A systematic review and meta-analysis of clinical trials of thyroid hormone administration to brain dead potential organ donors*

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Objectives: **To review all published clinical studies of thyroid hormone administration to brain-dead potential organ donors.**

Methods: **A search of PubMed using multiple search terms retrieved 401 publications including 35 original reports describing administration of thyroid hormone to brain-dead potential organ donors. Detailed review of the 35 original reports led to identification of two additional publications not retrieved in the original search. The 37 original publications reported findings from 16 separate case series or retrospective audits and seven randomized controlled trials, four of which were placebo-controlled. Meta-analysis was restricted to the four placebo-controlled randomized controlled trials.**

Results: **Whereas all case series and retrospective audits reported a beneficial effect of thyroid hormone administration, all seven randomized controlled trials reported no benefit of thyroid hormone administration either alone or in combination with other hormonal therapies. In four placebo-controlled trials including 209 donors, administration of thyroid hormone (n = 108) compared with placebo (n = 101) had no significant effect on donor cardiac index (pooled mean difference, 0.15 L/min/m^2; 95% confidence interval –0.18 to 0.48). The major limitation of the case series and retrospective audits was the lack of consideration of uncontrolled variables that confound interpretation of the results. A limitation of the randomized controlled trials was that the proportion of donors who were hemodynamically unstable or marginal in other ways was too small to exclude a benefit of thyroid hormone in this subgroup.**

Conclusions: **The findings of this systematic review do not support a role for routine administration of thyroid hormone in the brain-dead potential organ donor. Existing recommendations regarding the use of thyroid hormone in marginal donors are based on low-level evidence. (Crit Care Med 2012; 40: 1635–1644)**

Key Words: donor management; thyoid hormone

Organ transplantation is the most effective therapy currently available to treat end-stage failure of a number of organs, including the heart, lung, liver, and kidney (1). The most common source of donor organs is the deceased multi-organ donor (1). Most deceased organ donors have undergone brain death and have respiration artificially maintained by mechanical ventilation while cardiac function and blood pressure are commonly supported by vasoactive drug therapy. After death, the sole purpose of these therapies is to facilitate organ donation. The optimal management of the brain-dead potential organ donor in the period between brain death declaration and organ procurement for transplantation has not been established.

There are conflicting data regarding the endogenous hormonal changes that occur during and after brain death and their effect on hemodynamic variables and organ quality (2–7). Observational studies in brain-dead human donors have almost always documented a reduction in the free plasma triiodothyronine (T3) concentration, but changes in the serum concentration of other hormone levels (such as thyroid-stimulating hormone, thyroxine [T4], and cortisol) are variable (8–15). When measured, reverse T3 has been normal or increased after brain death, consistent with a "sick euthyroid" rather than a true hypothyroid state (8, 11, 13–15). These studies have also failed to identify a consistent association between circulating thyroid hormone concentrations in the brain-dead donor and donor hemodynamic instability (8, 10–12, 15, 16), cardiac dysfunction as assessed by echocardiography (9), or circulating troponin levels (12). Nor has any association been observed between donor thyroid hormone levels and early post-transplant outcomes in heart (8, 15), kidney (8, 11), or liver transplantation (10).

There is also controversy over the benefits of administrating thyroid hormone to brain-dead potential organ donors. Despite this controversy, thyroid hormone administration in conjunction with other hormonal therapies has been recommended as part of an aggressive management protocol for the potential cardiothoracic donor and has been incorporated into the UNOS Critical Pathway for the Organ Donor (17). In this systematic review, we analyzed published clinical studies in which thyroid hormone, either thyroxine (T4) and triiodothyronine (T3), was administered to brain-dead potential organ donors as part of their management protocol between determination of brain death and organ retrieval. The aim of the review was to examine the strength of the evidence in support of the use of thyroid hormone administration to brain-dead donors and to identify if there were particular donors who might benefit from this therapy. Specifically, we assessed whether administration of

***See also p. 1689.**

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The authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e3182416ee7

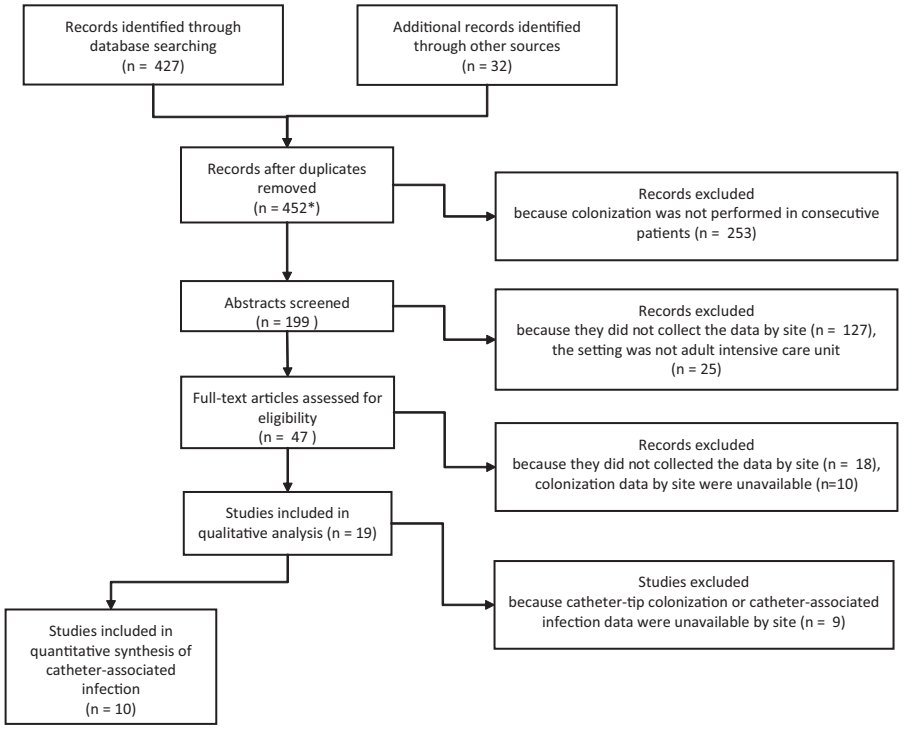

Figure 1. Process of publication searching and selection for inclusion in systematic review. *One publication reported results of a case series and a randomized controlled trial (33).

thyroid hormone was associated with improvement in hemodynamic stability and reduced dosage of vasoactive agents, as well as the number and quality of organs procured for transplantation.

MATERIALS AND METHODS

Search Strategy and Study Selection

A search of PubMed using the following search terms was undertaken: ("thyroid hormone" or "thyroxine" or "triiodothyronine" or "hormonal therapy") and ("brain death" or "brain dead donor" or "deceased donor" or "organ donor" or "donor management"). We retrieved all publications published before November 2010. The process of selection of publications for inclusion in the systematic review is summarized in Figure 1. Four-hundred one publications were retrieved, 262 of which were unrelated to the topic of interest. Of the remaining 139 publications, there were 29 experimental studies in tissues or animals, 36 observational reports of changes in hormonal concentrations in human brain-dead donors without the administration of hormonal therapy, and 36 reviews, editorials, or letters to the editor. Of the remaining 38 clinical studies, there were three original reports of interventions that did not include thyroid hormone, leaving 35 original publications reporting the administration of thyroxine or triiodothyronine to brain-dead potential organ donors (7, 9, 18–50). Detailed review of the 35 original reports led to identification of two additional publications not retrieved in the original search (51, 52). Fifteen of the publications reported additional findings in the same patient population that were included in separate reports from the same authors. Others included substantial overlap in the study populations.

Assessment of Study Quality

The studies were initially graded for study quality using the grading system developed by the National Health and Medical Research Council, Australia (53). Given the heterogeneity in study design and quality, the studies were stratified by study quality before further analysis. The randomized controlled trials identified in the initial grading were then scored against the criteria proposed by Jadad (54).

Data Synthesis and Analysis

Meta-analysis of the four placebo-controlled trials was performed by computing the mean difference with 95% confidence intervals between thyroid hormone (T3) and placebo using an inverse-variance random-effects model. Data on cardiac index and dose of concomitant vasoactive drug therapy at the completion of study drug administration were analyzed. Between-studies heterogeneity was analyzed by means of the I^2 method, considering values between 0% and 30% of little importance. All analyses were performed with the Review Manager 5.1.4 (RevMan) software (2011, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Of the 37 original studies, there were 16 separate case series or retrospective audits (Table 1) and seven randomized controlled trials (Table 2). The 16 case series comprised 11 studies that included a concurrent nonrandomized control population (7, 28, 31, 33, 34, 36–39, 42, 52), three studies that included historical controls (19, 41, 49), and two that were uncontrolled (22, 44). These nonrandomized case series resulted in eight additional publications (18, 20, 21, 27, 30, 32, 35, 51), which were not analyzed further because their major findings were contained within the studies included in Table 1. The seven randomized controlled trials (9, 23–25, 33, 40, 47) gave rise to seven additional publications apart from the publication reporting the primary outcome of the trial (26, 29, 43, 45, 46, 48, 50). One study reported the results of both a randomized controlled trial as well as a nonrandomized study (33).

Case Series and Study Populations

Most studies restricted enrollment to potential heart or lung donors. Seven studies further restricted administration of thyroid hormone therapy to donors who were either hemodynamically unstable or receiving high doses of vasoactive support (28, 31, 33, 34, 39, 42, 52). In these studies, untreated hemodynamically stable donors were used as a control group. In five studies, thyroid hormone therapy was administered to consecutive donors irrespective of the hemodynamic status or level of support (19, 22, 41, 44, 49). In the two large retrospective UNOS audits, data regarding the hemodynamic status or level of support for the donor were not available (36, 37).

Thyroid Hormone Protocol

Seven studies administered T3 and seven administered T4. The two large UNOS audits did not distinguish between

T3 and T4 (36, 37). There was greater consistency between studies in which T4 was administered both in terms of dose and use of coadministered drugs. With the exception of the study by Zuppa et al (39) in pediatric donors in whom the dose of T4 was weight-adjusted and age-adjusted, all other studies administered T4 as a 20-μg bolus intravenously followed by a constant infusion at 10 μg/hour (28, 38, 41, 42, 44, 49). In these studies, T4 was coadministered with bolus doses of methylprednisolone, insulin, and dextrose followed by an infusion of insulin. In five of these studies, vasopressin was also administered as an infusion with the dose titrated according to systemic arterial pressure or urine output (38, 41, 42, 44, 49).

The dose and form of administration of T3 in the studies that examined the use of this drug were more variable. T3 was administered intravenously in all studies except that of Taniguchi et al (7), who administered T3 via the nasogastric tube as a single oral daily dose of 1.5 μg/kg/day for up to 7 days after determination of brain death. In four studies, T3 was administered as repeated intravenous bolus injections (19, 22, 31, 33). The bolus was administered as a fixed dose of 2 μg in two studies and as a weight-adjusted dose of 0.2–0.4 μg/kg in two studies. In two studies, it was administered as a constant infusion with or without an initial bolus (34, 52).

The duration of administration of thyroid hormone was not recorded in all studies. In the eight studies in which it was recorded, the duration of administration of thyroid hormone was highly variable both within and between studies. With the exception of the study by Taniguchi et al (7), the duration of administration ranged from approximately 2 hrs (31, 33) up to >15 hrs (44). One study stratified analysis between donors who had received thyroid hormone for <15 hrs or >15 hrs (44).

Outcome Measures

All case series reported an improvement in donor outcome measures after administration of thyroid hormone, although the measured outcomes differed between studies. Ten studies reported donor hemodynamic stabilization or improved metabolism (reduced lactate) and reduced vasoactive agent requirements (7, 19, 31, 33, 34, 38, 39, 41, 42, 52). Three studies reported improved donor heart function (22, 33, 52) and six studies reported an increase in the number of organs procured per donor in the thyroid hormone group (37, 41, 42, 44, 49, 52). Finally, four studies reported improvement in posttransplant graft function or patient survival in the thyroid hormone group (22, 28, 33, 36).

Randomized Controlled Trials and Study Populations

As with the case series, the randomized controlled trials restricted enrollment to potential heart or lung organ donors. The study populations ranged from 25 to 80 subjects. Six randomized controlled trials recruited consecutive unselected donors, the majority of whom were hemodynamically stable at trial entry. One trial restricted enrolment to hemodynamically stable donors (33). In one randomized controlled trial, 20 of 37 enrolled subjects had echocardiographic evidence of impaired cardiac function at baseline (9). In the largest randomized controlled trial reported to date, 50% of enrolled donors were described as "marginal" at the time of initial assessment based on suboptimal hemodynamic indices or high vasoactive medication requirements (47).

Thyroid Hormone Protocol

In four randomized controlled trials, a double-blind, placebo-controlled design was used (9, 24, 40, 47). In three studies, the investigators were unblinded (23, 25, 33); however, one of these involved blinded end point assessment (23). Most randomized controlled trials utilized invasive hemodynamic monitoring (arterial line and pulmonary arterial catheterization) instituted before commencement of hormonal therapy. All randomized controlled trials evaluated intravenous T3. In five randomized controlled trials, T3 was the sole study drug administered. In another two studies, T3 was coadministered with a corticosteroid (24, 47), with one of these trials assessing T3, methylprednisolone, and the combination against placebo (47). In this trial, all study subjects irrespective of assigned group were commenced on a vasopressin infusion with attempted weaning of any concurrent vasoactive medication infusions.

As with the case series, there was considerable interstudy heterogeneity in the dose and form of administration of T3. In six studies, the duration of study drug administration varied between 3 and 6 hrs until donor organ procurement (9, 24, 25, 33, 40, 47). In the remaining study, T3 was administered for up to 72 hrs (23). In all four studies in which plasma free T3 levels were remeasured after commencement of T3 treatment (9, 23, 40, 47), an increase in the plasma T3 to normal or supraphysiologic levels was demonstrated.

Outcome Measures

The primary end-point varied between trials; however, all studies reported no beneficial effect of T3 (alone or in combination with steroid) on donor hemodynamics, donor acid–base balance, or donor vasoactive medication requirements. Four placebo-controlled trials compared the effect of T3 compared with placebo on cardiac index at the time of organ procurement (9, 24, 40, 47). Meta-analysis of these trials including 209 donors revealed that administration of thyroid hormone (n = 108) compared with placebo (n = 101) had no significant effect on donor cardiac index (pooled mean difference, 0.15 L/min/m^2; 95% CI, –0.18 to 0.48) (Fig. 2). Three of these studies also reported the effect of T3 on concomitant vasoactive drug administration (9, 24, 40). Dopamine was used as the vasoactive agent in two studies (9, 40) and dobutamine was used in the other (24). Meta-analysis of these studies is shown in Figure 3 and demonstrates no effect of T3 administration on inotropic drug administration. Norepinephrine was the vasoactive drug administered to donors in the study of Venkateswaran et al (47). These investigators reported that routine administration of vasopressin to all donors in their study was associated with a reduction or withdrawal of norepinephrine (and increase in cardiac index) with no additional effect of T3 administration.

One study reported a worsening metabolic acidosis in the T3 group (25), whereas another reported lower lactate levels in the T3-treated donors (40). Garcia-Fages et al (23) reported a significant increase in adenine nucleotide levels in the donor pancreas and kidney in response to T3 but no change in the heart, lung, or liver. In contrast, a subsequent

Table 1. Nonrandomised open-label clinical studies of thyroid hormone replacement in brain-dead donors

Author/Year	No.	Design	Active Treatment
Novitzky 1987 (19)	47	Case series A: 21 consecutive potential donors C: 26 historical	T3 2 μg, cortisol 100 mg, Insulin 20 U stat, repeated 1–2 hourly
Novitzky, 1990 (22)	116	Case series A: 116 consecutive potential donors C: No control group	T3 2 μg, cortisol 100 mg, insulin 20 U stat, repeated 1–2 hourly
Taniguchi, 1992 (7)	16	Case series A: 4 potential donors C: 12 concurrent	T3 1–1.5 μg/kg/day orally Cortisol 3–5 mg/kg IV
Orlowski, 1993 (28)	69	Case series A: 21 potential donors on high-dose inotrope infusion C: 48 concurrent donors on low-dose inotrope infusion	T4 20 μg IV bolus then 10 μg/hr Insulin 20 U + dextrose MP 2 g IV bolus
Jeevanandam, 1994 (31)	24	Case series A: 6 H/D instability ± cardiac dysfunction C: 18 concurrent, H/D stable	T3 0.2 μg/kg IV bolus repeated hourly to a maximum of 0.6 μg/kg total dose
Wheeldon, 1995 (52)	52	Retrospective audit A: 52 H/D instability ± cardiac dysfunction C: No control group	T3 4 μg bolus + 3 μg/hr infusion MP 15 mg/kg, VP 1 u bolus + 1.5 U/hr, Insulin 1 U/hr
Jeevanandam,1997 (33)	74	Case series A: 22 H/D unstable with poor LV function C: 52 concurrent, H/D stable	T3 0.4 μg/kg IV bolus repeated ×3 at hourly intervals
Roels, 2000 (34)	47	Retrospective audit A: 19 H/D unstable C: 28 concurrent, H/D stable	T3 2–4 μg/hr infusion Hydrocortisone 100 mg Insulin 1-2 U/hr
Rosendale, 2003 (37)	10,292	Retrospective audit of 10,292 UNOS donors between January 1, 2000 and September 30, 2001 A: 701 3HR C: 9591 concurrent	3 HR (T3 or T4 + MP + VP) Doses and indications for HR not available
Rosendale, 2003 (36)	4543	Retrospective audit of 4543 UNOS HTx recipients between January 11, 1999 and December 31, 2001 A: 394 3-HR C: 4,148 concurrent	3 HR (T3 or T4 + MP + VP)
Van Bakel, 2004 (38)	133	Retrospective audit 133 consecutive donors from a single OPO A: 36 MP + insulin + T4 C1: 64 concurrent C2: 19 MP alone	MP 1–2 g + T4 20 μg bolus + 10 μg/hr + insulin vs. control vs. MP 1 g alone
Zuppa et al, 2004 (39)	171	Retrospective audit 171 of 183 donors younger than age 18 yrs on vasopressor support A: 91 H/D unstable C: 80 concurrent H/D stable	T4 5–0.8 μg/kg bolus then 1.4–0.8 μg/kg/hr infusion dependent on age
Salim, 2005 (41)	469	Retrospective audit, A: 255 potential donors treated with aggressive donor management C: 214 historical	T4 bolus 20 μg + infusion 10 μg/hr Insulin 20 U + dextrose MP 2 g, VP
Salim, 2007 (42)	123	Retrospective audit, A: 96 H/D unstable donors (all on dopamine >10 μg/kg/min) C: 27 concurrent, H/D stable	T4 20 μg bolus + 10 μg/hr infusion Insulin 20 U + dextrose MP 2 g, VP
Abdelnour, 2009 (44)	219	Retrospective audit of consecutive donors between 10 and 60 yrs of age A: 146 donors with HR >15 hrs C: 73 concurrent donors with HR < 15 hrs	20 μg T4 bolus + infusion starting at 10 μg/hr, Insulin and dextrose MP
Nath, 2010 (49)	574	Retrospective audit of 574 consecutive donors A: 301 consecutive donors C: 273 historical	20 μg T4 bolus + infusion 10 μg/hr MP 15 mg/kg bolus, VP 1 U bolus + 0.5 –4 U/hr infusion

A, active; BD, brain dead; C, control; CO, cardiac output; CV, cardiovascular; CVA, cerebrovascular accident; CVP, central venous pressure; DM, diabetes mellitus; H/D, hemodynamics; HR, hormone replacement; H/T, hypertension; HTx, heart transplant; IV, intravenous; LV, left ventricular; MP, methylprednisolone; Rx, treatment; T3, triiodothyronine; T4, thyroxine; TH, thyroid hormone; VP, vasopressin.

Table 1.— *Continued*

Primary End Point	Outcome	Author Conclusion Regarding Thyroid Hormone	Comment
Donor H/D Metabolic responses	Improved H/D, reduced plasma lactate Increased donor heart utilization	Beneficial	Average Rx 5–7 hrs Concurrent weaning of inotrope/vasopressor Plasma T3 levels increased to normal or elevated during Rx
Immediate posttransplant cardiac function	Good early graft function in all but three	Beneficial	70 recipients received T3 as well Includes patients from Novitzky, 1987 Duration of Rx not stated
Donor H/D	Improved H/D, delayed time to cardiac arrest	Beneficial	Kidneys only retrieved Hormonal Rx up to 7 d after brain death T3 levels normalized
Posttransplant heart graft survival	Higher posttransplanation graft survival from T4-treated donors	Beneficial	Plasma T4 levels not measured Duration of Rx not stated
Donor H/D Donor inotrope requirement	H/D stabilization	Beneficial	Average duration of Rx 2–3 hrs Plasma T3 levels not measured No comment regarding concomitant steroid usage
Donor H/D Posttransplant heart graft survival	H/D stabilization Improved cardiac function Increased organ retrieval	Beneficial	Art line + Swan-Ganz in all "Unacceptable donors": Donors with H/D instability or impaired heart function Duration of Rx not stated TH levels not measured
Donor H/D Posttransplant heart graft function	H/D stabilization and improved myocardial function in 17 of 22; all transplanted with good function	Beneficial	Art line + LA pressure line Donors with myocardial dysfunction or H/D instability Mean duration of T3 Rx 139 mins Plasma T3 levels not measured
Donor H/D Donor inotrope requirement	H/D stabilization, reduced inotrope requirement	Beneficial	Art line + CVP H/D unstable donors Average duration of T3 Rx 11 hrs Plasma T3 levels not measured
Donor organ retrieval	Higher yield of all organs from donors who received 3-HR (3.8 vs. 3.1)	3-HR beneficial for all organs	3-HR donors younger, lower rates of DM, H/T, CVA death, better terminal renal function Doses and indications for HR not available
Posttransplant heart graft survival and function	Higher graft + patient survival at 1 mo and reduced risk of early graft dysfunction in 3-HR group	3-HR beneficial for post HTx function and survival	3-HR donors older Recipients of HR donors older
Donor inotrope requirement	Reduced inotrope requirement in steroid + T4 group	Beneficial	Swan-Ganz in 85% VP infusion (to control diabetes insipidus) Trend to improvement in steroid alone group Average duration of T4 Rx 12 hrs
Donor H/D Donor inotrope requirement (vasopressor score)	Reduced vasopressor requirement	Beneficial	Children younger than age 18 yrs VP, MP + insulin discretionary Increased MP and insulin usage in T4 group Duration of Rx not stated TH levels not measured
Conversion of potential to actual donors Donors lost because of cardiovascular collapse	Increased ratio of actual/potential donors: from 27% to 41% Fewer donors lost because of CV collapse: from 39% to 5%	Beneficial	Art line + Swan-Ganz in all Includes patients in Salim, 2001 Duration of Rx >4 hrs
Donor H/D Donor organ retrieval	H/D stabilization Increased organs per donor: 3.9 ± 1.7 vs. 3.2 ± 1.7	Beneficial	Art line + Swan-Ganz in all H/D unstable donors: mainly donors with high vasopressor requirements Duration of Rx not stated
Donor organ retrieval	Organ donor increased from 3.36 to 4.31 when T4 > 15 hrs ($p = 0.08$) Heart donor increased from 0.33 to 0.59 ($p = 0.001$)	Beneficial when administered for >15 hrs	Art line + CVP Extended criteria donors excluded Significant increase in donor heart retrievals Interaction between T4 > 15 hrs and final donor CVP < 10 mm Hg
Donor organ retrieval	Increased retrieval of hearts (22%) and lungs (107%) in HR cohort	Beneficial	Duration of Rx, minimum of 4 hrs

Table 2. Prospective randomized trials of thyroid hormone replacement in brain-dead donors

Author, Year (Reference)	No.	Study Design	Jadad Score	Study Population
Mariot, 1991 (24)	40	Double-blind, placebo-controlled A: 20 C: 20	3	Unselected donors All H/D stable at trial entry
Garcia-Fages, 1991 (23)	44	Open-label, blinded analysis of nucleotide levels A: 20 C: 24	1	Unselected donors
Randell, 1992 (25)	25	Open-label A: 12 C: 13	2	Unselected donors All H/D stable at baseline
Goarin, 1996 (9)	37	Double-blind, placebo-controlled A: 19 C: 18	3	Unselected donors, including 20 with LV dysfunction
Jeevanadam, 1997 (33)	30	Nonblinded placebo-controlled A: 15 C:15	1	All donors H/D stable at trial entry, including <10 μg/kg/min dopamine
Perez-Blanco, 2005 (40)	52	Double-blind, placebo-controlled A: 29 C: 23	3	Consecutive unselected donors
Venkateswaran, 2009 (47)	80	Double-blind, placebo-controlled Factorial T3 alone 20 MP alone 19 T3 + MP 20 Placebo 21	4	80 of 116 eligible donors 50% marginal/suboptimal at baseline

A, active; Art line, systemic arterial pressure line; BD, brain death; BP, systemic blood pressure; C, control; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; H/D, hemodynamics; HR, heart rate; IV, intravenous; LV, left ventricular; MP, methylprednisolone; NA, noradrenaline; Rx, treatment, T3, triiodothyronine; VP, vasopressin.

study by Perez-Blanco et al (40) found no changes in adenine nucleotide levels in any donor organs in response to T3.

Post hoc analysis of donors with echocardiographic evidence of cardiac dysfunction in the trial of Goarin et al (9) and of "marginal" donors in the trial of Venkateswaran et al (47) failed to demonstrate any beneficial effect of T3 compared with placebo in these subgroups. Three trials also examined the number of organs procured per donor. All three trials reported that T3 treatment had no effect on this outcome when compared with placebo (24, 25, 47).

DISCUSSION

Summary of Review Findings

We conducted a systematic review of studies reporting effects of thyroid hormone on hemodynamic stability, vasoactive medication dosage, and the quality and number of procured organs in brain dead potential organ donors. We found that the majority of available studies were of low quality and heterogeneous in nature. The most striking finding of this review is the contrast in the conclusion regarding the efficacy of thyroid hormone treatment depending on the study design. Without exception, the authors of all nonrandomized case series concluded that thyroid hormone therapy was beneficial. In contrast, the authors of every randomized controlled trial concluded that there was no clinical benefit of thyroid hormone therapy. One trial raised the possibility that thyroid hormone may be detrimental (25). Meta-analysis of the four placebo-controlled trials failed to identify any benefit of thyroid hormone on donor cardiac index or vasoactive drug requirements.

Table 2.— *Continued*

Intervention	End Point	Results	Author Conclusion	Comment
T3 2 –4 μg IV bolus Hydrocortisone 100 mg IV bolus Both doses repeated every 30-60 min	Donor H/D (HR, BP and CVP) Donor inotrope requirement (dobutamine)	No significant differences in H/D, acidosis, inotropic dose, or organs/donor retrieved	Neutral	Art line + CVP + Noninvasive CO Repeated doses dependent on H/D response Average duration of active Rx 3 hrs
T3 0.5 μg/kg bolus, then 0.05 μg/kg/hr	Donor organ adenine nucleotide levels (ATP, ADP, AMP)	Plasma T3 normalized within 3 hrs in active group Increase adenine nucleotide levels in pancreas + kidney; no difference in heart, lung, liver	Neutral or possible benefit	Art line + Swan-Ganz T3 Rx for up to 72 hrs from BD Follow-up publication in 1993 reporting no difference in donor H/D (unblinded analysis)
T3 infusion (2 μg/hr)	Donor inotrope requirement (dopamine) Donor metabolic response Organs/donor	All donors H/D stable with no difference in H/D or in organs/donor Metabolic acidosis in active group	Neutral or possible harm	Art line + CVP T3 commenced immediately before the start of retrieval surgery Ave duration of Rx 3 hrs
T3 0.2 μg/kg IV bolus	Donor H/D HR, MAP, CVP, CI) Donor cardiac function (echocardiograph)	Normalization of T3 within 30 mins in T3 Rx group No change in H/D or echo (including subset with LV dysfunction on echocardiograph)	Neutral	Art line + Swan-Ganz Echocardiography No correlation between serum T3 and cardiac dysfunction in control group. T3 Rx up to 6 hrs
T3 0.6 μg/kg IV bolus vs. placebo	Donor H/D (HR, BP) Donor inotrope requirement (dopamine)	No difference	Neutral	Art line + Swan-Ganz Duration of T3 not stated
T3 1 μg/kg bolus then IV infusion at 0.08 μg/kg/hr	Donor H/D (CI) Donor inotrope requirement (dopamine) Donor lactate levels Donor organ adenine nucleotide levels	Normalization of T3 within 90 mins in T3 Rx group No change in CI, inotrope dose, adenine nucleotide levels Lower lactate levels in T3 group	Neutral	Art line + Swan-Ganz T3 administered over 270 mins
T3 0.8 μg/kg bolus + 0.113 μg/kg/hr infusion MP 1000 mg	Donor H/D (CI) Organ retrieval	T3 increased to supraphysiological levels in T3 Rx groups No effect of T3, MP or the combination on H/D or organ retrieval	Neutral effect of T3 and MP	Art line + Swan-Ganz No relationship between plasma T3 levels and H/D status VP and weaning of NA in all– improved H/D and heart function Ave duration of Rx 6 hrs Multiple substudies published separately

Explanation and Possible Mechanisms of Findings

There are several possible explanations for the discordant results observed in the clinical studies to date. These include variable study design, outcomes measures used, patient cohorts enrolled, and use of concurrent hormone therapies.

The apparent benefit of thyroid hormone in the observational case series may relate to the lack of consideration of uncontrolled variables that confound the interpretation of the results. These include but are not limited to the absence of a control group in some studies, comparison with historical or poorly matched concurrent control groups in others, the unblinded administration of thyroid hormone, and the likely conviction regarding the efficacy of thyroid hormone of personnel managing the donor. In addition, in most of the case series, commencement of thyroid hormone coincided with institution of invasive hemodynamic monitoring and the use of other measures aimed at optimizing donor hemodynamic and metabolic status, including acid–base balance, blood glucose, and hemoglobin. Thyroid hormone is only one element of such aggressive donor management policies (17, 52). Furthermore, studies involving repeated echocardiographic examination of the brain-dead donor have revealed that left ventricular systolic dysfunction is common after brain death and that it commonly improves together with hemodynamic status after a period of aggressive donor management that does not include thyroid hormone (50, 55).

In most case series, thyroid hormone was coadministered with other hormonal therapies including a corticosteroid as well as insulin or vasopressin, which may

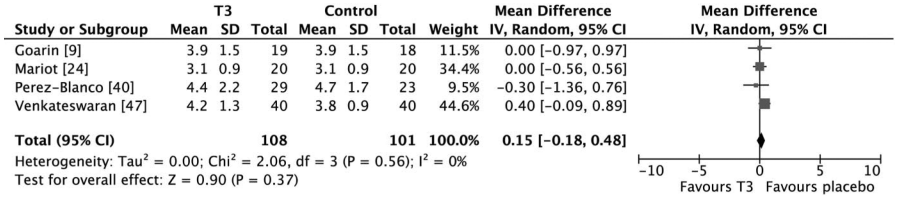

Figure 2. Forest plot comparing the effect of triiodothyronine (*T3*) vs. placebo on cardiac index at the end of study drug administration. *CI*, confidence interval; *IV*, intravenous. Number in brackets indicates reference number.

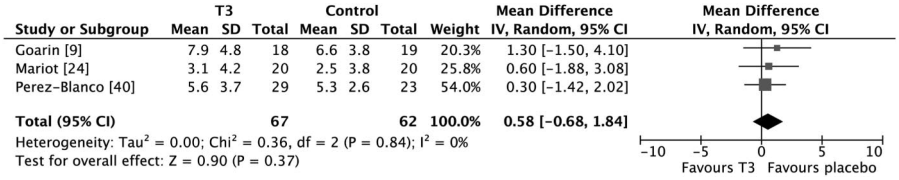

Figure 3. Forest plot comparing the effect of triiodothyronine vs. placebo on the dose of inotropic agent at the time of organ retrieval. Dopamine was the inotropic agent used in the studies of Goarin et al (9) and Perez-Blanco et al (40). Dobutamine was used in the study of Mariot et al (24). *CI*, confidence interval; *IV*, intravenous. Number in brackets indicates reference number.

assist in weaning of the donor from catecholamine support. Highlighting this concern, in one large retrospective study, Rosendale et al (36) reported that T3 or T4 was administered as the sole hormonal supplement in only 5% of donors. Primary graft failure and early heart transplant mortality were lower when thyroid hormone was administered as part of a combined three-drug hormonal protocol (thyroid hormone, corticosteroid, and vasopressin) compared to all other hormonal combinations including thyroid hormone alone (36). In those studies in which thyroid hormone levels were measured after brain death, there was no correlation between plasma thyroid hormone levels in the donor and donor hemodynamic status, inotropic/vasopressor requirement, or cardiac function (9, 40, 47). Finally, all randomized controlled trials that tested T3 as the sole therapy failed to demonstrate any benefit of T3 on donor hemodynamics, organ retrieval, or posttransplant outcome.

Effect of Thyroid Hormone on Different Donor Organs

The focus on most studies included in this review was the impact of thyroid hormone on the hemodynamic status of the donor, on donor heart function, and on utilization. There was limited reporting of the effect of thyroid hormone on other organs. The six case series that reported increased organs retrieved per donor generally attributed this to donor stabilization rather than to a direct effect of thyroid or combined hormonal therapy on different organs. Among the randomized trials, Garcia-Fages et al (23) reported an increase in adenine nucleotide levels in the pancreas and kidney of donors who received thyroid hormone but no effect on adenine nucleotide levels in the heart, lung, or liver. Perez-Blanco et al (40) performed similar measurements but found no effect of thyroid hormone on adenine nucleotide levels in any organ. Venkateswaran et al (43) reported that thyroid hormone alone or in combination with corticosteroids had no effect on lung function. None of the randomized trials has observed an effect (positive or negative) of thyroid hormone on the function or retrieval rate of any intra-thoracic or intra-abdominal organs.

Thyroid Hormone Alone Compared With Combined Hormonal Therapy

Although the available evidence does not support a role for thyroid hormone as single therapy, there may still be a role for it as part of a combined hormonal therapy. The large retrospective studies conducted by Rosendale et al (36, 37) reported that donors treated with the three-drug combination of thyroid hormone, corticosteroid, and vasopressin yielded more transplantable organs than donors who did not receive this combination. However, only a small proportion of the donors in these reviews received all three drugs, their characteristics differed significantly from other donors, and the decision-making process that led to the use of all three drugs in these donors and not others was unclear. Only one of the randomized controlled trials examined the combination of thyroid hormone, corticosteroid, and vasopressin (47). In that study, 80 donors were randomized to one of four treatment groups: control; T3 alone; methylprednisolone alone; and T3 and methylprednisolone in combination. In all four treatment groups, a pulmonary artery catheter-guided hemodynamic management algorithm was used and vasopressin infusion was commenced with concomitant weaning of catecholamine infusion at the commencement of blinded trial medication. There was no benefit of combination therapy on donor hemodynamic status or organ retrieval compared with control or single supplements. Thus, the limited data available from the randomized controlled trials do not support the hypothesis that triple hormonal supplementation is more effective than other hormonal combinations in maintaining donor hemodnyamics.

Impact of Donor Variables on Response to Thyroid Hormone

As discussed, the putative benefit of thyroid hormone in combination with other hormonal therapies may be restricted to a subset of brain-dead donors such as those who are hemodynamically unstable, those who require high doses of inotropic/vasopressor support, or those with echocardiographic evidence of cardiac dysfunction. Several case series restricted administration of thyroid hormone to such donors (28, 31, 34, 39, 42, 52). In contrast, a number of the randomized controlled trials did not include hemodynamically unstable donors (24, 25, 33), whereas all the others included both stable and unstable donors. Hence, one of the limitations of the randomized controlled trials is that the majority of donors were hemodynamically stable at entry and therefore less likely to demonstrate hemodynamic improvement in response to the intervention (56). Inclusion of hemodynamically stable donors may have obscured a beneficial effect of hormonal therapy in a hemodynamically unstable subgroup. Nonetheless, two randomized controlled trials did include donors with impaired heart function or who were "marginal" in other ways (9, 47). Post hoc analysis of these donors failed to demonstrate any beneficial effect of single or combined hormonal therapy compared with placebo; however, as acknowledged by the authors, the numbers of "marginal" donors in these trials were small.

Strengths and Limitations of Our Review

There have been several reviews of thyroid hormone administration to brain-dead donors published recently. In two of these, a review of clinical studies was undertaken as part of a broader review of both experimental and clinical studies of thyroid hormone in this setting (57, 58). In neither review did the authors attempt to stratify the clinical studies in terms of study quality. While mentioning that there were both positive and negative studies, the authors concluded that thyroid hormone, specifically T3, played a critical role in the reversal of donor organ dysfunction after brain death and recommended that T3 administration be incorporated into donor management protocols. In contrast, Powner and Hernandez (16) performed a systematic review of clinical studies in which they graded studies according to quality of study design. They concluded that although routine administration of thyroid hormone was not supported by the published literature, administration of "rescue" hormones including thyroid hormone appeared justified in hemodynamically unstable donors. Their review, however, was based on only 11 publications.

In the current systematic review, we were able to analyze 37 original publications, including the largest randomized controlled trial published to date (47). The conclusion of the present review is largely in agreement with that of Powner and Hernandez with regard to the routine administration of thyroid hormone to brain-dead potential organ donors, namely that there is no demonstrable benefit in donors who are hemodynamically stable. The evidence to support the use of thyroid hormone in hemodynamically unstable donors is of low quality.

Areas for Future Research

The major limitation of the randomized controlled trials is that they have been too small to conclusively rule out any benefit of single or combined hormonal therapy in donor management. Nonetheless, meta-analysis of the four placebo-controlled trials did not suggest any benefit of thyroid hormone administration. Most randomized trials have focused on donor hemodynamics or inotropic requirements as the primary end points, with only one study providing a power calculation to justify the sample size (47). Arguably, more relevant end points are the number of organs retrieved per donor and the outcome of transplanted organs. Recruitment of substantially larger numbers of donors would be required for any prospective clinical trial to have adequate power to demonstrate a significant impact of any intervention on these end points. Based on these considerations, it is apparent that only a large-scale, multicentered, randomized, placebo-controlled trial would have sufficient power to test the hypothesis that thyroid hormone administration to brain-dead donors is beneficial, particularly if recruitment is restricted to marginal donors.

CONCLUSION

The findings of this systematic review highlight the ongoing uncertainty regarding the purported benefits of thyroid hormone administration to brain-dead potential organ donors. Our review findings do not support a role for routine administration of thyroid hormone therapy in the brain-dead potential organ donor. The randomized controlled trials uniformly demonstrate no benefit of thyroid hormone administration either alone or in combination with other hormonal therapies in either hemodynamically stable or unstable donors. Our review findings also indicate that existing recommendations regarding the use of thyroid hormone in marginal donors, including those who are hemodynamically unstable, are based on low-level evidence (17). These recommendations need to be tested, and this can only be performed through a large-scale, multicentered, prospective, double-blind, placebo-controlled trial of thyroid hormone therapy. The trial should focus on marginal donors and should be adequately powered to detect a significant impact on the number of organs procured per donor.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Assistant Professor Stephen McDonald for providing the descriptive statistical analysis for organs per donor for the year 2010, and to Professor Matthew Law for providing an independent statistical review of the manuscript.

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