Original Article

The Effect of Oral Triiodothyronine in Outcome of Pediatric Congenital Cardiac Surgery

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Abstract

Background: Cardiac surgery especially in small children is associated with a marked decrease in thyroid hormone levels consistent with the phenomenon referred to as Sick Euthyroid Syndrome (SES). The purpose of the present study was to determine if oral triiodothyronine could reduce the length of ICU stay, vasoactive inotropic score (VIS), and promote ejection fraction in infants and children undergoing cardiac surgery with CPB.

Materials and Methods: In a double-blind clinical trial, one hundred and twenty children aged 6 to 60 months and scheduled for different types of cardiac surgery with CPB, were randomized into two groups to receive either 2 mcg/Kg triiodothyronine (trial group) or 5% dextrose water (placebo group), immediately after anesthesia and 24 hours after surgery. The perioperative serum thyroid hormone levels and hemodynamic variables were determined. The intubation time, ICU stay length, ICU inotropic use, and cardiac ejection fraction was recorded.

Results: The basic demographic data were comparable in two groups. No significant side effects or adverse reactions were seen due to hormone therapy. Intubation time, ICU stay, and VIS values were significantly shorter between the two groups.

Conclusion: In children undergoing cardiac surgery with CPB, perioperative oral small-dose triiodothyronine therapy could improve clinical indices of perioperative care.

Keywords: Pediatric congenital cardiac surgery, Sick Euthyroid Syndrome, Thyroid hormone replacement therapy

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Introduction

Cardiac surgery produces a generalized systemic inflammatory reaction, resulting in increased postoperative complications (1-3). Cardiac surgery with or without cardiopulmonary bypass, mainly in small children, is associated with a marked decrease in thyroid hormone levels consistent with the phenomenon referred to as Sick Euthyroid Syndrome (SES) (4-9). Thyroid Hormones (THs) have a cardioprotective role through direct or indirect actions at the level of the myocytes, the interstitium, and the vasculature. THs have also an antiapoptotic effect on myocytes.

The contractile apparatus of the cardiac myocyte contains the α and β myosin heavy chains, which are positively and negatively regulated by T3,

respectively. Cardiac contractility is further regulated by several important cardiac proteins (1, 3), including the Sarco/endoplasmic reticulum Ca2+-ATPase (SERCA2) and its inhibiting counterpart phospholamban (PLB). SERCA2 is positively regulated by T3, whereas PLB is negatively regulated. Together, they are responsible for the kinetics of calcium ion influx into (and subsequent efflux from) the sarcoplasmic reticulum. This lusitropic effect of TH is a characteristic of T3 regulation of myocyte contractility (2, 9).

The present study aimed to determine whether in pediatric congenital surgeries oral triiodothyronine could reduce the length of stay in ICU and hospital, vasoactive inotropic score (VIS), pump, and clamp time, and promote ejection fraction in infants and children undergoing open-heart surgery using CPB.

Methods

After institutional ethics committee approval (IR.SBMU.MSP.REC.1397.609), and Iranian Clinical Trial Database registration (IRCT registration number: IRCT20180502039507N1), children aged 6 to 60 months and scheduled for open-heart surgery with CPB under general anesthesia were recruited from Modarres Hospital, Shahid Beheshti University of Medical Sciences in Tehran (April 2018-February 2019). Informed written consent was obtained from the parents by the principal investigator.

One hundred and twenty children were enrolled in this study. Of them, 48 had ventricular septal defects, 28 atrial septal defects, 15 ventricular septal defects combined with atrial septal defects, and 21 had tetralogy of Fallot, 3 aortic stenoses, and 5 had single ventricle anomaly.

Exclusion criteria were abnormal baseline thyroid function, thyroid diseases and other endocrine diseases, use of drugs affecting thyroid function, and preoperative use of inotropic drugs for circulatory support.

Patients were randomized into 2 groups of equal size to receive the following treatments in a double-blind manner: placebo (control group) and trial group. Six hours before surgery, the patients were randomly assigned to receive either triiodothyronine or placebo. Cases assigned to triiodothyronine received an oral dose of 2 mcg/kg of body weight. The patients in the placebo group received a 5 percent dextrose solution. Repeated doses were administered immediately after anesthesia (via a gastric tube) and 24 hours after surgery.

Samples of arterial blood, for determination of serum total T3, total T4, and TSH concentrations (by radioimmunoassay method) were checked one day before surgery, 24 and 48 hours after surgery.

All physicians and nurses involved in the patients' care were unaware of the treatment assignments, and except for the administration of the study drug, care during and after surgery did not differ in the two groups.

The operation was performed by a single cardiac surgery team using a standardized protocol for anesthesia and surgery. In the operating room, at first, 5-lead electrocardiogram, invasive blood pressure, central venous pressure, cerebral oximetry, and pulse oximeter were monitored.

After routine preoxygenation, anesthesia was induced. Neuromuscular blockade was provided. After intubation, the lungs were ventilated with intermittent positive pressure ventilation, with a tidal volume of 8 to 10 ml/kg, a respiratory rate of 18-25 breaths/min, 3-5 cm water of PEEP, an inspiratory/expiratory ratio of 1:2, FiO2 equal to 40% to 60% and an oxygen flow of 2.5 l/min.

All children received standardized surgical and CPB management. Mild hypothermia (30–34 °C) was used for performing the procedures. During CPB, we maintained hematocrit at 24% to 28%. Besides, the cold blood cardioplegia solution (4 °C) was perfused to provide cardioprotection. The duration of aortic clamp and CPB were recorded. After performing the surgical procedure and systemic rewarming, the patients were transferred to ICU, where standardized institutional postoperative protocols were applied.

The perioperative serum thyroid hormone levels and hemodynamic variables were assessed. Intubation time, ICU stay duration, and the use of inotropic drugs in ICU were recorded. VIS was used to evaluate the inotropic need for cardiovascular support in children after the surgery (9). However, the inotropic support

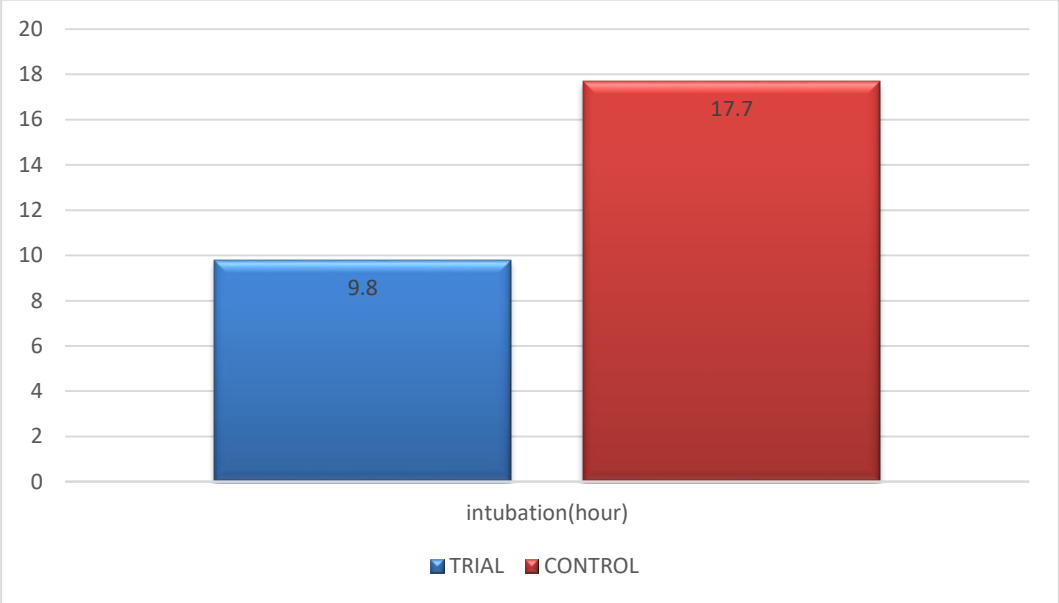

Figure 1. Intubation time in trial and control groups.

was measured using the following formula; where VIS was defined as Vasoactive Inotropic Support:

VIS = dopamine (mcg/kg/min) + dobutamine (mcg/kg/min) + 100 x epinephrine (mcg/kg/min) + 100 x norepinephrine(mcg/kg/min) + 10 x milrinone (mcg/kg/min) + 10,000 x vasopressin (mUnits/kg/min)

The patients in the trial group received triiodothyronine immediately after anesthesia and 24 hours later. Postoperative care including weaning and ICU discharge were based on the standard institutional protocols.

We compared intubation time, ICU stays, and VIS in the first postoperative 24 hours, cardiac ejection fraction; while we assessed total T3 (TT3), total T4 (TT4), and TSH levels during postoperative 48 hours.

Data were analyzed using Statistical Package for Social Sciences, version 14 (SPSS Inc., Chicago, IL, USA). The correlation between quantitative data was tested using a T-test; however, P values less than 0.05 were considered statistically significant.

Results

The demographic characteristics and clinical data of the cases are shown in Table-1. There were no significant differences in age (P value=0.43), weight (P value=0.37), duration of CPB (P value=0.32), and aortic clamp time (P value=0.36) between groups.

In both groups, the mean serum T3, T4, and TSH concentrations were in the normal range before surgery. Serum T_3, T_4, and TSH levels on the first and second postoperative days were not significantly different in 2 groups (Table 2).

The median intubation time and duration of ICU stay were 17.7 hours and 6 days in the control group, respectively, 9.8 hours and 5 days in the trial group. VIS was 17.38±5.63 and 11.48±5.22 in the control and trial group, respectively. There were significant differences in ICU stay length (P value= 0.02), VIS (P value=0.0001) and intubation time (P value=0.0001) between groups (Figure 1, 2, and 3).

Discussion

To the best of the authors' knowledge, this is the first clinical trial study of triiodothyronine therapy effect in children undergoing congenital cardiac surgery in Iran. Previous studies have shown that the metabolism of thyroid hormones was altered in children after

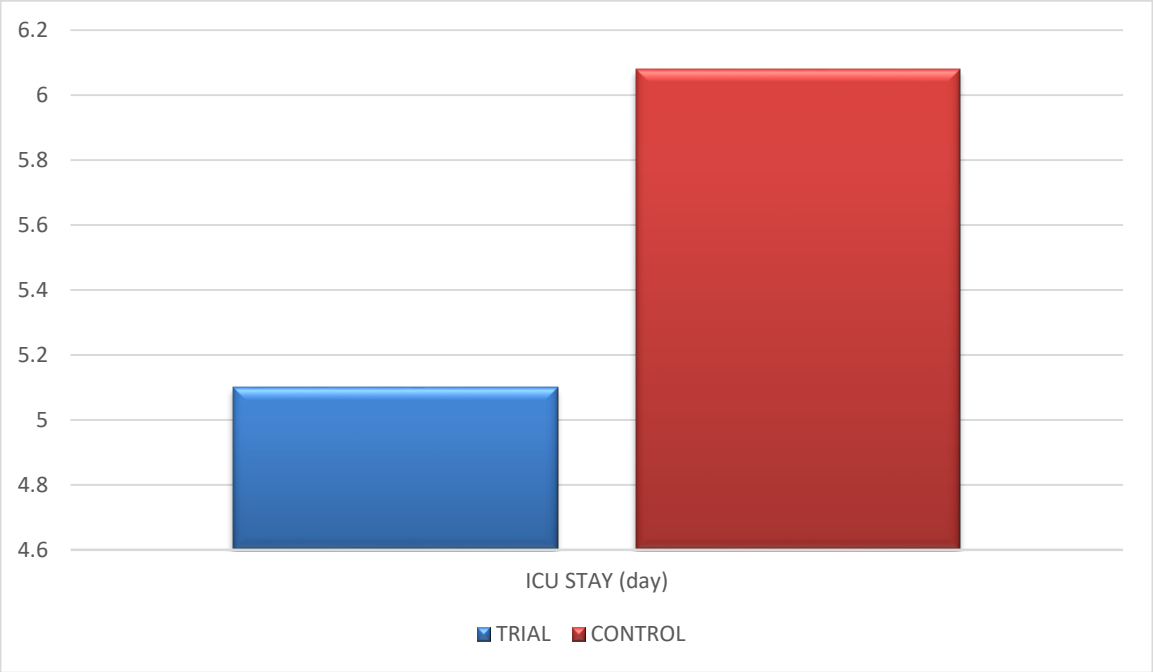

Figure 2. ICU stay in trial and control groups.

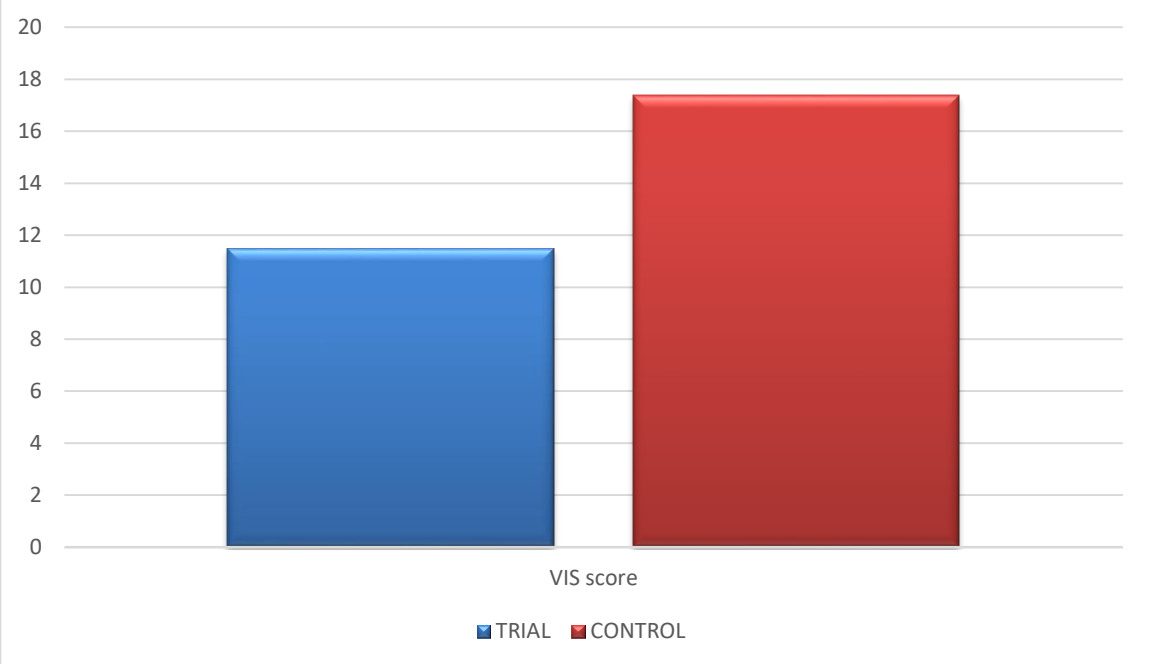

Figure 3. VIS score in trial and control groups.

congenital heart surgery. As a matter of fact, it is CPB that results in a significant and persistent depression of circulating thyroid hormones (10-13). Considering this concept, it would be rational to supply these hormones perioperative to improve patients' postoperative course.

As oral hormone therapy is very simple, available, and inexpensive, regarding the selection of route of administration to be effective, either orally or parenterally, Choi et al (14, 15) demonstrated that oral T3 therapy significantly attenuated the postoperative decline in the serum concentration of T3. Marwali and

Table 1: Demographic and clinical data in two groups. Data are expressed as mean ± SD; n=60 in each group.

variable	Trial group	Control group	P value
Gender (F/M)	29/31	32/28	0.2
Age (month)	24.2±13.1	22.3±13.1	0.43
Weight (Kg)	11.2±5.4	10.9±4.7	0.37
Intubation time (hour)	9.8±4.9	17.7±8.8	0.00
ICU stay (day)	5.1±2.2	6.08±2.36	0.02
Duration of CPB (min)	92.73±30.62	102.4±33.17	0.32
Aortic Clamp Time (minutes)	48.75±24.73	56.08±21.89	0.36
Vasoactive Inotropic Score: VIS	11.48±5.22	17.38±5.63	0.0001
Ejection Fraction (%)	49±4	41±3	0.16

Table 2: Serum of thyroid hormone levels in 2 groups. TSH (mIU/l) T4 (mcg/dl); T3 (ng/dl). Data are expressed as means ± SD; n=60 in each group.

variable	Trial group	Control group	P value
TSH FIRST (1)	2.55±1.24	2.3±1.7	0.47
TSH SECOND (2)	2.2±1.2	2.2±1.2	0.11
TSH THIRD (3)	2.3±1.4	2.1±.89	0.42
T3 FIRST (1)	1.2±1.44	1.2±.3	0.24
T3 SECOND (2)	1.5±.44	1.3±.36	0.13
T3 THIRD (3)	6.1±1.4	1.4±.67	0.07
T4 FIRST (1)	9.4±2.1	8.49±3.3	0.059
T4 SECOND (2)	8.07±2.4	8.04±2.6	0.25
T4 THIRD (3)	8.44±1.8	9.12±1.9	0.05

colleagues (16) concluded that hormone supplementation by an oral dose of 0.5 mcg/Kg every 12 hours for three days could maintain total and free T3 levels within normal limits after pediatric open-heart surgery.

It seems that the degree of thyroid hormone derangement is closely related to the difficulties of postoperative management. Dagan et al (17) have shown that in neonates treated with high doses of inotropes, the level of free T4 was significantly lower than patients with low doses of inotropes and this decrease persisted for a longer period.

The effect of thyroid hormone supplementation on the postoperative course of pediatric surgical patients was studied in previous researches. Although most of them proved its beneficial effect, some did not show any statistically significant result. A study by Haas et al (18) reported that thyroid hormone

replacement therapy could be a desirable option in terms of mortality and morbidity decrease, especially in high-risk pediatric cardiac patients. Aaron et al (19) proved that supplementation with triiodothyronine could achieve three important goals namely, improvement of hemodynamic function, reduction of inotrope usage, and shortening the duration of mechanical circulatory support. On the other, it is demonstrated that thyroid hormone replacement therapy is not necessary for patients under cardiac surgery, as this Sick Euthyroid Syndrome will recover spontaneously within one week (20). It has been concluded that with oral levothyroxine supplement therapy, the time to extubation and length in ICU and hospital stay would be decreased (21). Although this difference was just clinically, not statistically significant. Our study proved the effect of perioperative oral triiodothyronine therapy on the reduction of VIS, intubation time, ICU stays, and hospital stay, which is in agreement with the previously mentioned studies.

Regarding the effect of the patient's age, there is some emphasis on the more obvious benefit of hormone therapy for infants and neonates. In other studies, intravenous triiodothyronine supplementation has been demonstrated safe, resulting in better clinical outcome scores and more rapid achievement of negative fluid balance in a group of neonates undergoing Norwood operation or repair of the aortic arch; however, there was no significant improvement in postoperative cardiac index (22-24).

A study by Portman et al (25) reported that triiodothyronine therapy in Infants undergoing ventricular septal defect or tetralogy of Fallot repair could enhance cardiac function reserve. This effect was through the improvement of myocardial oxygen consumption. A multicenter randomized trial (TRICC trial) proved that triiodothyronine supplementation was safe in infants and children after cardiopulmonary bypass and could result in clinical advantages in patients younger than 5 months (24). This is not in accordance with our study. The range of our patients was from six to sixty months and we could show the significant effect of T3 supplementation beyond infancy.

To reach to a briefing, our experience in children undergoing cardiac surgery with CPB suggests that preoperative and postoperative short-term oral small-dose triiodothyronine treatment can reduce intubation time, VIS, ICU stay, and hospital stay.

At least, part of the oral triiodothyronine effect in reducing intubation time, VIS, ICU stay, and hospital stay can be attributed to the cardioprotective effects of thyroid hormones. The most important shortcoming of this study was the limited sample size. The inclusion of both cyanotic and acyanotic patients might have also affected our results.

Conclusion

In the present study, we found a relationship between thyroid hormone replacement therapy and reducing the length of ICU stay, intubation time, and VIS in patients undergone CPB. We recommend perioperative triiodothyronine supplementation in pediatric congenital cardiac surgery, especially in high-risk operations.

Acknowledgment

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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