

# Effect of Perioperative Use of Oral Triiodothyronine for Infants Undergoing Complex Congenital Cardiac Surgeries Under Cardiopulmonary Bypass: A Double-Blinded Randomised Controlled Study

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## ABSTRACT

**Background:** Thyroid hormone metabolism disrupts after cardiopulmonary bypass both in adults and pediatric patients. This is known as Euthyroid sick syndrome, and it is more evident in pediatric patients who were undergoing complex cardiac surgeries compared to adults. This decrease in serum T3 levels increases the incidence of low cardiac output, requirement of inotropes, prolonged mechanical ventilation, and prolonged intensive care unit (ICU) stay.

**Aims and Objectives:** The primary objective was to compare the mean Vasoactive-inotropic score (VIS) at 72 hours postoperatively between T3 and Placebo groups.

**Materials and Methods:** One hundred patients were screened, and 88 patients were included in the study. Triiodothyronine 1 mic/kg 10 doses 8<sup>th</sup> hourly was given orally postoperatively to cases and sugar sachets to controls. The blood samples for analysis of FT3, FT4, and TSH were taken every 24 hours postoperatively, and baseline values were taken after induction. Mean VIS scores, ejection Fraction (EF), Left ventricular outflow tract velocity time integral (LVOT VTI), hemodynamics and partial pressure of oxygen/ fraction of inspired oxygen (PaO<sub>2</sub>/ FiO<sub>2</sub>) were recorded daily.

**Results:** The Mean VIS scores at 72 Hours postoperatively were significantly less in the T3 group (5.49 ± 6.2) compared to the Placebo group (13.6 ± 11.7). The PaO<sub>2</sub>/FiO<sub>2</sub> ratios were comparatively more in the T3 group than the Placebo group. The serum levels of FT3 FT4 were significantly higher in the T3-supplemented group than the Placebo group. The VIS scores were significantly lower from 48 hours postoperatively in children < 6 months of age.

**Conclusion:** In this study, we observed that supplementing T3 postoperatively decreases the inotropic requirement from 72 hours postoperatively. This is more useful in children <6 months of age undergoing complex cardiac surgeries.

**Keywords:** Cardiopulmonary bypass, Risk Adjustment for congenital heart surgery, triiodothyronine, VIS Score,

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## INTRODUCTION

Cardiopulmonary Bypass (CPB) causes disruption of normal homeostatic mechanisms and leads to various effects on different organ systems.<sup>[1]</sup> Thyroid functions are also deranged by CPB, leading to transient secondary 'hypothyroidism and sick euthyroid' syndrome (SES).<sup>[2]</sup> Sick euthyroid syndrome and transient secondary hypothyroidism are two conditions which are caused by a reduction in 'circulating thyroid' hormone levels' without primary thyroid disease.<sup>[3]</sup> It is more evident in infants and younger children who undergo congenital cardiac surgeries under CPB than in adults.<sup>[4-6]</sup> Beside their roles in development, metabolism, and homeostasis, thyroid hormones have been shown to play a major role in cardiac repair after injury. So, we hypothesized that giving oral triiodothyronine would decrease the inotropic requirement and help in the enhancement of postoperative recovery. In this study, we used oral triiodothyronine in children undergoing complex cardiac surgeries in addition to routine standard management.

## MATERIALS AND METHODOLOGY

After taking approval from institutional Ethics committee No. INT/IEC/2020/000471 dated 16/5/2020 and registered under CTRI with ref no. CTRI/2021/03/032122, our study is conducted in Advanced Cardiac Centre of Postgraduate Institute of Medical Education and Research, Chandigarh from January 2020 to May 2021. It is a prospective double blinded (data collector, surgeon) randomized controlled study.

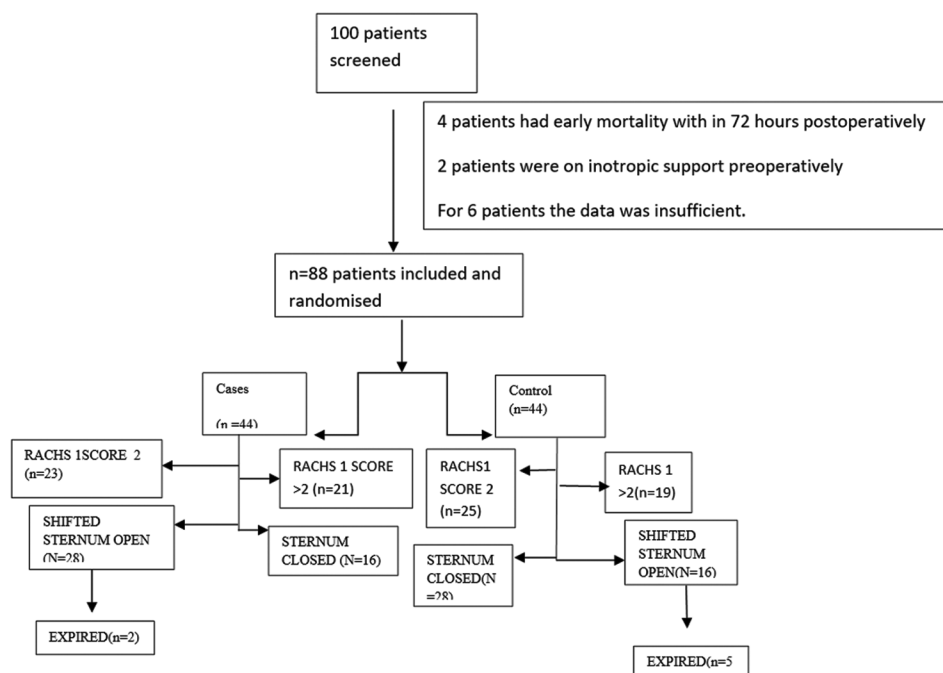
We included 88 patients who underwent complex cardiac surgeries of RACHS-1 (Risk Adjustment for Congenital Heart Surgery) for category 2–5 of  $\leq 1$  year of age. The distribution of patients is shown in Figure 1. Children who had a history of thyroid diseases and other endocrine diseases, abnormal baseline thyroid function, preoperative thyroid hormone therapy, radiation therapy, use of drugs affecting thyroid function, preoperative use of inotropic drugs for circulatory support, serum level of creatinine  $>2.0$  mg/dL, "downs syndrome, mortality during the study were excluded from the study. Randomization was done by computer-generated numbers using the sealed envelope technique. The medication and sugar sachets were prepared and administered by an independent assistant who was not involved in the study. Sachets were prepared in the pharmacy. Investigators and participants were blinded to the assigned groups till the end of the study.

All the patients were evaluated one day prior to surgery, and demographic data like age, sex, and weight were recorded. In addition, baseline hemoglobin and total leucocyte count, and echocardiographic findings were recorded. The induction of general anesthesia was done according to our institute's protocol. To assess baseline, free T3, free T4, and thyroid-stimulating hormone (TSH) samples were collected before going on to CPB. A standard CPB technique according to the institutional protocol was followed. Cardioplegia was administered using del Nido. Surgeries were performed under mild and moderate hypothermia. Post CPB appropriate 'inotropes and dilators were added to maintain patient hemodynamics by attending anesthesiologists who were blinded to the drug used in either group. Mean arterial pressure (MAP) was maintained  $>45$  mm of Hg, heart rate between 100–160/min, and saturation  $>95$ . In the ICU, inotropic scores were monitored hourly, and daily mean scores were calculated. After the patient was shifted to the ICU, triiodothyronine 1 mic/kg and Placebo were administered 8<sup>th</sup> hourly for five days according to randomization. Cardiac functions were assessed daily by measuring left ventricular outflow tract obstruction velocity time integral (LVOT VTI) and ejection fraction (EF). To evaluate serum free T3, T4 levels and TSH levels, blood samples were collected daily; centrifuged samples and ultrafiltrate were stored at  $-80^{\circ}$  C. All the stored samples were analyzed at the end using the enzyme-linked immunoassay (ELISA) test. Serum procalcitonin levels were sent for patients having fever episodes during the ICU stay. Daily fluid balance was noted. Post cardiac surgery Mechanical ventilation duration and ICU length of stay were noted. Twenty four hours vasoactive inotropic score on the 3<sup>rd</sup> day was compared between the triiodothyronine group and placebo group. A decrease of 20% in the inotropic score was taken as significant.

## Statistical analysis

The present study sample size was estimated on the basis of survival analysis, taking the hazard ratio as 1.86 (33). The sample size came out to be 82 subjects with a power of 80% and a level of significance of 5% to detect a hazard ratio of 1.8. For possible attrition, it was decided to include 100 subjects (10% attrition).

Data was analyzed by using a 'statistical package for social sciences (SPSS Inc., Chicago, IL version 21.0). Continuous data with a normal distribution were expressed as mean  $\pm$  standard deviation (SD). Komolgorov- Smirnov's 'one-sample test was used to assess the normality of distribution of the continuous data.' All tests were two-tailed with a 95% confidence interval and a *P* value



**Figure 1:** Consort diagram, RACHS 1 score- Risk Adjustment For Congenital Heart Surgery

considered significant below the 0.05 alpha level. All the statistical tests were two-sided. Two-tailed unpaired T-tests were used for the analysis of parametric data. Non-parametric data was analyzed by the Mann-Whitney test. Paired T-test was used for the intragroup analysis of parametric data.

**RESULTS**

The baseline demographic and surgical characteristics of the patients are summarized in Table 1. Both the groups were well-matched, except for the age.

**VIS SCORES**

Vasoactive-inotropic scores (VIS) were significantly less in the T3 group compared to the Placebo Group at 72, 96, and 120 hours ( $P < 0.001$ ). The primary outcome of our study was that the VIS score at 72 hours showed a significant decrease in the T3-treated group, the median VIS score was 4 (0–33), and the  $P$  value  $< 0.01$ . At 96 and 120 hours, the median VIS scores were 3 (0–44)  $P$  value  $< 0.01$  and 0 (0–44)  $P$  value  $< 0.01$ , respectively. It is graphically represented in Figure 2.

Except for baseline values which showed no significant difference, partial pressure of oxygen/fraction of inspired oxygen (PaO2/FiO2) ratio was better in the T3 group as compared to the Placebo group [Table 2]. Sepsis markers like total leukocyte count (TLC) and procalcitonin levels

were comparable in both groups at all time points [Table 2]. Mixed venous was comparable at all time points [Table 2]. There was no significant difference in the duration of minute ventilation (MV) and ICU stay. Five children in the T3 group and ten children in the Placebo group had new onset of Arrhythmias [Table 2]. Two patients in the T3 group and five patients in the Placebo group expired [Table 2].

Table 3: Comparison of thyroid hormone profile (free T3, freeT4, and TSH)

In our study, we could demonstrate the euthyroid sick syndrome as the FT3, FT4 levels were decreased when compared to the baseline in the Placebo group.

The serum levels of FT3 and FT4 were comparable at the baseline. There was a significant increase in serum FT3 levels from 24 hours time intervals in the T3-supplemented group compared to the Placebo group. The serum FT4 levels were also significantly higher in the T3 group than in the Placebo group except at 72 hours time point. TSH values were comparable in both groups at all time points. FT3 baseline levels were compared with 24, 48, 72, 96 hours within the groups. There was a significant decrease in FT3 levels post surgery from baseline in the Placebo group.

**Subgroup analysis**

The VIS scores were compared between  $\leq 6$  months and  $>6$  months groups, and RACHS-1 scores 2 and  $>2$ .

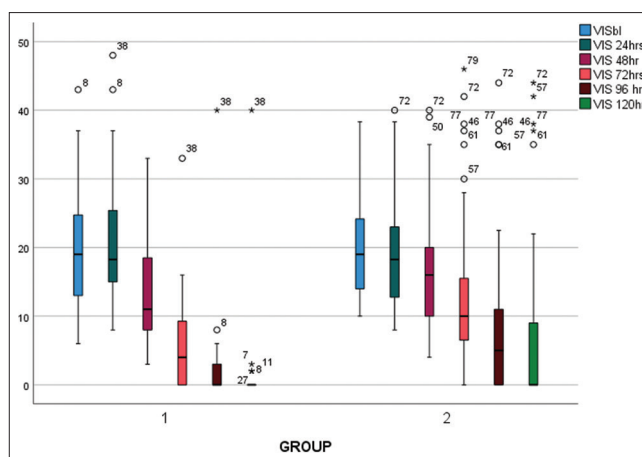
**Table 1: Demographic characteristics, preoperative and intraoperative data**

|                                 | MEAN±SD                        |                                  | P     |
|---------------------------------|--------------------------------|----------------------------------|-------|
|                                 | T3 GROUP (44)                  | PLACEBO GROUP (44)               |       |
| Age (MONTHS)                    | 4.42±3.8                       | 6.26±4.19                        | 0.03* |
| Sex (M/F %)                     | 32 (M)(72.7%)<br>12 (F)(27.3%) | 30 (M) (68.1%)<br>14 (F) (31.8%) |       |
| Length (cm)                     | 57.33±7.76                     | 61.29±13.7                       | 0.1   |
| Body weight (kg)                | 4.28±1.57                      | 4.33±1.8                         | 0.132 |
| Diagnosis :                     | n (mortality)                  | n (mortality)                    |       |
| VSD                             | 11                             | 15 (1)                           |       |
| TAPVC                           | 10 (1)                         | 5                                |       |
| DTGA                            | 12 (1)                         | 7 (2)                            |       |
| TOF PHYSIOLOGY                  | 7                              | 11 (2)                           |       |
| TRUNCUS ARTERIOSUS              | 1                              | 2                                |       |
| Others                          | 3                              | 3                                |       |
| RACHS 1 SCORE                   |                                |                                  |       |
| CATEGORY 1 (n)                  | 0                              | 0                                |       |
| CATEGORY 2 (n)                  | 23                             | 25                               |       |
| CATEGORY 3 (n)                  | 1                              | 8                                |       |
| CATEGORY 4 (n)                  | 19                             | 9                                |       |
| CATEGORY 5 (n)                  | 1                              | 2                                |       |
| Preoperative medication         |                                |                                  |       |
| Diuretics (n)                   | 28                             | 23                               |       |
| Betablockers (n)                | 10                             | 6                                |       |
| Ace inhibitors (n)              | 3                              | 1                                |       |
| Cardiac glycosides (n)          | 2                              | 2                                |       |
| Pde5-inhibitors (n)             | 8                              | 7                                |       |
| Pge1 infusion (n)               | 12                             | 7                                |       |
| Iron supplementation (n)        | 30                             | 34                               |       |
| AXC time (mins)                 | 124.38±60.6                    | 109.88±60.8                      | 0.26  |
| CPB time (mins)                 | 179.95±81.01                   | 164.38±79.7                      | 0.36  |
| Surgery time (mins)             | 359±129.3                      | 319±122                          | 0.13  |
| Fluid balance on pump           | 9.86±65.17                     | 20.7±57.34                       | 0.4   |
| Baseline hb (g/dl)              | 13.44±1.8                      | 12.7±1.9                         | 0.8   |
| Baseline TLC                    | 9264.7±2308                    | 9232.9±2056                      | 0.9   |
| Postoperative medications (n)   |                                |                                  |       |
| ACE inhibitors                  | 42                             | 43                               |       |
| Cardiac glycosides              | 15                             | 20                               |       |
| PDE 5 inhibitor                 | 13                             | 15                               |       |
| Endothelin receptor antagonists | 3                              | 5                                |       |
| NO                              | 3                              | 3                                |       |

Both groups were comparable except for age, i.e., the Placebo group children were older than the T3 group (P<0.05). n=number of patients, () cases of mortality. Severe mitral regurgitation, Patent ductus arteriosus, Anomalous left coronary originating from pulmonary artery reappear, Interrupted aortic arch, atrial septal defect, pulmonary vein stenosis, congenital mitral stenosis

There was a significant decrease in VIS scores in the T3 group at time intervals of 48 hours, 72 hours, 96 hours, and 120 hours in the age group <6 months [Figure 3]. There was a significant decrease in VIS scores at 72 hours in the age >6 months group [Figure 3].

Baseline VIS scores were comparable in both groups. In the T3 group, there was a significant decrease in VIS score at 72 and 96 hours post surgery in infants having RACHS-1 score of less than or equal to 2. However, VIS scores remained significantly lower in the T3 group at 72,96 and 120 hours postsurgery in patients having RACHS-1 score more than 2. [Figure 4].



**Figure 2: Box Whisker Plot Comparing VIS scores post surgery, at 24, 48, 72, 96, and 120 hours postoperatively.** The upper and lower borders of the box were upper and lower quartiles. The middle horizontal line was the median. The upper and lower whiskers were the maximum and minimum values of nonoutliers. \* represents the outliers. VIS scores were significantly on the lower side in the T3 group from 72 hours post surgery : Group 1 = T3 group, Group 2 = Placebo Group., VIS BL = VIS score immediately post surgery. (VIS score with which the patient was shifted to ICU), VIS 24 HRS = Mean VIS scores of first 24 hours post surgery, VIS 48 HRS = Mean VIS score of 24 to 48 hours post surgery, VIS 48 hours = mean VIS score from 48 to 72 hours post surgery. VIS 72 HRS = mean VIS score from 72 to 96 hours post surgery. VIS 96 hrs = mean VIS score from 96 hours to 120 hours, VIS 120 HRS = mean VIS scores from 120 hours to next 24 hours

## DISCUSSION

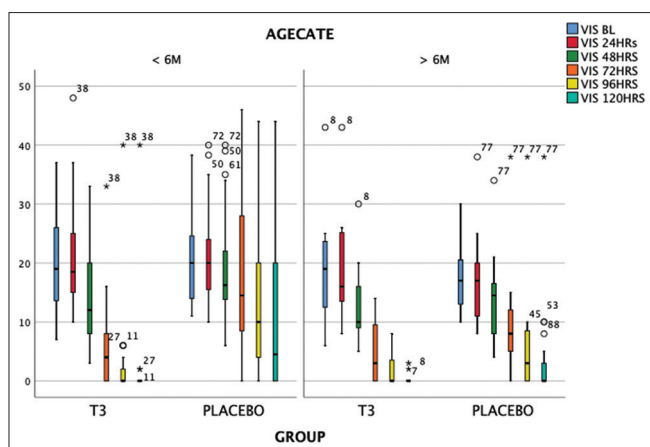
After pediatric cardiac surgery, abnormal thyroid hormone level is found due to prolonged cardiopulmonary bypass time and physiological stress of inflammation, even with a normal preoperative thyroid functions in the patient. This clinical condition is described as sick euthyroid syndrome. In type 1 sick euthyroid syndrome, there decrease in total and unbound T3 level with normal TSH level and it is attributed to inflammatory response,<sup>[7]</sup> elevated steroid hormone level due to surgical stress<sup>(20)</sup> or due to tissue hypoxia during perioperative period due to low cardiac output syndrome.<sup>[8]</sup> In type 2 sick euthyroid syndrome total T3 and T4 levels are decreased due to reduced levels of thyroid binding globulin.<sup>[9]</sup> Several studies have proposed that the thyroid hormone levels in patients undergoing surgery under CPB, decline in the first 24-48 hours post surgery and then levels normalizes by 5-7 days after surgery, especially in patients having a uncomplicated course in ICU.<sup>[10]</sup>

So, in this study, oral triiodothyronine was administered to see the effect on inotropic support requirement. Oral triiodothyronine was available in developing countries, the injectable form is expensive and not available easily.

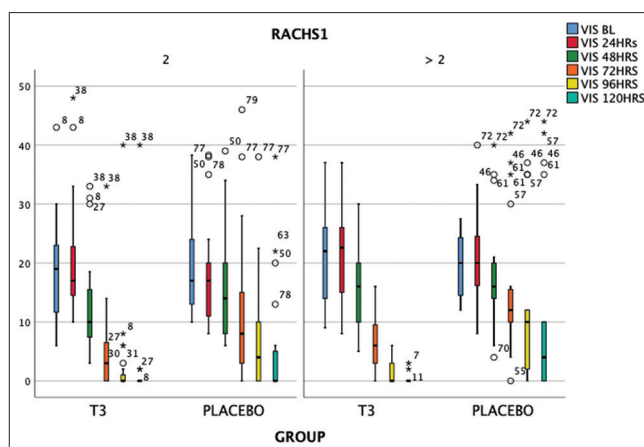
## Inotropic score

The primary outcome VIS score at 72 hours was





**Figure 3:** Box Whisker Plot Comparing VIS scores post surgery, at 24, 48, 72, 96, and 120 hours postoperatively in age group <6 months and >6 months between T3 and placebo group. The upper and lower borders of the box were upper and lower quartiles. The middle horizontal line was the median. The upper and lower whiskers were the maximum and minimum values of nonoutliers. \* represents the outliers. VIS scores were significantly on the lower side in the T3 group from 72 hours post surgery VIS- Vasoactiveinotropic score, BL- base line, VIS BL- VIS score immediately post surgery



**Figure 4:** Box Whisker Plot Comparing VIS scores post surgery, at 24, 48, 72, 96, and 120 hours postoperatively in RACHS 1 score 2 and >2 between T3 and placebo group. The upper and lower borders of the box were upper and lower quartiles. The middle horizontal line was the median. The upper and lower whiskers were the maximum and minimum values of nonoutliers. \* represents the outliers. VIS scores were significantly on the lower side in the T3 group from 72 hours post surgery VIS- Vasoactiveinotropic score, BL- base line, VIS BL- VIS score immediately post surgery. RACHS score 1: Risk Adjustment for Congenital Heart surgery Score

significantly less in the T3 group compared to the Placebo group. This might be due to the peak action of oral triiodothyronine being 48 hours and fluid shifts and myocardial edema post-cardiac surgery settled during the initial 48 hours. In our study, we found that oral T3 was more effective in the reduction of VIS scores in children  $\leq 6$  months of age than in  $>6$  months of age. The Transfusion Requirements in Critical Care (TRICC) trial conducted by Portman *et al.*<sup>[11]</sup> also concluded that intravenous triiodothyronine therapy (0.4 mcg/kg before commencing CPB and 0.4 mcg/kg at aortic cross clamp time release, 0.2 mcg/kg at 3, 6, 9 hours after AXC release) was beneficial in children  $<5$  months of age undergoing complex cardiac surgeries to reduce inotropic scores and less mechanical ventilation duration. There was no benefit in children  $>5$  months of age. We also found that patients undergoing complex surgeries (RACHS-1 score  $>2$ ) benefitted more with oral T3 therapy compared to patients undergoing simple surgeries. However, we could not get any difference in cardiac function in both the groups due to maintenance with inotropic support.

### Serum levels of thyroid hormones

Mainwaring<sup>[12]</sup> and Bettendorf and their colleagues,<sup>[13]</sup> in their studies saw that the decrease in levels of free T3, reverse T3, TSH levels led to delayed recovery. In another study by Bettendorf and colleagues, they administered an infusion of triiodothyronine 2 mcg/kg to children undergoing complex cardiac surgeries and compared levels of T4, FT4, T3, FT3. They were decreased compared to

the baseline in the T3 group, and reverse T3 levels were increased in the Placebo group where the levels were maintained in the treatment group.<sup>[14]</sup> In the current study, there was a significant decrease in the levels of free T3 and free T4 compared to baseline in the Placebo group, and the levels were maintained in the same range in the T3 group. Most of these patients had undergone complex surgeries. Bartkowski concluded that a larger amount of T3 was removed by ultrafiltration during CPB.<sup>[15]</sup> In the present study, there was a significant difference in the serum FT3 and FT4 levels at all time points. TSH was within normal range in both the groups. This represents the good bioavailability of oral T3. It is not inferior to injectable. Oral T3 can be used instead of the injectable form as the latter form was not affordable to common people.

### Hemodynamic parameters

In the present study, there were significantly lower heat rates in the T3 group, but the mean arterial pressure (MAP) was comparable in both the groups. The mean arterial pressures were lower in the T3 group than in the Placebo group but not statistically significant. "This may be due to action of T3, which increases the contractility of the heart<sup>[16]</sup> and decreases systemic vascular resistance via dilation of resistance arterioles in the peripheral circulation.<sup>[17]</sup>" The heart rates were on the lower side compared to the Placebo group. This can be explained by the lesser inotropic requirement in the T3 group than the Placebo group. The heart rate on the lower side implies that the incidence of

**Table 2: Comparison of secondary outcomes in both the groups**

|   | MEAN±SD         |                      | P        |
|---|-----------------|----------------------|----------|
|   | T3 GROUP (n=44) | PLACEBO GROUP (n=44) |          |
| <b>HEMODYNAMICS</b>                             |                 |                      |          |
| <b>MAP</b>                                      |                 |                      |          |
| BASELINE  | 53±7.1          | 54.9±6.8             | 0.24     |
| POST SURGERY                                    | 52.42±6.5       | 55.43±6.6            | 0.2      |
| 24 HOURS  | 52.9±6.3        | 55.43±6.6            | 0.03     |
| 48 HOURS  | 52.9±6.3        | 55.48±6.1            | 0.57     |
| 72 HOURS  | 53.4±6.02       | 55.6±6.4             | 0.1      |
| 96 HOURS  | 53.4±6.1        | 55.6±6.4             | 0.19     |
| 120 HOURS                                       | 54.3±6.04       | 55.3±7.82            | 0.12     |
| <b>HR</b>                                       |                 |                      |          |
| BASELINE  | 119.3±6.38      | 121.7±10.74          | 0.16     |
| POST SURGERY                                    | 130.1±11        | 133.43±10.97         | 0.14     |
| 24 HOURS  | 129.4±12.8      | 138.4±12.8           | 0.02     |
| 48 HOURS  | 129.38±13.5     | 136±12.5             | 0.019    |
| 72 HOURS  | 128.37±15.8     | 135.77±13.2          | 0.02     |
| 96 HOURS  | 127.9±17.4      | 134.36±12.32         | 0.048    |
| 120 HOURS                                       | 126.58±17.53    | 131.8±13.9           | 0.121    |
| <b>SERUM LEVELS OF THYROID HORMONES</b>         |                 |                      |          |
| <b>FT3 (pg/ml)</b>                              |                 |                      |          |
| BASELINE  | 3.38±0.73       | 3.38±0.69            | 0.99     |
| 24 HOURS  | 3.32±0.74       | 1.9±1.0 ^            | < 0.01*  |
| 48 HOURS  | 3.41±0.8        | 2.07 1.09 ^          | < 0.01*  |
| 72 HOURS  | 3.41±0.9        | 2.18±2.09 ^          | < 0.01*  |
| 96 HOURS  | 3.38±0.7        | 2.14±1.23 ^          | < 0.01*  |
| <b>FT4 (ng/dl)</b>                              |                 |                      |          |
| BASELINE  | 1.5±0.34        | 1.4±0.35             | 0.17     |
| 24 HOURS  | 1.37±0.45       | 1.16±0.44 ^          | 0.03*    |
| 48 HOURS  | 1.44±0.48       | 1.1±0.45 ^           | 0.01*    |
| 72 HOURS  | 1.36±0.43       | 1.09±0.46 ^          | 0.002*   |
| 96 HOURS  | 1.35±0.37       | 1.08±0.49 ^          | 0.06     |
| <b>TSH (µIU/ml)</b>                             |                 |                      |          |
| BASELINE  | 2.52±1.87       | 3.03±1.69            | 0.18     |
| 24 HOURS  | 1.89±1.93 ^     | 1.79±1.38 ^          | 0.78     |
| 48 HOURS  | 2.2±2.1         | 1.80±1.33 ^          | 0.312    |
| 72 HOURS  | 2.1±2           | 2±1.5 ^              | 0.9      |
| 96 HOURS  | 2.38±2.21       | 2.3±1.47 ^           | 0.8      |
| <b>ECHO PARAMETERS</b>                          |                 |                      |          |
| <b>LVOT VTI (Centimeters)</b>                   |                 |                      |          |
| BASELINE  | 11.9±1.87       | 12.5±1.98            | 0.14     |
| POST SURGERY                                    | 10.1±1.41       | 10.4±1.59            | 0.36     |
| 24 HOURS  | 10.1±1.38       | 10.53±1.63           | 0.18     |
| 48 HOURS  | 10.6±1.9        | 10.56±1.67           | 0.9      |
| 72 HOURS  | 10.33±1.4       | 10.6±1.5             | 0.36     |
| 96 HOURS  | 10.32±1.4       | 10.6±1.6             | 0.38     |
| 120 HOURS                                       | 10.34±1.4       | 12.7±1.4             | 0.27     |
| <b>EF (%)</b>                                   |                 |                      |          |
| BASELINE  | 49.9±7.35       | 49.45±7.1            | 0.75     |
| POST SURGERY                                    | 43.18±6.74      | 42±8.3               | 0.48     |
| 24 HOURS  | 42.37±8.08      | 42.1±8.3             | 0.88     |
| 48 HOURS  | 42.9±8.37       | 42.5±8.38            | 0.8      |
| 72 HOURS  | 44.4±6          | 42.9±8.4             | 0.32     |
| 96 HOURS  | 45.2±6.47       | 43±8.2               | 0.93     |
| 120 HOURS                                       | 45.1±6.4        | 42.7±8.3             | 0.14     |
| <b>OXYGENATION PARAMETERS (PaO2/FiO2 Ratio)</b> |                 |                      |          |
| POST SURGERY                                    | 314.9±49.2      | 260±67.8             | < 0.01   |
| 24 HOURS  | 343±44          | 282.2±71.7           | < 0.001* |
| 48 HOURS  | 347.26±46.68    | 289±74.3             | 0.002*   |
| 72 HOURS  | 355±51.3        | 294±77.8             | 0.001*   |
| 96 HOURS  | 357±59          | 293±78               | 0.001*   |
| 120 HOURS                                       | 372.4±78        | 311±90               | < 0.001  |
| <b>SCVO2</b>                                    |                 |                      |          |
| POST SURGERY                                    | 74.5±1.68 (39)  | 74.6±1.53 (42)       | 0.9      |
| 24 HOURS  | 74.1±1.6 (28)   | 74.9±1.5 (34)        | 0.6      |
| 48 HOURS  | 73.7±1.42 (32)  | 73.4±3.1 (39)        | 0.03*    |

Contd...

Table 2: Contd...

|                           | MEAN±SD             |                      | P     |
|---------------------------|---------------------|----------------------|-------|
|                           | T3 GROUP (n=44)     | PLACEBO GROUP (n=44) |       |
| 72 HOURS                  | 73.8±1.9 (26)       | 73.4±3.1 (29)        | 0.5   |
| 96 HOURS                  | 73.7±3.6 (18)       | 73.3±5.5 (12)        | 0.8   |
| <b>SEPSIS MARKERS</b>     |                     |                      |       |
| <b>TLC COUNT</b>          |                     |                      |       |
| 24 HOURS                  | 13311±3513          | 11753±2638           | 0.02* |
| 48 HOURS                  | 13308±4173          | 11965±2685           | 0.07  |
| 72 HOURS                  | 12556±3704          | 12054±2823           | 0.47  |
| 96 HOURS                  | 12416±3870          | 11751±2621           | 0.34  |
| <b>PROCAL (ng/dl)</b>     |                     |                      |       |
| 48 HRS                    | 27.7 (6-100) (n=24) | 8.3 (2.3-99) (n=16)  | 0.28  |
| 72 HRS                    | 9 (3-100) (n=19)    | 6.5 (0.15-99) (n=36) | 0.7   |
| 96 HRS                    | 6.7 (3-100) (n=23)  | 4.15 (0.8-99) (n=14) | 0.7   |
| 120 HRS                   | 2 (0.15-100) (n=25) | 4.2 (0.25-99) (n=23) | 0.6   |
| ARRYTHMIAS (n)            | 5                   | 10                   |       |
| IN HOSPITAL MORTALITY (n) | 2                   | 5                    |       |

\*P<0.05 ^ significant difference within the group. Procal at 48,72,96,120 hours were represented in median and range

Table 3: Comparison of thyroid hormone profile (free T3, free T4, and TSH)

|                    | T3 GROUP    | PLACEBO GROUP | P      |
|--------------------|-------------|---------------|--------|
| <b>FT3 (pg/ml)</b> |             |               |        |
| BASELINE           | 3.38±0.73   | 3.38±0.69     | 0.99   |
| 24 HOURS           | 3.32±0.74   | 1.9±1.0 ^     | <0.01* |
| 48 HOURS           | 3.41±0.8    | 2.07±1.09 ^   | <0.01* |
| 72 HOURS           | 3.41±0.9    | 2.18±2.09 ^   | <0.01* |
| 96 HOURS           | 3.38±0.7    | 2.14±1.23 ^   | <0.01* |
| <b>FT4 (ng/dl)</b> |             |               |        |
| BASELINE           | 1.5±0.34    | 1.4±0.35      | 0.17   |
| 24 HOURS           | 1.37±0.45   | 1.16±0.44 ^   | 0.03*  |
| 48 HOURS           | 1.44±0.48   | 1.1±0.45 ^    | 0.01*  |
| 72 HOURS           | 1.36±0.43   | 1.09±0.46 ^   | 0.002* |
| 96 HOURS           | 1.35±0.37   | 1.08±0.49 ^   | 0.06   |
| <b>TSH (µU/ml)</b> |             |               |        |
| BASELINE           | 2.52±1.87   | 3.03±1.69     | 0.18   |
| 24 HOURS           | 1.89±1.93 ^ | 1.79±1.38 ^   | 0.78   |
| 48 HOURS           | 2.2±2.1     | 1.80±1.33 ^   | 0.312  |
| 72 HOURS           | 2.1±2       | 2±1.5 ^       | 0.9    |
| 96 HOURS           | 2.38±2.21   | 2.3±1.47 ^    | 0.8    |

^ Significant difference p value <0.05 with in the group,\*significant difference p value <0.05 among the groups

low cardiac output syndrome was less in the T3 group. A similar finding of a decrease in heart rate was observed by Portman *et al.*<sup>[11]</sup> in the TRICC trial. Kumar *et al.*,<sup>[18]</sup> given oral thyroxine at a dose of 10 mcg/kg/day started from post operative day (POD) 0 and continued till POD 5; they found that there were no significant differences in heart rate, systolic blood pressure, diastolic blood pressure, mean blood pressure in the T4-treated group. Kokkonen *et al* measured free T3 levels in adult patients undergoing cardiac surgery and found that, a significant low level of T3 occurred on POD 4, coinciding with higher incidence of Atrial fibrillation at that time.<sup>[21]</sup> In Coronary Artery Bypass Graft(CABG) Surgery a bolus of 0.8 mic/kg of IV T3 at AXC release followed by infusion of 0.113 mics/kg/hour for 6 hours decreased the postoperative arrythmia.<sup>[20]</sup> Similarly in another study conducted in CABG patients

by giving IV T3 0.4 mic/kg after AXC release followed by 0.1mic/kg/hour for 6 hours improved the left ventricular function, decreased inotropic and mechanical devices support. Reduced incidence of myocardial Ischemia ,slightly decreased Atrial fibrillation and reduced the need of pacemaker support.<sup>[19]</sup>

### Fluid balance and oxygenation

In this study, there was a significant increase in Pao2/FiO2 ratio in the T3 group than the Placebo group. This may be explained by less time to achieve negative balance in the T3 group. Mackie *et al.*<sup>[22]</sup> noted that the T3 therapy reduces the time to get the first negative balance than the Placebo. This can be explained by the fact that thyroid hormones are necessary for the normal functioning of all organs, and low free T3 levels in the Placebo group may have impaired the intrinsic renal function.

### Effect of triiodothyronine on cases shifted with Open sternum

In the case of neonatal surgery, patients are shifted with open sternum due to prolonged bypass time and postoperative biventricular dysfunction. There was no significant difference in sternal closure time between the two groups. The sternum was reopened in one patient in the T3 group and for two patients in the Placebo group due to a low cardiac output state. [Table 4] The sternum of the patient in the T3 group was closed after 24 hours of reopening. But for the two patients in the Placebo group, sternal closure was not possible, and later, the patients expired. Postoperative T3 therapy is associated with a positive inotropic effect and reduced third space fluid loss. This was evident by better oxygenation and negative fluid balance in the T3 group. Mackie *et al.*,<sup>[22]</sup> in their study, concluded that the time to get the first negative balance is significantly less in the T3-treated group than in the Placebo group. In the

**Table 4: Comparison of VIS scores in patients shifted to ICU with open sternum**

|                  | T3 GROUP       |      | PLACEBO GROUP  |      | P      |
|------------------|----------------|------|----------------|------|--------|
|                  | MEDIAN (RANGE) | IQR  | MEDIAN (RANGE) | IQR  |        |
| VIS POST SURGERY | 21.8 (8-37)    | 12.3 | 20 (11-30)     | 10.3 | 0.5    |
| VIS 24 HRS       | 21.8 (8-48)    | 9.5  | 20 (10-40)     | 16.5 | 0.41   |
| VIS 48 HRS       | 5.5 (5-33)     | 10   | 16 (6-46)      | 17   | 0.53   |
| VIS 72 HRS       | 0 (0-33)       | 10.5 | 10 (0-46)      | 31   | 0.02*  |
| VIS 96 HRS       | 0 (0-40)       | 3.8  | 10 (0-44)      | 33.5 | 0.001* |
| VIS 120 HRS      | 0 (0-40)       | 0    | 4 (0-44)       | 36   | 0.001* |

\*P<0.05, VIS: score vasoactiveinotropic score, IQR: interquartile range

present study, there was no significant difference in time for the closure of the sternum. But the mean time for sternal closure was less in the T3 group (56.57 ± 16.28) [Table 4] than in the Placebo group (63.18 ± 26.8), which was similar to Mackie *et al.* (2.5 and 4 days) observation. Heart rate was age-appropriate in the T3 group than in the Placebo group, where slight tachycardia was present. This was also indirect evidence that these patients were less likely to have low cardiac output states.

### Duration of ICU stay and mechanical ventilation

There was no statistically significant difference in hours of mechanical ventilation duration and ICU stay in both the groups; however, the mean duration of mechanical ventilation duration and ICU stay were on the lower side in the T3 group. According to a metaanalysis by Flores *et al.*,<sup>[23]</sup> there is no difference in mechanical ventilation duration and ICU length of stay in both groups. Even the duration of mechanical ventilation was longer in the T3 group than in the Placebo group but not statistically significant. In our study, mean mechanical ventilation is lesser for the T3 group but not significant. Talwar *et al.*<sup>[24]</sup> administered oral T4 to children undergoing congenital heart surgery. They found that the duration of mechanical ventilation and ICU stay were significantly lesser in the T3 group.

**Sepsis:** Procalcitonin and total leucocyte count were comparable in both groups.

Limitations of our study are single centered study; we had given only ten doses of drugs and followed the patient for 120 hours postoperatively. So we could not demonstrate the prolonged effects of drugs. Due to the coronavirus pandemic, we could not administer the drug preoperatively.

### CONCLUSION

Supplementing triiodothyronine postoperatively decreases the requirement of vaso ionotropic agents and improvement in oxygenation. T3 therapy may be more beneficial in

children <6 months of age undergoing complex cardiac surgeries.

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### Conflicts of interest

There are no conflicts of interest.

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