Original Article

A Comparative Study of Serum Thyroxine, Tri-Iodothyronine and Thyrotropin Between Low Birth Weight and Normal Birth Weight Neonate.

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Abstract

This was a prospective randomized study. The period of study was from April 2005 to May 2006 and conducted in the department of Pediatrics and obstetrics in BSMMU, in DMCH and in the Institute of nuclear Medicine (INM). A total of 90 neonates of either sex of postnatal age ranging from 3-6 days were selected for this study. They were divided into three groups of 30 preterm LBW (gestational age < 37weeks & birth weight < 2.5 kg) neonates, 30 full-term small for gestational (SGA) age (gestational age ≥ 37weeks & birth weight < 2.5 kg) and 30 full-term appropriate for gestational (AGA) age (gestational age ≥ 37weeks & birth weight ≥ 2.5 kg) neonates. The mean of gestational age of preterm LBW, full term SGA and full term AGA were 34.73 ± 0.20 weeks, 38.6 ± 0.21 weeks and 38.80 ± 0.15 weeks respectively. We studied their thyroid function status by estimating serum T_3, T_4 and their controlling homone TSH and then the results were compared between the groups. We observed that the mean serum T_3 & T_4 level in low birth weight neonates were significantly lower in comparison to those of the full term AGA neonates. The estimated mean values of serum T_3, T_4 levels were lowest in preterm LBW neonates-(T_3 =0.93 ± 0.05 nmol/1 and T_4 = 129.29± 6.33 nmol/1), highest in full-term AGA neonates (T_3 = 1.98 ± 0.05 nmol/1 and T_4 188.47 ± 3.66 nmol/l) and intermediate in full term SGA neonates (T3 =1.49 ± 0.03 nmol/l and T4= 152.66 ± 2.87 nmol/l). Regarding TSH value there was no significant difference between the groups (TSH in preterm LBW 6.52 ±0.46 miu/l, in full term SGA 6.37 ±0.30 miu/l, full term AGA 5.69 ± 0.35 miu/l).There were positive correlation (r) found between T_3 & T_4 with birth weight and gestational age and negative correlation between TSH and birth weight and no correlation with gestational age. It found that higher the birth weight higher was the value of serum T_3 and T_4 but TSH level did not differ. From our study as serum T_3 and T_4 levels were lower in LBW neonates than that of the full term (AGA) and TSH level did not vary between groups So we concluded that during thyroid screening program both T_4 and TSH are considered. On the basis of our findings we recommended that in preterm LBW or in low birth weight neonates where serum T_4 level is at hypothyroid level (<64.5nmol/l) with normal TSH should be kept under regular follow up till T_4 value become normal.

Key words: thyroxine (T_4), triiodothyronine (T_3), thyroid stimulating hormone (TSH) congenital hypothyroidism, hypothyroxinemia.

Introduction

Disorder of the thyroid function has been considered as one of the most important endocrine problem in newborn babies. The prevalence of congenital hypothyroidism based on worldwide program for neonatal screening is 1/4000 infants[12] Maternal thyroid hormones are important in fetal development in first trimester before establishment of the fetal Hypothalamic-Pituitary-thyroid (HPT) axis. Late transfer of maternal hormones is not as important to the fetus but may be neuroprotective for a fetus with congenital hypothyroidism. The clinical manifestations of congenital hypothyroidism are often subtle at birth so the mass neonatal screening programs have allowed for early identification of hypothyroid neonates. The growth and development disorders due to hypothyroidism may be prevented by replacement therapy during first few weeks[3,4] to 45 days of birth. During screening for congenital hypothyroidism serum levels of T_4 and TSH of cord blood or venous blood were measured in first week of life. The serum levels of T_4 and TSH vary at different birth weight and gestational age. The T_4 concentration appear to increase near term. The T_4 values in premature neonates have been shown to increase progressively with the increase of birth weight and gestational age. Serum T_4 level should be standardized according to birth weight and gestational age during screening. It has been found in different studies[1,3,4,6]

that serum T_4 level in low birth weight newborn is lower than the full-term appropriate for gestational age (full-term AGA) neonates. But serum TSH level between the groups have no significant difference. Thus these hormone levels in low birth weight newborn have an implication in regard to screening programs for congenital hypothyroidism. The high percentage of false positive results were found in pre term low birth weight neonates if only serum T_4 level is considered during screening.[5] The incidence of hypothyroidism may be increased in a population consisting of low birth weight (premature low birth and term SGA neonates) infants. Larson et al reported the incidence of hypothyroidism in low birth weight infant is 1:250.[17]

A large part of Bangladesh is the zone of iodine deficiency area and iodine deficiency disorder (1DD) are very common in this part. So incidence of congenital hypothyroidism is suspected to be high in this part. Delange F et al told the daily iodine requirement of pre-term infant is more than twice than the term infant.[18] Considering this condition the study of thyroid function in low birth weight neonates were carried out. In this study we considered low birth weight neonates (preterm LBW & Full term SGA) as study group and full-term appropriate for gestational age (AGA) as control group. Here serum levels of thyroxine (T_4), triiodothyronine (T_3) and their controlling pituitary hormone TSH were measured.

In low birth weight newborn the pattern of thyroid function is qualitatively similar but quantitatively smaller than that of the full term AGA newborn . At birth serum thyrotrophin (TSH) level is increased in response to cooling by first 30 minutes after birth. This high level of TSH stimulates increase secretion of thyroxin (T_4) and triiodothyronine (T_3) to a peak values at 24-48 hours of age. In low birth weight newborn babies even with this postnatal TSH surge the serum level of T_4 remain significantly lower than the full term AGA neonates. This low serum level of T_4 is known as hypothyroxinemia[7] which is transient in nature. Some authors has recommended that thyriod hormone supplementation should not be used for the infants with low thyriod hormone level unless they have elevated TSH level.[21]

Materials and Methods

This was a prospective randomized study. The period of study was from May 2005 to April 2006 and conducted in the Dept. of Pediatrics, Obstetric in BSMMU, in DMCH and the Institute of Nuclear Medicine (1NM). A total of 90 neonates of both sex were included in this study. They were divided into three groups of thirty full-term AGA, thirty full term small for gestational age (SGA) and thirty preterm low birth weight (preterm LBW) neonates. In all the groups 15 males and 15 females of postnatal age ranging from 3 to 6 days were selected. They were selected randomly from obstetric ward in BSMMU and in DMCH. The neonates whose birth weight were recorded at the time of delivery were selected in the study group. The gestational age was calculated from the first date of last menstrual period of mother (calculated in the obstetric unit) and confirmed by Dubowitz score. (Dubowitz et al.,1970) when needed. Weight of neonates were taken from history sheet of obstetric ward which recorded just after delivery.

The inclusion criteria were:

Apparently healthy preterm LBW, full-term SGA and full term AGA neonates up to 6 days of postnatal age were selected.

Exclusion criteria:

Extremely low birth weight neonates (birth weight <1000g), Any history of maternal endocrine disease or systemic illness and history of maternal drug abuse. The attendants of the subjects were put through an oral questionnaire and a detail history was taken and findings of physical examination were noted in a predesigned case record form.

Observation and Results

Clinical characteristics (postnatal age, birth weight in kg and gestational age) of full-term AGA, full term SGA and preterm LBW neonates and level of significance are shown in Table- 1 & 2.

Table-1: Shows clinical characteristics i.e. post-natal age, birth weight and gestational age with their mean.

Groups	Age in days (Post-natal age) and mean	Birth Wt. in kg, and mean	Gestational age in weeks, and mean
Group 1 n=30	3.83 :1=0.14	2.92±0.05	38.80±0.15
Full term AGA	(4.11-3.55)	(2.92-2.90)	3(8.3-38.77)
Group 2 n=30	3.73±0.14	1.91±0.04	38.6±30.21
Full term SGA	(4.01-3.45)	(1.99-1.83)	(39.05-38.21)
Group 3 n=30		1.62±0.03	37.73±0.02
Full term LBW		(1.68-1.56)	(.13-34.33)

Table-2: Level of significance of clinical characteristics between the groups

Groups	Gestational Age	Birth weight
Full term AGA vs Full term SGA	t = 0.658 p = 0.538>0.50	t = 15.694 p = 0.000<0.001
Full term AGA vs Preterm LBW	t = 16.223 p = 0.000<0.001	t = 20.423 p = 0.000<0.001

Table-3: Biochemical characteristics i.e. serum T_3, T_4 & TSH levels of different groups with mean.

Groups	T_3 nmol/l and Mean	T_4 nmol/l and Mean	TSH mui/l and Mean
Group 1 n=30 Full term AGA	1.98±05 (2.08-1.88)	188.47±3.66 (195.79-181.15)	5.69±0.35 (6.39-4.99)
Group 2 n=30 Full term SGA	1.49±0.03 (1.55-1.43)	152.66±2.87 (158.40-146.92)	6.37±0.30 (6.97-5.77)
Group 3 n=30 Full term LBW	0.93±0.05 (1.03-0.83)	129.29±6.33 (141.95-116.63)	6.52±0.46 (7.44-5.6)

Table-4: Level of significance of serum T_3, T_4 & TSH of different groups by 'p' values and 't' values.

Groups	T_3 nmol/l and Mean	T_4 nmol/l and Mean	TSH mui/l and Mean
Full term vs Full term SGA	t = 8.001 p<0.001	t = 7.691 p<0.001	t = 1.485 p = 0.143 >0.5
Full term vs Preterm LBW	t = 15.032 p<0.001	t = 8.090 p<0.001	t = -1.427 p = 0.159 >0.1
Full term SGA vs Preterm LBW	t = 9.652 p<0.001	t = 9.652 p<0.001	t = 0.271 p = 0.787

Table-5: Correlation coefficient for serum of T_3, T_4 and TSH vs Gestational age in whole population (n=90)

Correlation ship	Correlation Coefficient	Probability
Correlation of gestational age with serum T3	r = 0.777 t = 11.566	p<0.001
Correlation of gestational age with serum T4	r = 0.585 t = 6.764	p<0.001
Correlation of gestational age with serum TSH	r = 0.107 t = 1.006	p = 0.1/NS

In Table 2 the mean birth weight of low birth weight (SGA and preterm LBW) neonates were significantly (p <0.00 1) lower as compared to full term AGA. In preterm LBW neonates the mean gestational age was significantly lower (p < 0.00 1) than full term AGA. The mean gestational age did not differ significantly (p> 0.5) between full term SGA and full term AGA.

In Table 3 our estimated mean serum T_4 level in preterm LBW neonates was 129.29 ± 6.33 nmol/1. The mean serum T_4 value was little lower than the values found by Frank 14 1±32 nmol/l.1997[5], Jacobsen 155 nmol/l'[2] and Ubnnann 140±32 nmol/l.[11] Our observed lower value may be due to absence of any stress factor during delivery or less exposure to environmental temperature or environmental temperature variation was minimum. The mean serum T_4 level in full term SGA neonates was 152.66 ± 2.87 nmol/l. Jacobsen et al, in 1977 found 206 nmol/1.[12] The comparative lower value in our study was probably due to the absence of any stress during delivery. We found the mean serum T_4 level in full-term neonates was 188.47 ± 3.66 nmol/1. Di amond, F.B found 191±58.5 nmol/1[12] and Jacobsen B.B et al found 267 nmol/1. The mean serum T_4 level in our study was similar to Diamond's reported value but lower than Jacobsen's value.

We found the mean serum T_3 in preterm LBW neonates 0.90 ± 0.05 nmol/l. Jacobsen et al found 0.89 nmol/l and Adams LM et al found 0.89 ± 0.15 nmol/1.[12,14] The value in our study was similar to values found by others. The mean serum T_3 level in full term SGA neonates was 1.49 ± 0.03 nmol/1. Jacobsen et al found 1.88 mu/l.[12] Our observed lower value may be due to lower serum T_4 level. The mean serum T_3 level in full term newborn babies was 1.98 ±0.05 nmol/1, Jacobsen B, B et al found 2.33 mnol/l. The mean serum T_3 value in our study was lower than the value observed by Jacobsen et al. This low value may be due to low serum T_4 level.

In our study the mean serum TSH level in full term AGA was 5.69 ± 0.35 miul/l, in full SGA 6.37 ± 0.46 miu/l and in preterm LBW 6.52 ±0.46 miu/l. Jacobsen et al found median serum TSH level 2.3 miu/l.[12] Our observed higher serum TSH value than Jacobsen's study may be due to low serum T_4 and T_3 levels.

In Table 4. We found the mean serum T_4 and T_3 level in preterm LBW newborn and full term SGA was significantly (P <0.001) lower than the full term AGA babies. The mean serum T_4 and T_3 value of preterm LBW babies was significantly lower than the full term SGA babies (P< 0.001). The statistical significant difference regarding mean serum T_4 & T_3 levels between full term AGA and fullterm SGA as well as preterm LBW neonates were in conformity with study done by Jacobsen et al and Frank J.E et al.[4,12] Regarding level of significance of TSH between full-term AGA and full term SGA (p> 0.5) and between full term AGA and preterm LBW neonates (P >0.1) were non significant. Same result also found by Jacobsen et al and Frank J.E et al[4,12]. They observed that after 22 weeks of gestation the serum level of TSH did not show any significant difference.

The range of gestational age of whole population in our study was 34 to 40 weeks. Jacobsen B. B. et al.

Discussion

The thyroid dysfunction leading to congenital hypothyroidism is a relatively common disorder in neonates. Several published studies reported marked lower serum T_4 and T_3 level in low birth weight neonates than that of full-term neonates. The main factors that influence thyrioid function in pre-term infants are immaturity of the hypothalamic-pituitary-thyriod axis, immature thyroid hormone synthesis, immature thyroid hormone metabolism and systemic diseases. Insufficient or excessive iodine intake also influence pre-term thyroid function.[16] lower values give false impression that the baby has been suffering from congenital hypothyroidism (or transient hypothyroxinemia/transient hypothyroidism). So serum TSH level measurement is mandatory. In our study we selected LBW newborn babies as study group and considered clinical characteristics (gestational age, birth weight and postnatal age) in Table I and biochemical characteristics (serum T_4, T_3 & TSH) in Table 3. The results were compared with full term neonates of the control group to find out any influence of gestational age and birth weight on measured thyroid hormones and TSH. Jacobson found no statistically significant difference of serum TSH level among full-term AGA, fuilterm SGA and preterm LBW.

According to our laboratory reference serum T_4 level was mentioned 64.5-152 nmol/l. Serum level less than 64.5 nmol/l considered as hypothyroid level. In our study, the serum T_4 levels of 4 preterm LBW neonates were below 64.5 nmol/l but their TSH level within normal range (<20 mlu/l). So out of 30 preterm LBW neonates we got 4 who were having transient hypothyroxinemia i,e 13.33%. Urhmann found 16% hypothyroxinemia in preterm neonates at 72 hours of age and 18% at one week of age.[10] Hadeed A. J.et al reported 11.2% of transient hypothyroxinemia in preterm infants of 34 to 36 weeks' gestational age.[18] The gestational age of our studied preterm were 34 to 36 weeks.

In Table 5 we have found significant positive correlation between birth weight and serum T_3 ($r = 0.795$, $t = 12.28$ 1, $P<0.001$) and serumT_4 ($r = 0.700$, $t = 9.204$, $P <0.001$) in both control and study group (n= 90). The findings of the present study were in conformity with the studies of Bongers-Schokking JJ, et al,[14] Oddie TH.[15] But we found significant negative correlation between birth weight and serum TSH ($r = -0.354$, t -3.548, $P< 0.00$ 1) in the whole population. Our observation agrees with Bongers-Schokking JJ, et al.[14]

In Table 6. We found significant positive correlation between gestational age and serum T_3 ($r = 0.777$, $t=$ 11.566, $P< 0.001$), serum T_4 (r 0.585, t 6.764, $P <0.001$) and found no correlation of gestational age with serum TSH ($r = 0.107$, t 1.006 $P>0$. 1) in whole population which was also found by J.J. Bongers-Schokldng et al and Oddie TH.[14,15]

Conclusion

From our study it may be concluded that serum T_3 and T_4 levels were lower in LBW neonates than that of full-term AGA neonates where as serum TSH level was slightly higher in LBW babies.

Thyroid screening is one of the important program considered in neonatal life. This depends on estimation of T_4 and TSH levels. In case of low birth weight neonates particularly in preterm LBW neonates false positive results often found if only T_4 value is considered. As the T_4 level is varied with gestational age and birth weight so normal value should be adjusted according to the gestational age and birth weight. For better understanding and to arrive a definite conclusion in interpreting T_4 screening values in LBW neonates, birth weight and gestational age must be taken into account as well as following suggestion can be made:

1. Follow up estimation, i.e. after screening in the first week of life the LBW neonates (with low T_4) should have additional screening at least at 2 and 4 to 6 weeks with T_4 and TSH assays so that late onset , transient hypothyroidism can be diagnosed as early as possible.
2. Further prospective studies consisting larger number of neonates with multistage sampling, including estimation of TBG, TBPA, FT_3 and FT_4 should be carried out.

Recommendation

In LBW newborn babies with serum thyroxine (T_4) values at hypothyroid level (< 64.5 nmol/1) with normal serum TSH should be kept under regular follow up for estimating serum T_4 weekly for 6 weeks or more until serum T_4 value become normal. They should also be kept under regular clinical assessment of neurological and physical development for further evaluation for at least one year. American Academy of Pediatrics: Newborn screening of hypothyroidism recommended guidelines. Pediatrics 1993; 91:1203.

References

1. Fisher DA, Dussault JH, Foley TP, Kaline AH, LaFranchi S, et al. 1979, Screening for congenital hypothyroidism: result of screining one million North American infants. J. of Padeatrics 94: 700-5.

2 . Toft AD. Thyroxin therapy. N Engl J Med. 1994; 331 : 174-180.

3 . Fisher DA, Foley BL. 1989. Early treatment of congenital hypothyroidism 83:785-9.

4 . Frank JE. Faix JE. Hermox RI. et. Al Thyroid function in very low birth weight infants: Effect on neonatels thyroid screening J Pediatr 1996: 128 :548.

5 . Schonberger W, Grimm W, Emmrich P. Ge Mpp W,1979. Reduction of motality rate in Preterm infants by substitutin of thyroid hormone J Pediat. 135:245 -53.

6 . Fisher DA. Thyroid function in premature infant: The hypothyroxinamea of prematurity. Clin. Perinatal 1998; 25:999 - 1014,

7 . Mercado M, Vu WH, Fancis I, Szymono W, Gold H, 1988, Thyroid function in preterm infant. Early Hum Dev 16: 131 -141.

8 . Hadeed AJ, Asay LD, Kelin AH, Fisher DA, 1981 Significance of transient postnatal hypothyroxinemia in premature infant with or without respiratory distress syndrome. Pedatrics 68:494-8.

9 . Diamond FB, Park iS Tenore A,Bmarinoe JM, Bongiovanni AM. 1979 Hypothyroxinemia in sick and well preterm infant. Clin Pediatr. 18: 555-561.

10. Uhrmann 5, Mark KH, Maisel Mi, Kuhn HE, Kaplan M, tiger R, 1981. Frequency of transient hypothyroinemia in low birth weight infant: Potential pitfall for neonatal screening programmes Arch Dis Child 56: 214-7.

11. Weichsel ME Jr. 1978. Thyroid hormone replacement therapy in the peririatal period neurological consideration. J Pediatr. 92: 1035.

12. Jacobsen BB, Anderson Hi, Petersen B, Dige Petersen H, Hummer L, 1977. Serum level of thyrotropin, thyroxin and triiodothyronine in full term, small for gestational age and preterm newborn. Acta Paediatr. Scand. 66: 681-7.

13. Adams LM, Emary JR. Clark Si, Canton El, Nelson IC, 1995. Reference ranges for newer thyroid fu.nction tests in premature infant J. Pediat. 126: 122-7.

14. Bongers - Schokking ii, Schopman W 1984. Thyroid function in healthy normal, low birth weight and preterm infant. Eur.j Pediat. 143:117-22.

15. Oddie TH, Bernard B, Klein AR, Fisher DA, 1979. Comparison of T3, T4 and TSH Concentration in cord blood serum of infant up to 3 month of age Early Hum. Dev 3: 239-244.

16. Van wassenaer AG, KOKJH, Hypothyroxinemia and thyroid function after preterm birth. Semen Neonatal. 2004; 9:3-11 [Pub Med].

17. Larson C, Hermos R, Delaney A, Daley D, Mitechell M. Risk factors associated with delayed thyrotropin elevations in congenital hypothyroidism. J Pediatr. 2003; 143:587-591 [Pub Med]

18. Delange F. Optimal iodine nutrition during pregnancy, lactation and neonatal period. Int J Endocrine Metab. 2004; 2:1-12.

19. Rapaport R, Rose S R, Freemark M. Hypothyroxinaemia in the pre term infant: the benefit & risk of thyroxin treatment. J Pediatr. 2001; 139:182-188 [Pub Med]