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Study title: Thyroid hormone levels with change in HIE stages in term neonates.

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Abstract

Background: Perinatal asphyxia causes reduced supply of oxygen to almost all organs of the body. It causes Hypoxic Ischaemic Encephalopathy (HIE) in the brain which alters the level of thyroid hormones. There are very few studies which suggest how hypoxia and ischemia affects the level of thyroid hormone.

Aims: To study the change in level of thyroid hormones(T3, T4 and TSH) in cord blood and venous blood at 18-24 hrs of life in different grades of HIE (Stage I, II, and III)

Material and Methods: It was a Prospective Cohort study with a total of 60 full term neonates that required ventilation by bag and mask for >1min or APGAR scored < 7at 1 and 5 minutes or required intubation.According to Sarnat and Sarnat staging criteria babies staged as stage I, II and III. Cord blood samples and venous blood samples at 18-24 hours of life were taken and changes in level of thyroid hormones (T3, T4, TSH) were observed with radioimmunoassay.Student's T test used to assess continuous variables with a confidence limit of 95% and significance level of 5%.

Results: In newborns of HIE Stage I, there was no significant difference betweenthe mean levelsof T3, T4 and TSH in cord bloodand 18-24 hours sample. On the contrary in newborns with HIE Stage II and III we found a statistically significant decrease in the mean levels of T3, T4 and TSH in 18-24 hours sample after birth as compared to that of cord blood.

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Conclusion: InNeonates with higher grades of HIE there is decrease in physiological TSH surge which leads to diminished increase in T3 and T4.

Key words: Hypoxic-Ischemic Encephalopathy, Hypothyroidism, Cord Blood, Apgar score, Thyroid Stimulating Hormone

INTRODUCTION:

Hypoxic Ischemic Encephalopathy (HIE) is one of the major cause of neonatal mortality in both developed and developing countries. In neonates, birth asphyxia is the most common cause for HIE. HIE affects about 1.5 per 1000 live births in developed countries while in developing countries incidence rate varies from 2.3 to 26.5 per 1000 live births [1,2]. In HIE, hypoxic and ischaemic episodes lead to anaerobic metabolism which in turn generates large amount of lactate and inorganic phosphates. Excitatory and toxic amino acids like glutamate accumulate in the tissues. NMDA(N-Methyl-D-Aspartate), AMPA(α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)and Kainate receptors are over activated leading to increase sodium and calcium ions permeability which causes intracellular accumulation of ions leading to cytotoxic edema and neuronal death [3]. These cellular injuries can be immediate or delayed as secondary energy failure which occurs approximately 6-24 hours later and these injuries can be necrotic or apoptotic.

Effect of hypoxia on thyroid metabolism has been studied in adults and older children.[4] Thyroid hormone has an important role in development of central nervous system. Several perinatal factors like gestational age, mode of delivery, maternal age, maternal thyroid status, HIV status, history of PROM, APH, sex, weight and perinatal asphyxia etc. which influence the level of cord blood thyroid hormones have been studied.[5-11] Effect of HIE on thyroid hormone in term neonates is much underexplored subject. In this study researchershave evaluated the change in the level of thyroid hormones in full term neonates and degree of change in different grades of HIE.Thyroid hormone plays a vital role in the neurodevelopment of the baby, so knowing the thyroid status and rectifying it timely will save a child from poor mental development.

METHODS

It was a Prospective Cohort Study conducted in 60 randomly selected full term neonates with birth asphyxia delivered in maternity unit of aTertiary care center in Central India in duration of 1 year from Nov 2014 to Oct 2015 after getting ethical approval from the institutional committee.

This sample size was calculated considering a significance of 0.05 and a statistical power of 90% based on prevelancepresented by Pareira et al.[12]

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Inclusion Criteria:

Full Term asphyxiated newborns born with one of these criteria:

- Required bag & mask ventilation for at least 1 minute immediately after birth.
- Required intubation for resuscitation.
- APGAR score at 1 and 5 minute <7

Exclusion Criteria:

- Preterm newborns (< 37 weeks of gestation)
- Newborns with any congenital malformations or diseases
- Baby born to mother with any thyroid disorder.
- Baby born to mother who were treated with antihypertensive, diuretics, corticosteroids and antithyroid drugs.
- Parents of the baby not giving consent to be included in the study.

Gestational age of the newborn was determined by Naegele's formula [13] and confirmed by clinical examination by New Ballard Score.[14]If there was a difference of more than 2 weeks then clinical parameters were considered.

Umbilical cord blood from babies born with asphyxia was sent for T3, T4 and TSH levels via radioimmunoassay. Hypoxic ischaemic encephalopathy grading was done with Sarnat and Sarnat Staging (Table 1). Severity of encephalopathy graded as HIE I, HIE II and HIE III. Again at 18-24 hours venous blood sample were taken from cases and sent for T3, T4, and TSH measurement. Values expressed as T3 in ng/dl, total T4 in µg/dl and TSH in mIU/dl.

Table 1: Sarnat and Sarnat staging for HIE in term neonates: [15]

SIGNS	STAGE I	STAGE II	STAGE III
Level of consciousness	Hyperalert	Lethargic	Stuporous, Coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/Clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent

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Pupils	Mydriasis	Myosis	Unequal, Poor light reflex
Seizures	None	Common	Decerebration
EEG findings	Normal	Low voltage changing to seizure activity	Burst suppression to isoelectric
Duration	< 24 hrs if progresses, otherwise may remain normal	24 hrs to 14 days	Days to weeks
Outcome	Good	Variable	Death, Severe deficits

Statistical analysis was done with SPSS 16 software. Continuous variables were described as mean, median, standard deviation and categorical variables in percentage.For categorical variables chi square test was used. Student's T test used to assess continuous variables with a confidence limit of 95% and significance at a level of 5%.

RESULTS

Table 2: Characteristics of cases in our study.

Characteristics		Number	Percentage (%)
Sex of Baby	**Male**	36	60
	Female	24	40
Parity	**1**	36	60
	2	18	30
	>3	6	10
Mode of delivery	**Vaginal**	35	58.3
	Cesarean	25	41.7
Mother's age (years)	**<20**	10	16.7
	20-25	35	58.3
	>25	15	25
Mother's thyroid hormone levels (Mean+SD)	**T3 (ng/dl)**	129.15+21.12	-
	T4 (µg/dl)	8.1+1.47	-
	TSH (mIU/dl)	4.08+0.89	-
HIE Stage	**I**	3	5
	II	30	50
	III	27	45
APGAR Score at 1min after birth	**5-6**	0	0
	3-4	11	18.3
	<3	49	81.7
APGAR Score at 5min after birth	**5-6**	13	21.7
	3-4	44	73.3
	<3	3	5

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There was no significant difference in level of thyroid hormones in cord blood samples of the cases. In HIE stage I the mean level of T_3, T_4 and TSH in cord blood in asphyxiated babies were 90.67ng/dl, 9.60 µg/dl, 8.76mIU/dl and in sample from 18-24 hours after birth were 68ng/dl, 8.37 µg/dl, 4.35mIU/dl with P value of 0.09, 0.66, 0.07 respectively**[Table 3]**. These results were not statistically significant. In contrast to HIE I, the mean level of T_3, T_4 and TSH in cord bloodin HIE stage II were 85.21ng/dl, 8.69 µg/dl, 9.30mIU/dland andin sample from 18-24 hours after birth were 73.5ng/dl, 6.67 µg/dl, 4.67 mIU/dlrespectively with a P value < 0.05 in all which suggest a significant decrease in level of thyroid hormone**[Table 4]**. Similarly in stage III the mean level of T_3, T_4 and TSH in cord blood were 74.93ng/dl, 8.61 µg/dl, 8.51mIU/dl and at 18-24 hour were 63.82ng/dl, 6.06 µg/dl, 3.95 mIU/dlrespectively with a P value of <0.05 which again showed a statistically significant decrease in all T_3, T_4 and TSH**[Table 5]**. Thus, this study concludes that as the severity of HIE increases, the derangement of thyroid hormones also increases significantly.

Table 3: Level of thyroid hormones in HIE stage I in cord blood and 18-24 hours sample

HIE STAGE I			
Thyroid Hormone Levels	**Cord Blood**	**18-24 Hour Sample**	**P Value**
	MEAN + SD	MEAN + SD	
T3 (ng/dl)	90.67 + 17.01	68 + 5.29	0.09
T4 (µg/dl)	9.6 + 4.36	8.37 + 1.12	0.66
TSH (mIU/dl)	8.76 + 0.71	4.35 + 3.05	0.07

Table 4:Level of thyroid hormones in HIE stage II in cord blood and 18-24 hours sample

HIE STAGE II			
Thyroid hormone levels	**Cord Blood**	**18-24 Hour Sample**	**P Value**
	MEAN + SD	MEAN + SD	
T3	85.21 + 14.48	73.5 + 16.21	0.004
T4	8.69 + 2.12	6.67 + 2.07	0.0004
TSH	9.3 + 4.49	4.67 + 3.48	<0.0001

Table 5: Level of thyroid hormones in HIE stage III in cord blood and 18-24 hours sample

HIE STAGE III			
Thyroid hormone levels	**Cord Blood**	**18-24 Hour Sample**	**P Value**
	MEAN + SD	MEAN + SD	
T3	74.93 + 21.87	63.82 + 25.72	0.09
T4	8.61 + 2.51	6.06 + 2.79	0.0009
TSH	8.51 + 3.53	3.95 + 5.35	0.0005

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DISCUSSION:

Thyroid function can be affected by several factors acting on different stages of metabolism. The effect of hypoxia on thyroid hormone has long been recognized. In the present study researchers have evaluated that as the stage of HIE increases more and more thyroid hormones are affected. It was observed that decrease in physiological TSH surge in newborn with HIE was due to asphyxia. After this low TSH surge the corresponding increase in T3 and T4 was diminished due to hypoxia and ischemia.

Borges et alobserved that the mean fT3, and fT4 levels were significantly lower at 24 hours and 48 hours in the asphyxiated group than the control group but the mean level of TSH were similar. They observed that asphyxiated newborns failed to increase their circulating thyroid hormone levels appropriately in spite of the normal TSH surge. They suggested that the reason for it may be lack of increase in thyroid function in study group of newborns has occurred so as to diminish the oxygen consumption and metabolic rate.[4]

In this study researchers found that there is significant decrease in T3, T4 and TSH from cord blood to 18-24 hours sample in both HIE II and HIEIII.Pareira et al found lower level of T4, T3, fT4, and TSH in asphyxiated newborns at 18-24 hours after birth. They concluded that it may be due to central hypothyroidism secondary to asphyxia.They observed that moderate/severe hypoxic-ischemic encephalopathy presents a greater involvement of the thyroid function and consequently a greater risk of death.[12,16] Frank et al observed that prenatal treatment with thyroxine and thyroid releasing hormone (TRH)accelerates surfactant system maturation and has opposite effect on the antioxidant enzyme in the lung.[17]

Qureshi et al, Etuk et al and Siva et al observed more mortality as the HIE stage increases and highest mortality in HIE stage III.[18,19,20]

Gurjar et al found that mean value of fT3 was significantly decreased in HIE stage II and III than HIE stage I. It was also observed that fT4 was significantly low in all 3 stages. The mean value of TSH was significantly low only in HIE stage III when compared to HIE stage I.[21]

In euthyroid sick syndrome T3 and T4 are deficient without an elevation of TSH. It is non-thyroid illness syndrome which is combined central and peripheral hypothyroidism often associated with other vital hormone deficiencies.[22] It can occur in sepsis, post-operative surgeries, meconium aspiration, protein energy malnutrition and use of certain drugs like corticosteroid, dopamine, and ionized contrasts.[16]

This study concludes that neonates with higher grades of HIE has decrease in physiological TSH surge and there is corresponding diminished increase in T3 and T4. It suggests that the central hypothyroidism is due to reduced production of TSH. So, timely detecting this pathology and

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supplementing thyroid hormones may remove the hindrance in the neurodevelopment of the growing baby.

This study was short termed with smaller sample size, so to establish the above findings and to evaluate whether these changes are transient or permanent, studies with larger sample size and with multiple thyroid samples in follow up are needed.

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