The effects of topical iodine containing antiseptics on thyroidal status of preterm versus term babies

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ABSTRACT

الأهداف: تحديد أثر عنصر الأيودين المحتوي على مضادات الأنتان على وظيفة الغدة الدرقية خلال الأسابيع الثلاثة الأولى من الحياة للمواليد الذين تعتبر أوزانهم غير منخفضة كثيراً والمواليد مكتملي فترة الحمل، وتقييم وظيفة الغدة الدرقية لديهم والحالة السلوكية بعد سبع سنوات.

الطريقة: أجريت الدراسة (كوهيرت1) خلال الفترة ما بين عام 1997م وحتى عام 1998م. تمت دراسة عدد 57 مولوداً خديجاً (الأسبوع 30–35 من الحمل)، وعدد 29 مولوداً مكتمل النمو. بعد مرور سبعة أعوام (في عام 2005م) أجريت الدراسة الثانية (كوهيرت2) على نفس الـ28 خديج و الـ18 رضيع مكتمل فترة الحمل بمستشفى بيهسيت يو – بتركيا. تم قياس مصلال ثايروتروبين، هيريودوثايرونين والثايوركسين الكامل والحر في الأيام السبعة الأولى والواحد والعشرين (كوهيرت1) وعمر سبع سنوات (كوهيرت2). بناء على مضادات الانتان المستعملة، تم تقسيم المرضى إلى مجموعتين. تم إجراء تقييم المرضى وفقا لطريقة تورجاي (DSM–2) المبنية على فحص اضطرابات سلوك الأطفال، المراهقين ونقاط التصنيف.

النتائج: في اليوم السابع من الحياة، كان لدى المواليد الذين تعرضوا للأيودين ميتويات ثايروتروبين أعلى بشكل ملحوظ و كانت مستويات (FT–4) و (T–3) اقل، وفي الأيام الإحدى والعشرين الأولى كانت مستويات الثايروتروبين للمواليد مشابهة لمجموعة التحكم. أظهرت نتائج (كوهيرت2) أن وظيفة الغدة الدرقية طبيعية لدى جميع المرضى مع زيادة في فرط النشاط بين الأطفال المولودين قبل أوانهم (خدج) وخاصة الذين تعرضوا للأيودين.

خاتمة: فرط الأيودين قد يسبب انخفاض الثايروكسين لدى المواليد المكتمل فترة الحمل (أكثر من 30 أسبوع الحمل وأكثر من 1.5kg)، وقد يعتبر ذلك أحد أسباب مشاكل السلوك التي يتم ملاحظتها فيما بعد على هؤلاء الأطفال.

Objectives: To determine the effect of iodine containing antiseptics on thyroid function for the first 3 weeks in non-very-low-birth weight preterm and term babies, and to evaluate their thyroid function and behavioral status 7 years later.

Methods: Cohort I (between the years 1997-1998) was studied in 57 preterm (30-35 weeks) and 29 term newborns, 7 years later cohort II (in the year 2005) was created from same 28 preterm and 18 term infants at Behcet Uz Children's Hospital, Izmir, Turkey. Serum thyrotropin, triiodothyronine, total and free thyroxine were measured on the first, seventh, and twenty-first days (cohort I), and at the age of 7 (cohort II). In respect of used antiseptics, the patients were divided into 2 groups. The evaluation of patients was performed according to the Turgay Diagnostic and Statistical Manual for Psychiatric Disorders, 4th edition based child and adolescent behavior disorders screening and rating scale.

Results: On the seventh day of life, iodine-exposed newborns had significantly higher mean thyrotropin levels and lower free thyroxine, total thyroxine, and triiodothyronine levels. On the twenty-first day, thyrotropin levels of iodine-exposed newborns were similar to controls. The cohort II results showed normal thyroid function in all patents with increased hyperactivity among children born prematurely, and particularly experienced exposure to iodine.

Conclusion: Iodine excess may cause transient hypothyroxinemia in preterm babies (>30 weeks gestational age, >1.5 kg) and this may be one of the reasons for behavior problems observed later in these children.

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Iodine is known to induce transient hypothyroidism in term infants undergoing major iodine exposure.[1] Principally, 2 different ways are generally responsible for excess exposure of iodine: direct ingestion of iodine via adsorption from the skin and mucous membrane, and administration of organic iodine from drugs (for example, amiodarone, and radiologic contrast agents).[2] Known as the Wolff-Chaikoff effect, this excess iodine inhibits synthesis and release of thyroid hormones. The mature thyroid gland can escape from inhibition for around 2 days,[3] however, the premature infants' thyroid cannot overcome it. Moreover, the higher adsorption ability of premature subcutaneous tissue leads to adsorption of larger amount of iodine from iodine containing topical disinfectant,[4] In the literature, the effect of repeated and single dose of povidone-iodine on thyroid function on full-term and preterm neonates has been well described.[5-9] Moreover, iodine exposure was reported in 23% of very-low-birth weight (VLBW) newborns, in whom hypothyroidism is principally 14-times higher than in non-VLBW.[10] In relation to these reports, povidone-iodine disinfection for newborns below 1.5 kg and under 32 gestational weeks was restrained. The aim of this study was to determine the effect of iodine containing antiseptics (ICA) on thyroid function in non-VLBW preterm with gestational age between 30 and 35 weeks in comparison with term newborns. Additionally, the thyroid hormone levels and behavior status are measured at the later period to elucidate whether thyroid dysfunction provoked by exposure to ICA at the newborn period, contains any clue for thyroid dysfunction for the next years, and to investigate the impact of neonatal transient hypothyroxinemia on patients' later behavior.

Methods. Newborns at Dr. Behcet Uz and Atatürk Research and Training Hospital, Izmir, Turkey were enrolled in a prospective study approved by the Local Research Ethics Committee of the hospitals. Both neonatal intensive care units were tertiary care centers with similar treatment protocols. Exclusion criteria were life threatening disease, major congenital abnormalities, malnutrition, and treatment with drugs affecting thyroid function. The design of the study included: cross-sectional comparison of thyroid hormone measurements in blood specimens from premature and full term infants; and longitudinal comparison of values 7 years later. The first cohort of patients was studied in 1997-1998 and comprised 57 preterm and 29 full term newborns (cohort I). The studies were repeated in 2005 in 28 preterm and 18 term infants (cohort II). The preterm neonates were chosen according to their gestational age: greater than 30 and smaller than 35 weeks, and body weight: greater than 1500 grams. The gestational age was determined from the obstetric data, and postpartum by the Ballard score. Serum thyrotropin (TSH), total thyroxine (T4), free thyroxine (fT4), and triiodothyronine (T3) were measured before applying 10% povidone-iodine (P-I) or 70% ethyl alcohol (EA) containing antiseptics. Both antiseptics were used for invasive procedures such as an insertion of intravenous or umbilical cord care. The samples were obtained on their first, seventh, and twenty-first days (cohort I) and at 7 years (cohort II) of life. Blood samples were drawn from an antecubital vein and centrifuged after coagulation. The serum was stored at -20°C until analysis. The serum TSH, T4, T3, and fT4 levels were determined in all patients by electro chemiluminescence immunoassay method (Roche, Modular System E170, Mannheim, Germany). The hyperactivity and disruptive behavior level of children were evaluated regarding the scores of mothers for their children on the Turgay Diagnostic and Statistical Manual for Psychiatric Disorders, 4th edition (DSM IV) Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S).[11,12] The Turgay Scale: the T-DSM-IV Scale was developed by Turgay and translated/adapted in Turkish by Ercan et al.[12] It is based on the DSM-IV diagnostic criteria and assesses hyperactivity/impulsivity (9 items), inattention (9 items), opposition/defiance (8 items), and conduct disorder (15 items). The symptoms are scored by assigning a severity estimate for each symptom on a 4-point Likert-type scale (namely: 0=not at all, 1=just a little, 2=quite a bit, 3=very much).

Student's t-test, chi-squared test, Spearman's correlation analysis, and Pearson's correlation analysis was used for statistical evaluation of the data. A p value of <0.05 was accepted as significant.

Results. The evaluation of the patients according to their clinical findings is shown in **Table 1**. The groups did not differ significantly in gestational age, gender, or birth weight ($p>0.05$). Levels of thyroxine and TSH for mature and premature newborns according to time of sampling are shown in **Table 2**. On the seventh day of life, iodine-exposed newborns: term and preterm had significantly higher mean thyrotropin levels and lower T4 and T3 levels. On the twenty-first day, TSH levels of iodine-exposed newborns, term and preterm as well, were significantly indifferent than controls. However, T3, fT4, and T4 levels were slightly higher. Cohort II results obtained after 7 years showed similar values for TSH, fT4, T4, and T3. No statistical difference in hormone levels was found between preterm and term babies at any time of sampling. Moreover, no statistically significant difference was detected between groups regarding type of delivery, gender, and duration of hospitalization. According to the T-DSM-IV-S, scores

Table 1 - Clinical findings of the patients (results are mean±SE).

Variable	10% povidione-iodine (P-I)			70% ethyl alcohol (EA)		
	Term (N=16)	Preterm (N=31)	Total (N=47)	Term (N=13)	Preterm (N=26)	Total (N=39)
Gestational age (weeks)	37.5 ± 2.6	31.2 ± 2.4	34.3 ± 2.2	37.2 ± 2.4	32.2 ± 2.0	34.7 ± 2.2
Birth weight (g)	2706 ± 702	2100 ± 664	2403 ± 683	2655 ± 694	2267 ± 788	2461 ± 741
Apgar Score (5 min)	8.0 ± 0.8	7.0 ± 0.3	7.5 ± 0.5	8.4 ± 0.1	7.2 ± 0.4	7.8 ± 0.2
Female/Male	7/9	15/16	22/25	8/5	9/17	17/22
CS/NSVD	6/10	21/10	26/20	7/6	15/11	22/17
Duration of hospitalization (days)	5.9 ± 0.6	7.8 ± 1.0	9.8 ± 0.8	4.9 ± 0.4	12.7 ± 0.6	8.8 ± 1.0

CS - cesarean section, NSVD - normal spontaneous vaginal delivery

Table 2 - Serum thyroid hormone levels of the patients (results are mean±SE).

Hormone	PI Group				EA Group			
	1st day	7th day (*p*-value)	21st day	7th year	1st day	7th day	21st day	7th year
TSH (µU/ml)								
Preterm	11.0 ± 6.3	15.3 ± 4.5 (0.04)	3.7 ± 5.3	2.0 ± 1.5	13.2 ± 5.8	4.2 ± 3.5	3.1 ± 4.9	1.9 ± 1.4
Full term	15.3 ± 5.4	15.1 ± 4.9 (0.04)	3.4 ± 1.4	1.9 ± 1.8	14.2 ± 5.8	4.3 ± 0.7	4.4 ± 0.9	1.8 ± 1.6
Total	**13.0 ± 6.1**	**15.3 ± 4.6** (0.04)	**3.6 ± 4.4**	**1.9 ± 1.6**	**11.1 ± 5.7**	**4.3 ± 2.9**	**3.9 ± 3.7**	**1.9 ± 1.5**
T3 (ng/ml)								
Preterm	0.9 ± 0.3	0.5 ± 0.5 (0.03)	2.1 ± 1.4	1.2 ± 1.2	1.2 ± 0.73	1.4 ± 0.5	1.2 ± 0.6	1.5 ± 0.9
Full term	1.5 ± 0.4	0.9 ± 0.4 (0.02)	1.4 ± 0.5	1.6 ± 0.8	1.4 ± 0.4	1.4 ± 0.4	1.2 ± 0.4	1.6 ± 1.4
Total	**1.1 ± 0.4**	**0.7 ± 0.6** (0.03)	**1.9 ± 1.2**	**1.4 ± 1.0**	**1.4 ± 0.6**	**1.4 ± 0.5**	**1.2 ± 0.5**	**1.6 ± 1.5**
T4 (µg/dl)								
Preterm	8.1 ± 3.0	3.7 ± 2.8 (0.02)	6.6 ± 2.3	6.5 ± 2.5	10.9 ± 6.0	7.7 ± 3.1	6.0 ± 2.6	7.2 ± 2.4
Full term	13.0 ± 7.3	5.5 ± 2.2 (0.03)	7.4 ± 2.1	7.1 ± 1.8	13.0 ± 2.7	7.7 ± 2.6	7.2 ± 1.5	7.3 ± 1.8
Total	**9.7 ± 5.4**	**4.3 ± 2.7** (0.03)	**7.0 ± 6.8**	**6.8 ± 2.1**	**12.6 ± 5.4**	**7.7 ± 2.9**	**6.8 ± 2.3**	**7.2 ± 2.1**
FT4 (ng/dl)								
Preterm	1.8 ± 0.6	0.7 ± 0.6 (0.02)	0.9 ± 0.3	1.2 ± 0.5	2.4 ± 1.3	1.8 ± 0.7	1.4 ± 0.6	1.3 ± 0.4
Full term	3.1 ± 1.4	.9 ± 0.06 (0.03)	1.0 ± 0.3	1.3 ± 0.3	3.1 ± 0.6	1.0 ± 0.3	1.2 ± 0.2	1.3 ± 0.3
Total	**2.4 ± 1.0**	**0.8 ± 0.3** (0.03)	**1.0 ± 0.3**	**1.2 ± 0.4**	**2.7 ± 0.9**	**1.4 ± 0.5**	**1.3 ± 0.4**	**1.3 ± 0.3**

TSH - thyrotropin, T3 - triiodothyronine, T4 - total thyroxine, fT4 - free thyroxine

Table 3 - Psychometric evaluation of preterm and term babies at the age of 7 years (mean values of scores ± SD).

Groups	T-DSM-IV-S		
	Hyperactivity	Opposition/defiance	Conduct disorders
10% povidione-iodine (P-I)			
Born as preterm	13.25 ± 8.57†	5.25 ± 3.57	6.66 ± 4.92
Born as term	7.25 ± 3.47	5.58 ± 3.26	5.58 ± 3.26
70% ethyl alcohol (EA)			
Born as preterm	1 1.58 ± 7.26*	5.58 ± 2.26	5.08 ± 3.88
Born as term	6.58 ± 2.16	5.48 ± 1.26	3.58 ± 1.26

T-DSM-IV-S - Turgay DSM IV based child and adolescent behavior disorders screening and rating scale,
*p=0.02, †p=0.00

for hyperactivity at the age of 7 years were highest in the P-I preterm babies. There was no significant difference in the scores for opposition/defiance between groups. The conduct disorder scores were slightly elevated in the preterm in comparison with term babies, independent of kind of antiseptics used (**Table 3**).

Discussion. In the past 30 years, many reports have been published on the severity of transient hypothyroxinemia in VLBW preterm babies, and its relationship with maturation and iodine exposure, and clinical and developmental outcome. In this study, we studied the profile of thyroid function regarding iodine exposure in preterm infants, who were born between 30 and 35 weeks, and are not VLBW, compared with term infants. After delivery, a dramatic surge of TSH, remaining high for 3-5 days, occurs in term babies. The TSH surge leads to a rise in T4 and T3, which reaches their highest concentrations at 24-36 hours after birth. Infants born prematurely have variably low levels of T4 and TSH due to their immature hypothalamic-pituitary thyroid axis. With progressive maturation, the transient hypothyroxinemia spontaneously resolves by 8-10 weeks after birth. The findings are compatible with the physiological immaturity of the hypothalamic-pituitary-thyroid axis at this stage of gestation.[13] Another factor worsening the transient hypothyroxinemia is iodine: excess and deficiency.

Transient hypothyroidism in neonates due to such exposure has been mainly reported in areas with low or borderline iodine intake.[14-16] High TSH levels on the fourteenth day in iodine exposed VLBW (below 1500g) neonates was reported by Smerdely et al.[7] Severe hypothyroxinemia (44.1 nmol/l) was documented in the iodine-containing antiseptic (ICA) group compared with the normal group. The TSH levels of the control group (83 nmol/l) did not differ from the ICA exposed group, showing that serum TSH levels did not rise despite low thyroxine levels in ICA patients. Parravicini et al[5] found similar results from the investigation of 44 VLBW infants with gestational ages at birth of 30±2.3 weeks, and weights of 1223±231. According to their outcomes on the seventh day, the ICA exposed patients had higher TSH levels than control subjects, but at the twenty-eighth day, the hypothyroxinemia and hypotriiodotropinemia was detected. Moreover, the small for gestational age patients group demonstrated decreased thyroid hormone levels in umbilical cord and at the first month after birth. The findings from these studies are compatible with the present investigations for the first measured thyroid function on the seventh day. In contrast to them, the results from AvRuskin et al[17] demonstrated that both T3 and T4 levels were lower in the subgroups versus controls (p<0.01-0.05), TSH levels however did not rise in any group in 30 preterm neonates examined 5 days after topical exposure to 10% P-I application. This data suggest partial failure of thyroid hormone synthesis, in a population of high-risk infants possibly already exhibiting features of the euthyroid-sick syndrome. Yılmaz et al[9] investigated the effect of single dose P-I on serum TSH and thyroxine levels and urinary iodine excretion in 30 preterm, 40 full-term newborns, and 50 infants. Surprisingly, they found a decline in TSH and an increase in T4 levels. The authors believed that the decrease in TSH and the increase in T4 levels was due to a change in metabolism of the thyroid gland.[9] The present study, and the other investigations in this area concluded that ICA may alter the thyroid function at very early stage of life.[18] The thyroid dysfunction seems to be transient, as thyroid functions are normalized quickly and persist at normal values later. However, the impact of neonatal hypothyroxinemia on brain development is very important. There are many studies documenting the link between impaired brain development, measured as nerve conduction velocity, lower scores in Bayley mental and motor scale, or Wechsler Intelligence Scale.[19-21] The results of the present study support the hypothesis on the late effects of neonatal hypothyroxinemia. There are multiple factors that can affect thyroid function, brain development, and behavior in premature babies in prenatal and postnatal life. Therefore, collection of further data is needed to clarify the association between behavior problems and neonatal hypothyroxinemia due to ICA exposure.

The present study has several limitations. First, the data for urine iodine content were not presented. We are aware that urine iodine levels, in addition to T4 and TSH are mandatory for evaluation of thyroid dysfunction due to iodine overload. However, we could not provide a reliable collection of 24-hour urine excretion. Second, we do not have VLBW group patients, as the usage of ICA in these patients was restrained.

In conclusion, iodine exposure may cause transient hypothyroxinemia in preterm babies (>30 weeks gestational age, and >1.5 kg), and this may be one of the reasons for behavior problems later observed in these children.

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