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Original Article

The Effects of Thyroid Hormone Levels on Patent Ductus Arteriosus Closure in Newborns

Yenidoğanlarda Tiroid Hormon Düzeylerinin Patent Ductus Arteriosus Kapanması Üzerine Etkisi

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ABSTRACT

Objective: Although the role of thyroid hormones in functional and anatomical closure of patent ductus arteriosus (PDA) is well known, their effects on the medical or surgical closure of PDA in newborns remain unclear. This study aimed to assess the correlation between thyroid function tests and PDA closure through medical or surgical interventions in newborns.

Methods: This retrospective study was conducted on 65 newborns diagnosed with hemodynamically significant PDA (hs-PDA), with a premature rate of 81.5% (n=53). The subjects were divided into two groups according to the nature of the ductal closure as medically responsive "MR-PDA" or surgically treated "ST-PDA". The groups were compared in terms of thyroid hormone levels and other clinical parameters.

Results: Thirty-three (51%) of all 65 patients had PDA and responded to medical treatment. Gestational week, birth weight, and mode of delivery were similar between the medical and surgical treatment groups (p>0.05). Free thyroxine levels were significantly lower in the MR-PDA group than in the ST-PDA group (p=0.01).

Conclusions: Because hs-PDA is associated with increased morbidity and mortality in the neonatal period, especially in premature infants, we hypothesize that thyroid hormone levels may play a role in the closure of hs-PDA.

Keywords: Newborn, premature, patent ductus arteriosus, thyroid function tests

ÖZ

Amaç: Tiroid hormonlarının, patent duktus arteriozusun (PDA) fonksiyonel ve anatomik kapanmasında etkinliği bilinmekle beraber medikal ve/veya cerrahi olarak kapanan PDA'lı yenidoğan bebeklerdeki etkinliği bilinmemektedir. Bu çalışmada yenidoğan bebeklerde tiroid fonksiyon testleri ile medikal ve cerrahi olarak kapatılan PDA arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntemler: Bu çalışma retrospektif bir çalışma olup, 65 hemodinamik anlamlı PDA'lı (hs-PDA) yenidoğan çalışmaya alınmıştır. Çalışmaya alınan yenidoğanların 53'ünü (%81,5) preterm bebekler oluşturmaktaydı. Olgular duktal kapanma tiplerine göre medikal yanıtlı "MR-PDA" veya cerrahi tedavi gereken "ST-PDA" olarak iki gruba ayrıldı. Medikal tedaviye duyarlı ve dirençli PDA'sı olan yenidoğanlarda, tiroid hormon düzeyleri ile bu düzeylere etki eden faktörler karşılaştırıldı.

Bulgular: Çalışmaya alınan hastaların 33'ünü (%51) medikal tedaviye duyarlı PDA'sı olan yenidoğan bebekler oluşturmaktaydı. PDA'sı medikal ve cerrahi tedavi ile kapatılan gruplar arasında gestasyon haftası, doğum ağırlığı ve doğum şekli benzer idi (p>0,05). Medikal tedaviye duyarlı PDA'lı grubun serbest tiroksin düzeyleri, medikal tedaviye dirençli gruba göre anlamlı olarak düşüktü (p=0,01).

Sonuçlar: hs-PDA, yenidoğan döneminde, özellikle de prematüre bebeklerde artmış morbidite ve mortalite ile ilişkili olduğundan, tiroid hormon düzeylerinin hs-PDA kapanmasında etkili olabileceğini düşünmekteyiz.

Anahtar kelimeler: Yenidoğan, prematüre, patent duktus arteriozus, tiroid fonksiyon testleri

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INTRODUCTION

Patent ductus arteriosus (PDA) is defined when the ductus arteriosus remains unclosed even after the first 72 hours of life. The frequency of PDA is inversely proportional to the gestational week and birth weight[1]. Closure of DA in premature and term infants is affected by various factors and mechanisms. The effectiveness of prostaglandins, prostaglandin synthase inhibitors, and tissue oxygen levels of DA vary according to the gestational week and age. Due to the immature structures of prematures and their responses to the constrictive mechanisms, DA often does not close[2]. Thyroid hormones can affect the functional and anatomical closure of DA. It has been suggested that thyroid hormones play important roles in the closure of PDA by increasing the synthesis of von Willebrand factor, fibronectin, and endothelin-1 proteins by inducing the mRNA expression of endothelial proteins[3,4]. There are few studies showing a relationship between PDA and lower thyroid hormone levels in newborns. It has also been stated that medical treatment-resistant PDA may be associated with congenital hypothyroidism[5,6]. Nakagawa[7] reported that PDA resistance to medical treatment in a preterm infant with transient hypothyroidism was reduced with L-thyroxine treatment. Bozkaya et al.[8] compared thyroid hormone levels in newborns with PDA that closed spontaneously or required medical treatment. In addition, a meta-analysis reported a decrease in the incidence of PDA in preterm infants who were diagnosed with hypothyroidism and received thyroid hormone replacement[9]. Some newborn babies' ducts resist spontaneous closing. Although resistance to the closure of the ductal structure is often overcome by medical treatments, some patients require surgical intervention. In this way, we thought that "Could there be a relationship between increased resistance of the PDA to closure and thyroid hormone levels?". Unlike previous studies, we evaluated the effects of thyroid hormone levels on PDA closure rates in newborns whose PDA did not spontaneously close.

MATERIALS and METHODS

This study was retrospectively conducted on newborns who were followed up in our tertiary neonatal intensive care unit (NICU) and diagnosed with PDA between 2012 and 2022. Clinical and laboratory data of the patients were obtained by scanning medical documents extracted from the hospital database system. Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee approval was obtained for this study (decision no: 2688, date: 12.04.2023). Newborn infants who were defined as having hemodynamically significant PDA (hs-PDA) and underwent medical or surgical treatment were eligible for the study. Newborns whose PDA closed spontaneously, who died without ductal closure, and whose thyroid function test values could not be reached via the system were not included in the study.

The diagnosis of hs-PDA was made by pediatric cardiologists by demonstrating high flow velocity (left atrium/aorta >1.4 and PDA diameter/kg>1.5) on echocardiography[10]. Newborns diagnosed with hs-PDA were divided into two groups as sensitive or resistant to medical treatment. Approximately 3-5 of all 65 babies were under 32 weeks of gestation; routine echocardiography was performed in these babies in the first three postnatal days. Echocardiography was needed on babies over 32 weeks of gestation based on physical examination and clinical findings (such as cardiac murmur, unresponsiveness to treatment, pulmonary congestion findings). It was observed that babies with hs-PDA received medical treatment at the earliest on the 3rd day and at the latest in the first month. Until 2016, patients with hs-PDA were administered only ibuprofen after 2016, ibuprofen was the first choice. However, paracetamol treatment was administered in cases where ibuprofen was contraindicated or there was no response to ibuprofen. The dose of ibuprofen was 10 mg/kg/day for the first day and 5 mg/kg/day for the next two days. Repeated doses of ibuprofen were administered by increasing the dose when necessary (such as 15 and 8 and 8 mg/kg/day). Paracetamol was administered four times at a dose of 15 mg/kg/day for a duration of 3-5 days, in the absence of contraindications. Infants who did not respond to several courses of medical treatment and showed congestive heart failure underwent PDA ligation with the approval of the cardiac council, which included pediatric cardiologist, pediatric cardiovascular surgeon, and neonatology specialists.

The thyroid function test results of the patients obtained from the postnatal 5th to 7th day were retrospectively evaluated. It was observed that treatment (levothyroxine) was started 3-7 days after the patients with abnormal thyroid function tests, according to the thyroid function tests performed for the second time. It was thought that the first abnormal result might have been wrong due to birth stress. It was observed that thyroid function tests were checked 2-3 times in the first month of follow-up of patients who were started on levothyroxine. It was observed that dexamethasone treatment was given to patients who could not be weaned from the mechanical ventilator. All patients had received at least 1 cure of

medical treatment before receiving dexamethasone treatment. Some patients needed dopamine treatment because of hypotension. The endocrinological diagnoses of the patients were divided into three groups by the pediatric endocrinologist as "premature transient hypothyroxinemia", "sick euthyroid patient syndrome", and "congenital hypothyroidism". The diagnosis of transient hypothyroxinemia of prematurity was made with normal thyroid-stimulating hormone (TSH) levels together with temporarily low levels of circulating thyroid hormones, and the diagnosis of sick euthyroid syndrome was made with free triiodothyronine (fT_3) level or fT_3, fT_4 level below normal, and TSH level normal, low, or high in severe disease states without pathology in the thyroid gland. In addition, demographic data of the patients (gestational week, gestational weight, gender, mode of delivery, 5th min APGAR scores), medical treatments applied for PDA closure treatment (paracetamol, ibuprofen), number of medical treatment courses, accompanying pulmonary hypertension, inotropes administered to the baby while he was hospitalized in our cardiac center, and surfactant and dexamethasone treatments administered in the postnatal period were recorded in the previously prepared study forms.

Statistical Analysis

Demographic and clinical data of the patients are shown as frequency and percentage by descriptive statistical analyzes quantitative variables were defined on the basis of mean and standard deviation. For statistical analyzes to compare qualitative data in independent groups, Student's t-test or Mann-Whitney U test was used, as appropriate. Statistical analyzes were performed using the IBM SPSS Statistics-Version 23.0 software. P<0.05 was considered statistically significant.

RESULTS

Initially, 71 newborn infants were included in the study; six infants were excluded from the study. Thyroid function test results could not be obtained in four patients, and two died due to sepsis before PDA treatment was completed. Finally, 65 patients were evaluated for the study. The demographic and clinical data of the patients are shown in Table 1.

The fT_4 levels in the group whose PDA was closed with medical treatment (MT-PDA) were significantly lower than those in the group whose PDA was closed with surgical treatment (ST-PDA) (p=0.01). Congenital hypothyroidism was diagnosed in 5 babies, transient hypothyroxinemia of prematurity in 2 babies, and sick euthyroid syndrome in 3 babies in the MT-PDA group. L-thyroxine treatment was started in these babies according to the recommendations of the endocrinologists (Table 2). The mean day of initiation of L-thyroxine treatment was 14.8 postnatal days (8-35). A premature baby born at the 32nd gestational week was referred to our center for PDA ligation at

Table 1. Demographical and clinical data of the study patients.

Demographical data	Patients with PDA closing with medical treatment (n=33)	Patients whose PDA was closed by surgical treatment (n=32)	p-value
Gestational age (week)	30.4±4.3	31.4±5.5	p>0.05
Gestational weight (g)	1559.8±856.4	1819.5±1110.1	p>0.05
Gender (male) (%)	48.5	53.1	p>0.05
Birth by cesarean (%)	81.8	68.8	p>0.05
APGAR (5th min)	7.5±1.6	7.21±1.40	p>0.05
Clinical data			
Application time to our unit (minimum-maximum day)	10 (0-72)	21 (0-80)	p>0.05
Surfactant treatment (%)	66.1	56.3	p>0.05
Dexamethasone treatment (%)	12.3	38	p=0.018
Pulmonary hypertension (%)	39.3	48.4	p>0.05
Dopamine treatment (%)	35.7	27.8	p>0.05
Number of PDA medical courses (%)			
≤2	35.8	22.6	p>0.05
3-4	64.2	77.4	
Dead (%)	15.1	9.3	p>0.05

PDA: Patent ductus arteriosus

Table 2. Weeks of gestation and diagnosis of patients with hypothyroidism.						
	Patients with PDA closing with medical treatment (n=33)			Patients whose PDA was closed by surgical treatment (n=32)		
Gestational week	23-30	30-37	>37	23-30	30-37	>37
Number of patients (n)	17	12	4	13	11	8
Primary congenital hypothyroidism (n)	-	2	3			
Transient hypothyroxinemia of premature (n)	-	2	-			
Sick euthyroid syndrome (n)	3	-				
PDA: Patent ductus arteriosus						

the postnatal 4th week because of no response to medical treatment at repeated doses of ibuprofen or paracetamol. We detected that thyroid hormone levels were below normal values and observed that PDA was closed with levothyroxine treatment alone in this patient. After the exclusion of patients with proven hypothyroidism (n=10) from the MT-PDA group, fT_4 levels were compared between the two groups. There were no statistically significant differences in fT_4 levels between the two groups ($p>0.05$). There was also no statistical difference between the TSH hormone levels between the MT-PDA group and the ST-PDA group ($p>0.05$). Only four patients in the medical treatment group received dexamethasone treatment after their ducts were closed. In the surgical group, 12 patients received dexamethasone. When the data of patients receiving dopamine and dexamethasone were analyzed separately, there was no statistical difference between the groups in terms of fT_4 and TSH levels ($p>0.05$).

DISCUSSION

In this study, we evaluated thyroid function tests in newborns whose PDA was closed with medical or surgical treatment. We found that the mean fT_4 levels in the group whose PDA was closed with medical treatment were lower than those in the group whose PDA was closed with surgical treatment.

Advances in neonatal care and the increase in the survival rate of premature infants bring new problems and challenges to the fore. In particular, thyroid function abnormalities are commonly observed in hospitalized premature infants[11]. In our study, most of the treated hypothyroid babies were preterm babies, which is in line with the literature. The risk of preterm birth in the neonatal period and the predisposition to hypothyroidism in these babies pose a separate risk. Hypothyroidism also worsens oxidative stress by decreasing antioxidant levels in the body[12,13]. In a previously published case series in term infants, it was shown that the coexistence of hypothyroidism and PDA and the closure of PDA with L-thyroxine treatment. thyroid hormone affects the maturation of the ductus arteriosus[14,15]. In our study, we found lower fT_4 levels in the group whose duct was closed with medical treatment than in the group whose duct was closed with surgical treatment. In the comparison of the two groups after the hypothyroid patients were excluded, we did not find any difference between fT_4 levels. This suggests that all hypothyroid patients were in the group whose ducts were closed with medical treatment. This suggests that thyroid hormones may affect the closure of the duct in patients with only hypothyroidism. We observed that the PDA was closed with only L-thyroxine administration in the patient who was diagnosed with hypothyroidism and was at 32 weeks of gestation and was referred to our unit for surgical closure because he was resistant to medical treatments. This is consistent with previous studies and case series reported in the literature[5-7].

In a few studies, it has been shown that non-thyroid diseases (respiratory distress syndrome, sepsis, intraventricular hemorrhage, necrotizing enterocolitis, PDA) cause premature transient hypothyroxinemia with the diagnosis of sick euthyroid syndrome[16-19]. The degree of hypothyroxinemia is associated with the severity of these diseases[17,20]. This picture, which is caused by this prolonged critical illness, is often observed in babies under 30 weeks of gestation. Low circulating fT_4 levels are thought to protect the body from hypercatabolism caused by the disease, reduce metabolic rate, and provide a response to stress by conserving energy[13]. Parallel to clinical improvement, there was an increase in serum TSH, followed by an increase in serum T4 and T3. In our study, 3 preterm infants (below 30 weeks of gestation) with PDA received L-thyroxine supplementation because of the diagnosis of sick euthyroid syndrome.

Some drugs also affect thyroid function in preterm infants. Of these drugs, dopamine and steroids are the most commonly used in NICUs. Dopamine directly inhibits anterior pituitary function via inhibitory dopamine receptors, resulting in decreased TSH secretion. TSH is released within 20 minutes of dopamine cessation.

Because of the short serum T4 and T3 half-lives, long-term use of inotropic agents leads to a significant (up to 56%) decrease in fT4 levels[21]. In a study by Carrascosa et al.[22], hypothyroxinemia was found in 30-36 weeks-old preterm infants, especially those treated with dopamine and/or PDA. However, in our study, we did not find a relationship with the effect of dopamine on thyroid hormone levels.

Steroid therapy can alter serum T3 levels (approximately 12 h after initiation of therapy). Steroid use can also reduce the TSH response and peripheral conversion of T4 to T3. In the study by Arai et al.[23], TSH levels of babies who received dexamethasone in the first 2 weeks postnatally were significantly lower than those who did not receive steroids. In our study, we did not detect any effect of dexamethasone on thyroid hormone levels. We believe that this is because our patients did not receive dexamethasone treatment during the evaluation of thyroid function tests.

Yılmaz et al.[24], in their study on premature babies, found a significant relationship between transient hypothyroxinemia of prematurity and congenital heart diseases (especially PDA) and SGA. A trend toward lower PDA formation was found in infants treated with thyroid hormone[25]. In our study, two of our patients received L-thyroxine therapy because of the diagnosis of transient hypothyroxinemia of prematurity, which resulted in the closure of their PDAs.

The fact that it was a study conducted in a specific patient group (newborns with hs-PDA) containing 10-year cardiac center data was the strength of our study. Unfortunately, our study also had some limitations. Because it was a retrospective study, data from certain patients could not be accessed, thereby limiting the possibility of achieving a much larger sample size.

CONCLUSION

We found that the fT_4 levels in the group whose PDA was closed with MT-PDA were significantly lower than those in the group whose PDA was closed with ST-PDA. Additionally, thyroid hormone replacement may have a positive effect on PDA closure in newborns, especially preterms, with PDA accompanied by hypothyroidism and resistance to spontaneous closure. We believe that prospective studies with larger series are needed to obtain more meaningful results on this issue.

Ethics

Ethics Committee Approval: Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee approval was obtained for this study (decision no: 2688, date: 12.04.2023).

Informed Consent: Since our study was a retrospective study, informed consent was not obtained.

Peer-review: Externally and internally peer-reviewed.

Author Contributions

Surgical and Medical Practices: B.K., H.A., D.D., S.C., A.O., U.A.O., M.T., A.Z., Concept: B.K., H.A., D.D., Design: B.K., H.A., S.C., A.Z., Data Collection and/or Processing: B.K., A.O., M.T., Analysis and/or Interpretation: B.K., U.A.O., A.Z., Literature Search: B.K., S.C., A.O., Writing: B.K., H.A.

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