Oral thyroxin supplementation in infants undergoing cardiac surgery: A double-blind placebo-controlled randomized clinical trial

Sachin Talwar, MCh, Amolkumar Bhoje, MS, Rajesh Khadagawat, DM, Pradeep Chaturvedi, MD, Vishnubhatla Sreenivas, PhD, Neeti Makhija, MD, Manoj Sahu, DM, Shiv Kumar Choudhary, MCh, and Balram Airan, MCh

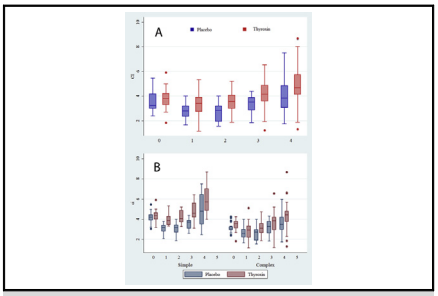
ABSTRACT

Background: Decreases in serum total thyroxin and total triiodothyronine occurs after cardiopulmonary bypass, and is reflected as poor immediate outcome. We studied effects of oral thyroxin supplementation in infants who underwent open-heart surgery.

Methods: In this prospective study, 100 patients were randomized into 2 groups: 50 in the thyroxin group (TH) and 50 in the placebo group (PL). Patients in the TH group received oral thyroxin (5 μg/kg) 12 hours before surgery and once daily for the remainder of their intensive care unit (ICU) stay. Data on intraoperative and postoperative variables were recorded. Cardiac index (CI) was measured. Perioperative serum thyroid hormone levels and serum interleukin-6 and tumor necrosis factor-α were measured. Secondary analysis was performed by dividing patients into simple and complex subcategories.

Results: Results of the primary analysis indicated a higher CI in the TH compared with the PL. In the complex category, the mean duration of mechanical ventilation was 3.85 $\pm$ 0.93 and 4.66 $\pm$ 1.55 days in the TH and PL, respectively ($P = .001$). Mean ICU stay was 6.79 $\pm$ 2.26 and 8.33 $\pm$ 3.09 days ($P = .03$), and mean hospital stay was 15.70 $\pm$ 4.77 and 18.90 $\pm$ 4.48 days ($P = .01$) in the TH and PL, respectively. There were no significant differences between the TH and the PL in the simple category. CI was higher in the TH at all time points ($P = .004$). The average therapeutic intervention scoring system scores for the first 2 days were higher in the PL in the complex category.

Conclusions: Oral thyroxin supplementation improves the CI and reduces the inotropic requirement. In addition, it reduces the duration of mechanical ventilation, ICU and hospital stay, and therapeutic intervention scoring system in infants after surgery for complex congenital heart defects. (J Thorac Cardiovasc Surg 2018;156:1209-17)



Comparison of cardiac indices.

Central Message

Oral thyroxin supplementation improves postoperative outcomes in infants who undergo surgery for complex congenital heart diseases with better immediate postoperative outcomes.

Perspective

We performed a placebo-controlled, double-blind, randomized controlled trial involving 100 patients, 50 in the thyroxin group and 50 in the placebo group. It was found that oral thyroxin supplementation is associated with higher cardiac indices compared with placebo in infants who undergo open-heart surgery for complex congenital heart diseases with better immediate postoperative outcomes.

See Editorial Commentary page 1218.

See Editorial page 1207.

Thyroid hormones regulate every aspect of the cardiovascular system. A decrease in thyroid hormone levels is observed after cardiopulmonary bypass (CPB) in children who undergo open-heart surgery.[1] The decrease in thyroid hormone levels after CPB is more profound in neonates and infants compared with adults. This makes them vulnerable to the harmful effects of a CPB-induced temporary hypothyroid state.[2] Nonpulsatile flow to the brain depressing

From the Cardiothoracic Center, All India Institute of Medical Sciences, New Delhi, India

Read at the 96th Annual Meeting of The American Association for Thoracic Surgery, Baltimore, Maryland, May 14-18, 2016.

Received for publication June 14, 2016; revisions received May 7, 2018; accepted for publication May 13, 2018.

Address for reprints: Sachin Talwar, MCh, Department of Cardiothoracic and Vascular Surgery, All India Institute of Medical Sciences, New Delhi 10029, India (E-mail: sachintalwar@hotmail.com).

0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2018.05.044

Scanning this QR code will take you to the supplemental video and figures for the article.

Abbreviations and Acronyms

CI = cardiac index
CPB = cardiopulmonary bypass
ICU = intensive care unit
IL = interleukin
IS = inotropic score
LCOS = low cardiac output syndrome
T4 = thyroxin
TISS = therapeutic intervention score
TT3 = total triiodothyronine
TT4 = total thyroxin

the hypothalamus–pituitary–thyroid axis, hypothermia, hemodilution, and ultrafiltration during CPB have been identified to be responsible for a decrease in thyroid hormone levels after CPB.[3] These hormones regulate cardiac output by their effects on heart rate, cardiac contractility, and systemic vascular resistance,[4] with lower levels being associated with poor postoperative outcomes.[1,5] We conducted a double-blind placebo-controlled prospective randomized study to assess the efficacy of oral thyroxin (T4) supplementation in infants who underwent open-heart surgery.

METHODS

This prospective, double-blind, placebo-controlled randomized trial was conducted at the Cardiothoracic Sciences Center of the All India Institute of Medical Sciences, New Delhi, India, between April 2014 and July 2015. The study protocol was approved by the Institute Ethics Committee (IEC/NP-235 and RP-14/17.06.03) and the study protocol was duly registered with the clinical trials registry of India (CTRI/03/058263). Informed consent was obtained from the parents/guardians of all of the patients. We aimed to evaluate the effects of oral T4 supplementation in infants 6 months of age or younger, who underwent open-heart surgery with CPB. The primary end point was change in the cardiac index (CI). The secondary end points were change in inotropic score (IS), and levels of serum inflammatory markers. Clinical end points were time to extubation, intensive care unit (ICU) stay, and occurrence of low cardiac output syndrome (LCOS), which was defined as per standard criteria that include subjective determination of reduced peripheral perfusion, diminishing urine output, and increasing lactate levels with acidosis, and hemodynamic instability despite optimal inotropic support.[1] In the absence of data on mixed venous saturations, a rising lactate level was used as a surrogate for occurrence of LCOS.

The study population was further stratified into complex and simple categories for purposes of secondary analysis and to clarify the differences between the 2 groups of patients that exhibited different intraoperative and postoperative behavior. The simple category included 38 patients and the complex category included 62 patients. The complex category consisted of 56 patients with dextra-transposition of the great arteries (20 with intact ventricular septum and 36 with associated ventricular septal defect), 3 with tetralogy of Fallot, 2 with total anomalous pulmonary venous connection, and 1 with truncus arteriosus. The simple category consisted of patients with varying types of ventricular septal defects.

Sample Size and Randomization

In our experience, the preoperative CI in the patients in this study is expected to be 3.5 L/min/m^2. We expect an average improvement/change in the CI of 0.4 L/min/m^2. Assuming this increases by 1 L/min/m^2 in the thyroid group, with a common SD of 1 L/min/m^2, we require 44 patients in each of the placebo and T4 groups to detect this difference to be statistically significant in a 2-sided test with 5% α error and 80% power. Giving an allowance for attrition, a sample size of 50 was chosen in each group. The number of patients in the simple and complex groups were not defined beforehand for calculation of the sample size. A randomization list was generated using the nQuery advisor version 7.0 (Statistical Solutions Ltd, Cork, Ireland). We used stratified randomization with blocks of 4 separately for the simple and complex groups to have an even distribution between the patients with different severities of diagnosis. This randomization sequence was transferred to sealed envelopes, which were opened just before administering T4/placebo (Figure E1).

T4 Administration and Dosage

Preoperative thyroid hormone levels were tested on an outpatient basis and patients with abnormal values were excluded from the study. The patients were allocated to either the drug A (T4) or drug B (placebo) group using random number allocation in sealed covers. The preparation of the drug/placebo was performed by a person who labeled them as A or B and handed it over to another person who was blinded to the contents of the drug and was responsible for the storage, maintenance, and administration. To prepare the drug, 1 tablet of Eltroxin (containing 25 μg of levothyroxine sodium; GlaxoSmithKline Pharmaceuticals Ltd, Mumbai, India) was crushed and dissolved in 5 mL of saline so that the concentration of levothyroxine was 5 μg/mL. The placebo was prepared by dissolving an identical plain sugar tablet in 5 mL saline. The calculated dose of the drug was 5 μg/kg body weight per dose or 1 mL/kg of the prepared solution. The assigned solution was administered in such a dose that patients in the test group received 1 dose equivalent to 5 μg/kg of levothyroxine sodium 12 hours before surgery. This dose was repeated once daily at 7 AM for the duration of the remaining ICU stay via a nasogastric tube. The control group received placebo in a similar fashion. All babies received similar standard preanesthetic medication and were breastfed up to 4 hours before surgery.

Anesthesia Technique

The anesthesia technique was standardized for all patients. Intravenous induction with ketamine 2 mg/kg, fentanyl 2 μg/kg, and rocuronium 1 mg/kg was used. Sevoflurane with air and oxygen was used for maintenance to maintain a minimum alveolar concentration of 0.8 to 1. Midazolam 0.1 mg/kg, fentanyl 0.1 μg/kg, and vecuronium 0.1 mg/kg were used intermittently. Heparin (3 mg/kg) was administered and supplemented as required to maintain an active clotting time of 480 seconds or greater on CPB.

Surgical Technique

Before making the skin incision, venous blood samples were taken in a plain vial. CI was measured using noninvasive impedance cardiometry method with an ICON monitor (ICON Osypka Medical GmBH, Berlin, Germany).[6] ICON is an electrical cardiometry principle-based noninvasive technology to compute cardiac output. Four electrodes are placed on the skin (2 on the left side of the neck, one below the other, the third on the left midaxillary line at the level of the xiphisternum, and the fourth 2 cm below the third). These electrodes sense the electrical impedance of red blood cells and it is converted into CI by computer software. In infants with a short neck, the first electrode was placed on the forehead and the fourth one on the left femoral region whereas the position of the second and third were same as for other babies. The validity and reliability of this method of determination of CI has been proven by comparing it with a standard invasive method using a pulmonary artery catheter. This has been shown to be an accurate method of calculating the CI in previous studies from our institution (https://pdfs.semanticscholar.org/d837/133b554ac4a5e4bede29d75bef68f5612772.pdf).[6-8]

After median sternotomy, standard hypothermic (28°C-32°C) CPB was established after aortobicaval cannulation using a nonpulsatile roller pump,