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Comparison of Pituitary-thyroid Axis Changes between Minor and Major Cardiac Surgery in Patients Less than 18 years of Age

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Abstract

Comparison of pituitary-thyroid axis changes between minor and major cardiac surgery in patients less than 18 years of age

Background: During illnesses, some events occur in pituitary-thyroid axis including causing a disease state named non-thyroidal illness syndrome (NTIS). The aim of this study was to compare pituitary-thyroid axis changes in children less than 18 years old with minor versus major heart operations.

Method: This study was conducted on 52 patients less than 18 yr who had undergone surgery within a period of 8 months from fall 2010 through spring 2011 in heart center of Yazd, Iran. Three sample specimens were taken from every patient. Every sample was assessed for thyroid hormones.

Findings: All the patients in the major group and 90% of those in the minor group developed NTIS. The severity of NTIS was different between the two groups. (P< 0.001) Average admission days at the hospital ward were also more in the major than the minor group. (P= 0.014) The trend of changing in serum TSH level on days after surgery in the major group was significant (P< 0.001), but not in minor group. (P = 0.622) The trend of changing in serum FT4 level on days after surgery in major group was significant (P = 0.0 47), but not in minor group (P = 0.199). Almost all hormone levels reached normal levels at the 4th post-op day.

Conclusion: In major surgery, TSH and FT4 levels drop significantly after the operation and this makes diagnosis a real challenge, therefore treatment is based mainly on clinical grounds. In minor surgery, the changes in TSH and FT4 levels were not significant after the operation, so we recommend using laboratory tests to diagnose hypothyroidism after operations.

Keywords: Non-thyroidal illness syndrome (NTIS); Cardiac surgery; Thyroid hormones

Introduction

Euthyroid sick syndrome (ESS) is observed in patients with nonthyroidal illness syndrome (NTIS) characterized by abnormalities in TSH and thyroid hormone levels [1-6]. In its mild form, this causes only a decrease in serum T3 level. As the severity of the illness increases, both T3 and T4 decrease [2,4]. This decrease in level of serum thyroid hormone is seen in surgery, myocardial infarction, sepsis, bypass and probably any other severe illness [4]. These abnormalities result from variable, usually reversible, disturbances in the hypothalamo-pituitary-thyroid axis, binding of thyroid hormone to serum proteins, tissue uptake of thyroid hormones and thyroid hormone metabolism [2,5]. It's not clear that NTIS is adaptive or maladaptive. Some studies suggested that NTIS affects the outcome adversely. There are limited studies which have assessed NTIS only in children undergoing major cardiac surgery [6]. To the best of our knowledge, this is the first study in children undergoing cardiac surgery to compare NTIS in major and minor surgery together.

Congenital Heart Disease	Group		Total
	Major	Minor	
VSD	10 (40%)	4(14.8%)	14(26.9%)
VSD + PDA	0	3(11.1%)	3(5.8%)
VSD + Pulmonary stenosis (PS)	2(8%)	0	2(3.8%)
TOF	4(16%)	10(37%)	14(26.9%)
TGA	3(12%)	4(14.8%)	7(13.5%)
ASD	4(16%)	0	4(7.7%)
PDA	0	3(11.1%)	3(5.8%)
AS + PS	2(8%)	0	2(3.8%)
Complete Atrio-Ventricular Canal	0	2(7.4%)	2(3.8%)
Tricuspid Atresia	0	1(3.7%)	1(1.9%)
Total	25 (100%)	27(100%)	52(100%)

Table 1: Frequency distribution of congenital heart diseases.

Materials and Methods

A cross-sectional study was conducted on 52 patients with congenital heart diseases undergoing cardiac surgery (age under 18yr) between Sep 2010 and May 2011 in Afshar heart center, Yazd, Iran. Those who had a preexisting endocrine disease including thyroid,

Severity	FT3	FT4	rT3	TSH
Mild	↓		↑	normal
Moderate	↓↓	normal ,↑ , ↓	↑↑	normal, ↓
Severe	↓↓↓	↓	↑	↓↓
Recovery	↓	↓	↑	↑

Table 2: Severity of NTIS.

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adrenal or pituitary dysfunction or a condition predisposing them to thyroid dysfunction (e.g. trisomy 21) and patients undergoing surgery during 2 months before the study were excluded from the study. All patients were euthyroid before surgery, without consuming drugs that could have influenced thyroid hormone tests. Informed consent was obtained from their parents. The study was approved by the ethics committee of Shahid Sadoughi University of medical sciences. The subjects were selected by nonrandom sampling to major and minor surgery. The frequency distribution of congenital heart diseases is summarized in table 1. Thyroid hormone status was assessed in 52 patients before surgery, and 1 day and 4 days after surgery. Pediatric intensive care unit (PICU) and ward hospitalization days were determined. The patients were evaluated at 0800 AM, in the supine position following an overnight fast. Plasma levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), total thyroxine (TT4), free triiodothyronine (fT3), total triiodothyronine (TT3), and triiodothyronine uptake (T3U) were measured. Samples were stored at -20°C before assay. Serum concentrations of hormones were measured by Enzyme-linked immunosorbent assay (ELISA) kit (Delaware Biotech lnc, USA). Data were extracted by chart reviews. Analysis was performed by SPSS version16. Hormone concentration changes over time points were assessed by paired t test in each group and ANOVA test between two groups. Level of significance was set at P-Value< 0.05. Results were expressed as the mean ± SD. Severity of NTIS was defined as mentioned in table 2.

Results

Fifty two patients (22 females and 30 males)were prospectively studied: major group, 25 patients (mean age 4.98 ± 4.94 yr, 16 males, 9 females) undergoing cardiopulmonary bypass surgery and minor group, 27 patients (mean age 1.18 ± 1.09 yr, 14 males, 13 females) were studied 1 and 4 days after surgery. There were no deaths. A total of 156 hormone measurements were performed. Preoperative levels were normal in all patients. All the patients in major group and 24 patients (88.9%) in minor group developed NTIS, without a statistically significant difference between two groups (p=0.132). In major group there were 16 (64%) patients with severe and 9 (36%) patients with moderate NTIS. No patients developed mild NTIS. In minor group there were 1(3.7%) patient with severe NTIS, 18(66.7%) with moderate and 5 (18.5%) with mild NTIS and 3 (11.1%) patients without NTIS. The observed difference was statistically significant (p<0/001).The mean of PICU stay was 2.52 ± 1 and 2.4 ± 0.93 days in major and minor groups, respectively with no significant difference (p= 0.78). The mean of hospital stay was 3.12 ± 1.73 days in major group and 2.19 ± 0.63 days in minor group and the difference was statistically significant (p = 0.014). Changes in serum thyroid hormone levels over time are shown in table 3. TSH in two groups decreased below preoperative levels at postoperative day 1 and rose to preoperative levels at postoperative day 4 (Figure 1). In major group there were no significant changes in serum TT4 (although a trend toward an increase 4 days after operation was seen) (p= 0.390).The average level of TT4 in minor group decreased 1 day after operation and returned to preoperative level at day 4 after operation, but it was not statistically significant (p= 0.444) (Figure 2). The average level of FT4 in major group reduced regarding its baseline values at day 1 after operation and returned to its preoperative level by the fourth postoperative day. In minor group value of FT4 depressed at day 1after operation and remained without changes at day 4 after operation (Figure 3). In both groups the mean serum TT3 level remained unchanged throughout the periods of observation in major and minor group (Figure 4). The average level of FT3 decreased from preoperative levels and returned to baseline levels at day 4 after operation in both groups in major and minor group (Figure 5). The mean serum T3U concentrations didn't change significantly during the time in both groups (Figure 6).

Discussion

This study showed major and minor cardiac surgeries affect thyroid hormone concentrations and cause NTIS. A marked reduction in the levels of TT3, FT3 and TSH was detected during the time frame of the study. The serum levels of T3 and T4 decrease within hours after the onset of severe physical stress and they can remain low until recovery occurs. In general, the frequency and extent of these changes differ with severity of the illness or injury [3,4,7-9]. In illness, the production and serum concentrations of T3 decrease due to reduced conversion of T4 to T3 [9]. A decrease in TSH secretion may reduce the thyroidal secretion and further may lead to low serum T4 and T3 concentrations [3,8,9]. In addition to these two reasonable changes, there are some other mechanisms. The production of one or more serum thyroid hormone

Tyroid Hormone	Normal Values	Type of surgery	Mean ± SD			P-Value
			Before surgery	1 day after surgery	4 days after surgery	
TSH	0.35-5.3 µIU/l	Major	2.62 ± 1.74	1.08 ± 0.73	2.76 ± 1.38	< 0.001
		Minor	2.07 ± 1.45	1.87 ± 1.5	2.23 ± 1.32	0.622
		P-Value	0.169	0.023	0.221	
TT4	4.5-13.2 µg/ml	Major	8.93 ± 1.59	8.87 ± 1.70	9.68 ± 1.89	0.390
		Minor	10.40 ± 2.51	9.6 ± 1.78	10.15 ± 1.74	0.444
		P-Value	0.360	0.118	0.016	
FT4	9-23 Pmol/l	Major	12.27 ± 6.17	8.82 ± 4.47	12.87 ± 17.18	0.047
		Minor	14.3 ± 6.02	12.48 ± 5.50	12.57 ± 5.47	0.199
		P-Value	0.236	0.012	0.896	
TT3	0.5-2.3 ng/ml	Major	1.43 ± 0.47	1.11 ± 0.61	1.12 ± 0.33	0.085
		Minor	1.47 ± 0.71	1.20 ± 0.54	1.36 ± 0.80	0.151
		P-Value	0.818	0.558	0.176	
FT3	3.5-6.5 Pmol/l	Major	6.30 ± 2.68	4.06 ± 3.15	5.36 ± 2.63	0.006
		Minor	7.74 ± 5.9	5.05 ± 3.23	6.15 ± 3.51	0.011
		P-Value	0.227	0.268	0.360	
T3U	25-37%	Major	31.24 ± 2.12	31.26 ± 2.63	31.32 ± 2.30	0.986
		Minor	30.65 ± 2.95	31.22 ± 3.17	30.69 ± 2.55	0.681
		P-Value	0.420	0.963	0.359	

Table 3: Serum Thyroid Hormone Concentrations in two groups before, one day after, and four days after cardiac surgery.

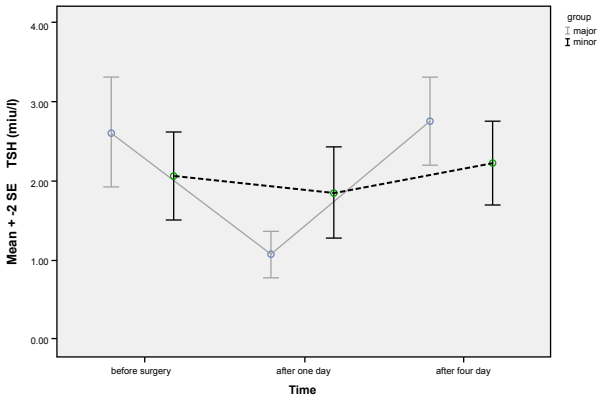


Figure 1: Serum TSH changes in two groups before, 1 day after and 4 day after operation.

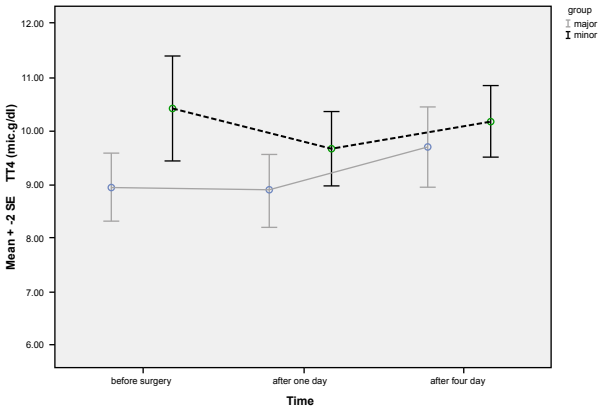


Figure 2: Serum TT4 changes in two groups before, 1 day after and 4 day after operation.

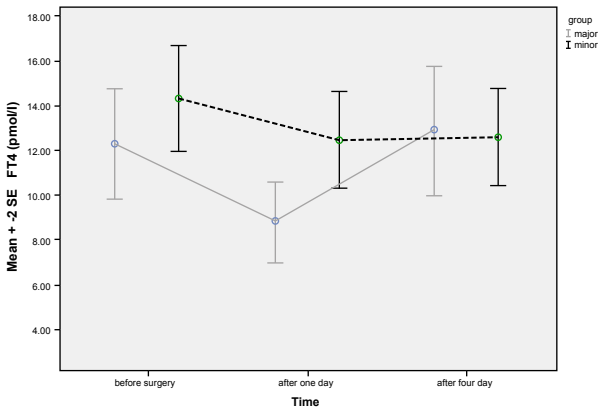


Figure 3: Serum FT4 changes in two groups before, 1 day after and 4 day after operation.

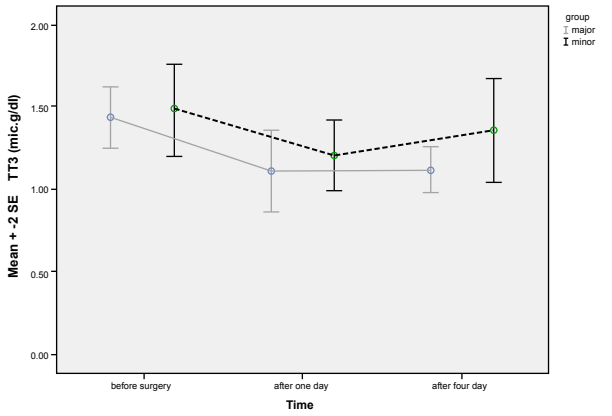


Figure 4: Serum TT3 changes in two groups before, 1 day after and 4 day after operation.

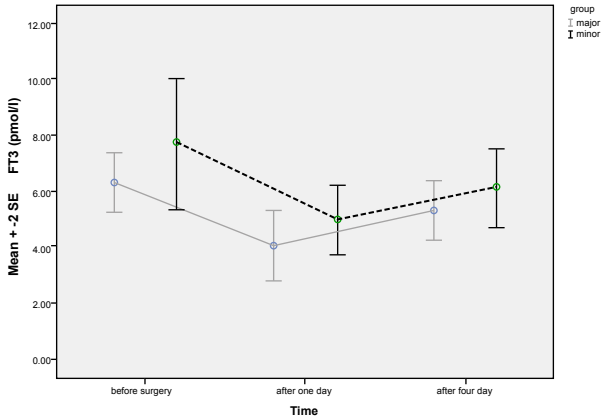


Figure 5: Serum FT3 changes in two groups before, 1 day after and 4 day after operation.

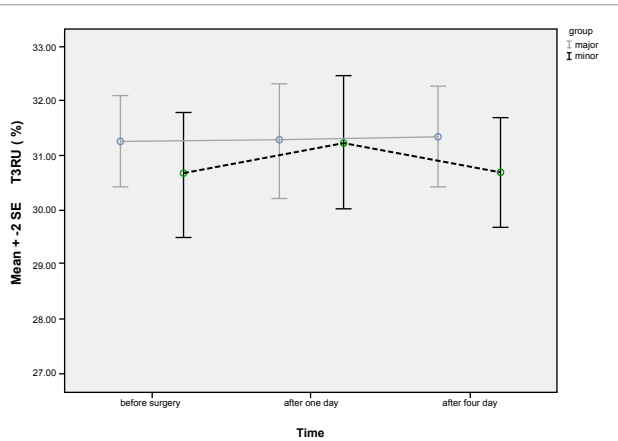


Figure 6: Serum T3U changes in two groups before, 1 day after and 4 day after operation.

binding proteins (T4-binding globulin, transthyretin, and albumin) or their affinity for the thyroid hormones may decrease [4,7,9].The serum concentration of rT3 increases as a result of impaired deiodination and Tissue uptake of T4 and T3 may decrease. Little is known about the causes of these changes, but glucocorticoids, dopamine, cytokines, and nutrition have been proposed as contributing factors [3,4,8,9]. In general, lower serum T3 or T4 concentration may be associated with poorer outcome, but causality cannot be found. Among hospitalized patients low serum TSH and T4 reflect higher mortality [4,7,11]. All patients in major group demonstrated NTIS. Several authors showed these results as well [2,6,7,10,11]. Most of the children in minor group developed NTIS. Other studies have evaluated NTIS only in patients undergoing major cardiac surgery and according to our knowledge

this study was the first study to compare NTIS in both major and minor cardiac groups. We found more severe NTIS and also more hospitalization days in major group than minor group. We can explain this difference by difficulty of operation in major group rather than minor group. Marks et al. in 2008 studied 21 children aged 1–11 yr and underwent cardiopulmonary bypass. Patients with TT3 ≤ 0.7 nmol/l were 12 times more likely to be in the PICU for 10 or more days. Patients with T3U ≥ 0.5nmol/l were 20 times more likely to be in the hospital for 20 or more days [6]. In the current study, one patient was hospitalized 5 days in PICU and 10 days in cardiology ward as a consequence of arrhythmia. Murzi et al. in 1995 measured thyroid hormones in 14 pediatric patients aged between 18 months and 14 years before, during and after cardiopulmonary bypass. TSH level returned to normal range 3 days after surgery [11]. In Marks study this change occurred at 4 days after surgery [6] such as our study. The changes of TSH level in minor group were not significant. It's related to NTIS severity in this group. In mild to moderate NTIS, TSH is mostly in normal range or reduced. More reduction of TSH level in major group rather than minor group is correlated with more suppression of pituitary-thyroid axis [1,6,7]. Other researchers [2,6,7] found that serum TT4 levels were reduced significantly after surgery, but we found no significant changes in serum TT4 level after surgery. It may be related to this fact that 36% patients developed moderate NTIS. As mentioned before, in moderate NTIS, TT4 and TSH levels are in normal range. It's the case in minor group, because 85.2% of this group had mild to moderate NTIS and no significant changes were found in TT4 level in the group. Similar to others [2,6,7,10,11], we found marked decrease and then increase in FT4 level in major group. In the current study, FT4 returned to preoperative level 4 days after surgery. Marks et al. [6] and Zagola et al. [7] found that FT4 level returns to preoperative level 3 and 7 days after surgery, respectively. Bartkowskia et al. in 2000 studied 20 infants with congenital heart defects undergoing cardiac surgery (age range: 7 days-11 months). In their study FT4 returned to normal range 8 days after surgery [2]. We didn't find any significant changes in FT4 level in minor group. It is explained by this fact that most patients had mild to moderate NTIS in this group. In our study, TT3 level decreased postoperatively and did not return to normal range 4 days after surgery. In the minor group, same as the major group, the changes were not significant. In Zagola et al. [7] study, TT3 fell to a low level after surgery and did not return to normal range 7 days after surgery. We found that changes of FT3 level in patients who underwent cardiopulmonary bypass were significant which was consistent with other studies [2,6,7,10,11]. We also found that it was marked in minor group. It can be explained considering the severity of NTIS. In our study, T3U increased 1 day after surgery and remained elevated during postoperative period, but the changes were not significant. In other studies the change was more significant [6,7]. It may be related to heterogeneity of evaluated patients, because in other studies all patients had severe NTIS. In minor group the changes were not significant. The major limitations of the present study were: 1) Lack of serum rT3 measurement 2) We planned to measure thyroid hormone 7 days after operation but most of the patients were discharged before that time.

Conclusion

We conclude that NTIS occurs in children undergoing major and minor cardiac surgeries for congenital heart lesions. The exact mechanism responsible for causing these changes is not completely understood. Clinically, thyroid function may be used as a marker of clinical status and as a predictor of outcome in this population. We know that normal thyroid function is very important for cardiovascular system. Hypothyroidism may cause decreased heart rate, cardiac output, contractility and increased systemic vascular resistance and can be dangerous after cardiac surgery. In our study, all patients undergoing major surgery developed severe NTIS. We noticed using clinical manifestations for diagnosis of hypothyroidism. Patients undergoing minor surgery developed mild to moderate NTIS in which serum TSH level is usually normal. In these patients, clinicians can use laboratory data for diagnosis of hypothyroidism. Future studies should include a longer period to determine when serum thyroid function tests exactly return to normal ranges in minor cardiac surgeries.

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