

Effect of Altered Thyroid Hormone (FT3&FT4) and Thyroid Stimulating Hormone Levels on Asphyxia Related Neonatal Mortality

Gurjar Umesh*, Gupta Palak and Gupta ML

Department of Paediatrics, SMS Medical College, Jaipur, Rajasthan India

*Corresponding author: Dr. Umesh Gurjar

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Abstract

Original Research Article

To study the effect of altered thyroid hormone (FT3&FT4) and Thyroid Stimulating Hormone (TSH) levels on asphyxia related neonatal mortality. It was a hospital based observational, Analytical study, 32 Term babies with perinatal asphyxia (as per NNF definition) were taken, Thyroid hormones (FT3&FT4) and TSH levels were measured and Outcome results were analysed using student 't' test and Receiver operating characteristic (ROC) curve. P value <0.05 was considered significant. Cases of perinatal asphyxia expired had significant low level of S.FT4 (1.22 ± 0.27 ng/dl) as compare to discharged (1.58 ± 0.38 ng/dl). Cut off value of S.FT4 ≤ 1.39 ng/dl & S.TSH ≤ 3.8 μ U/ml combined was having a good predictive value (SN- 77.2, SP- 90, PPV- 94.44 & NPV- 64.29) for asphyxia related neonatal mortality. Cut off value of combined S.FT4 ≤ 1.39 ng/dl & S.TSH ≤ 3.8 μ U/ml have good predictive value for asphyxia related neonatal mortality.

Keywords: Asphyxia, Hypoxic ischemic encephalopathy, thyroid hormones, hypothyroidism.

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INTRODUCTION

Thyroid hormones play an important role in the synthesis of mitochondrial enzymes and structural elements; in addition they have role in the thermogenesis, water and electrolyte transportation and in the growth and development of central nervous system [1].

Perinatal asphyxia triggers rapid alterations in the concentration of several hormones such as thyroid hormones, catecholamine, glucocorticoids, antidiuretic hormone, aldosterone, renin, atrial natriuretic peptide and insulin [2-5]. Less is known about the effect of perinatal asphyxia on fetal and neonatal level of thyroid hormones despite their importance. Only few studies carried out so far on this subject and these have produced conflicting results. One study performed with asphyxiated newborns using blood samples collected after 4th day of life did not show altered level of thyroid hormone and thyroid-stimulating hormone (TSH) [6]. However, another study performed with seven asphyxiated newborns during the 1st 48 hr of life showed decrease level of free T4 (FT4) in comparison to seven control newborns [7].

Previous studies shows that low levels of thyroid hormone in non thyroid illnesses have been associated with a poor prognosis and high mortality [8].

The objective of our study was to study the effect of altered thyroid hormones (FT3&FT4) & TSH levels on asphyxia related neonatal mortality and to determine whether we can use the serum levels of these hormones to predict asphyxia related mortality.

MATERIAL & METHODS

A hospital based prospective, observational, analytical study was conducted in the Neonatal units of department of paediatrics S.M.S. Medical College, Jaipur during the period of May 2014 to August 2015. Detailed history was taken, that included antenatal, natal and postnatal history, detailed physical examination was done and clinical course of these newborns were followed during their hospital stay (Discharged/Expired). Term babies having gasping, inadequate breathing or no breathing at 1 minute as per NNF definition [9] were considered asphyxiated and were included in the study.

The neonate of mothers who had used antihypertensive, corticosteroids, thyroid or antithyroid drugs during pregnancy, Preterm babies of <37 wk of age, neonates with septicemia, metabolic disorders or any congenital malformations and parent of newborn that refuse to give consent were excluded from the study. Considering a significance level of $\alpha=0.05$ (type I

error) and a statistical power of 90% (B=0.10) to detect a difference of 0.95, in the level of FT4, the sample size required was 30, we included 32 newborns.

Cases underwent physical examination including their neurological assessment and HIE staging, according to the Levene’s modification of Sarnat and Sarnat staging [10]. In all study subjects, serum FT3, FT4 and TSH were measured between 18 and 24 hours of life. Blood sampling included 5 ml of blood in a plain vial collected and processed within 2-3 hours of sampling. Meanwhile, the samples were stored at room temperature. Chemiluminiscence immunoassay was used for the determination of hormone levels. All samples were tested at central laboratory SMS hospital Jaipur, blinded to the patient’s data .FT3 values were expressed in pg/ml; FT4 values were expressed in ng/dl and TSH values were expressed in ulu/ml.

Statistical analysis was performed with the SPSS, version 20 for Windows statistical software package (SPSS inc., Chicago, IL, USA). Mean and SD compared using student ‘t’ test. Receiver operating

characteristic (ROC) curve analysis was performed to determine the optimal cut off values of significant variables. Probability P value <0.05 was considered statistically significant.

RESULTS

A total of 32 asphyxiated newborns were included in the study and the clinical course was followed until final outcome either they Expired or Discharged from the hospital.

In our study a total of 10 out of the 32 (31.25%) cases expired. This percentage was much higher 8 out of 10 (80%) among babies with HIE stage 3. In our study significantly lower mean S.FT4 (ng/dl) was observed among the 10 expired cases (1.22±0.27) as compared to 22 Discharged (1.58±0.38) cases. No significant difference was observed in S.FT3 (pg/ml) [Expired 2.63±0.91, V/S Discharged 3.15±0.88] and TSH (uIU/ml) [Expired 5.01±2.58, V/S Discharged 7.34±3.52] levels.

Table-1: Comparison of Neonatal Outcome in relation to Thyroid Hormone Profile

Outcome		S.FT3(pg/ml)	S.FT4(ng/dl)	TSH(uIU/ml)
Discharged (N=22)	Mean	3.15	1.58	7.34
	SD	0.88	0.38	3.52
Expired (N=10)	Mean	2.63	1.22	5.01
	SD	0.91	0.27	2.58
P Value LS		0.139NS	<0.05S	0.07NS

We also tried to find the sensitivity and specificity of Thyroid hormones and TSH levels for predicting mortality in asphyxiated babies. To get the data in form of true positives and negatives and false

positives and negatives, we need to decide a cut off value for these tests. For this purpose ROC Curves were used.

S.FT3 Level for prediction of asphyxia related mortality at the optimal cut-off points of the ROC analysis curves

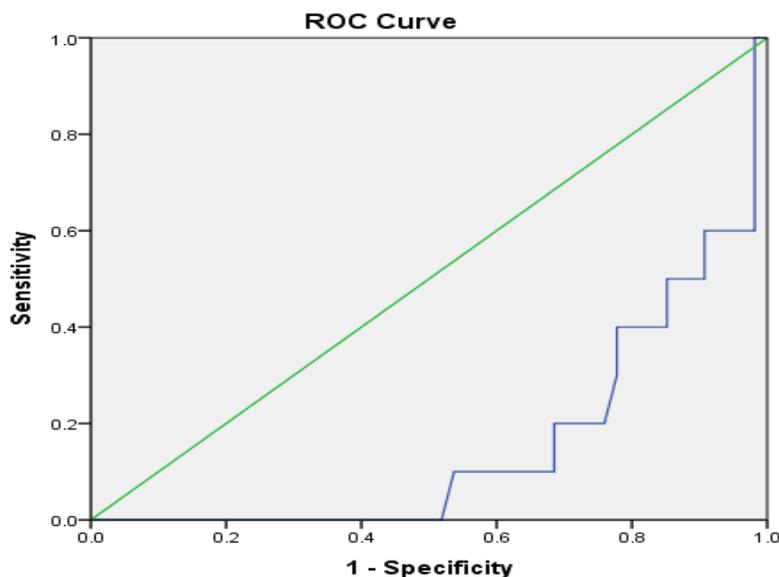


Fig-1: ROC plot of S.FT3 in reference to death in asphyxiated neonates

The ROC curve of FT3 for predicting death in asphyxiated neonates was constructed. The area under curve (AUC) was found to be 0.156 (95% confidence interval =0.044 to 0.267). The optimum cut off value was obtained by points of test values that grants the highest Youden Index that is (SN+SP)-1 .The best cut

off value for S FT3 for predicting mortality was $\leq 1.43 \mu\text{g/ml}$ (at youdon index 0.019 where max SN and SP exist) Sensitivity 32% and specificity 0.02 % was determined with SE 0.101.This was not found to be a good predictive test.

FT4 Level for prediction of asphyxia related mortality at the optimal cut-off points of the ROC analysis curves

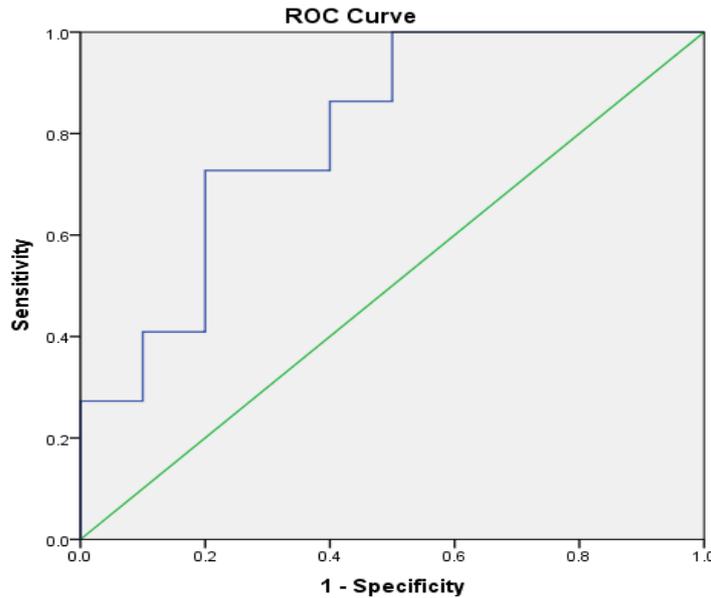


Fig-2: ROC plot of S.FT4 in reference to death in asphyxiated neonates

The ROC curve of S.FT4 (ng/dl) for predicting death in asphyxiated neonates was constructed .The area under curve (AUC) was found to be 0.8 (95% confidence interval =0.623 to 0.977). The optimum cut off value was obtained by points of test values that

grants the highest Youden Index that is (SN+SP)-1 .The best cut off value for S FT4 for predicting mortality was ≤ 1.39 (at youdon index 0.527 where max SN and SP exist) Sensitivity 72.7% and specificity 80 %, was determined with SE 0.09S.

TSH Level for asphyxia related mortality at the optimal cut-off points of the ROC analysis curve

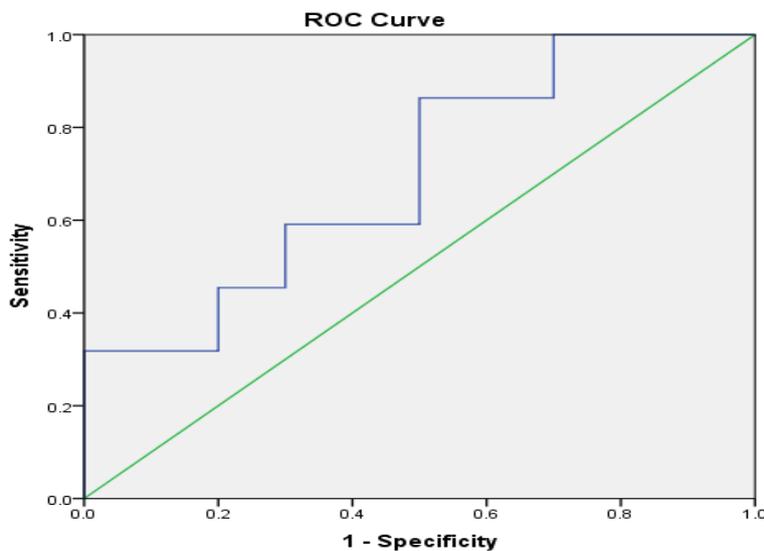


Fig-3: ROC plot of TSH in reference to death in asphyxiated neonates

The ROC curve of TSH for predicting death in asphyxiated neonates was constructed. The area under curve (AUC) was found to be 0.7 (95% confidence interval =0.502 to 0.898). The optimum cut off value was obtained by points of test values that grants the highest Youden Index that is (SN+SP)-1. The best cut off value for S TSH for predicting mortality was ≤ 3.88 uIU/ml (at youdon index 0.364 where max SN and SP exist) Sensitivity 86.4% and specificity 50%, was determined with SE 0.101.

Our results showed that a cut off value of S.FT4 ≤ 1.39 ng/dl was having SN- 72.73, SP- 80,

PPV- 88.89 & NPV- 57.14 and cut off value of S.TSH ≤ 3.8 uIU/ml is having SN- 86.36, SP- 50, PPV- 79.17 & NPV- 62.5, while cut off value of S.FT4 ≤ 1.39 ng/dl & S.TSH ≤ 3.8 uIU/ml combined was having SN- 77.2, SP- 90, PPV- 94.44 & NPV- 64.29.

Sensitivity of cut off level of S.FT4 (≤ 1.39 ng/dl) for predicting mortality in asphyxiated newborns is good (73%) with high specificity (80%) and positive predictive value (89%). Sensitivity of cut off level of S.TSH (≤ 3.88 uIU/ml) for predicting mortality in asphyxiated newborns is higher (86%) than S.FT4 but specificity (50%) is not so good.

Table-2: Predictive value of cut off level of S.FT4 ≤ 1.39 ng/dl, S.TSH ≤ 3.88 uIU/ml and combined S.FT4 (≤ 1.39 ng/dl) & S.TSH (≤ 3.88 uIU/ml) for neonatal mortality in Asphyxiated newborns

Cutoff value	Predicted Outcome	Observed Outcome			Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
		Expired	Discharged	Total				
S.FT4 ≤ 1.39 ng/dl	Expired	8	6	14				
	Discharged	2	16	18	72.73	80	88.89	57.14
	Total	10	22	32				
S.TSH ≤ 3.88 uIU/ml	Expired	5	3	8				
	Discharged	5	19	24	86.36	50	79.17	62.5
	Total	10	22	32				
Combined S.FT4 (≤ 1.39 ng/dl) & S.TSH (≤ 3.88 uIU/ml)	Expired	9	5	14				
	Discharged	1	17	18	77.27	90	94.44	64.29
	Total	10	22	32				

Our observations shows that a cut off value of S.FT4 ≤ 1.39 ng/dl & S.TSH ≤ 3.8 uIU/ml combined is having a good (SN- 77.2, SP- 90, PPV- 94.44 & NPV- 64.29) predictive value for asphyxia related neonatal mortality compared to S.FT4 or S.TSH alone.

DISCUSSION

In our study, we assessed thyroid hormone and TSH levels in the blood (between 18 and 24 h after birth) of asphyxiated newborns in order to investigate the effect of these hormone concentrations on outcome. We also tried to find the sensitivity and specificity of Thyroid hormones and TSH levels for predicting mortality in asphyxiated babies. To get the data in form of true positives and negatives and false positives and negatives, we need to decide a cut off value for these tests. For this purpose ROC Curves were used.

The best cut off value for S FT3 for predicting mortality was ≤ 1.43 uIU/ml (at youdon index 0.019 where max SN and Sp exist) Sensitivity 32% and specificity 0.02 % was determined with SE 0.101. This was not found to be a good predictive test.

The best cut off value for S. FT4 for predicting mortality was ≤ 1.39 ng/dl (at youdon index 0.527 where max SN And Sp exist) with Sensitivity 72.7% and specificity 80 % (determined with SE 0.09).

The best cut off value for S. TSH for predicting mortality was ≤ 3.8 uIU/ml (at youdon index 0.364 where max SN And Sp exist) (Sensitivity 86.4% and specificity and 50 %), was determined with SE 0.101.

To determine the Predictive value of S.FT4, TSH and combined FT4 & TSH for mortality among perinatal asphyxia cases tables were constructed separately for S.FT4, S.TSH and for combined S.FT4&TSH. From these tables sensitivity, specificity and positive & negative predictive values were obtained for each parameter. Our results shows that a cut off value of S.FT4 ≤ 1.39 ng/dl is having SN- 72.73, SP- 80, PPV- 88.89 & NPV- 57.14, cut off value of S.TSH ≤ 3.8 uIU/ml is having SN- 86.36, SP- 50, PPV- 79.17 & NPV- 62.5 and cut off value of S.FT4 ≤ 1.39 ng/dl & S.TSH ≤ 3.8 uIU/ml is having SN- 77.2, SP- 90, PPV- 94.44 & NPV- 64.29 when these two used combindly.

Study done by *DN Pereira et al.* [11] on the 11 babies from the asphyxiated group with FT4 < 2.0 ng/dl between 18 and 24 hr of life, 6(54.5%) died. There were no deaths among the 6 neonates with FT4 > 2.0 ng/dl (p=0.0427). Low FT4 presented 100% sensitivity (CI 95%, 52-100) and 55% specificity (CI 95%, 25-82) in

predicting death of asphyxiated neonates. The positive predictive value was 55% (CI 95%, 25-82) and the negative predictive value was 100% (CI 95%, 52-100). They have not studied effect of TSH.

Our observations showed that a cut off value of $S.FT4 \leq 1.39$ ng/dl & $S.TSH \leq 3.8$ μ U/ml combined was having a good predictive value for asphyxia related neonatal mortality. However a larger study is needed to verify our observations and to make further recommendations.

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