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The effects of thyroid hormones levels on prognosis after pediatric heart surgery

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Abstract
In this study, we aimed to evaluate the effects of thyroid hormone levels on the prognosis of patients who underwent congenital heart surgery under cardiopulmonary bypass. A total of 40 children who underwent congenital heart surgery were enrolled to this prospective study. The patients were divided into two groups according to the presence or absence of postoperative low cardiac output state. Plasma free thyroxine, free triiodothyronine and thyroid stimulating hormone levels were measured preoperatively and at 24 and 48 hours postoperatively. Postoperative low cardiac output state was observed in five patients (12.5 %). Preoperative free thyroxine levels were significantly higher in the low cardiac output state group (p=0.021). Postoperative free triiodothyronine and free thyroxine levels were significantly lower, and lactate levels, inotropic index were significantly higher in the low cardiac output state group. Duration of mechanical ventilation, intensive care unit stay, operation and cardiopulmonary bypass were significantly higher in the low cardiac output state group. Four patients (10 %) died in the early postoperative period, and all of them were in the low cardiac output state group. Our findings showed that the occurrence of low cardiac output state after congenital heart surgery was associated with the high levels of preoperative free thyroxine and the reduction in percentage of free triiodothyronine and free thyroxine levels at the 24th and 48th hours postoperatively.

Keywords: Cardiopulmonary bypass, pediatric heart surgery, thyroid hormones, prognosis

Introduction

Despite the recently developed diagnosis and treatment methods, congenital heart diseases continue to be one of the most important causes of death in the first year of life after birth [1]. Low cardiac output state (LCOS) might occur following a congenital heart surgery under cardiopulmonary bypass (CPB). This adverse state occurs 9-12 hours after the CPB is over and cardiac functions resumes normally in 24 hours. The decrease in cardiac output elicites clinical evidences such as hypotension, tachycardia, bradycardia, inotropic drug requirement for maintaining normal blood pressure (dopamine > 5 µg/kg/min or any dose of dobutamine, epinephrine, norepinephrine infusion), oliguria, anuria, acidosis, respiratory failure, confusion, central hyperthermia, peripheral hypothermia, and gastrointestinal disorders [2-4]. An inotropic index is defined as the support of the cardiovascular system with inotrop medicine in the cases of decreased cardiac output [5]. Many studies show that inotropic index is an important independent indicator in the mortality and the morbidity of children operated for congenital heart disease [5,6].

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Many studies show that in cases of congenital heart diseases after surgeries under CPB, thyroid hormone levels are depressed [7-9]. The changes in thyroid hormone levels during CPB is described as sick euthyroid syndrome type-1 or nonthyroidal illness syndrome (NIS). NIS is a malfunction in the hypothalamus-pituitary-thyroid axis which may be in a low form with only a decrease in triiodothyronine (T3) levels or which may be in a more complex form with a decrease at T3 and thyroxine (T4) levels at the same time [10,11]. NIS developing after cardiac surgery under CPB is believed that hemodilution non-pulsatil flow usage, systemic heparinization and hypothermia are responsible for its development and it results in a decrease in cardiac contractility and an increase in peripheral vascular resistance [12,13].

In this study, we aimed to evaluate the relationship between thyroid hormone levels on prognosis in infant patients undergoing congenital heart surgery under CPB and the possible LCOS after surgery.

Material and Methods

The patients' parents were informed about the study, and their written consents were obtained. The study protocol was approved by the institutional ethics committee. This study was conducted in accordance with the principles of the Helsinki Declaration.

A total of 40 children that were planned to undergo congenital heart surgery under CPB at our hospital were included in this prospective study. Firstly, the demographic and clinical characteristics of patients were recorded, then intraoperatif data and postoperative outcomes of patients were also recorded. In addition to preoperative data, the recorded perioperative parameters were as follows: CPB time, aortic cross clamp time, duration of surgery, duration of mechanical ventilation, inotropic index, length of stay in intensive care unit (ICU), length of stay in hospital, amount of diuresis per hour, and plasma lactate levels in arterial blood gas measured 6 times in 24 hours, as well as in-hospital mortality. The patients were divided into two groups according to the presence or absence of postoperative LCOS, and were then compared with each other. The patients with the absence of LCOS were named as Group 1, whereas the patients with the presence of LCOS were named as Group 2. The patients who had previous thyroid illness or had used thyroid hormones before the surgery were excluded from the study.

Operations were performed by same cardiothoracic surgery team. All operations were performed through median sternotomy under general anaesthesia, and normothermic conditions with no ultrafiltration during CPB.

Blood samples were collected from patients preoperatively and postoperatively at the 24th and 48th hours. Thyroid stimulating hormone (TSH), free thyroxine (fT4) and free triiodothyronine (fT3) levels were measured with the Electro Chemi Luminesence Immuno Assay (ECLIA) method.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 20 was used for the analysis. Mann-Whitney U or independent sample t tests were used for differences in continuous variables between the groups, while Fisher's exact test was used for differences in categorical variables. Spearman correlation analysis was used to show the relationships between variables. Continuous variables were presented as mean ± Standard deviation or median (minimum-maximum), whereas categorical variables were presented as frequency and percentage. A p value of less than 0.05 was considered as statistically significant.

Results

Cardiac output did not decrease in 35 of 40 cases in the study group (87.5 %), whereas 5 of the cases (12.5 %) had LCOS. Four of the cases (10 %) died. Those who died were all in the group with the presence of LCOS (80 %). Table 1 shows both the names of the diseases and the operations that the cases in the study groups had. Procedures performed on the four cases that have died were; ventricular septal defect was closed in one patient, tetralogy of Fallot was corrected in one patient, total anomalous pulmonary venous connection was corrected in one patient, total cavopulmonary shunt was performed in one patient.

Table 2 shows the median, minimum and maximum values and p values of the patients' preoperative data. Twenty five of 40 patients in the study group (62.5 %) consisted of the boys, whereas other 15 of patients (37.5 %) were girls. The youngest patient was 1 month old, whereas the oldest one was 171 months old (median=37 months). Weights were ranging between 4 and 64 kg (median=12 kg), heights were ranging between 50 and 168 cm (median=90.5 cm) and the body surface areas (BSA) were ranging between 0.21 and 1.72 (median=0.53). When patients were compared according to their ages, weights, heights, BSA and genders, no statistically significant difference was found. Preoperative fT3 value of the patients was 3.70 (2.64 - 4.82) pg/dL in Group 1, whereas it was 3.72 (2.76 - 3.99) pg/dL in Group 2. There was no statistically significant difference in terms of preoperative fT4 between two groups (p=0.781). Preoperative fT4 value was found to be 1.33 (0.9 - 1.98) ng/dL in Group 1 and 1.60 (1.32 - 1.74) ng/dL in Group 2 with a statistically significant high level of preoperative fT4 in Group 2 (p=0.021). Preoperative TSH value was found to be 2.66 (1.07 - 13.24) µIU/mL in Group 1 and 3.10 (2.43 - 6.57) µIU/mL in Group 2 with no statistically significant difference between two groups (p=0.317).

Table 1. Diseases and operations of patients

Disease	Operation	Group 1 (n=35)	Group 2 (n=5)
VSD	VSD closure	8	1
ASD	ASD closure	7	
TOF	Total correction	5	1
AVSD	Total correction	3	
Subaortic stenosis	Resection of the stenosis	3	
Single ventricle, RV hypoplasia	BCPC	1	1
TAPVD	Total correction		1
VSD + Subaortic stenosis	VSD closure, resection of the stenosis	1	
ASD + Pulmonary stenosis	ASD closure, reconstruction of the RVOT	1	
Supra-annular aortic stenosis	Aortoplasty	1	
ALCAPA	Transposition	1	
RV hypoplasia, BCPC	TCPC		1
Operated AVSD, Mitral regurgitation	Mitral valve repair	1	
Pulmonary conduit stenosis	Pulmonary conduit replacement	1	
Pulmonary stenosis	Reconstruction of the RVOT	1	
c-TGA, VSD, Glenn shunt	Fontan circulation	1	

VSD: Ventricular septal defect, ASD: Atrial septal defect, TOF: Tetralogy of Fallot, AVSD: Atrioventricular septal defect, BCPC: Bidirectional cavapulmonary circulation, TAPVD: Total anomalous pulmonary venous return, RVOT: Right ventricular outflow tract, ALCAPA: Anomalous Left Coronary Artery From the Pulmonary Artery, RV: Right ventricle, TCPC: Total cavapulmonary circulation, c-TGA: Corrected transposition of the great arteries

Table 2. Preoperative data of groups

	Group 1 (n=35)	Group 2 (n=5)	p value
Age (month)	42 (4-171)	18 (1-45)	0.170
Height (cm)	96 (55-168)	72 (50-105)	0.094
Weight (kg)	14 (5-64)	9 (4-19)	0.103
BSA	0.58 (0.27-1.72)	0.41 (0.21-0.73)	0.113
Gender			1.00
Male	13 (86.7%)	2 (13.3%)	
Female	22 (88%)	3 (12%)	
fT3	3.70 (2.64-4.82)	3.72 (2.76-3.99)	0.781
fT4	1.33 (0.9-1.98)	1.60 (1.32-1.74)	0.021
TSH	2.66 (1.07-13.24)	3.10 (2.43-6.57)	0.317

BSA: Body surface area, fT3: Free triiyodothyronine, fT4: Free thyroxine, TSH: Thyroid stimulating hormone.

Table 3 shows intraoperative and postoperative data of patients. CPB time was found to be significantly higher in Group 2 (p=0.007). No statistically significant difference was found between two groups in aortic cross clamp time (p=0.086). Operation time was found to be significantly higher in Group 2 (p=0.038). Duration of mechanical ventilation was found to be significantly higher in Group 2 (p<0.001). Duration of ICU stay was found to be significantly higher in Group 2 (p=0.002). No significant difference was found between two groups for in-hospital stay duration (p=0.968). Inotropic index was found to be significantly higher in Group 2 (p<0.001). Plasma lactate level in Group 2 was found to be significantly higher (p=0.005). Diuresis was found to be significantly higher in Group 2 (p=0.018).

Table 3. Intraoperative and postoperative data of groups

	Group 1 (n=35)	Group 2 (n=5)	p value
CPB time (min)	86.6 ± 37.4	138.4 ± 35.5	0.007
Aortic cross clamp time (min)	46.6 ± 28.7	67.2 ± 16.5	0.086
Duration of surgery (min)	170.2 ± 43.6	236 ± 81.7	0.038
Duration of MV (h)	8.8 ± 7.2	146.0 ± 80.0	<0.001
Length of ICU stay (h)	35.7 ± 16.6	106.4 ± 79.6	0.002
Length of hospital stay (days)	5.6 ± 3.0	11.2 ± 11.1	0.968
İnotropic index	0 (0-7)	50 (9-100)	<0.001
Plasma lactate levels (mg/dL)	23.1 ± 9.7	54.8 ± 26.3	0.005
Diuresis (mL/h)	56.6 ± 39.2	23.6 ± 13.7	0.018

CPB: Cardiopulmonary bypass, ICU: İntensive care unit, MV: Mechanical ventilation.

Percentage changes (PC) between the preoperative and postoperative results of patients' thyroid hormone values were calculated. The change between preoperative median value and postoperative 24th hour median value was named as PC1. The change between preoperative median value and postoperative 48th hour median value was named as PC2. The results according to groups are shown in Table 4 as median, minimum and maximum values with their p values. The course of thyroid hormones levels, and percentage changes are also shown in Figure 1.

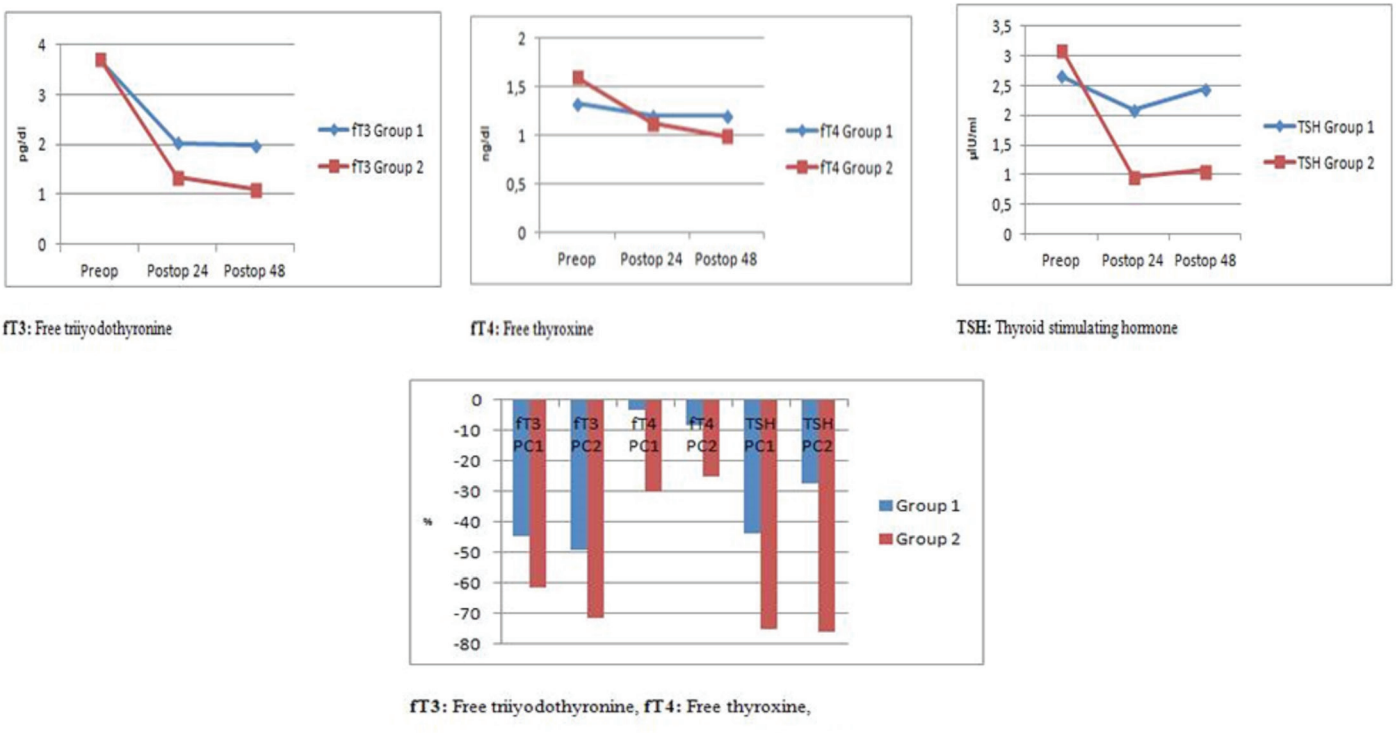

Figure 1. The course of thyroid hormones levels and percentage changes

Table 4. Postoperative quantitative data of groups

	Group 1 (n=35)	Group 2 (n=5)	p value
fT3 PC1	-44.8 (-73, 0)	-61.6 (-75, -48)	0.018
fT3 PC2	-49.4 (-77, -22)	-71.7 (-76, -34)	0.053
fT4 PC1	-3.4 (-38, +126)	-30 (-52, -15)	0.002
fT4 PC2	-8.1 (-41, +16)	-25 (-58, -19)	0.006
TSH PC1	-43.7 (-94, +179)	-75.1 (-90, -28)	0.058
TSH PC2	-27.2 (-94, +224)	-76.1 (-94, +1624)	0.123

fT3: Free triiyodothyronine, fT4: Free thyroxine, TSH: Thyroid stimulating hormone, PC: Percentage change.

A correlation analysis was conducted between preoperative values of thyroid hormones and inotropic index which is an independent indicator in LCOS presence. No statistically significant relationship was found between inotropic index and preoperative fT3 and TSH values. A statistically significant positive relationship was found between inotropic index and preoperative fT4 value (Table 5).

Table 5. Results of the correlation analysis of preoperative values of thyroid hormones and inotropic index

	fT3	fT4	TSH
r	0.28	0.373	0.141
p	0.864	0.018	0.385

fT3: Free triiyodothyronine, fT4: Free thyroxine, TSH: Thyroid stimulating hormone.

Table 6 shows the results of the percentage changes of inotopic index and thyroid hormones in the correlation analysis. A statistically significant negative relationship was found between intropic index and fT3 PC1, fT3 PC2, fT4 PC1, fT4 PC2 and TSH PC1 values. No significant relationship was found between inotropic index and TSH PC2 value.

Table 6. Results of the correlation analysis of percentage changes of inotopic index and thyroid hormones

	fT3 PC1	fT3 PC2	fT4 PC1	fT4 PC2	TSH PC1	TSH PC2
r	-0.385	-0.358	-0.426	-0.322	-0.398	-0.278
p	0.014	0.023	0.006	0.043	0.011	0.082

fT3: Free triiyodothyronine, fT4: Free thyroxine, TSH: Thyroid stimulating hormone, PC: Percentage change.

Table 7 shows the results of the correlation analysis between inotropic index and peroperative and postoperative variables. A statistically significant positive relationship was found between intropic index and CPB time, aortic cross clamp time, duration of ventilation and duration of ICU stay. No significant relationship was found between inotropic index and operation duration.

Table 7. Results of the correlation analysis between inotopic index and preoperative and postoperative variables

	CPB time	Aortic cross clamp time	Operation time	MV time	ICU time
r	0.392	0.331	0.214	0.659	0.615
p	0.012	0.037	0.185	<0.001	<0.001

CPB: Cardiopulmonary bypass, MV: Mechanical ventilation, ICU: Intensive care unit.

Discussion

Heart surgery techniques have improved since that the CPB has been in place in heart surgery practice, but at the same time some side effects caused by extracorporeal circulation have been also seen. To prevent or minimize these side effects, many studies have been performed and are still being performed. As the studies on congenital heart surgery have increased, our knowledge have also increased and we have tried to define the preoperative risk factors more clearly.

In human physiology, T4 concentration in blood is approximately 70 times more than T3. After secreted from thyroid gland T3 and T4 are quickly attached to plasma proteins. Only a very small amounts of T3 and T4 are found free form in blood. This free fraction determines the metabolic activity of the hormones. Compared to T4, T3 is 4 times more active. Three plasma proteins which are called thyroid binding globulin, thyroid binding prealbumin and albumin, carry the thyroid hormones in bind. Although not accepted as an inotrop, positive inotropic effects of thyroid hormones are known. T3 improves the contractility of the heart muscle by stimulating the transcription of myosin heavy chain α and inhibiting myosin heavy chain β. It increases β-adrenergic receptors and G proteins by changing the isoforms of Na-K-ATP-ase genes. In this way, it makes positive inotropic and chronotropic effects in the heart. Thyroid hormones increase the β-adrenergic receptors in heart and skeleton muscles while decreasing α adrenergic receptors in heart muscles. They also increase the effect of catecholamines by increasing adenylcyclase activation and cAMP production in postreceptor levels [14-16].

In our study, LCOS was observed in 5 of 40 patients (12.5 %), whereas in other 35 of them (87.5 %) it was not observed. Four of all patients (10 %) died. Those who died were all in the group with the presence of LCOS (80 %).

In their study with 36 infant patients who had congenital heart surgery under CPB, Plumpton and Haas [17] found that the extension in CPB period was related with low preoperative fT3 and TSH values. The study also showed that babies younger than 3 months had low preoperative fT3 values and they had the need for mechanical ventilation for more than 48 hours. In another study with 16 infant patients who had congenital heart surgery under CPB, McMahon et al. [18] reported a similar relationship between CPB period and total plasma T3 value.

In our study, we found no statistically significant difference between both groups in terms of the demographic features including age, gender, weight, height and body surface area. In addition, we found that preoperative fT4 level is significantly higher in the group with the presence of LCOS than in the group with the absence of LCOS. No significant difference was found between two groups regarding the preoperative fT3 and TSH values. Moreover, it was found that perioperative CPB time and operation time were significantly longer in patients with the presence of LCOS and aortic cross clamp timed was longer in cases with the presence of LCOS but that was not significant. Also the duration of mechanical ventilation and the duration of ICU stay were found to be significantly longer in patients with the presence of LCOS whereas there was not a significant difference between two groups for the duration of in-hospital stay. It was found that thyroid hormones

decreased postoperatively in both groups. It was seen that in the group with the presence of LCOS, fT3 had decreased significantly more in postoperative 24th hour borderline significantly decreased further in postoperative 48th hour. It was also seen that in the group with the presence of LCOS, fT4 had decreased significantly more in postoperative 24th and 48th hour and TSH had borderline significantly decreased more in postoperative 24th hour but not significantly decreased in postoperative 48th hour. It was seen that postoperative lactate level had increased in both groups in the first 24 hours but the increase in the group with the presence of LCOS was found to be significantly higher. Also the inotropic index was found to be significantly higher in the group with the presence of LCOS.

In a study in which children with congenital heart diseases had operations under CPB, Baysal et al. [19] demonstrated that plasma fT3, total T3 and total T4 values had decreased, TSH and fT4 values had no significant change, fT3 and total T3 values in the postoperative 48th hour had significantly decreased in children with the presence of LCOS and preoperative total T4 level was an independent indicator of LCOS. In another study in which 20 infants had congenital heart operation under CPB and ultrafiltration, Bartkowski et al. [20] reported the decreased postoperative thyroid hormone levels in plasma, and the authors also found thyroid hormones in the dialysis ultrafiltrate. It was seen that the recovery period was longer for the patients who had more decrease in T3 levels, therefore they suggested that T3 replacement therapy could be beneficial for the postoperative recovery. In a randomized controlled study in which 20 patients had congenital heart operations under CPB and received T3 treatment for 5 days, Bettendorf et al. [21] showed the increased average cardiac index in patients who had T3 treatment and increased systolic function for especially the ones whose CPB time was lasted longer. In a study performed by Talwar et al. [8] in which 100 infant patients had congenital heart operations under CPB, the authors evaluated thyroid hormones, survival, inotropic score, duration of mechanical ventilation and postoperative complications and found the decreased thyroid hormones levels postoperatively in all patients. They found that the patients who died in the first postoperative 72 hours had lower total T4 levels when compared to the patients who did not die. For the patients who who did not die, total T4 levels were found to be lower in the ones with the presence of complications when compared to the ones with the absence of complication. They also found that total T4 level had a significant inverse correlation with inotropic score and borderline significant inverse correlation with mechanical ventilation. They stated that to improve the postoperative results, more researches should be conducted on prophylactic management of total T4.

In our study, we also found that the inotropic index was significantly positively correlated with preoperative fT4, inversely correlated with PC in fT3 and fT4, and PC in TSH in postoperative 24th hour, and it was not correlated with the PC in TSH in postoperative 48th hour.

Limitations of the Study

This present study had several limitations. The major limation of the study was small sample size. The other important limitations were non-randomized study design or lack of adjustment in comparability between the groups, heterogeneity and irregular distribution of the groups in terms of both the wide range of disease spectrum and patient numbers of groups, and the lack of the mid and long-term outcomes of patients.

Conclusion

Our findings showed that the development of LCOS after a pediatric heart surgery was related with the increase of preoperative fT4 and the decrease in fT3 and fT4 levels in the first postoperative 24 and 48 hours. As a result, in our study with the patients who had congenital heart surgery under CPB, we found a decrease in thyroid hormone levels and determined that this could be related to deterioration of myocardial function. Therefore, we believe that preoperative and postoperative thyroid hormone levels of the patients could be used in intensive care and clinical follow-ups. There is not enough studies and meta-analyzes on patients who had congenital heart surgery comparing thyroid hormone levels with prognosis; but in view of the available data in the literature, there is a belief that the thyroid hormone tests might be important tools at early diagnosis for preventing the development of LCOS. In accordance with these data, the follow-up of thyroid hormone levels might be an important parameter in the establishment of proactive treatment. As we had a limited number of patients in our study, we believe that more researches should be done on the related topic and the findings should be supported with wider studies.

Competing interests
The authors declare that they have no competing interest

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Ethical approval
Available from Uludag University Medical Research Ethics Committee (Decision number: 2012-24/5 and date: November 06, 2012).

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