Has Triiodothyronine Treatment of Children after Cardiopulmonary Bypass Surgery Any Long-Term Effects?

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Surgery requiring cardiopulmonary bypass (CBP) induces nonthyroidal illness syndrome (NTIS) in adults and children. While adult patients generally show isolated low triiodothyronine (T3), children and infants present with a more global depression of the thyrotrope axis (decreased TRH, TSH and thyroid hormones), resulting in low T3 after CBP surgery. Experimental data suggest that low T3 is an adaptive mechanism induced by the activation of deiodinase type 3, which reduces the metabolic demand to the hypoxic heart [1]. However, low T3 has been associated with poorer postoperative outcomes in pediatric patients [2]. The effect of triiodothyronine supplementation on early postoperative outcomes has been assessed in a number of pilot randomized controlled trials conducted in pediatric patients and have suggested some short-term benefit of T3 supplementation [3–6]. Limitations of these randomized controlled trials included a limited number of patients with an inherent lack of power, different inclusion criteria, different ages, differences in the T3 dose and regimen, and different outcome measures. These studies did not permit strong determination of whether perioperative T3 supplementation was beneficial or harmful, especially for infants <1 year old (see Cochrane Reviews and its 2007 update [7]). In 2010, Portman et al. [8] published a larger randomized controlled trial (98 treated vs. 95 placebo; <1 year old), which showed that T3 repletion appeared safe but did not have beneficial effects for the entire study population. In secondary analysis adjusted for age, a subgroup of infants younger than 5 months seemed to have some benefit (a shorter time to extubation and a lower inotrope score), while treatment showed some detrimental effect on the cardiac output of infants older than 5 months. Consequently, whether T3 supplementation after cardiac surgery brings definitive benefits in infants still remains an open question, and randomized controlled trials including stratification by age are needed.

Beyond the immediate postoperative period, whether T3 treatment after CBP surgery has either a positive or a negative effect on long-term neurodevelopment is not a trivial question. Adverse neurological outcomes are common in children with congenital heart disease, and some factors may be modifiable [9]. Consideration of a possible role of thyroid supplementation is important because hypothyroidism [10, 11] or transient hypothyroidism [12] (this latter point being more controversial [13]) in infancy are associated with poorer neurocognitive outcomes.

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Consequently, overtreatment as well as the absence of treatment might have detrimental consequences. In this context, Mittnacht et al. [14] performed a follow-up study on 28 children 10 years after their initial randomized controlled trial [4]. The original study evaluated 40 patients who had a median age of 0.6 years (range 2 days to 10.4 years) at the time of surgery. These 28 children (14 girls) are now 10.7 years old on average and have similar auxological data. Fourteen patients of the T3-treated group were compared to 14 patients of the placebo group using (i) three tests to assess the neuropsychological functions (the Wechsler Intelligence Scale for Children-III, the d2 Test of Attention and the Trail Making Test Part B), (ii) a test to assess the motor development (the Lincoln-Osretzky Motor Development Scale), and (iii) echography and Doppler ultrasonography to assess the cardiac function. The authors found no significant differences between the T3-treated and placebo groups for full-scale IQ, attention and concentration, executive function, motor development, and cardiac function.

Randomized controlled trials in pediatric intensive care are notoriously difficult, and long-term follow-up of these cohorts are rare. Mittnacht et al. [14] should therefore be commended for their efforts, but their study has several limitations. Among these is the relatively low frequency of any given cardiac malformation and the different ages of the patients at the time of surgery. The result is a study population that is quite heterogeneous and has numerous confounding factors which, taken together, does not allow for strong conclusions to be drawn. The limited sample size precludes any subgroup analysis. Nevertheless, this study seems to suggest that the long-term consequence of either treated or untreated nonthyroidal illness syndrome on cardiac and neurological functions is neutral. This long-term safety signal allows investigators to design new multicenter randomized controlled studies to assess the short-term effect of T3 treatment with sufficient power and with, at least, some confidence that their intervention has no long-term detrimental consequences.

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