. The finding of present study indicates that thyroid abnormalities at admission in septic neonates could be of prognostic value, perhaps even independent of other such markers. Further studies are required on larger sample size to substantiate the findings and should aim to clearly establish the strength of the above-mentioned association in neonates with sepsis whether thyroid supplementation during initial course of NICU stay can affect the outcome, among neonates with severe sepsis need to be systematically evaluated.

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