A prospective randomized clinical study of perioperative oral thyroid hormone treatment for children undergoing surgery for congenital heart diseases

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ABSTRACT

Context : **Thyroid hormone deficiency is known to occur after cardiac surgery and known as nonthyroid illness (NTI). The beneficial role of perioperative thyroid hormone supplementation in children has been debatable more so with oral supplementation.**

Aims : **The aim is to evaluate the role of pre-operative oral thyroid hormone therapy in preventing NTI. To assess its effect on post-operative thyroid hormone levels, hemodynamic parameters, and cardiac function of infants and small children undergoing pediatric cardiac surgery.**

Settings and Design : **Prospective randomized, double-blinded controlled trial at a tertiary level pediatric cardiothoracic center.**

Materials and Methods : **Sixty-five children aged under 18 months undergoing corrective surgeries on cardiopulmonary bypass were included. Patients were randomized into two equal groups: placebo group (given placebo) and thyroxine group (given thyroxine tablet 10 μg/kg) orally once a day starting on the preoperative evening till the fifth postoperative day. The postoperative hemodynamics, inotropic requirement, ventilatory requirement, and cardiac function on echocardiography were observed.**

Statistical Tests : **Shapiro–Wilk test, Mann–Whitney/*t*-test, Chi-square test, ANOVA with Tukey correction were used.**

Results : **Serum triiodothyronine and thyroxine levels postoperatively were significantly higher in the thyroxine group than in the placebo group. There was no significant difference in left ventricular ejection fraction, hemodynamic variables, extubation time, and length of intensive care unit (ICU) stay between the two groups.**

Conclusions : **In infants and small children undergoing corrective cardiac surgery, perioperative oral thyroid hormone therapy reduces the severity of postoperative NTI. It increases the serum level of thyroid hormones but the therapy does not translate to better hemodynamics, reduced inotropic requirement, reduced ventilatory requirement, improved myocardial function or reduced ICU stay when compared to placebo.**

Keywords : Cardiopulmonary bypass, congenital heart surgery, fast track, nonthyroid illness, thyroxine

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INTRODUCTION

Thyroid hormone has an effect on multiple organ systems, including cardiovascular function, especially in infants. Infants require and produce higher levels of thryoxine (T4) and triiodothyronine (T3) compared to older children and adults. The blood levels of T4 and T3 fall transiently in children under physiological stress like any critical illness or cardiac surgery.[1] This transient hypothyroidism has been termed as nonthyroid illness (NTI) or euthyroid sick syndrome and been observed after cardiac surgery under cardiopulmonary bypass (CPB) in children. It can blunt postoperative physiological response of children undergoing cardiac surgery affecting cardiac afterload, ventricular function, and ventilation.[2-4] This has the potential to adversely affect their outcome after cardiac surgery under CPB. It has been reported in pediatric patients that T3 supplements have beneficial inotropic effects and can prevent Low cardiac output state (LCOS) in the immediate postoperative course.[5,6] The T3 supplements have been administered either intravenously (IV) or enterally by different workers.[7-9] The benefit of supplemental T3 or T4 in reducing hospital stay postoperatively makes it an attractive proposition as an adjunct to fast tracking which is practiced by some centers.[10,11] However, the studies on the beneficial effects of thyroid hormone supplements have been undertaken with varied end points; thus, their results are conflicting. The jury is still out and more so with the effect of enteral T4 supplementation.[12,13] Therefore, we conducted this study to see the effect of enteral T4 on the blood levels of T3, T4, thyroid-stimulating hormone (TSH) and on the postoperative hemodynamics and cardiac function.

Aim and primary objective

To measure the effect of perioperative enteral thyroid hormone administration on the blood levels of free T3, T4, and TSH levels of infants and small children undergoing pediatric cardiac surgery under CPB.

Secondary objective

To study the effect of enteral thyroid hormone administration on the postoperative outcome variables, namely left ventricular ejection fraction, mechanical ventilation (MV) duration, length of intensive care unit (ICU) stay, and mortality after pediatric cardiac surgery.

MATERIALS AND METHODS

It was a prospective, double-blind, placebo-controlled randomized trial at tertiary level cardiothoracic center, between January 2019 and December 2019. The study was approved by the Institutional Ethics Committee and study protocol registered with the clinical trials registry of India (CTRI/2019/01/017334). A written informed consent was obtained from the parents. Pediatric patients (<10 kg and 18 months) undergoing cardiac surgery under CPB for congenital heart diseases (CHDs) (RACHS ≥2) were included. Patients with multiple congenital anomalies, genetic abnormalities, preoperative arrhythmias and patients on preoperative inotropes were excluded. Block randomization was done to ensure an equal number of participants in both groups. The random number was generated using Microsoft Excel®, Microsoft Inc. USA. Patients were randomized into two groups using blind envelop technique, thyroxine group, and placebo group. The groups formed were sealed in a sequentially numbered opaque envelope and opened by the duty staff after a participant met the inclusion criteria. The thyroxine group received tablet L-thyroxin 10 μg/kg (Tab Eltroxin®, GlaxoSmithKline, NZ) orally 1 day before surgery and 10 μg/kg/day every postoperative day through nasogastric tube till inotropes were stopped or a maximum of five consecutive days. The placebo group received sterile glucose powder of similar appearance in the same dosage. The attending intensivist, nursing staff, and the individual recording data were blinded.

Anesthetic technique was as per standard institutional protocol, i.e., balanced general anesthesia (GA) technique with continuous thoracic epidural analgesia (TEA). Premedication with intranasal ketamine 7 mg/kg and nasal midazolam 0.3–0.5 mg/kg was given. GA induced with ketamine (1–2 mg/kg), fentanyl (2 μg/kg), and rocuronium (1 mg/kg). Lungs were ventilated by a semi-closed circle system with a tidal volume of 6–8 mL/kg, breath rate and fraction of inhaled oxygen concentration adjusted as per the requirement. Anesthesia was maintained with 2% sevoflurane and vecuronium injection. TEA was administered after induction as an initial bolus of 1 ml/kg bupivacaine 0.25% with 50 μg/kg morphine (no epidural morphine used in patients <5 kg) followed by infusion of 0.125% bupivacaine at the rate of 0.2 ml/kg/h. CPB was carried out uniformly as per unit protocol. Moderate hypothermic (28°C–32°C) CPB was established with a nonpulsatile flow of 3 - 3.2 *body surface area L/minute and a mean arterial pressure (MAP) as per age with additional filtration. Coagulation was offset by 300 IU/kg heparin aiming at an activated clotting time >480 s. In addition, all patients received tranexamic acid 100 mg/kg. Cardioplegic arrest induced and maintained by intermittent administration of antegrade Delnido cardioplegia solution. Perioperative goal-oriented hemodynamic support was established according to institutional protocol. Hematocrit >35% was maintained in all patients. Extubation protocol and postoperative sedation protocol was as per the pediatric cardiac surgical team. Postoperative analgesia in ICU was maintained with TEA and rescue analgesia as intermittent intravenous fentanyl 1 mcg/kg boluses.

The data collected was the demographic parameters and intra-operative data, including CPB time and aortic cross-clamping (AXC) time. Post-operative data included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressures (BPs) (MAP) and arterial base deficit twelve hourly, postoperative length of stay in ICU, duration of MV, the incidence of low cardiac output state (LCOS), incidence of sepsis, mortality, chest tube drainage in milliliters, and any adverse events. Transthoracic echocardiography was done at 12 h postoperatively and every 24 h subsequently for 5 days by the pediatric cardiologist on Philips IE 33 (Philips Healthcare, Netherlands) echocardiography machine. The left ventricle ejection fraction (LVEF) was measured by the Simpson biplane method. The inotropic requirement was assessed in terms of Vasopressor-Inotropic Score (VIS) using the formula:[14]

VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (IU/kg/min) + 100 × norepinephrine dose (μg/kg/min).

LCOS was defined as a maximum VIS >15 for >30 min or requirement of extracorporeal membrane oxygenation support.

The laboratory parameters recorded included serum thyroid hormone levels preoperatively, at 24-h (day 1) and 48 h (day 2) after the surgery. Separated serum assay was done for the estimation of serum-free T3, freeT4, and TSH. Thyroid hormones were measured by radio-immune assay technique on the fully automated Elecsys 2010 analyzer (Roche Diagnostics) using gamma counter instrument (manufactured by Oakfield Company, England). (reference range for free T3: 2.2–4.2 pg/mL; free T4: 0.8–1.7 ng/dL; TSH: 0.3–3.6 mIU/mL)

Statistical analysis

Distribution of the continuous data was analyzed with the Shapiro–Wilk test. Continuous variables with a normal distribution were expressed as mean ± standard deviation. Dichotomous data were expressed as numbers and percentages. Based on the distribution of the data for continuous variable, Mann–Whitney or *t*-test was used for comparing two groups. The Chi-square test was used for a categorical variable. Mixed factor repeated measures ANOVA with Tukey correction was used to find any significant impact of the thyroxine treatment on thyroid hormone levels, hemodynamic variables, and other postoperative outcomes. The sample size was calculated for the serum-free T3 level. Assuming mean free T3 level to be 3.15 pg/ml + 0.2 and to find a difference of 0.15 in between two groups postoperatively, with 80% power and 5% alpha error, the calculated sample size is 28 in each group. With a 10% margin, we decided to recruit a minimum of 31 patients in each group. The data analysis was performed using SPSS software (IBM SPSS Statistics 21, Chicago, IL, USA). A value of $P < 0.05$ was taken as statistically significant.

RESULTS

Ninety patients under 18 months were operated between January 2019 and December 2019. Parents of two patients did not consent, whereas 18 patients were excluded. A total of 70 patients were included in the study. Thirty-five were randomly assigned to the thyroxine group and 35 to the placebo group. Finally, 32 and 33 patients completed study in thyroxine and placebo group, respectively [Figure 1]. The distribution of patients based on the underlying cardiac diagnosis is represented in Figure 2.

Patients in both the groups were comparable in respect to age, height, weight, BSA, and gender ratio [Table 1]. The CPB time, AXC time, the hematological parameters, base deficit, and biochemical parameters were comparable between the two groups [Table 1].

There was a significant difference in the serum T3, T4, and TSH levels between both groups [Table 2]. The mean values of free T3 (2.9 vs. 3.4 pg/mL) and free T4 (1.15 vs. 1.45 ng/dL) were lower in the placebo group and TSH (3.6 vs. 1.9 mIU/mL) higher when compared to the thyroxine group. There was a significant interaction between time period and use of oral thyroxine (T3: F [1.4, 58.8] = 5.1, P = 0.02, ηp2 = 0.11; T4: F [1.3, 47.6] =3.9, P = 0.04, ηp2 = 0.1; TSH: F [1.4, 45.1] = 2.9, P = 0.08, ηp2 = 0.08). There was about 8% decrease in free T3 levels on day 1 and about 12% on day 2 when compared to baseline values in the placebo group. Similarly, free T4 levels dropped 10% on day 1 and about 14% on day 2 in the placebo group, while 11% and 13% increase

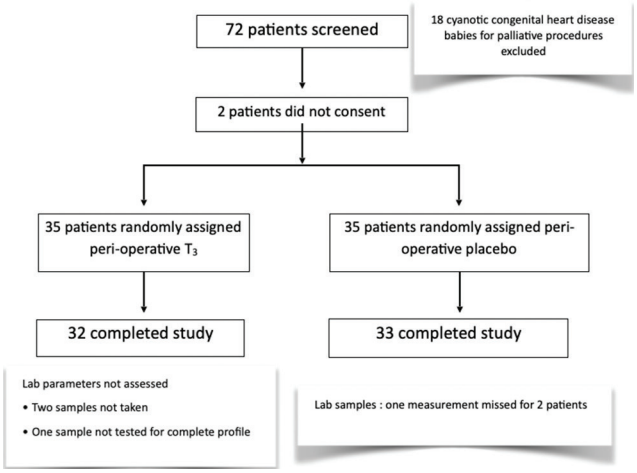

Figure 1: Consort diagram: to depict the distribution of patients inclusion, randomization and final completion of the study

Table 1: The distribution of the demographic characteristics, laboratory investigations and hemodynamic variables of the study population in both groups

Parameters	Mean±SD		*T*/χ^2	*P*
	Thyroxine (*n*=32)	Placebo (*n*=33)		
Age (months)	7.3±6	6.2±3.7	0.92	0.36
Sex (male)	21 (65.6%)	14 (42.4%)	3.52	0.06
Height (cm)	61.2±7.8	62.5±7.9	−0.33	0.74
Weight (kg)	5.1±2.5	4.6±1.3	1.00	0.32
BSA (m^2)	0.26±0.07	0.25±0.1	0.37	0.71
CPB (min)	113.6±54.7	111.3±50.5	0.18	0.86
AXC (min)	70.9±42.3	73.8±39.2	−0.28	0.78
Preoperative investigations				
Haemoglobin (g/dL)	12.03±3.3	12.3±1.65	−0.43	0.67
TLC (/cu mm)	9993±2305	10505±2501	−2.53	0.06
Platelet count (lac/cu mm)	3.49±1.5	3.61±1.4	−0.33	0.74
BUN (mg/dL)	9.1±4.7	11.1±4.8	−1.72	0.09
Serum creatinine (mg/dL)	0.29±0.14	0.36±0.17	−1.78	0.08
Serum sodium (mEq/L)	138.3±2.7	139.7±4.3	−1.56	0.12
Serum potassium (mEq/L)	5.0±0.98	5.0±0.39	0.05	096
Serum total bilirubin (mg/dL)	1.06±1.03	0.98±1.6	0.24	0.81
Serum AST (IU/mL)	55.7±35	56.7±38	−0.10	0.91
Serum ALT (IU/mL)	35.8±14.4	39.6±9.6	−1.26	0.21
PT (second)	13.4±1.4	12.9±0.6	1.90	0.06
APTT (second)	35.9±9.4	38.4±5.2	−0.65	0.52
INR	1.2±0.32	1.1±0.27	1.87	0.07
Base excess (mEq)	0.57±4.6	1.1±4.1	−0.49	0.62
Preoperative haemodynamic paramaters				
Systolic blood pressure (mmHg)	86±12.5	81±12.4	1.36	0.18
Diastolic blood pressure (mmHg)	54±7.8	52±9.6	1.26	0.21
Mean blood pressure (mmHg)	65±8.3	62±10.2	1.37	0.18
Heart rate (bpm)	128±19	135±17	−1.65	0.10
Preoperative LVEF (%)	51.25±7.3	51.0±7.6	0.14	0.89
Baseline thyroid hormones assay				
T3 (pg/dL)	3.14±0.67	3.00±0.64	0.81	0.42
T4 (ng/dL)	1.34±0.23	1.28±0.23	0.89	0.38
TSH (mIU/mL)	3.55±2.68	3.86±4.49	−0.29	0.77
Duration of thyroxine/placebo therapy (median days with IQR)	4 (4-5)	4 (4-4.5)	0.57	0.75

P<0.05 is considered significant. BSA: Body surface area, CPB: Cardiopulmonary bypass, AXC: Aortic cross clamp time, TLC: Total leucocyte count, BUN: Blood urea-nitrogen, AST: Aspartate amino-transferase, ALT: Alanine transaminase, PT: Prothrombin time, APTT: Activated partial thromboplastin time, INR: International normalized ratio, LVEF: Left ventricle ejection fraction, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone/thyrotropin, IQR: Interquartile range

Table 2: The results of mixed ANOVA on the observation of the serum levels of thyroid hormones and the postoperative outcome variables

Parameter	df	*F*	ηP^2	*P*
Heart rate (beats/min)	1, 815.9	0.66	0.01	0.42
Systolic blood pressure (mmHg)	2.1, 133.7	1.33	0.02	0.3
Mean blood pressure (mmHg)	2, 127.7	2.6	0.04	0.08
Diastolic blood pressure (mmHg)	2.2,136.2	0.34	0.005	0.7
LVEF (%)	2.7,167.7	2.6	0.04	0.06
Vasopressor ionotropic score	1.4, 90.2	0.39	0.006	0.6
Base deficit (mEq)	21.7, 92.4	3.2	0.06	0.051
Serum free T3 level (pg/dL)	1, 7.1	20.1	0.33	<0.001
Serum free T4 level (ng/dL)	1, 2.45	58.5	0.62	<0.001
Serum TSH level (mIU/mL)	1, 73	4.2	0.11	0.048

P<0.05 is considered significant. LVEF: Left ventricle ejection fraction, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimlating hormone/thyrotropin, df: Degree of freedom

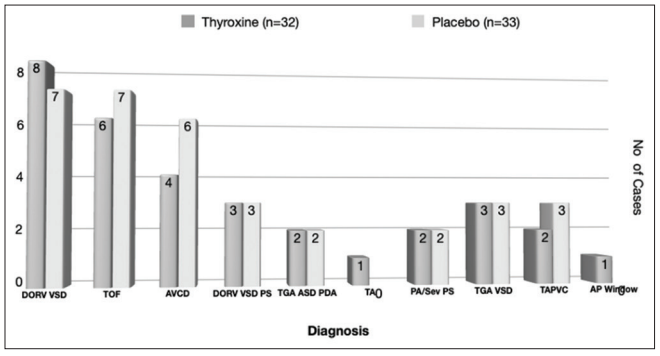

Figure 2: The distribution of the study population based on the underlying cardiac diagnosis in both the groups. DORV: Double outlet right ventricle, VSD: Ventricular septal defect, TOF: Tetralogy of Fallot, AVCD: Atrioventricular canal defect, PS: Pulmonary stenosis, TGA: Transposition of great arteries, ASD- Atrial septal defect, PDA: Patent ductus arteriosus, TA: Truncus arteriosus, PA: Pulmonary atresia, TAPVC: Total anomalous pulmonary venous connection, AP window-Aortopulmonary window

were noted in the thyroxine group on day 1 and day 2, respectively. In contrast, TSH increased by 60% in the placebo group, while it decreased by 74% in the thyroxine group on the first postoperative day. TSH levels, however, recovered in the placebo group on the second postoperative day [Figure 3].

There was no significant difference in HR, mean SBP, DBP, and MAP between both groups [Table 2]. The HR, SBP, DBP, and MAP variations temporally after the

administration of thyroxine and placebo are depicted in Table 2 and Figure 4. In both groups, an initial marginal increase in BP was noted postoperatively, which stabilized over the next 24 h [Figure 4]. LVEF, VIS, base deficit, postoperative transfusion requirements and chest tube drainage volumes showed no significant difference in both groups [Table 2 and Figure 5].

Thyroxine group patients had a prolonged duration of MV compared to the placebo group, though not statistically significant. However, the incidence of LCOS, length of ICU stay, and incidence of sepsis were comparable in both groups. Two patients in each group died in the immediate postoperative period, all four being small infants and neonates with RACHS ≥3 ($P = 0.97$) [Table 3]. There was no requirement for re-exploration in either group.

DISCUSSION

The commonest comorbidity in children with hypothyroidism is CHD.[14-16] Even euthyroid children undergoing cardiac surgery often exhibit NTI or sick euthyroid syndrome after CPB; generally, low T3, normal or decrease T4 with normal or suppressed TSH.[4,12,17,18] It is characterized by thyroid hormones reaching a nadir in the first 24–48 h and recovering over the 4th to 8th day.[19-22] NTI after cardiac surgery has been associated with longer ICU stay, prolonged ventilation, and increased use of inotropes.[4,19-23] T3 supplementation has been tried during and after cardiac surgery with the presumption that it will enhance cardiac function along with hemodynamics by its vasoactive inotropic effects.[5-7,9,12,24] The therapeutic dose of hypothyroidism in infants ranges from 10 to 15 μg/kg/day, with younger patients requiring higher dosages. We decided to uniformly administer a dose of 10 μg/kg/day in a single dose which is higher than doses administered in earlier studies. Earlier studies have used IV thyroxine due to the variable bioavailability of enteral T4, except by Marwali *et al.* and Talwar *et al.* who have used enteral thyroxine.[5,9,12,24]

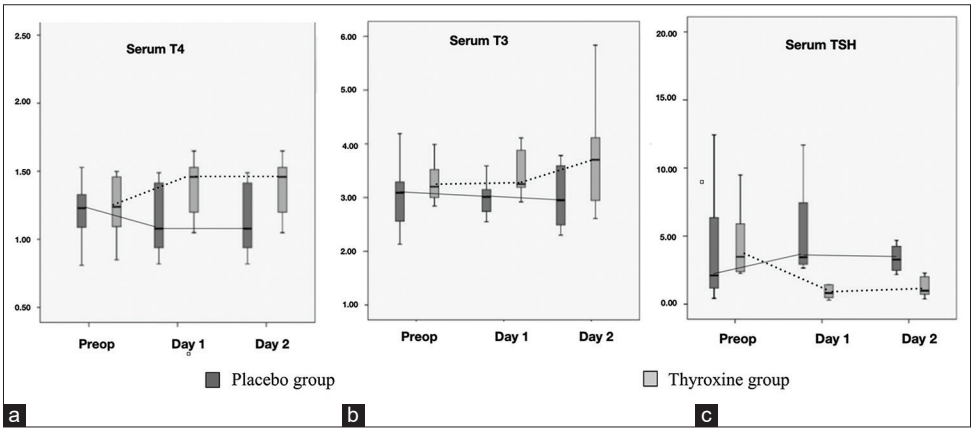

Figure 3: Box plot diagram of (a) serum T4 (thyroxine) assay, (b) serum T3 (triiodothyronine) assay and (c) serum thyroid stimulating hormone assay of the two groups (placebo and thyroxine) at different time periods (preoperative, Postoperative on day 1, and day 2)

Table 3: The distribution of the postoperative outcomes, hemodynamic variables, morbidity and mortality indicators in both groups of patients

Parameters	Thyroxine (*n*=32)	Placebo (*n*=33)	*T*/χ^2	*P*
Outcomes				
MV duration (h)	41.9±38.2	30.2±25.5	1.45	0.15
ICU Stay (days)	5.9±2.9	6.4±1.6	−0.80	0.43
Arrhythmias, *n* (%)	7 (21.9)	6 (18.2)	0.26	0.61
LCOS, *n* (%)	9 (28.1)	11 (33.3)	0.38	0.53
Sepsis, *n* (%)	5 (15.6)	4 (12.1)	0.17	0.68
In hospital mortality, *n*	2	2	0.001	0.97
Postoperative transfusion (mL/kg)				
PRBC	35.46±62.65	59.34±56.7	−1.12	0.07
FFP	78.12±28.53	96.06±54.02	−1.67	0.10
PC	8.26±10.00	10.00±11.37	−2.01	0.13
Cryoprecipitate	5.16±10.96	13.64±24.59	−1.78	0.08
Chest drain (mL/kg)				
Repeated measure ANOVA (h)				
At 12	120.6±49.4	127.8±55.9	3.17 (*F*)	0.058
At 24	61.1±54.9	75±73.6		
At 48	12.8±19.2	18.9±14.7		

P<0.05 is considered significant. MV: Mechanical ventilation, ICU: Intensive care unit, LCOS: Low cardiac output state, PRBC: Packed red blood cells, FFP: Fresh frozen plasma, PC: Platelet concentrate

Availability of IV T4 is a limiting factor in developing countries. Talwar *et al.* demonstrated significant improvement in cardiac index, decreased inotropic requirement, lesser MV duration and shorter ICU stay in infants given enteral thyroxine while undergoing cardiac surgery.[9] The adequacy of absorption of enteral thyroxine supplementation has been questioned; therefore, we studied the serum levels of thyroid hormones after oral administration postoperatively. We could conclusively demonstrate that the serum concentration of thyroid hormones declined significantly and TSH levels increased in the placebo group postoperatively, which is in agreement with other studies.[12,19,21,23-25] In contrast, free T3 and T4 levels increased and TSH decreased in the Thyroxine group postoperatively, even though ischemic CPB times and underlying CHD distribution were similar in both the groups. However, unlike other studies[3,9,12,24] it did not translate to significant improvement in hemodynamics, ICU stay, MV duration, VIS score, sepsis or mortality. No adverse effects were reported due to cardiac rhythm or HR in either group. Chowdhury *et al.* did show a decrease in inotropic use and TISS score but also observed a similar outcome as ours viz. length of ICU stay, MV duration, BP, HR, rhythm.[3] The largest randomized controlled trials (TRICC trial) showed no difference in hemodynamics, ionotropic use or postoperative outcomes. However, on subgroup analysis decreased extubation time, improved myocardial function and decreased ionotropic use were noted in neonates and smaller infants[12] Talwar *et al.* have measured cardiac index by using noninvasive electrical cardiometry method with an ICON® monitor (ICON Osypka Medical GmBH, Berlin, Germany).[9] As an objective measure of cardiac output and perfusion, we recorded LVEF, base deficit and VIS score, which showed similar trends in both the groups.[26] Though cardiac output has been shown to improve with oral thyroid supplementation, we did not observe any significant clinical difference in the incidence of LCOS related to thyroxine supplementation.[9] Patients who developed LCOS were of significantly younger age, lesser height, weight, and BSA; they had longer CPB and AXC time ($P < 0.05$). Also, they remained significantly longer on MV and had longer ICU stay ($P < 0.05$), although no difference in thyroid hormone levels was observed. Thyroxine group did show a lesser VIS score, but not only the difference was insignificant, there was no difference after 48 h between the two groups. Talwar *et al.* demonstrated no correlation between LCOS and thyroid hormone levels on ICON monitoring.[9]

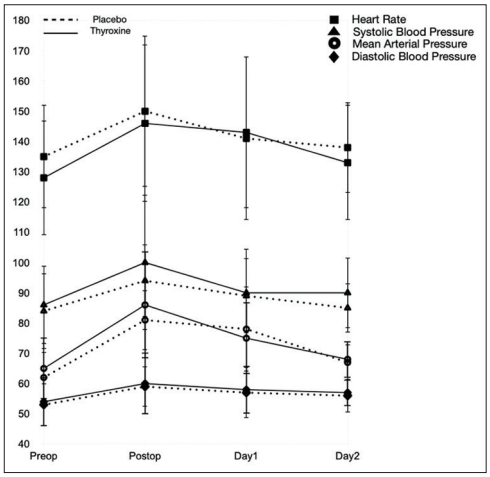

Figure 4: Line diagram with error bars depicting the temporal variations in heart rate, systolic blood pressure, mean blood pressure and diastolic blood pressure between the two groups (placebo and thyroxine) over different time periods (Preop- preoperative, Postop- postoperative, day 1–24 h after surgery, day 2–48 h after surgery)

The limitation of our study was that it was a single center study limited to immediate outcomes. The supplementation was of short duration. Our center practices fast-tracking with neuraxial analgesia;[27]

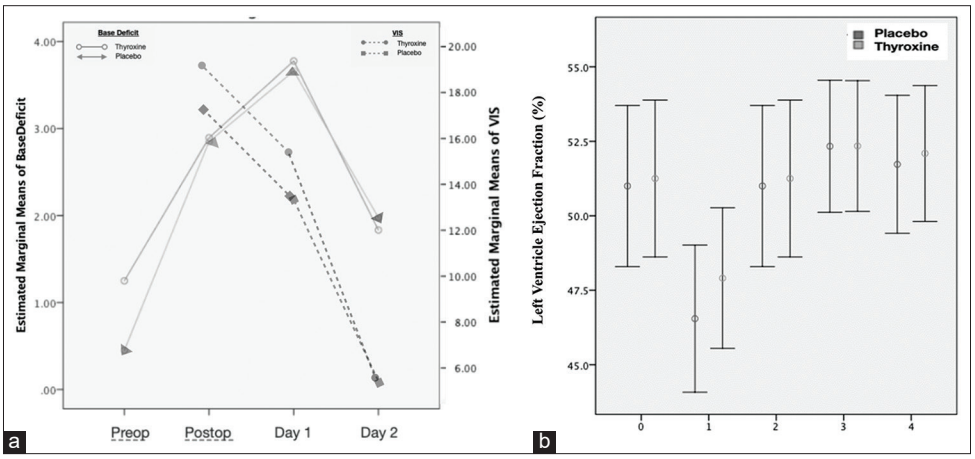

Figure 5: Profile Plot diagram depicting the temporal variation of means of (a) vassopressor -ionotropic score) and base deficit and (b) left ventricle ejection fraction %) of both groups (placebo and thyroxine) at different time periods (preoperative, postoperative-immediate postoperative, postoperative on day 1, and day 2 and before discharge)

therefore, we limited our study for a short postoperative time. The interaction of neuraxial analgesia with thyroid hormone levels was not studied by us. Furthermore, different age-groups have different hemodynamic and hormonal response to surgery-induced stress, which could have definitive impact on clinical outcome. We also could not objectively assess the impact of ultrafiltration on thyroid hormone depletion[4] and this could open another frontier for research.

CONCLUSIONS

NTI is not uncommon following cardiac surgery in the pediatric population with complex CHDs. Perioperative supplementation with oral thyroxine does increase serum free T3 and free T4 levels and mitigates NTI, but it does not translate into improved hemodynamic performance, decrease inotropic use, decrease MV duration, and ICU stay even when fast track protocol is followed. Larger population multi-centric studies with confirmatory designs and longer observation periods are required to determine the role of oral thyroxine supplementation in this cohort.

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Conflicts of interest

There are no conflicts of interest.

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