A prospective randomized clinical study of thyroid hormone treatment after operations for complex congenital heart disease

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Infants and children undergoing operations for complex congenital heart disease form a group of extremely sick patients who require specialized care in the postoperative period.¹⁻⁴ Treatment strategies to minimize morbidity and increase survival aim to improve cardiac function and optimize postoperative hemodynamic parameters. Changes in thyroid hormone metabolism have been documented in patients undergoing pediatric car-

diac surgery, as well as in adult patients.¹⁻⁶ A recent study in children undergoing cardiac surgery who received a single daily bolus dose of triiodothyronine (T_3) in the postoperative period showed significant improvement in cardiac function and decreased postoperative therapeutic intervention, especially in those patients undergoing more complex surgical procedures.⁶ The present report is the first prospective randomized study to use a continuous infusion protocol to achieve normal steady-state serum T_3 levels in children for up to 7 days after cardiac surgery and to assess clinical outcomes.

Methods

We evaluated 75 consecutive patients of either sex undergoing cardiac surgery between the ages of birth and 18 years. The protocol was approved by the institution's committee on human rights in research. Parents or guardians gave informed consent before the operation, and patients older than 7 years of age gave assent.

Serum thyroid hormone levels were measured preoperatively, immediately postoperatively, and then once a day. Criteria for assignment to the treatment arm of the study included a serum total T_3 level of less than 40 ng/dL (or <60 ng/dL for newborns) on postoperative days 0, 1, or 2 and a requirement for mechanical ventilation. Patients randomized to the T_3 treatment group received continuous T_3 infusion at 0.05 to 0.15 μ g/kg of body

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Figure 1. Preoperative and postoperative serum total T_3 levels in pediatric patients undergoing operations for congenital heart disease. Mean $\pm$ SE serum total T_3 concentrations in all study patients who were randomized to the T_3 -treated ($n = 14$) or the untreated ($n = 14$) groups or were not eligible for randomization (nonrandomized group, $n = 47$) are shown. Preoperative serum samples were drawn in the operating room after induction of anesthesia. Postoperative serum samples were drawn immediately after the operation. Day 0 of randomization into the study represents serum total T_3 values obtained 24 to 48 hours after the operation. To convert values for T_3 to nanomoles per liter, multiply by 0.015. All data points between postoperative day 1 and 5 are significantly different among the 3 groups ($P < .05$).

weight per hour to maintain serum levels within the normal range (80–200 ng/dL).⁴ Serum thyrotropin levels were analyzed to ensure that the treatment dose did not render the patient chemically hyperthyroid.

The degree of inotropic support required was calculated as previously described by Wernovsky and colleagues.⁷ Cardiac rhythm was continuously monitored with bedside monitors and telemetry. The overall degree of postoperative care was analyzed by calculating the Therapeutic Interventional Scoring System (TISS) score. Scores were given for 76 different therapeutic and monitoring procedures and reflected the invasiveness, intensity, and complexity of care rendered to the patient.^{4,6}

All demographic, baseline, and outcome variables were compared by the Mann-Whitney test. Categorical variables were compared by the Fisher exact test. Results are expressed as means $\pm$ standard deviation. A 2-factor repeated-measures analysis of variance with group and day as the main effects and including the interaction effect (group $\times$ day) in the model was initially carried out for the serum T_3 level. Bonferroni-adjusted pairwise comparisons between days were carried out.

Results

Twenty-eight of 75 patients were eligible for the study, with 14 patients randomized to T_3 treatment. Figure 1 shows serum total T_3 levels preoperatively and postoperatively in all study patients. Serum T_3 levels fell in all patients after operations with the lowest values consistently measured after 24 and 48 hours. Patients receiving continuous T_3 infusion achieved serum T_3 values equivalent to the mean preoperative levels within 24 hours of initiation of treatment. Of the 28 study patients, serum T_3 levels were equivalent at the time of randomization. T_3 treatment did not alter outcome measures in the randomized groups when all 28 patients were considered (Table 1). No differences were found for TISS score, inotropic score, or dose requirements for milrinone and furosemide. Similarly, no significant differences were measured between the 2 groups for days of mechanical ventilation or length of hospital stay.

Nine patients within the overall study group were newborns (<1 month of age); 5 were randomized to T_3 treatment and 4 to the untreated group (Table 1). No significant differences between the T_3 -treated and untreated newborns were found with respect to the number of patients requiring cardiopulmonary bypass, the total bypass time, duration of crossclamping, and duration of hypothermic cardiac arrest. Twenty-four hours after initiation of T_3 treatment, the serum total T_3 level was restored to normal at 130 ± 38 ng/dL, which was significantly higher than the level of 34 ± 7 ng/dL found in the untreated group.

The TISS score was not different on day 0 of randomization, but on randomization days 1, 2, and 3, scores were significantly lower ($P = .037$) in the T_3 -treated group (40 ± 7 ng/dL) compared with the untreated group (49 ± 3 ng/dL), indicating lower postoperative management requirements (Table 1). T_3 treatment significantly decreased the need for inotropic support, as documented by a lower mean daily inotropic score of 5 ± 3 compared with 23 ± 26 ($P = .037$) in the untreated group (Table 1). Mixed venous oxygen saturation (MVO_2) values were obtained in 8 newborns. The mean MVO_2 values at the time of randomization were similar at $53\% \pm 13\%$ and $42\% \pm 10\%$ for the T_3 -treated and untreated patient groups, respectively. After 18 to 24 hours, the mean MVO_2 increased to $70\% \pm 12\%$ in the T_3 -treated group and remained unchanged at $44\% \pm 18\%$ in the untreated group. These differences, however, did not reach statistical significance because of the small sample size. Although the length of hospital stay and days of mechanical ventilation were not significantly different between the 2 groups, the mean values showed a trend toward shorter times in the T_3 -treated group (Table 1).

Discussion

Previous studies in adult⁵ and pediatric heart surgery patients^{1-4,6,8} have reported alterations in thyroid hormone metabolism, leading to significant decreases in postoperative serum total T_3 levels and normal or reduced serum thyrotropin and thyroxine levels. A recent study showed that the half-life of serum T_3 in children after heart surgery was markedly decreased.⁹ Bettendorf and colleagues^{1,6} reported that a low serum T_3 level in children after cardiac surgery was a predictor of adverse outcome and that T_3 treatment significantly improved cardiac function. Because we and others have shown that thyroid hormones have both inotropic and vasoactive effects,¹⁰ we undertook a study to determine

TABLE 1. Characteristics and treatment outcomes of the T₃ study patients

	Untreated	T ₃ treatment	P value
<i>Overall study groups</i>			
No. of patients	14	14	
Age (y)	3.2 ± 5.1	1.3 ± 2.4	1.000
TISS*	36 ± 12	39 ± 12	.765
Inotropic score*	11 ± 2	8 ± 4	.696
Mechanical ventilation (d)	4 ± 3	4 ± 2	.746
Postoperative hospital stay (d)	24 ± 29	23 ± 24	.747
<i>Newborn patient subgroups</i>			
No. of patients	4	5	
Age (d)	9.5 ± 11.6	4.6 ± 2.3	.805
TISS*	49 ± 3	40 ± 7	.037
Inotropic score*	23 ± 26	5 ± 3	.037
Mechanical ventilation (d)	6 ± 2	4 ± 2	.171
Postoperative hospital stay (d)	56 ± 38	18 ± 17	.109

Values are listed as means ± SD where shown. The normal range for serum total T₃ is 80 to 200 ng/dL (1.2-3.0 nmol/L).

*Mean daily postrandomization score.

whether T₃ replacement by continuous infusion of pediatric patients after cardiac surgery would improve clinical outcome. Evaluation of 75 patients showed that serum total T₃ levels fell predictably within 72 hours of the operation to a mean nadir value of 42 ± 13 ng/dL. The present data are in agreement with the results reported by Mainwaring,² Bettendorf,^{1,6} and their colleagues, who showed that the fall in serum T₃ was greater in patients undergoing complex cardiac surgical procedures. In the present study T₃ treatment was accomplished safely with no untoward changes in blood pressure, heart rate, or cardiac rhythm. T₃ treatment of the overall study group did not significantly alter postoperative outcome measures, including the TISS, days of mechanical ventilation, or overall length of hospital stay. In contrast, newborn patients showed the tendency for a positive therapeutic response to T₃ treatment, as indicated by a significantly lower TISS score and lower inotropic requirements that persisted throughout the randomization period. As a measure of cardiac output and peripheral perfusion, the MVO₂ measurements in the newborns showed a 17% increase after T₃ treatment compared with a 2% increase in the untreated group.

This positive postoperative outcome can be explained in part by the known molecular effects of thyroid hormone to increase cardiac contractility and to lower systemic vascular resistance in cardiac disease,¹⁰ after cardiac surgery,⁴⁻⁶ and in the low-T₃ syndrome.¹⁰ In conclusion, the present data suggest a therapeutic benefit of T₃ in the postoperative period by using a continuous infusion protocol to normalize serum T₃ levels in newborn patients undergoing operations for complex congenital heart disease. A prospective randomized study of greater statistical power will be required to confirm these results.

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