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Oral triiodothyronine for the prevention of thyroid hormone reduction in adult valvular cardiac surgery

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Abstract

Treatment of non-thyroidal illness by intravenous triiodothyronine (T_3) after cardiac surgery causes a disproportional elevation of hormone levels. The administration of oral T_3, which has never been studied in this context, could cause physiological hormone levels. The aim of this study was to test oral T_3 for the prevention of T_3 reduction during the postoperative period of valvular cardiac surgery in adults. Eighteen patients who underwent cardiac surgery for valvular disease with invasive hemodynamic monitoring were randomly assigned to 2 groups: the T group received oral T_3 (N = 8), 25 µg three times/day, initiated 24 h before surgery and maintained for 48 h and the NT group (N = 10) received placebo. Serum T_3, thyroxine and thyrotropin were determined at baseline, 1 h before surgery, within 30 min of cardiopulmonary bypass and 6, 12, 24, and 48 h after removal of the aortic cross-clamp. Baseline T_3 was similar in both groups (T: 119 ± 13; NT: 131 ± 9 ng/dL). Serum T_3 increased during the first 24 h in the T group compared to the NT group (232 ± 18 *vs* 151 ± 13 ng/dL; $P < 0.001$). In the NT group, T_3 was reduced by 24% ($P = 0.007$) 6 h after removal of the aortic cross-clamp, confirming the non-thyroidal illness syndrome. There were no differences in clinical or hemodynamic parameters between groups. Administration of oral T_3 prevented its serum reduction after valvular cardiac surgery in adults, with normal serum levels for 48 h without disproportional elevations.

Key words
- Cardiac surgery
- Non-thyroidal illness syndrome
- Heart valve disease
- Postoperative period

Introduction

The non-thyroidal illness syndrome (NTIS) is observed in sepsis, acute myocardial infarction, and in cardiac and non-cardiac surgery and is likely to be present in any critically ill patient. The syndrome is characterized by low serum levels of triiodothyronine (T_3) and elevated reverse T_3, with initially normal levels of thyroxine (T_4) and thyrotropin (TSH) (1). This syndrome has been considered to be a normal adaptive response to decrease energy expenditure during an acute illness. The mechanisms involved in the genesis of NTIS are the inhibition of peripheral conversion of T_4 to T_3, due to decreased activity of type 1 iodothyronine deiodinase (2), and reduction of endogenous

secretion of thyrotropin-releasing hormone by the hypothalamus (1).

Serum levels of total T_3 and free T_3 usually decline by 50-75% during the immediate postoperative period in patients who undergo cardiac surgery with cardiopulmonary bypass (3), a decrease that can persist as long as 6 days postoperatively. Recent evidence showed that the time for recovery of serum T_3 levels after surgery is correlated with the number of days of postoperative hospitalization, a fact that emphasizes the association between NTIS and postoperative outcome (4).

The cardiovascular dysfunction observed after cardiopulmonary bypass, as well as in other non-thyroid diseases, is similar to that observed in hypothyroidism, which is characterized by low cardiac output and increased systemic vascular resistance (5). Recent studies have suggested that reduction of the serum levels of free T_3 and elevation of reverse T_3 are predictors of mortality in patients with ischemic heart disease, valvular cardiomyopathies and other cardiac diseases (6,7). Whether the NTIS is really adaptive or potentially harmful, and whether treatment to restore serum T_3 levels toward normal values is indicated has been a matter of debate.

Several studies have explored the intravenous administration of T_3 to adults (8-14) and, more recently, to children (15-17), during the cardiac surgery postoperative period. The results concerning clinical benefits, actual hemodynamic effects and need for inotropic drugs have been controversial. All of these studies have shown the occurrence of NTIS in this situation and that exogenous replacement of T_3 could definitely prevent the reduction of serum T_3 levels during the NTIS. However, in these experiments, T_3 was given intravenously in bolus, a procedure that caused a disproportional and artificial elevation of serum T_3 concentration in most of these studies. Hormone peak levels occurred soon after administration and no maintenance dose was given afterwards, provoking a subsequent drop in serum levels of T_3 over the following days. The only clinical trial using oral T_3 was performed in coronary bypass surgery, using a 7-day protocol before surgery, and attaining a hyperthyroid hormone profile that could be harmful (18).

On the basis of these considerations, we decided to determine experimentally if T_3 given orally three times a day results in more constant hormone levels within the normal range for a longer time during the postoperative period. Secondarily, we evaluated whether oral T_3 could improve the clinical and hemodynamic endpoints during the postoperative period of valvular cardiac surgery in adults.

Patients and Methods

Patient selection

Twenty-two consecutive patients who underwent valvular cardiac surgery at Hospital São Francisco, Santa Casa de Porto Alegre, Porto Alegre, RS, Brazil, between April and October 2003, were included in the study. Adult patients (aged 18 to 75 years) of either sex were eligible if they had: 1) left ventricular ejection fraction below 40% by transthoracic echocardiogram, 2) symptomatic New York Heart Association Class III or IV heart failure, and/or 3) systolic pulmonary artery pressure higher than 50 mmHg. All patients were submitted to invasive hemodynamic monitoring with a thermodilution catheter in the pulmonary artery during surgery. The exclusion criteria were: 1) history of previous thyroid disease, thyroid hormone therapy, abnormal baseline thyroid function, and use of drugs that could potentially interfere with thyroid metabolism, 2) concomitant coronary artery bypass graft surgery, history of coronary artery disease and/or its diagnosis defined as the presence of a lesion greater than 50% or any evidence of myocardial infarction during or after surgery, 3) preoperative use of inotrop-

ic drugs or mechanical circulatory support, and 4) serum creatinine >2.0 mg/dL.

The study was explained to each patient and written informed consent was obtained. The Hospital Research Ethics Committee approved the study protocol.

Study design

This was a randomized clinical trial comparing the use of oral T_3 and placebo for the prevention of serum T_3 reduction in the postoperative period of valvular cardiac surgery. Patients were randomly assigned,10 by 10, 5 to each group, to one of two groups (T = T_3 group; NT = placebo group) 48 h before the surgical procedure and 24 h before receiving the first oral dose of T_3 or placebo. All physicians and nurses involved in patient care were blind to study therapy. With the exception of the study drug, all other interventions were the same in both groups. Patients allocated to the T group received oral T_3 (Cynomel, Enila Laboratory, Rio de Janeiro, RJ, Brazil), 25 µg three times a day, started 24 h before surgery and kept for 48 h after surgery. During the immediate postoperative hours T_3 was administered by a nasogastric tube, which was kept closed for 1 h. Afterwards the medication was again administered orally. This dose was chosen because it is the usual dose used for patients who need hormone replacement therapy with oral T_3 and has been suggested by De Groot in his recent review of NTIS (1). Patients who were allocated to the NT group received placebo according to the same schedule.

Blood samples were collected for the determination of serum levels of total T_3, total T_4 and TSH at randomization (baseline), 24 h after the first dose of the drug or placebo (1 h before going into surgery), 30 min after starting cardiopulmonary bypass, and 6, 12, 24, and 48 h after removal of the aortic cross-clamp. Serum levels of T_3, T_4 and TSH were measured by chemoluminescence using a Bayer commercial kit (ADVIA Centaur, Tarrytown, NY, USA). The reference values were 70-210 ng/dL for total T_3, 4.8-12.5 µg/dL for total T_4, and 0.3-6.2 µIU/mL for TSH. The interassay coefficients of variation for each sample were less than 9.8% for T_3, 8.6% for T_4, and 8% for TSH.

Surgery and anesthesia

Three cardiothoracic surgeons performed the surgical procedures according to a routine practice guideline for surgery and anesthesia. All patients underwent median sternotomy and were submitted to total cardiopulmonary bypass by ascending aorta and right atrium or caval cannulation. The filling volume in the cardiopulmonary bypass circuit was 1700 mL and consisted of Ringer lactate and packed red blood cells in partial hemodilution. Myocardial protection was obtained by administration of induction cardioplegic solution with a blood solution (cardioplegic kit from Braile Biomédica, São Paulo, SP, Brazil). The surgical procedures were performed under mild hypothermia of 32°C. Anticoagulation was obtained with unfractionated heparin (5 mg/kg) and repeated hourly (1 mg/kg).

During surgery, the systolic arterial blood pressure was maintained between 100 and 120 mmHg, with the aid of vasodilator (sodium nitroprusside) and vasopressor (norepinephrine) drugs in continuous infusions. The changes in cardiac output were controlled by continuous infusion of dobutamine or dopamine. Hemodynamically significant blood losses associated with hemoglobin below 9 g/dL were treated with packed red blood cell infusions. At the end of surgery, patients were warmed up again to 36.5°C. Appropriate doses of protamine sulfate were used for recovery from anticoagulation. A cardiac pacemaker was used whenever necessary to maintain the heart rate above 70 beats per minute. Afterwards, patients were transferred to the intensive care unit (ICU).

Postoperative management

Patients were continuously monitored in the ICU of São Francisco Hospital. Vasodilators (sodium nitroprusside) and inotropic drugs (dobutamine, dopamine, norepinephrine) were administered as required to keep systolic blood pressure between 90 and 140 mmHg. The same inotropic drugs were used in both groups to maintain cardiac output above 2.1 L min^{-1} $(m^2)^{-1}$. For each patient, the doses of vasoactive drugs given, in µg kg^{-1} min^{-1}, were recorded throughout the intraoperative period and the first 24 h after surgery.

Hemodynamic measurements

Mean arterial pressure, heart rate, right atrial pressure, pulmonary wedge pressure, cardiac index, and systemic vascular resistance were recorded during the intraoperative period and throughout the first 24 h after removal of the aortic cross-clamp, according to the 7 pre-established periods previously described. All data were obtained from the anesthesia form for the patient or from the ICU flow sheets.

Clinical outcome

Clinical follow-up data, including the need for and amount of vasoactive drugs, were obtained from the ICU flow sheets. Cardiac rhythm was continuously monitored in the ICU and an electrocardiogram was performed immediately after the operation and on the morning of the day following surgery. Ventricular or supraventricular arrhythmias and their respective treatment were documented on the patients' charts. All medical notes and reports were reviewed to determine the incidence of postoperative complications and the patients' clinical evolution was monitored throughout the hospitalization period. Postoperative mortality was defined as the death rate during hospitalization or within 30 days after surgery. Morbidity parameters included prevalence of atrial fibrillation, pacemaker dependence, need for mechanical assistance, or any other adverse events that could prolong the stay in the ICU or in the hospital or that could cause significant clinical deterioration.

Statistical analysis

All values are reported as means ± SEM or median and interquartile intervals if asymmetric distributions were found. The demographic, baseline and one-time outcome variables for the two groups were compared by the Student *t*-test for independent samples or by the Mann-Whitney test. The chi-square test or Fisher exact test, if applicable, was used to compare the two groups studied for categorical data. Results regarding continuous variables at different time points and between groups were compared by analysis of variance for repeated measures (*post hoc* Student-Newman-Keuls test). All calculations were performed with SPSS for Windows software (version 11.0, SPSS Inc., Chicago, IL, USA).

Sample size calculation

Power analysis showed that we needed 8 patients per group to achieve 80% power to detect a difference of 50 ng/dL in serum T_3 level between the two groups, considering a pre-established significance level (alpha) of 0.05, using a two-sample *t*-test (19).

Results

Study population

Twenty-two patients were included in the study. Four patients were excluded, 3 from the T group (1 because of amiodarone use during surgery, 1 because no invasive monitoring catheter was inserted, and 1 because of acute myocardial infarction imme-

diately after surgery, possibly due to coronary embolization) and one from the NT group, due to altered baseline thyroid function. Eighteen patients completed the study, 8 in the T group and 10 in the NT group. There were no statistically significant differences between groups concerning the preoperative characteristics, with the exception of T_4 and TSH levels (Table 1). There were also no statistically significant differences between groups concerning the intraoperative characteristics: duration of cardiopulmonary bypass was 100 ± 12 *vs* 83 ± 14 min (P = 0.120), aortic clamping time was 64 ± 8 *vs* 50 ± 9 min (P = 0.083), hypothermia was 32.9 ± 0.5 *vs* 32.7 ± 0.4ºC (P = 0.772), and heparin dose was 296 ± 19 *vs* 313 ± 27 mg (P = 0.145) for the T and NT groups, respectively.

Serum hormone concentrations

After the beginning of the surgical procedure, serum T_3 levels progressively decreased in the NT group, with a significant reduction of 24% when comparing the 6th hour after release of aortic cross-clamp with baseline (P = 0.007). After the 6th hour, T_3 levels remained significantly decreased for the duration of the study. In the T group, T_3 levels rose during the first 24 h compared to basal levels, with a 95% increase (P < 0.001), but were maintained within normal limits. When comparing both groups after baseline, serum T_3 levels in the T group were significantly higher than those in the NT group, except at 24 h, where the difference did not reach statistical significance (P = 0.08), Figure 1. The serum levels of T_4 and TSH did not differ significantly between groups after baseline. However, when compared with baseline, the levels of T_4 (P < 0.001) and TSH (P < 0.001) were significantly reduced after the beginning of surgery (Figures 2 and 3).

Postoperative treatment

There were no significant differences between groups concerning the pharmacological support needed to wean the patient from cardiopulmonary bypass. Only 1 patient in the NT group had to return to cardiopulmonary bypass due to hemodynamic instability, and one in the T group required mechanical support with an intra-aortic balloon when weaned from cardiopulmonary bypass.

Inotropic requirements were measured during surgery and 24 h after removal of the

Table 1. Preoperative baseline characteristics of patients treated with triiodothyronine and controls.

Variables	Triiodothyronine-treated group (N = 8)	Placebo-treated group (N = 10)
Age (years)	50 ± 3	59 ± 4
Males	3 (37.5%)	7 (70%)
Caucasian	6 (75%)	10 (100%)
Weight (kg)	63 ± 5	65 ± 5
Hypertension	3 (37.5%)	4 (40%)
Diabetes mellitus	3 (37.5%)	1 (10%)
Preoperative medications		
Digoxin	7 (87.5%)	9 (90%)
Diuretics	8 (100%)	9 (90%)
ACE inhibitors	3 (37.5%)	3 (30%)
ß-blockers	3 (37.5%)	1 (10%)
Intravenous heparin	5 (62.5%)	2 (20%)
Systolic blood pressure (mmHg)	109 ± 5	111 ± 4
Heart rate (bpm)	82 ± 6	80 ± 4
NYHA functional class		
I	0 (0%)	0 (0%)
II	2 (25%)	0 (0%)
III	4 (50%)	9 (90%)
IV	2 (25%)	1 (10%)
Ejection fraction	46 ± 5%	57 ± 4%
Main valvular disease		
Aortic stenosis	1 (12.5%)	2 (20%)
Aortic insufficiency	1 (12.5%)	2 (20%)
Mitral stenosis	2 (25%)	5 (50%)
Mitral insufficiency	4 (50%)	1 (10%)
Reoperation	3 (37.5%)	4 (40%)
Atrial fibrillation	6 (75%)	6 (60%)
Serum hormones		
Triiodothyronine (ng/dL)	119 ± 13	131 ± 9
Thyroxin (µg/dL)	7.9 ± 0.4*	10.7 ± 0.9
Thyrotropin (µIU/mL)	2.7 ± 0.3*	1.5 ± 0.3

Data are reported as means ± SEM or as number of patients and percent in parentheses. ACE = angiotensin-converting enzyme; NYHA = New York Heart Association. There were no significant differences between groups except for thyroxin and thyrotropin.

*P < 0.05 compared to the placebo-treated group (Student *t*-test for all continuous variables; categorical data: chi-square test for sex and Fisher exact test for all others).

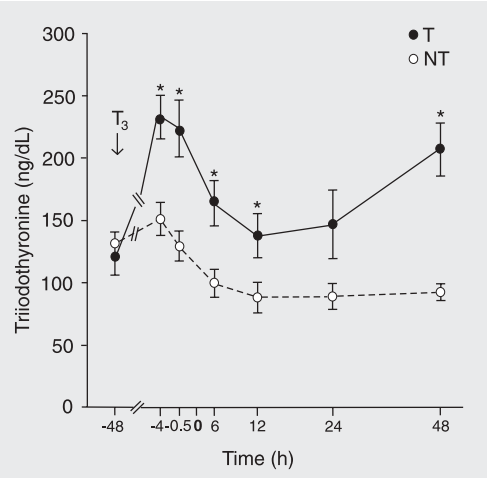

Figure 1. Serum triiodothyronine (T_3) in the groups studied. T = T_3-treated group, N = 8; NT = placebo-treated group, N = 10; -48 = 2 days before cross-clamp removal (baseline); -4 = 1 h before going into surgery and 4 h before cross-clamp removal (24 h after the beginning of T_3 or placebo); -0.5 = within 30 min of cardiopulmonary bypass; 0 = cross-clamp removal; 6 = 6 h after aortic cross-clamp removal; 12 = 12 h after aortic cross-clamp removal; 24 = 24 h after aortic cross-clamp removal; 48 = 48 h after aortic cross-clamp removal. *P < 0.05 compared to control (ANOVA for repeated measures; *post hoc* Student-Newman-Keuls test).

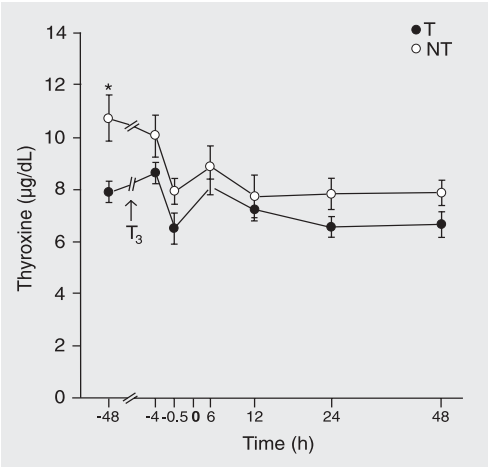

Figure 2. Serum thyroxine in the groups studied. T = T_3-treated group, N = 8; NT = placebo-treated group, N = 10; -48 = 2 days before cross-clamp removal (baseline); -4 = 1 h before going into surgery and 4 h before cross-clamp removal (24 h after the beginning of T_3 or placebo); -0.5 = within 30 min of cardiopulmonary bypass; 0 = cross-clamp removal; 6 = 6 h after aortic cross-clamp removal; 12 = 12 h after aortic cross-clamp removal; 24 = 24 h after aortic cross-clamp removal; 48 = 48 h after aortic cross-clamp removal. *P < 0.05 compared to control (ANOVA for repeated measures; *post hoc* Student-Newman-Keuls test).

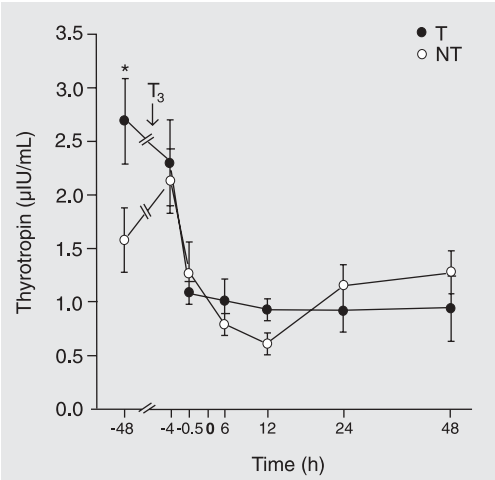

Figure 3. Serum thyrotropin in the groups studied. T = T_3-treated group, N = 8; NT = placebo-treated group, N = 10; -48 = 2 days before cross-clamp removal (baseline); -4 = 1 h before going into surgery and 4 h before cross-clamp removal (24 h after the beginning of T_3 or placebo); -0.5 = within 30 min of cardiopulmonary bypass; 0 = cross-clamp removal; 6 = 6 h after aortic cross-clamp removal; 12 = 12 h after aortic cross-clamp removal; 24 = 24 h after aortic cross-clamp removal; 48 = 48 h after aortic cross-clamp removal. *P < 0.05 compared to control (ANOVA for repeated measures; *post hoc* Student-Newman-Keuls test).

aortic cross-clamp. In the NT group, 80% of the patients were using dopamine and 10% were using dobutamine on arrival at the ICU, while in the T group, 75 and 62.5% of patients were receiving these drugs, respectively. Only 2 patients in each group received norepinephrine during the study. Regarding vasodilators, on arrival at the ICU, 20% in the NT group and 12.5% in the T group were using sodium nitroprusside. The heaviest use of sodium nitroprusside occurred during the surgical procedure. No statistically significant difference was observed between groups in the use of any vasoactive drug. The doses of sodium nitroprusside and dopamine (in μg kg^{-1} min^{-1}) used during and after surgery were similar for the two groups.

Hemodynamic measurements

Both groups were similar at baseline with respect to the hemodynamic parameters (mean arterial blood pressure, heart rate, right atrial pressure, pulmonary wedge pressure, cardiac index, and systemic vascular resistance). No statistically significant difference was observed between groups, with the exception of heart rate, which was significantly higher in the T group 24 h after removal of the aortic cross-clamp (Table 2). It is noteworthy that heart rate was also higher in the T group at the end of cardiopulmonary bypass and at the 6th hour following the aortic cross-clamp release, differences which did not attain statistical significance. The cardiac index was similar for the two groups studied at all pre-established periods previously described; at baseline it was 2.22 ± 0.8 *vs* 2.08 ± 0.6 L min^{-1} $(m^2)^{-1}$ and 24 h after surgery it was 2.83 ± 0.8 *vs* 2.80 ± 1.0 L min^{-1} $(m^2)^{-1}$ for T *vs* NT group, respectively. The systemic vascular resistance was also similar for the two groups studied at all pre-established periods previously described; at baseline it was 2429.9 ± 964 *vs* 2099.2 ± 738 dyn s^{-1} $(cm^{-5})^{-1}$ and 24 h after surgery it was 1979.3 ± 649 *vs* 1672.6 ± 547 dyn s^{-1} $(cm^{-5})^{-1}$ for T *vs* NT group, respectively.

Clinical results

There were no statistically significant differences between groups concerning intubation time, duration of ICU stay or hospitalization after surgery. There was no significant occurrence of ventricular arrhythmia in either study group, nor any decrease in the incidence of postoperative atrial fibrillation in the T group as compared to the NT

Table 2. Perioperative hemodynamic characteristics of patients treated with triiodothyronine and controls at different times during and after cardiopulmonary bypass surgery.

Variables	Anesthetic induction		End of CPB		Removal of the aortic cross-clamp			
	T	NT	T	NT	6 h after		24 h after	
					T	NT	T	NT
HR (bpm)	92 ± 6	91 ± 9	99 ± 6	91 ± 4	96 ± 6	89 ± 5	98 ± 4*	85 ± 2
MAP (mmHg)	78 ± 3	72 ± 3	64 ± 4	66 ± 2	75 ± 4	71 ± 3	77 ± 3	75 ± 4
RAP (mmHg)	14 ± 3	13 ± 3	12 ± 1	13 ± 1	10 ± 1	9 ± 1	11 ± 2	10 ± 2
PWP (mmHg)	24 ± 4	23 ± 3	18 ± 4	16 ± 1	14 ± 2	12 ± 1	16 ± 3	14 ± 2

Data are reported as means ± SEM. CPB = cardiopulmonary bypass; T = triiodothyronine-treated group; NT = placebo-treated group; HR = heart rate; MAP = mean arterial pressure; RAP = right atrial pressure; PWP = pulmonary wedge pressure.
*P = 0.01 for comparison between groups at 24 h after removal of the aortic cross-clamp (Student *t*-test for all comparisons).

group. The use of a temporary pacemaker after weaning from the cardiopulmonary bypass was also not prevented by the administration of T_3 (Table 3). No adverse effect attributed to the study drug was observed. With respect to mortality, there were 3 deaths in the T group: one during hemodialysis and two due to sepsis (endocarditis and mediastinitis); all of them occurred more than 30 days after surgery. These 2 patients underwent re-operation during the late postoperative period. Other major postoperative complications were similar in both groups (3 patients in the NT group and 2 in the T group presented heart failure and 1 patient in the NT group developed acute renal failure). These patients, however, had a favorable outcome and were discharged from the hospital.

Discussion

In this study, we demonstrated that the use of oral T_3 during the perioperative period of valvular cardiac surgery in adults prevented the occurrence of significant T_3 serum reduction, leading to normal hormone levels for longer periods of time than previously demonstrated by other studies using intravenous T_3 (9,11,15).

By administering T_3 in a 25-µg oral dose every 8 h, starting 24 h before surgery, we obtained significantly higher serum T_3 levels in the T group than in patients who received placebo. Interestingly, the T_3 levels of the patients treated with the hormone were kept within the normal variation for serum T_3, in contrast to what had been reported in most studies that used intravenous T_3 (9,11,15). Furthermore, the serum T_3 concentration remained more stable throughout the study compared to other studies, in which the bolus infusion caused an abrupt hormone rise and fall (9).

Sirlak et al. (18), in the only study that used oral T_3, showed similar results in a different clinical scenario (coronary bypass surgery). In their clinical trial, the drug began to be administered 1 week before the procedure. This longer protocol determined very low TSH and high free T3 levels, a hyperthyroid hormone profile that could be harmful, especially in ischemic subjects. Moreover, we began thyroid hormone administration 24 h before surgery, a protocol that could be easily performed in large-scale randomized trials.

The drop of T_3 levels in our NT group was not due to hemodilution during cardiopulmonary bypass since the levels of T_4 and TSH did not decrease to the same extent as T_3, data in accordance with those that demonstrated decreased levels of thyroid hormones in tissues and reversible alterations in the hypothalamo-pituitary-thyroid axis (1, 20,21). Although TSH and T_4 levels were similar for the two groups after the beginning of surgery, when the baseline levels of both groups were compared with the subsequent evaluations we found a significant reduction, starting as early as 30 min after the beginning of cardiopulmonary surgery in both groups. These results reinforce the hypothesis that there are changes at the hypothalamo-pituitary-thyroid axis level due to decreased thyrotropin-releasing hormone synthesis (22,23) and that the extent of suppression is related to disease severity (1).

Table 3. Clinical endpoints and postoperative complications of patients treated with triiodothyronine and controls.

Variables	T (N = 8)	NT (N = 10)
Time in intensive care unit (h)	72 (44-119)	45 (43-73)
Intubation time (h)	19 (16-24)	15 (12-20)
Postoperative time (days)	11 (8-44)	7 (7-21)
Atrial fibrillation	4 (50%)	4 (40%)
Need for pacemaker	3 (37.5%)	1 (10%)

Data for intensive care unit, intubation and postoperative times are reported as median and interquartile intervals (25-75th percentile). Other data are reported as number of patients and percent in parentheses. T = triiodothyronine-treated group; NT = placebo-treated group. There were no significant differences between groups (Mann-Whitney for all continuous variables; Fisher exact test for categorical data).

The fact that TSH and T_4 concentrations varied similarly in both groups is also in agreement with this hypothesis. Both heparin (used by all patients studied) and dopamine (used by a similar number of patients in the groups studied) may have contributed to the TSH reduction observed after surgery (24).

The differences observed between basal T_4 and TSH levels probably occurred by chance. This imbalance should be interpreted as a conservative bias, since the treated group had higher T_3 levels at the end of follow-up.

We observed a statistically significant increment in heart rate by the 24th hour after aortic cross-clamp removal in the T group compared to the NT group. In the other periods studied, a higher heart rate could be seen in patients who used T_3, although no statistically significant difference was reached. It is well known that the clinical effect of T_3 on heart rate is caused by an increase in number and affinity of ß-adrenergic receptors on cardiac myocytes (25). At the intracellular level, T_3 induces the expression of the HCN2 gene, which encodes an ion channel highly expressed on the sinus node, an effect that is partially responsible for the positive chronotropic effect of T_3 (26).

Concerning the increase in cardiac index and the reduction of systemic vascular resistance, we did not find significant differences between the two groups studied. However, other studies conducted on a larger number of adults (9) and children (15) did report this difference. It is important to consider the differences between timing and route of administration of T_3 in relation to cardiac index assessment in these studies.

We did not observe adverse cardiovascular effects due to T_3 administration at the doses used, including tachycardia or arrhythmia. Despite the occurrence of three deaths in the T group and none in the NT group, our study did not have enough statistical power to detect a difference between groups. The longer aortic clamping time and lower ejection fraction in the T group, although not statistically significant ($P = 0.083$ and 0.099, respectively), raise the possibility that the patients randomly allocated to this group had more complex cardiopathies and that their surgical procedure was more complicated. Other studies demonstrated that T_3 replacement reduced clinical endpoints postoperatively, such as the need for pacemaker and mechanical assistance, use of vasoactive drugs, need for intensive care, or prevalence of atrial fibrillation (8,10,12,15,18), and some studies have even suggested decreased mortality (13,14).

It should be emphasized that the present study had a methodological limitation due to the small sample. Our study could not show the clinical or hemodynamic effects of oral T_3 administration. Indeed, our main objective was to show whether oral T_3 administration could prevent NTIS. A study with a larger sample that could identify subgroups that would benefit more from this therapy is mandatory. Another difficulty encountered in our study was that it was limited to valvular cardiopathies, a fact that could compromise the extrapolation of our data to other modalities of cardiac surgery.

The clinical relevance of the present study is that it reproduced with oral T_3, a drug of very low cost, the same profile previously observed with intravenous T_3 to prevent its serum reduction postoperatively in valvular cardiac surgery. Because of the controversy surrounding the perioperative administration of T_3, a well-designed blind trial with sufficient power to detect critical postoperative clinical events is required to determine the safety of preoperative oral T_3 administration.

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