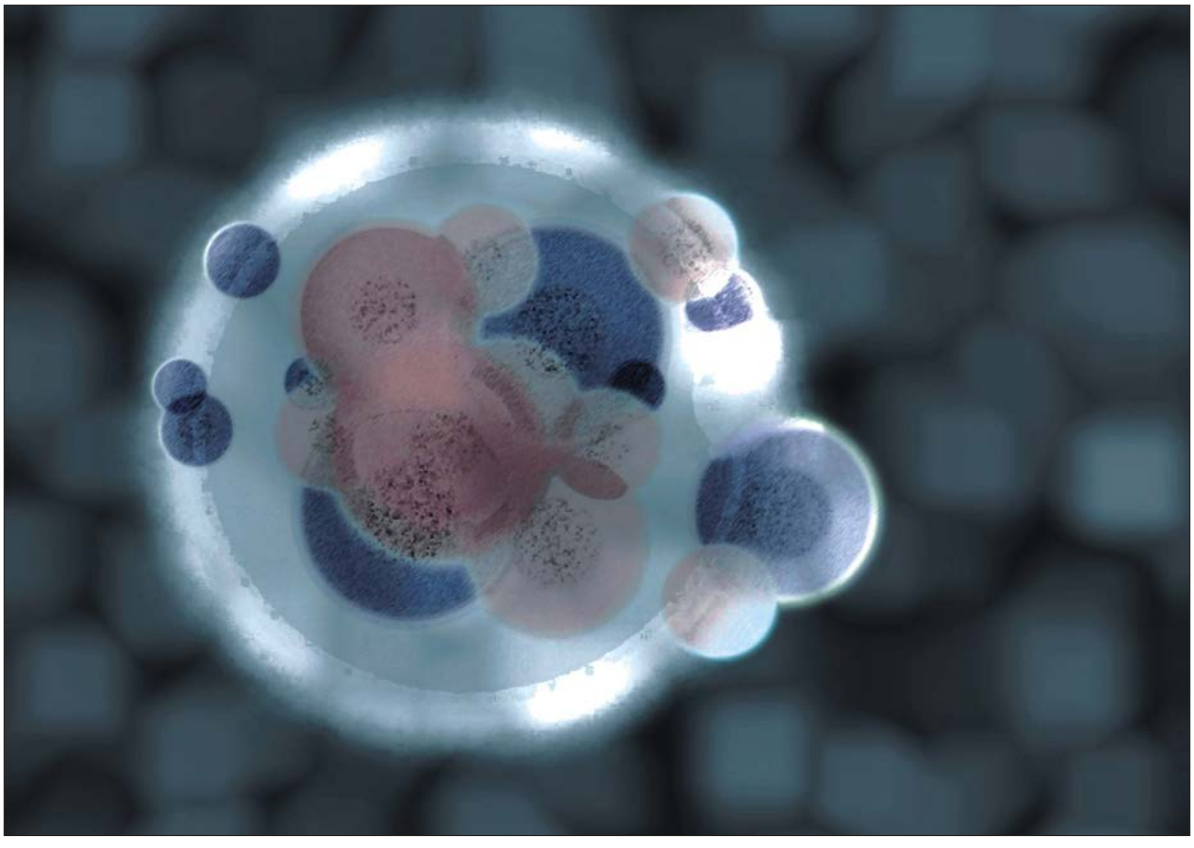

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Effect of Cardiopulmonary Bypass Duration on Thyroid Function Tests after Open Heart Surgery in Children

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Abstract: This study was designed to evaluate the effect of cardiopulmonary bypass duration on thyroid function in children undergoing open heart surgery. One hundred and five children with congenital heart disease in-need of open heart surgery with cardiopulmonary bypass were enrolled during a 12-month period. Patients categorized into two groups: Short-time cardiopulmonary bypass (<90 min) and long-time cardiopulmonary bypass (≥90 min). Serum levels of Triiodothyronine (T3), Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) were measured 2 h before surgery and 2 and 5 days after operation. If needed another laboratory investigation was carried out on week 2 after operation. There were 46 (28 males, 18 females with the mean age of 5.63±3.64 years) and 59 (30 males, 29 females with the mean age of 4.59±3.18 years) children in short-time and long-time cardiopulmonary bypass groups, respectively ($p>0.05$). The mean serum level of T3, T4 and TSH was not significantly different between the two groups. In each groups, serum TSH and thyroid hormones were decreased until 2 h and 2 days after post-operation, respectively, with gradual increase afterward. Decline of serum thyroid hormones was more longstanding in the long-time cardiopulmonary bypass group. Two weeks after operation, repeating the same laboratory tests in patients with defective results yielded normal consequences. According to our results, there is a transient laboratory abnormality in thyroid function tests in children undergoing cardiopulmonary bypass. This abnormality persists longer in patients with long-time cardiopulmonary bypass.

Key words: Congenital heart disease, transient thyroid dysfunction, cardiac surgery, children, long-time

INTRODUCTION

Different studies have shown that there is a significant compromise in thyroid function after open heart surgeries in children. This malfunction could be so extensive that may affect cardiac function (Haas *et al*., 2006). However, there is not general agreement about the supplemental use of thyroid hormones in children undergoing open heart surgery (Mainwaring and Nelson, 2002). In a study on 20 infants undergoing open heart surgery with delayed sternal closure it has been shown that exposure to povidone-iodine increases the risk of transient hypothyroidism (Kovacikova *et al*., 2003). In another series, it has been concluded that repetitive use of iodine-included antiseptics in pediatrics cardiac surgery may influence the thyroid function tests (Kovacikova *et al*., 2005). In a study in turkey on 289 children with congenital heart disease undergoing open heart surgery, it has been shown that perfusion mode (pulsatile vs. nonpulsatile) influences the plasma concentration of thyroid hormones. Results of that study showed that after Cardio Pulmonary Bypass (CPB), plasma levels of thyroid hormones were reduced but pulsatile perfusion had protective effect on thyroid hormone homeostasis in comparison to nonpulsatile mode (Akcevin *et al*., 2010). The role of chest tube insertion for a long period has also proposed in other study causing secondary hypothyroidism by Thyroxin Binding Globulin (TBG) loss after heart operation (Lynch *et al*., 2004). There is a strong association between postoperative decrease in thyroid hormones and atrial fibrillation. However it is not clear that preoperative replacement therapy can prevent this complication (Kokkonen *et al*., 2005; Park *et al*., 2009).

It has been shown that abnormalities in thyroid hormone levels occure after cardiac surgery using CPB (Haas *et al*., 2006). However, as far as we searched there is not any study covering about the effect of CPB duration on thyroid dysfunction after open heart surgery in children. This study aimed at answering this obscurity as well as evaluating other possible influencing parameters.

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MATERIALS AND METHODS

In an observational study between November 2007 and November 2008, 105 children aged 15 years or younger who were candidates for open heart operation due to congenital abnormalities were recruited in Shahid Madani Hospital, Tabriz, Iran. Patients with proven thyroid disease and abnormal primary thyroid tests were excluded. Open heart surgery was carried out by employment of CPB and intermediate hypothermia (25-28° C) in all patients. Serum Total Triiodothyronine (T3), Total Thyroxine (T4) and Thyroid Stimulating Hormone (TSH) were measured by ELISA method at baseline (before operation) and after that on hour 2 and days 2 and 5. Another thyroid function test was repeated 2 weeks after operation, in all patients with any abnormal result on day 5 post-operation. Based on duration of CPB, patients categorized in two groups; short-time CPB (<90 min) and long-time CPB (90 min≤). Any previous history of thyroid disease and/or taking drugs with potential effect on thyroid function tests was considered as exclusion criteria. Signed informed consent was taken from parents or legal sponsors of the children. This study is approved by the Ethics Committee of Tabriz University of Medical Sciences. Blood samples were taken during routine procedures and no extra sampling was applied.

Statistical analysis: Data were analyzed with the SPSS statistical software package (version 15.0; SPSS Inc, Chicago). Continuous variables were expressed as mean and categorical data were shown as frequency and percent. The contingency table (The Chi square and The Fisher's exact tests where appropriate) and the Independent samples t-test employed for comparisons (univariate studies). Statistically significant variables in a univariate study entered into a logistic regression analysis (multivariate study) for an independent predictive factor. Pearson's r was considered for evaluating correlations. The p-value below 0.05 was considered significant.

RESULTS

According to CPB time, there were 46 (43.8%) children in short-time group and 59 (56.2%) cases in long-time group. In short-time group, there were 28 (60.9%) males and 18 (39.1%) females with the mean age of 5.63±3.64 years. In long-time group, there were 30 (50.8%) males and 29 (49.2%) females with the mean age of 4.59±3.18 years. The two groups were comparable for gender (p = 0.306) and age (p = 0.225). Dopamine and dobutamine were administered in 8 (17.4%) and 9 (19.6%) cases in short-time group and 32 (54.2%) and 23 (39%) cases in long-time group, respectively. The rates of dopamine and dobutamine administrations were significantly higher in long-time group (p<0.001 and p = 0.032, respectively). There were not statistically meaningful difference between two groups regarding serum levels of TSH [before (0.485), 2 h (0.581), 2 days (0.819) and 5 days (0.526) after operation], T3 [before (0.108), 2 h (0.309), 2 days (0.452) and 5 days (0.318) after operation] and T4 [before (0.112), 2 h (0.617), 2 days (0.391) and 5 days (0.317) after operation]. The above mentioned results are summarized in Table 1.

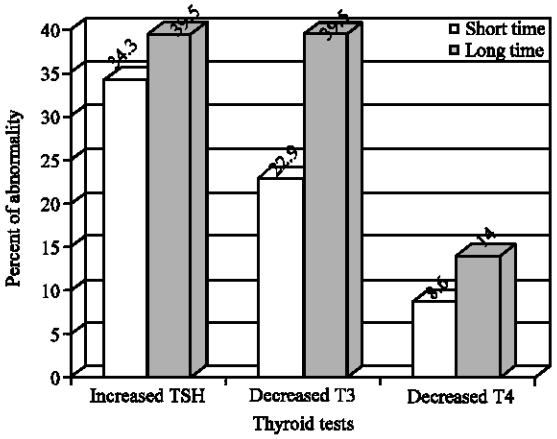

Fig. 1: Abnormal values of thyroid function tests on day 5 after operation

In short-time group, the mean serum TSH level at 2 h after operation was significantly decreased comparing with the baseline amount (p = 0.020). The mean serum T3 and T4 levels at 2 h and 2 days post-operation were significantly decreased comparing with the baseline readings (p = 0.001 and p<0.001 for T3, respectively; p = 0.002 and p = 0.001 for T4, respectively). Other parameters were not significantly different from the baseline values in this group. In long-time group, the mean serum TSH levels at 2 h and 2 days post-operation were significantly decreased comparing with the baseline readings (p = 0.035 and p = 0.003, respectively). The mean serum levels of T_3 and T4 were significantly decreased at 2 h and days 2 and 5 after operation (p = 0.003 for T4 in day 5, p<0.001 for the other values). Abnormal values of thyroid function tests on day 5 after operation are shown in Fig. 1. As the Fig. 1 shows, on day 5 after operation, 39.5, 39.5 and 14% of children in long-time group have abnormal levels of TSH, T3 and T4, respectively. These values in short-time group are 34.3, 22.9 and 8.6%. Accordingly there was no significant difference between the rates of cases with increased serum TSH (p = 0.633) and decreased serum T3 (p = 0.116) or T4 (p = 0.504) on

Table 1: Thyroid function test results in two groups with short-time and long-time cardiopulmonary bypass

Parameter	Short-time n = 46 (43.8%)	Long-time n = 59 (56.2%)	p-value
Gender: Male/Female	28/18	30/29	0.306
Age (year)	5.63±3.64	4.59±3.18	0.225
Administration of Dopamine N (%)	8 (17.4%)	32 (54.2%)	<0.001
Administration of Dobutamine N (%)	9 (19.6%)	23 (39%)	0.032
TSH (μIU mL^{-1}) (Normal = 0.4-6.21)			
Before operation	3.89±2.58	4.61±6.51	0.485
2 h after operation	2.51±2.98	2.99±4.94	0.581
2 days after operation	3.20±2.78	3.44±6.26	0.819
5 days after operation	4.52±3.01	5.27±6.41	0.526
T3 (ng mL^{-1}) (Normal = 0.52-1.85)			
Before operation	1.33±0.72	1.68±1.30	0.108
2 h after operation	0.97±0.43	1.09±0.70	0.309
2 days after operation	0.81±0.46	0.91±0.75	0.452
5 days after operation	1.04±1.05	0.85±0.54	0.318
T4 (μg dL^{-1}) (Normal = 4.8-11.6)			
Before operation	8.04±3.05	8.94±2.68	0.112
2 h after operation	7.10±2.46	7.34±2.31	0.617
2 days after operation	6.61±2.50	7.06±2.60	0.391
5 days after operation	8.03±2.70	7.44±2.48	0.317

$p<0.05$: significant

day 5 after surgery. Fourteen patients out of 29 primary ones with abnormal thyroid function tests on day 5 post-operation were connected and followed up to 2 weeks after operation. Based on these results there was no case with abnormal serum thyroid parameters. There was a significant reverse weak correlation between serum T4 and duration of CPB in all patients ($r = -0.268$, $p = 0.018$). Other parameters were not significantly correlated with duration of CPB. In multivariate analysis, age and gender of patients, duration of CPB and administration of dopamine were not significantly related with abnormal thyroid test results.

DISCUSSION

In this study, we showed that although the serum thyroid function test results were not significantly different between two groups with short-time or long-time CPB, it seems that longer CPB causes a more delay in return (increase) of serum T3 and T4 after surgery. Likewise we showed that in open heart operation in children, there is a decrement of serum TSH by 2 h after operation, with a gradual elevation afterward. Concomitantly, serum level of T3 and T4 were reduced by day 2 after operation with a subsequent progressive increase. Ririe *et al.* (1998) showed in study on 23 children underwent open heart operation with assistance of CPB that the serum levels of thyroid hormones and TSH decreased by the first day after surgery and gradually increased after that point. Murzi *et al.* (1995) in another series on 14 children reported a more longstanding decrease in serum levels of thyroid hormones (5-7 days after operation). In a study by Belgorosky *et al.* (1993), decreased serum levels of thyroid hormones after open heart surgery was reported. Bettendorf *et al.* (1997) emphasized con transitory of these findings. Mainwaring *et al.* (1994) reported similar trends in open heart operations in infants. Dagan *et al.* (2006) concluded that decreased levels of serum free T4 (FT4) and TSH was seen by the first day after heart operation in 20 newborns. Bartkowski *et al.* (2002) studied 20 children after heart operation and concluded a reduction of thyroid hormones and TSH after operation. Keceligil *et al.* (1996), on the other hand, did not show a change in FT4 and TSH after operation. As mentioned, change of thyroid function tests is universal finding in almost all relevant studies. However, the timing and types of involved parameters are not fully similar. Different sample sizes and type of thyroid function tests and their sensitivity may lead to this heterogeneity. There are diverse proposed mechanisms for changes in thyroid function tests after heart operation. Thyroid malfunctioning in response to decreased thyroid hormones during CPB is an example. Change in metabolism of thyroid hormones has been implicated in this regard (Chu *et al.*, 1991; Holland *et al.*, 1991; Novitzky *et al.*, 1989). In some studies, release of inflammatory factors such as IL-6, IL-1 and TNF-1, as well as elevation of steroids level have been put forward for sick euthyroid syndrome after heart operation. Haas *et al.* (2006) proposed a systemic inflammatory response during CPB as the main underlying cause of thyroid malfunctioning. Cellular hypoxia is another culprit in this regard (Peeters *et al.*, 2003). Holzer *et al.* (2004) reported a decrease of serum selenium after CPB and blamed this finding as the underlying etiology of abnormal thyroid function tests. Trauma of surgery, out-of-body circulation, hypothermia, blood dilution, anemia, heparin and dopamine use and ultrafiltration have all been proposed in this regard (Haas *et al.*, 2006; Bartkowski *et al.*, 2002; Plumpton and Haas, 2005;

Dimmick *et al*., 2004; Van den Berghe *et al*., 1994; Ghorashi *et al*., 2008). We did not find an independent predictor of thyroid hormone or TSH abnormality among gender, age, CPB duration and dopamine administration in the current study. It seems that this condition is a complex and multifactorial entity. Following up the patients with abnormal laboratory results on day 5 post-operation 2 weeks after surgery, we did not find any significant abnormality. This indicates a temporary abnormality of thyroid or upper controlling systems. In any way, presence of laboratory and transient hypothyroidism after open heart surgery, its effect on prognosis and necessity of correction are more important issues than the probable etiologies. There is not yet a consensus in this regard (Bartkowski *et al*., 2002; Klemperer, 2002).

The most important limitation of this study was that we lost some of our patients with abnormal tests on day 5, for evaluation on 2 weeks after operation.

CONCLUSION

Our results showed that thyroid function abnormalities after open heart surgery in children are aggravated with longer duration of cardio pulmonary bypass. These abnormalities are transient and return to normal status two weeks after surgery.

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