Review

Clinical review: Thyroid hormone replacement in children after cardiac surgery – is it worth a try?

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Abstract

Cardiac surgery using cardiopulmonary bypass produces a generalized systemic inflammatory response, resulting in increased postoperative morbidity and mortality. Under these circumstances, a typical pattern of thyroid abnormalities is seen in the absence of primary disease, defined as sick euthyroid syndrome (SES). The presence of postoperative SES mainly in small children and neonates exposed to long bypass times and the pharmacological profile of thyroid hormones and their effects on the cardiovascular physiology make supplementation therapy an attractive treatment option to improve postoperative morbidity and mortality. Many studies have been performed with conflicting results. In this article, we review the important literature on the development of SES in paediatric postoperative cardiac patients, analyse the existing information on thyroid hormone replacement therapy in this patient group and try to summarize the findings for a recommendation.

Introduction

During systemic illness, especially after cardiac surgery using cardiopulmonary bypass (CBP), abnormalities in the circulating thyroid hormone levels are found in the absence of primary thyroid disease; this is collectively called the sick euthyroid syndrome (SES). Some argue that it is unclear if the clinical picture of SES is an adaptive process, a marker of the severity of illness or even if treatment is warranted in these patients.

The many effects of thyroid hormones on the cardiovascular system have been described in detail elsewhere [1-3]. The biological actions of thyroid hormones on the cardiovascular system make these hormones attractive as a potential treatment option in the management of patients after cardiac surgery.

We review the actual literature on the development of SES in children after cardiac surgery and discuss the relevant literature on hormone replacement. Finally, a critical appraisal of the potential effects of hormone replacement and the studies performed is sought.

Sick euthyroid syndrome

It is well known that several severe diseases can cause abnormalities in the circulating thyroid hormone levels in the absence of primary thyroid disease (i.e., non-thyroidal illness or SES) [4].

The most common pattern is a decrease in total and unbound triiodothyronin (T3) with normal levels of thyroid stimulating hormone (TSH) and thyroxin (T4). This is classified as SES type 1 (SES-1) or low-T3 syndrome. The de-ionidation from T4 to T3 via peripheral (hepatic) enzymes (inhibition of 5′-deionidase, a selenoenzyme [5,6]) is impaired, leading to a decrease of T3 and an increase in reverse T3 that is biologically inactive [7]. Inflammatory cytokines have been linked to the development of SES [8] and the levels of cytokines seem to influence the severity of SES [9,10]. Elevated serum levels of steroids as part of a stress response may influence the de-ionidase activity and TSH and T3 response in SES [8,11-13]. Additionally, tissue-specific thyroid hormone bioactivity is reduced during cellular hypoxia and contributes to the low T(3) syndrome of severe illness [14]. In general, the severity of illness is correlated to the severity of SES [15-17].

Very sick patients may show a dramatic fall in total T3 and T4 levels; this state is called the low-T4 syndrome or SES type 2 (SES-2) and has a poor prognosis [18,19]. T4 metabolism may further be influenced by a decrease in thyroid binding globulin levels [20].

In both SES-1 and SES-2, serum levels of TSH are impaired and do not increase in reaction to low T3 or T4 levels.

CABG = coronary artery bypass graft; CBP = cardiopulmonary bypass; IL = interleukin; SES = sick euthyroid syndrome; SIRS = systemic inflammatory response syndrome; T3 = triiodothyronin; T4 = thyroxin; TRH = thyroid releasing hormone; TSH = thyroid stimulating hormone.

Patients with low or undetectable TSH show increased morbidity and mortality [15,21,22]. Additionally, the response of TSH to thyroid releasing hormone (TRH) is impaired in SES [23].

Prognostic impact of thyroid hormones on outcome

In addition to the results discussed above, SES does have a significant impact on outcome and survival. In 1995, Rothwell and Lawler [24] used thyroid hormone levels to predict outcome in adult intensive care patients and showed that an endocrine prognostic index based on intensive care unit admission measurements of these hormone levels is a superior discriminator of patient outcome than the APACHE II score. Similar results were obtained earlier [25], as well as by Jarek and colleagues in 1993 [26] and Koh and colleagues in 1996 [27] and was confirmed by Chinga-Alayo and colleagues in 2005 [28]. In their study with 113 patients, the addition of thyroid hormone levels to the APACHE score improved the prediction of mortality [28]. Similar results were reported by Iervasi and colleagues [29], who assessed prospectively the role of thyroid hormones in the prognosis of patients with heart disease. In their cohort of 573 consecutive patients, low levels of free T3 were found to be the highest independent predictor of death, especially in cardiac patients. Parle and colleagues [30] presented a large 10 year follow-up cohort study of 1,191 patients and were able to correlate a single measurement of low TSH in individuals aged 60 years and older with increased mortality from all causes and in particular mortality due to circulatory and cardiovascular diseases.

Thus, the degree of SES seems to have significant influence on a patient's outcome under various conditions.

Sick euthyroid syndrome in children

Classic SES-1 was found in several studies in children [31-33], including after bone marrow transplant [34], in meningitis [35,36], menigococcal disease [37], Hodgkin's disease [38], hepatitis [39], metabolic acidosis due to diarrhoea or diabetic ketoacidosis [40,41] and sepsis [42]. The thyroid function in neonates and premature babies is impaired and thyroid function disorders associated with neonatal adaption and illness are well described [43,44]. Dopamine infusion additionally induces or aggravates partial hypopituitarism and SES in critically ill infants and children [45].

In summary, there is significant evidence that SES plays an important role in children in various conditions; whereas SES-1 is related to good outcome and mild to moderate illness, SES-2 is related to severe illness and poor outcome.

Cardiac operations and the systemic inflammatory response in children

It is well known that cardiac surgery and CBP leads to a generalized systematic inflammatory response syndrome (SIRS), resulting in increased postoperative morbidity and mortality and organ failure [46,47]. Some of the main clinical features of postoperative SIRS are hemodynamic impairment, known as low cardiac output syndrome, capillary leak and fluid retention. SIRS is characterized by increased post-operative leucocyte counts, leucocyte activation, oxidative stress and release of cytokines such as tumor necrosis factor alpha and IL-6 and IL-8.

Various pharmacological techniques are used to modify or minimize this response, including the use of high dose steroids [48]. Other techniques applied routinely are hypothermia, the use of heparin bonded circuits and oxygenators, intraoperative continuous hemofiltration or conventional ultrafiltration, post-operative modified ultrafiltration, leucocyte filtration, and the postoperative use of peritoneal dialysis to remove inflammatory cytokines and their impact on postoperative fluid balance [48-50]. Finally, catecholamines (namely dopamine) and other drugs such as milrinone are used to support the circulation in low cardiac output syndrome [51].

In summary, CBP induced SIRS combines many risk factors contributing to the development of SES as outlined above and has significant impact on the postoperative course in paediatric patients.

Paediatric sick euthyroid syndrome after cardiac surgery

Cardiac surgery with or without cardiopulmonary bypass induces a marked and persistent depression of circulating thyroid hormones during the postoperative period in both adults and children [52-57].

Allen and colleagues [58] demonstrated SES in 12 postoperative cardiac children in 1989 regardless of the procedure complexity. Bartkowski and colleagues [54] showed that when a larger amount of T3 is removed by ultrafiltration, patients show a prolonged recovery. Murzi and colleagues [59] demonstrated in 14 patients a prolonged decrease in thyroid hormones for five to seven days. Belgorosky and colleagues [60] demonstrated similar effects in 20 prepubertal children undergoing cardiac surgery. Saatvedt and Lindberg [61] demonstrated a significant inverse correlation between T3 levels 24 and 48 hours postoperatively and total accumulated IL-6, and also between the percentage decrease in T3 concentrations and total accumulated IL-6.

Bettendorf and colleagues [53] showed in 139 patients a significant decrease in plasma thyroid hormone levels consistent with SES-2 and low TSH levels. In those patients with plasma T3 levels less then 0.6 nmol/l ($n = 52$), the period of mechanical ventilation and intensive care treatment was significantly prolonged. Neonates exposed to bypass and hypothermia uniformly show a pattern of SES-2 [62]; prolonged SES was demonstrated in older patients after a

Fontan procedure [63]. The magnitude of the fall in serum T3 predicts greater therapeutic requirements in the post-operative period, especially in neonates [64]. Lynch and colleagues [65] reported five cases of hypothyroidism possibly secondary to loss of thyroid binding globulin from prolonged chest tube drainage.

Peak serum levels of IL-6 were linked to the lowest T3 levels in 16 children after cardiac surgery [66]; the authors of this study postulated that treatments directed to diminish the rise in pro-inflammatory cytokines may prove effective in preventing postoperative SES. Ririe and colleagues [67] found no significant impact of deep hypothermic cardio-circulatory arrest on free T4, free T3 and TSH levels in children at day 1 and 2 after corrective surgery but this did lead to an increase of TSH while on bypass.

The concentration of plasma selenium in children undergoing cardiopulmonary bypass decreases significantly, resulting in diminished deiodinase activity and a subsequent reduction in the conversion of T4 to T3 [68]. Free T3 and selenium serum concentrations were correlated to the time spent in intensive care. Mitchell and colleagues [69] showed a correlation between low T3 and T4 levels and survival in 10 infants of less than 5 kg body weight. In the two patients that died in this small series, no increase in T3 and T4 or TSH was found after a trough was reached at 48 to 72 hours after surgery. Plumpton and Haas finally demonstrated that younger children (less than three months of age) with longer CBP time (greater than 120 minutes) showed prolonged ventilation after CBP and lower free T3 levels [52] and concluded that thyroid hormone replacement therapy in this high-risk group is warranted.

In conclusion, all children submitted to cardiac surgery with or without cardiopulmonary bypass show a persistent pattern of SES; in many patients, SES-2 with low T3 and T4 levels and a low TSH status is demonstrated and there is a close correlation between the age of the patients bypass time, postoperative morbidity and the degree of SES [58]. The profound decrease in thyroid hormones is thought to be of sufficient magnitude to affect cardiac function [70].

Other confounding factors

Dopamine and thyroid function

Dopamine is often used for treatment of low cardiac output syndrome. Dopamine directly inhibits anterior pituitary function through inhibitory dopamine receptors, resulting in diminished TSH release [71]. The intravenous administration of dopamine in healthy volunteers produced a reduction in serum prolactin, TSH, luteinizing hormone and follicle stimulating hormone while stimulating growth hormone release; TSH showed a sustained inhibition [72]. Additionally, dopamine lowers both basal and TRH-mediated TSH release [73]. This effect was even more sustained in patients with critical illness [74]. The dopamine-induced or aggravated pituitary dysfunction in critical illness warrants caution with prolonged infusion of this catecholamine, particularly in early life [75]. The administration of dopamine was correlated with the permanent suppression of TSH in children with meningococcal shock presenting with severe SES-2 [37]. In newborns, dopamine was found to suppress prolactin, growth hormone, and thyrotropin secretion consistently, and in children, dopamine suppressed prolactin and thyrotropin secretion, and a rebound release started within 20 minutes after dopamine withdrawal [45].

Thus, dopamine infusion induces or aggravates partial hypopituitarism and SES in critically ill infants and children.

Iodinated antiseptics in cardiac surgery

Infants may absorb significant quantities of iodine in iodinated topical antiseptics transcutaneously [76,77]. Premature and pre-term infants have been shown to absorb iodine when treated repeatedly with antiseptics such as povidone-iodine [78-81]; this patient group is specifically susceptible to iodine-induced hypothyroidism [82], the so called Wolff-Chiakoff effect [83]. This effect is detectable when compared with non-iodine skin disinfectant (chlorhexidine) [84]. Children with delayed sternal closure exposed to povidone-iodine for sternal wound protection display a more profound thyroid depression in the immediate postoperative period and significant iodine absorption [85]. In only one study did irrigation with povidone-iodine solutions for deep sternal wound infection not cause significant alteration in thyroid function in children [86].

Amiodarone

Amiodarone is a highly effective antiarrhythmic agent for supraventricular and ventricular arrhythmias, especially in the early postoperative setting [87]. The drug is known to affect thyroid homeostasis [88] by competitive inhibition of 5′-monodeiodinase, which converts T4 to T3 and reverse T3 to 3,3′-diodothyronine (T2), and also by the direct effects of its high iodine content (37% by weight) [89]; it is also structurally similar to the thyroid hormones [90]. The incidence of thyroid dysfunction in children is well reported [91] and hypothyroidisms as well as hyperthyroidism are reported with varying incidence rates, ranging from about 1% up to 24% [92-96]. The incidence and severity of side effects seem to be correlated with age and the dose used, with younger patients exposed to higher doses at increased risk [96,97].

Thus, the use of amiodarone in the early postoperative setting may contribute to the development of thyroid dysfunction, including SES.

Thyroid hormone replacement after cardiac surgery

The rationale of thyroid hormone replacement/ treatment

A vast literature is available on the changes of thyroid function during non-thyroidal illness or SES in adults. Therapy

with T3 has been suggested by many authors but is controversial. In SES-1 and SES-2, additional tissue-specific mechanisms are involved in the reduced supply of bioactive thyroid hormone and replacement of T3 can reverse these findings [98,99].

T3 administration is associated with improved hemodynamics, reduced peripheral vascular resistance, increased cardiac output and other effects, suggesting the potential utility of thyroid hormone replacement [100,101]. In patients after coronary artery bypass graft (CABG) surgery, an inverse correlation was found between days of post-operative hospitalisation and the slope of the recovery of T4 to T3 conversion [102].

Recently, Kokkonen and colleagues [103] demonstrated a strong association between atrial fibrillation and the low-T3 status. T3 replacement was shown to reduce the rate of arrhythmias and may be cardio-protective [104].

Novitzky and colleagues [105,106] performed two smaller randomised studies in 1989 using T3 supplementation and showed a significantly reduced need for conventional inotropic agents and diuretics as well as improved stroke volume, cardiac output, reduced systemic and pulmonary vascular resistances and survival.

Klemperer and colleagues [107] administered T3 in a randomised placebo controlled study in 142 high-risk patients undergoing coronary artery bypass surgery; they showed a significant increase in cardiac output and a decrease in systemic vascular resistance. Vavouranakis and colleagues [108] showed that T3 administration lessened the need for pharmacological vasodilator therapy, but may increase heart rate. Sirlak and colleagues [109] pre-treated patients for planned CABG surgery seven days pre-operatively and found postoperative lower catecholamine requirements and a better cardiac output.

Finally Mullis-Jansson [110] and colleagues showed in another similar study that parenteral T3 led to improved postoperative function, reduced the need for inotropic agents and mechanical devices, decreased the incidence of myocardial ischaemia and decreased the incidence of atrial fibrillation and pacemaker therapy.

Clinical treatment of children with thyroid hormones after cardiac surgery

Based on the findings after cardiac surgery and the pharmacological profile of thyroid hormones, it has been postulated that thyroid hormone replacement in infants may reduce postoperative morbidity and mortality [55].

The half-life of intravenous T3 in children is approximately one-third of that reported for adults and can be calculated at about 7 hours [111]. Thyronin treatment (T3) was used by Carrel and colleagues in seven children with severe low cardiac output syndrome in whom conventional treatment had failed [112]. All children showed metabolic acidosis and those with pulmonary hypertension received nitric oxide. Two patients died (one due to intractable right heart failure and one after cerebral embolism and who received left ventricular assist device) but the other five showed a continuous improvement in hemodynamics within the following 48 to 96 hours. Bialkowsky [113] showed a beneficial effect of T3 supplementation after CBP in children, including significant vasodilatation. Chowdhury and colleagues [114] initially reported a case series in 1999 of six children with low postoperative T3 levels. In these children, T3 treatment decreased the systemic vascular resistance by more than 25%, increased cardiac output by more than 20%, resolved the existing metabolic acidosis (base excess > 0) and reverted junctional rhythm to sinus rhythm in 3/3 patients. The same group later showed in a prospective trial that T3 levels are more likely to fall in children after cardiac surgery and that the magnitude of the fall in serum T3 predicts greater therapeutic requirements in the postoperative period, especially in neonates [64].

Mackie and colleagues [115] performed a randomised, double-blind placebo controlled trial of T3 treatment in a selective group of 42 patients undergoing a Norwood procedure or a two-ventricle repair of interrupted aortic arch and ventricular septum defect. In this high risk group of patients, T3 supplementation proved to be safe and resulted in a higher systolic blood pressure and a more rapid achievement of negative fluid balance. Cardiac index was not significantly improved. Fluid balance, however, is managed in many centres worldwide by the use of peritoneal dialysis and so the beneficial effects may be negligible [116].

Portman and colleagues [117] performed a small study with 14 patients and showed that T3 replacement prevented circulating T3 deficiencies and elevated heart rate without a concomitant decrease in systemic blood pressure, thus indicating increased cardiac output. Myocardial oxygen consumption improves with an elevation of peak systolic pressure and T3 repletion may thus enhance cardiac function reserve.

Potential side effects of thyroid hormone replacement

The acute application of thyroid hormone may have unexpected side effects based on the physiological profile of the hormones. Subclinical thyrotoxicosis may be associated with changes in cardiac performance and morphology; these may include increased heart rate, increased left ventricular mass index, increased cardiac contractility, diastolic dysfunction, and the induction of ectopic atrial beats or arrhythmias [118].

In adult patients undergoing coronary artery surgery, the intravenous infusion of T3 (0.8 μg/kg followed by 0.12 μg/kg/h for 6 hours) did not change hemodynamic variables or inotropic

drug requirements [119]. No significant differences were detected in the incidence of arrhythmia after T3 administration despite higher postoperative cardiac index and lower systemic vascular resistance [104,105,107,108,120].

Intravenous T3 (0.4 μg/kg bolus plus 0.1 μg/kg infusion) was administered over a 6 hour period without side effects in 170 patients undergoing elective coronary artery bypass grafting and resulted in a lower incidence of pacemaker dependence (14% versus 25%, $P = 0.013$) without side effects [110]. The oral administration of T3 (125 μg/day orally for 7 days preoperatively and from the first postoperative day until discharge) was without side effects in CABG patients [109].

T3 was well tolerated without episodes of ischemia or clinical arrhythmia in patients with advanced heart failure [121]. Finally, an intravenous bolus of 1 μg/kg T3 followed by continuous perfusion at 0.06 μg/kg/h was performed without haemodynamic impairment in 52 consecutive adult cadaveric organ donors [122].

In pre-term infants less than 28 weeks of gestational age, a single injection of T3 (0.5 μg/kg) given 22 to 26 hours after birth only leads to a two day increase of T3 levels and did not have negative effects on the cardiovascular system [123]. T4 administration reduced vasopressor needs in children with cessation of neurological function and hemodynamic instability; no side effects were seen [124].

After a mean bolus dosage of 2 ± 1.5 μg/h of T3, followed by a continuous infusion of 0.4 ± 0.3 μg/h for a mean duration of 48 ± 12 h, no side effects were demonstrated in a cohort of adult and paediatric patients suffering from severe low cardiac output [112]. Again, no side effects were found in 54 adult and seven paediatric patients suffering from severe low cardiac output in different clinical conditions with a mean bolus dosage of 2 ± 1.5 μg/h of T3 followed by a continuous infusion of 0.4 ± 0.3 μg/h for a mean duration of 48 ± 12 h [64,114].

In children, a once daily infusion of T3 (2 μg/kg bodyweight on day 1 after surgery and 1 μg/kg bodyweight on subsequent postoperative days up to 12 days after surgery) proved to be safe without side effects [125]; the cardiac index, however, improved significantly. The normalization of serum T3 levels in other studies was reflected in a marked decrease in the requirement for inotropic support, conversion to normal sinus rhythm, and progressively improving clinical course without clinically adverse effects [55,113]. In a cohort of children undergoing the modified Fontan procedure, the patients received intravenous T3 at dosages of 0.4, 0.6, and 0.8 μg/kg; no side effects were reported [111]. T3 (0.4 μg/kg) immediately before the start of CBP and again with myocardial reperfusion led to transient elevation in heart rate without a concomitant decrease in systemic blood pressure in infants less than 1 year old undergoing ventricular septal defect or tetralogy of Fallot repair [117].

When using a continuous infusion of T3 (0.05 μg/kg/h) in neonates undergoing aortic arch reconstruction, the study drug was discontinued prematurely in two children because of hypertension ($n = 1$) and ectopic atrial tachycardia ($n = 1$); heart rate and diastolic blood pressure, however, were not influenced by T3 supplementation, but systolic blood pressure was higher in the T3 group ($P < 0.001$). No serious adverse events were attributed to T3 administration [115].

In summary, the administration of T3 to adults and children of various ages after cardiac surgery as well as in various other conditions of critical illness proved to be safe and well tolerated; no side effects have been demonstrated so far.

Conclusion

The modern treatment of children with congenital heart defects provides worldwide excellent postoperative care with short ventilation times, short length of stay and low mortality and morbidity in the majority of clinical circumstances. Nevertheless, clinically significant SES can be detected, especially in neonates and children with long bypass times. At present, existing studies on treating SES in children have had relatively small subject numbers as well as age and diagnosis heterogeneity, thereby limiting the ability to determine significant clinical effects. Thus, to demonstrate a significant clinical effect of T3 supplementation, large numbers of patients are needed and the study must include patients at specific risk for SES and low cardiac output syndrome [52]. Treatment protocols in these patients, however, often include in the routine management peritoneal dialysis, inotropic support and afterload reduction as well as open chest strategies for a defined number of days; thus, common outcome parameters such as hours of ventilation, use of catecholamines, blood pressure, urine output, and so on may prove difficult to assess [116].

The Triiodothyronine for Infants and Children Undergoing Cardiopulmonary Bypass (TRICC) study is a multicenter, randomised, clinical trial designed to determine safety and efficacy of T3 supplementation in 200 children less than 2 years of age undergoing surgical procedures for congenital heart disease. Duration of mechanical ventilation after completion of cardiopulmonary bypass is the primary clinical outcome parameter and the study also follows multiple secondary clinical and hemodynamic parameters [126]. Based on the assumptions above, even the results of this study may fail to establish the routine administration of T3 to correct SES in children after cardiac surgery.

In summary, children after cardiac surgery are at specific risk to develop a clinically important SES peri-operatively. Despite clear evidence from the studies available, the demonstrated beneficial effects and the clear lack of negative effects make the prophylactic supplementation of T3 a desirable treatment option, especially in high-risk groups.

Competing interests

The authors declare that they have no competing interests.

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