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REPORTS OF ORIGINAL INVESTIGATIONS

Triiodothyronine replacement in critically ill adults with non-thyroidal illness syndrome

Remplacement de la triiodothyronine chez des patients en état critique avec syndrome d'hypothyroïdie non thyroïdienne

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Abstract

Purpose *Non-thyroidal illness syndrome is commonly encountered in critically ill patients, many of whom are treated with thyroid hormones despite uncertainty regarding their safety and effectiveness. This retrospective observational study sought to evaluate the utilization, safety, and effectiveness of triiodothyronine (T3) supplementation in critically ill adults admitted to either of two non-cardiac surgery mixed-medical/surgical intensive care units (ICU).*

Methods *Consecutive adults admitted to an ICU and treated with enterally administered T3 were identified over a two-year period. Data pertaining to demographics, T3 utilization, safety, and clinical outcomes were collected.*

Results *Data were extracted from the medical records of 70 consecutive patients. All had baseline serum free T3 concentrations below the lower limit of our laboratory's reference range and 22 (31%) patients also had low thyroxine (T4) concentrations. The most commonly prescribed replacement doses were 25 and 50 μg for a median of seven days and almost half of the patients also received concomitant T4 supplementation. Serum thyroid hormones were available in 48 of 70 patients (69%) at a median [interquartile range (IQR)] of 7 [6-38] days. Normalization of free T3 serum concentrations occurred in 30 of 48 patients (63%) at a median [IQR] of 8 [7-33] days. A dose-response relationship was identifiable. New adverse events (atrial fibrillation/flutter, hypertension, sinus tachycardia, myocardial infarction) during therapy were less frequent than at baseline.*

Conclusions *This study suggests that with T3 supplementation there was evidence of serum free T3 normalization without evidence of associated harms. A definitive trial is needed to evaluate clinical effectiveness.*

Résumé

Objectif *Le syndrome d'hypothyroïdie d'étiologie non thyroïdienne est fréquemment observé chez des patients en état critique; beaucoup d'entre eux sont traités avec des hormones thyroïdiennes en dépit de l'incertitude concernant leur innocuité et leur efficacité. Cette étude observationnelle rétrospective a voulu évaluer l'utilisation, l'innocuité et l'efficacité de l'apport de triiodothyronine (T3) chez des patients en état critique admis dans deux unités de soins intensifs (USI) mixtes médico-chirurgicales non-cardiaques.*

Méthodes *Les adultes consécutifs admis en USI et recevant un traitement par T3 administré par voie entérale ont été identifiés sur une période de deux ans. Les données sur les caractéristiques démographiques, l'utilisation de T3, l'innocuité et l'évolution clinique ont été collectées.*

Résultats *Les données ont été extraites des dossiers médicaux de 70 patients consécutifs. Tous les patients avaient des concentrations initiales de T3 libre sérique inférieure à la limite inférieure de référence de notre*

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laboratoire et 22 patients (31 %) avaient également des concentrations basses de thyroxine (T4). Les doses de substitution le plus souvent prescrites étaient de 25 et 50 μg pendant une médiane de sept jours et presque la moitié des patients a aussi reçu un supplément concomitant en T4. Les taux d'hormones thyroïdiennes sériques ont été disponibles pour 48 des 70 patients (69 %) pour une durée médiane [écart interquartile (EIQ)] de 7 [6 – 38] jours. La normalisation des concentrations de T3 libre sérique est survenue chez 30 des 48 patients (63 %) au bout d'une durée médiane [EIQ] de 8 [7 – 33] jours. Un effet dose-réponse a été identifié. La survenue de nouveaux événements indésirables (fibrillation auriculaire/flutter, hypertension, tachycardie sinusale, infarctus du myocarde) au cours du traitement a été moins fréquente qu'à l'inclusion.

Conclusions *Cette étude suggère qu'un supplément de T3 s'accompagne d'une normalisation de la T3 libre sérique sans données probantes d'effets délétères associés. Une étude clinique est nécessaire pour évaluer l'efficacité clinique.*

Serum thyroid hormone concentrations decline during starvation and critical illness. In mild illness, deiodination of thyroxine (T4) to triiodothyronine (T3) by type 1 iodothyronine-deiodinase is inhibited in the liver, thus inhibiting generation of T3. Traditionally, this syndrome (non-thyroidal illness syndrome [NTIS]) was thought to be an adaptive response to reduce the metabolic rate and has not been associated with negative outcomes in non-critically ill patients. Nevertheless, as the chronicity and severity of critical illness (or starvation) increase, a more complex disorder of hormone metabolism and synthesis manifests as low T4 *and* T3 concentrations. Some published evidence suggests that in severely ill patients NTIS is associated with morbidity and mortality.[1-3] Despite a lack of evidence to support treatment recommendations and clinical guidelines that recommend no treatment in the absence of data, intensivists are often inclined to treat these patients with enteral T3. Given the vulnerability of these critically ill patients, especially intensive care unit (ICU) survivors, it is possible that T3 replacement may cause dose-dependent dysrhythmias and hypertensive urgency/emergencies. Acknowledging that currently both the risks and benefits T3 replacement are not well quantified in critically ill patients, we evaluated the safety of our practice of T3 replacement therapy. This evaluation may inform future efficacy trials.

The purpose of this retrospective analysis is to describe the utilization and safety of T3 replacement in critically ill adults admitted to either of the ICUs of the Ottawa Hospital.

Methods

Research questions

Specific research questions addressed by this study are: 1) What are the demographic and clinical characteristics of critically ill adults prescribed T3? 2) How is T3 prescribed in terms of dose and duration? 3) What is the incidence of adverse events associated with T3 replacement, specifically tachydysrhythmias, hypertension, and myocardial infarction? 4) What proportion of treated patients achieves normalization of serum T3, T4, and thyroid-stimulating hormone (TSH) during therapy? 5) Is there a correlation between T3 usage and hospital mortality?

Study design and patient selection

We conducted a retrospective analysis of critically ill adults treated with enterally administered T3 in either ICU of The Ottawa Hospital. All patients prescribed enteral T3 were identified from 1 January 2014 to 31 December 2015 from pharmacy records. Eligible patients must have received at least one dose of T3 confirmed by nursing administration records. T3 prescription is typically at the discretion of the multidisciplinary clinical team and occasionally in consultation with an endocrinologist.

Data collection

Relevant demographic and clinical data related to T3 utilization, efficacy, and safety were extracted from eligible patients' electronic medical record using a pre-piloted standardized case report form by a single investigator. Accuracy and quality of data extraction were monitored via random audits of 20% of included cases.

Demographic data collected included age, gender, reason for admission, and comorbidities (limited to thyroid disease, hypertension, diabetes requiring drug therapy or insulin, dialysis dependent kidney disease, chronic obstructive pulmonary disease requiring home oxygen therapy, and history of arrhythmias). Clinical data included T3 (and, if applicable, T4) daily dosing, duration of therapy, and serum thyroid hormone (TSH, T3, T4, freeT3, freeT4) values if measured at any time during the patient's hospital stay. Clinical outcomes included hospital and ICU length of stay as well as survival. For patients who

died during T3 therapy, the cause of death was extracted from clinical notes and death summaries. This was adjudicated by an investigator blinded to whether the patient was receiving any form of thyroid hormone replacement. Clinical safety data included tachydysrhythmias (confirmed by two consecutive 12-lead electrocardiogram at least one hour apart), hypertension (systolic blood pressure > 180 mmHg or mean arterial pressure > 100 mmHg for two consecutive readings one hour apart), sinus tachycardia (defined as a heart rate >120 for two consecutive readings at least one hour apart), or myocardial infarction (confirmed serial troponin enzymes and dynamic ST changes on 12-lead electrocardiogram). Clinical safety outcomes were assessed at the initiation of T3 therapy and also during T3 therapy. Safety outcomes were considered to be new if they were not documented at the time of T3 initiation and occurred during T3 therapy.

Statistical analysis

Demographic data were collated and described for the entire cohort using descriptive statistics. The safety of T3 administration was addressed by reporting the proportion of patients in whom adverse events were identified. Drug dosing, treatment duration, and serum thyroid hormone concentrations at baseline (defined as the concentrations drawn closest but prior to the onset of T3 replacement) are presented using measures of central tendency and descriptive statistics as appropriate. T3 (and potentially T4) replacement efficacy was evaluated by the change in individual hormone concentrations from baseline. If multiple sets of serum thyroid hormone concentrations are measured during T3 therapy, the greatest difference is reported. Normalization of previously abnormal serum hormone values is defined as a return to the reference range reported by our local laboratory. Predictors of serum free T3 normalization are explored by logistic regression. Covariates were determined a priori and included dose ($\geq$ 25 μg *vs* > 25 μg), baseline serum free T3 values, and Acute Physiology And Chronic Health Evaluation (APACHE) II scores. Clinical safety outcomes are reported at baseline and then again if they occurred during therapy. Safety outcomes were considered new if they were not recorded at baseline but were observed during T3 therapy. The relationship between T3 and T4 serum concentrations and mortality is explored by logistic regression analysis to identify predictors of mortality. Covariates identified a priori include serum T3 concentration, serum T4 concentration, mechanical ventilation, and occurrence of any adverse event. All data were collated in Microsoft Excel (version 16.12, Microsoft Corporation, Redmond, WA, USA) and analyzed using SPSS version 20.0 (version 20.0, IBM, Armonk, NY, USA).

Results

From January 2014 to December 2015, 5,878 patients were admitted to the two participating ICUs of which 76 patients were prescribed T3. Data were extracted from 70/76 patients. Medical records could not be obtained for two patients. Four patients had oral T3 prescribed but never received it. Demographic data are provided in Table 1. The majority of patients were mechanically ventilated during oral T3 therapy and less than half had a history of hypothyroid disease requiring T4 replacement.

All 70 patients had baseline serum thyroid hormones measured (T3, T4, TSH) (Table 2). All patients had baseline T3 concentrations below the lower limit of the reference range (< 3.3 pmol·L^{-1}) while 12 (17%) patients had baseline concentrations less than 1.8 pmol·L^{-1}. Twenty-two (31%) patients had T4 concentrations below the lower limit of normal (9 pmol·L^{-1}) and no patients had T4 concentrations below 3.1 pmol·L^{-1}. The most commonly prescribed T3 replacement dose was 25 μg for a median of seven days and almost half of the patients also received concomitant T4 supplementation (Table 3). Follow-up serum thyroid hormones were available in 48 of 70 patients (69%) at a median [IQR] of 7 [6-38] days. Normalization of free T3 serum concentrations occurred in 30 of 48 patients (63%) at a median [IQR] of 8 [7-33] days. Twelve of these 30 patients (40%) also received concomitant T4 replacement. The relationship between change in serum free T3 concentrations and time is presented in Fig. 1 and that between change in free T3 concentrations and dose in Fig. 2. A significant difference in the change in free T3 concentrations was observed between the 25 and 50 μg dose (relative change in free T3, 31.8 ± 60.1% and 83.9 ± 42.5% for the 25 and 50 μg dose, respectively, $P = 0.015$ [independent samples t test]). The only predictor of achieving normal serum free T3 concentrations was dose (50 μg or greater was predictive of normalization; odds ratio [OR], 6.0; 95% confidence interval [CI], 1.1 to 25.0).

Sinus tachycardia hypertension, myocardial infarction, and supraventricular tachyarrhythmias were relatively common at baseline ranging from 14-34% prior to the start of T3 therapy (Table 1). There were no observations of ventricular dysrhythmias or myocardial infarction during T3 therapy. New atrial fibrillation/flutter occurred in 12 (17%) patients, new sinus tachycardia was observed in 10 (14%), and new hypertension was observed in 2 (3%) (Table 4). Forty-one patients (59%) died while in hospital. Eighteen patients died during T3 therapy, three of which

Table 1 Patient demographics

Variable	Entire Cohort (n = 70)*
Age (yr)	69 (26)
Sex (male)	42 (60%)
Reason for admission	
Septic shock	19 (27.1%)
Postoperative care	10 (14.3%)
Pneumonia	8 (11.4%)
Gastrointestinal bleeding	8 (11.4%)
COPD exacerbation	6 (8.6%)
Cardiac arrest	4 (5.7%)
Congestive heart failure	4 (5.7%)
Pulmonary edema	4 (5.7%)
Acute kidney injury	3 (4.3%)
Rapid atrial fibrillation	2 (2.9%)
Multiple trauma	2 (2.9%)
APACHE II score on admission	28 [22-34]
Mechanical ventilation during T3 therapy	59 (84%)
Vasopressor dependent shock during T3 therapy	41 (59%)
Tachycardia at start of T3 therapy	14 (20%)
Hypertension at start of T3 therapy	10 (14%)
Atrial fibrillation/flutter at start of T3 therapy	24 (34%)
Myocardial infarction on this admission prior to start of therapy	16 (23%)
Comorbidities	
Clinical hypothyroid disease	30 (43%)
Hypertension	46 (66%)
Atrial fibrillation/flutter	16 (23%)
Diabetes	42 (60%)
Chronic obstructive pulmonary disease	13 (19%)
End-stage renal disease	11 (16%)

*Reported as proportion (%), mean (standard deviation), or median [interquartile range]. APACHE = Acute Physiology And Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; T3 = triiodothyronine

Table 2 Thyroid hormone concentrations

Variable	Entire Cohort (n = 70)
Baseline free T3 ($pmol \cdot L^{-1}$)	
Mean (SD)	2.4 (0.54)
Median [IQR]	2.5 [2.0-2.8]
3.3-6.0 (reference range)	0 (0%)
≤ 3.3	70 (100%)
≤ 2.5	50 (71.4%)
≤ 1.8	12 (17.1%)
Baseline free T4 ($pmol \cdot L^{-1}$)	
Mean (SD)	10.3 (3.7)
Median (IQR)	10.2 [7.2-13.4]
9.0-23.0 (reference range)	48 (68.6%)
< 9	22 (31.4%)
≤ 3.1	0 (0%)
Baseline TSH ($mU \cdot L^{-1}$)	
Mean (SD)	11.5 (17.3)
Median [IQR]	6.4 [2.5-13.5]
0.32-5.0 (reference range)	14 (20%)
< 0.32	2 (2.9%)
> 5.0	54 (77%)
> 20	6 (8.6%)
Absolute change in free T3 (median [IQR]) (n = 48)	0.95 [0.23-1.67]
Absolute change in free T4 (median [IQR]) (n = 48)	−0.85 [−4.23-2.75]
Absolute change in TSH (median [IQR]) (n = 48)	−1.1 [−5.9-1.3]
Normalization of T3 (n = 48)	30 (62.5%)
Days to normalization of T3 (median [IQR]) (n = 30)	8 [7-33]

IQR = interquartile range; SD = standard deviation; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

were unanticipated (pulmonary hemorrhage, perforated duodenal ulcer, multisystem organ failure from septic shock). None of the documented causes of death were directly attributable to the known effects of T3 supplementation. From the logistic regression analysis, only age was predictive of death (OR, 1.3; 95% CI, 1.1 to 1.6).

Discussion

This single-centre observational exploratory study describes the utilization and outcomes of 70 consecutive critically ill adults with varying severities of NTIS, all treated with enteral T3 supplementation. All patients had low serum free T3 concentrations and normalization of these concentrations was observed in 63% of patients after a median duration of eight days. The most commonly used doses were 25 and 50 μg daily and a dose-response relationship was observed with respect to normalization of low serum T3 concentrations. Predictable safety outcomes (i.e., tachyarrhythmias, myocardial infarction, and hypertension) were more prevalent at the initiation of T3 therapy than during therapy. Hospital mortality was higher than expected (59%) but could not be directly attributed to T3 therapy. The aggregate crude mortality rate in the participating ICUs during the study period was 18% with an average length of stay of 7.7 days. This likely represents selection bias in that clinicians are more likely to treat NTIS in patients with chronic critical illness, which is a new disease state that has emerged where patients survive,

but do not recover. The biochemical changes seen in the NTIS have long been thought to represent an adaptive response that requires no treatment and will resolve as the illness resolves. With today's advances in mechanical life support, however, it is possible that life support has evolved faster than our ability as a species can adapt. As such, it is possible that that these biochemical changes represent true hypothyroidism at a time of unprecedented biologic stress.

The debate concerning in whom, when, and how to treat NTIS has waned because of a paucity of new evidence rather than resolution of outstanding concerns. Older literature suggests that NTIS is most often described in critically ill patients, correlates with APACHE II scores, and has been associated with increased mortality in trauma, septic, surgical, and bone marrow transplant patients.[4-6] In fact, when serum T4 concentrations drop below 3.1 pmol·L^{-1}, the probability of death has been reported to approach 50%, and with concentrations below 1.6 pmol·L^{-1}, the probability of death reaches 80% in small studies.[13] Rothwell and Lawler found an "Endocrine Index" that combines thyroxine, TSH, and cortisol values to perform better than APACHE II scores in predicting mortality.[7]

Table 3 Drug dosing and clinical characteristics

Variable	Entire Cohort (n = 70)
Maximal daily T3 dose	
12.5 μg	4 (5.7)
25 μg	50 (71.4)
50 μg	12 (17.1)
100 μg	4 (5.7)
Concomitant T4 replacement	32 (45.7)
Duration of T3 therapy in days	7 [3-26]

Data are presented as percentage (%) or median [interquartile range], as indicated

IQR = interquartile range; T3 = triiodothyronine; T4 = thyroxine

While NTIS is commonly encountered in adults with varying severity of critical illness, its association with negative outcomes such as mortality is derived from small studies and causality has not been described.[4,6,8]

Clinical practice guidelines do not advocate hormone replacement and cite a lack of unequivocal evidence that replacement improves outcomes but acknowledge a paucity of evidence from controlled trials.[9] The most studied population is that of cardiac surgery. Post-cardiac surgery, NTIS is commonly encountered and associated with negative outcomes such as prolonged vasopressor dependence, reduced cardiac output, and postoperative atrial fibrillation. Randomized-controlled trials conducted in the perioperative setting have shown an improvement in certain cardiac markers such as cardiac output but no impact on postoperative morbidity or mortality.[10-14] There is a dearth of trials of hormone replacement for NTIS in non-cardiac critically ill patients. In one randomized placebo-controlled trial of 12 patients in a medical ICU, intravenous T4 replacement was associated with normalization of serum T4 but not T3 concentrations,

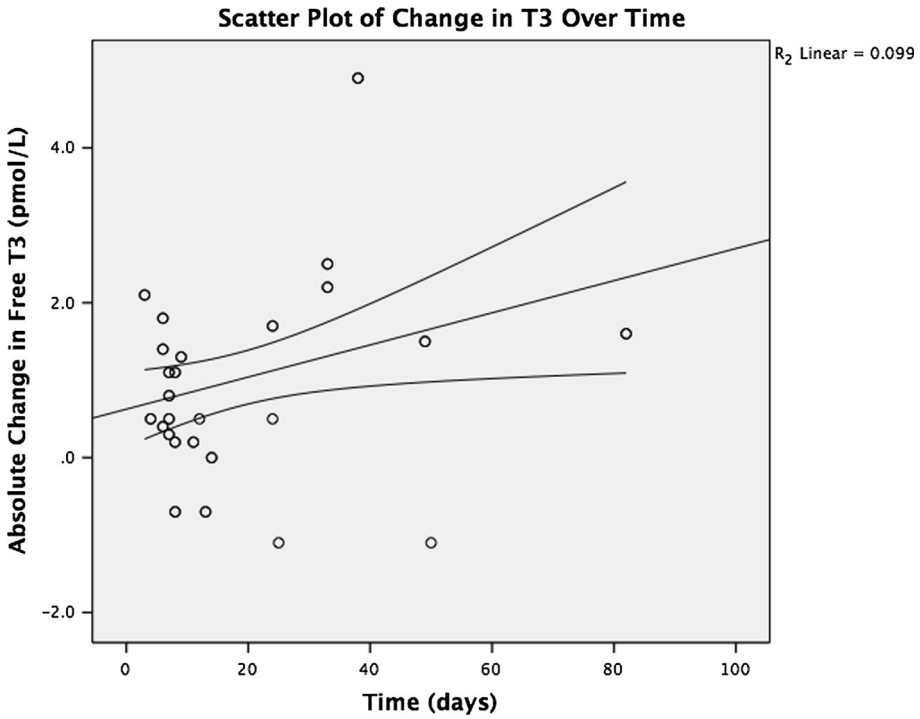

Fig. 1 Scatter plot of change in triiodothyronine (T3) (pmol·L^{-1}) over time (days). The straight line represents the regression line and the two curved lines are the relevant 95% confidence limits. (R^2 = 0.099, suggesting that duration of therapy explains 9.9% of the variability in absolute change in free T3 serum concentrations)

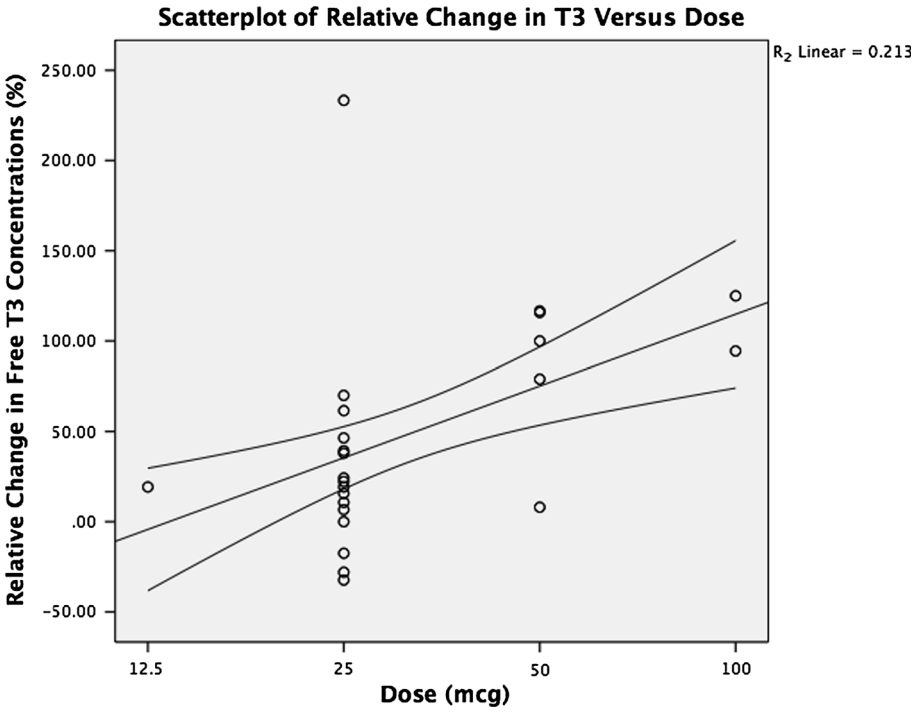

Fig. 2 Scatterplot of relative change in triiodothyronine (T3) (pmol·L^{-1}) *vs* dose (μg). The straight line represents the regression line and the two curved lines are the relevant 95% confidence limits. (R^2 = 0.213, suggesting that dose explains 21.3% of the variability in absolute change in free T3 serum concentrations)

and mortality was 80% in both groups.[15] In another trial of 36 burn patients with NTIS, T3 replacement was associated with normalization of free T3 serum concentrations but did not affect the resting metabolic rate or mortality.[16] Despite this lack of evidence, replacement of T4 and T3 in severe forms of NTIS is common.[17]

In our study we observed that enterally administered T3 was associated with normalization of serum free T3 concentrations and a dose-response relationship exists for this normalization when comparing 25 and 50 μg per day of enteral T3. While other studies have reported infrequent or no side effects, none has systematically reviewed drug safety concerns. Consequently, we investigated the prevalence of expected cardiac adverse events before and during therapy using strict definitions and a standardized approach to screening. Additionally, the cause of death for each patient who died while receiving enteral T3 was adjudicated. We observed no association of T3 replacement with cardiac morbidity or overall mortality. In fact, we found that the prevalence of expected cardiac adverse events was greater at the initiation of replacement treatment than the incidence of such during therapy with the most commonly used doses of 25 and 50 μg·day^{-1}. This suggests that historical concerns over cardiac adverse effects of replacement T3 therapy may be overstated. Unfortunately, none of the previously published T3 replacement trials in ICU populations reported rates of adverse events for comparison.

Our exploratory study is not without limitations. The absence of a control group prevents any statistical comparisons to similar patients who do not receive treatment. Additionally, selection bias compromises our ability to match patients based on their thyroid hormone serum concentrations because the most severely critically ill patients were typically prescribed replacement treatment. Given that critically ill patients are being prescribed this largely unproven therapy in the absence appropriately designed and powered efficacy trials, a definitive trial informed by dose-finding and mechanistic studies is warranted.

Table 4 Clinical and safety outcomes

Clinical Outcomes	Entire Cohort (n = 70)
ICU mortality	39 (55.7%)
Hospital mortality	41 (58.6%)
ICU length of stay, days	27 [7-54]
Hospital length of stay, days	32 [8-60]
Safety Outcomes*	
New ventricular tachydysrhythmias	0 (0%)
New atrial fibrillation/flutter	12 (17.1%)
New hypertension	2 (2.9%)
New or worsening sinus tachycardia	10 (14.3%)
New myocardial infarction	0 (0%)

Data are presented as percentage (%) or median [interquartile range], as indicated

*Safety outcomes were considered to be new if they were not documented at the time of T3 (T3 initiation and occurred during T3) therapy. ICU = intensive care unit; IQR = interquartile range; T3 = triiodothyronine

Conclusion

Non-thyroidal illness syndrome is commonly encountered in our ICU population and often treated with T3 replacement. In this study all patients were treated with enterally administered T3 and almost two thirds of patients had normalization of serum free T3 concentrations. The most commonly used daily doses were 25 and 50 μg and incidence of cardiac adverse events during therapy was less frequent than their prevalence at baseline. In the ICU, support is provided for most major organ systems outside of the endocrine system. Had the teleologic argument been applied to organ failure, there would be no dialysis, vasoactive medications, intra-aortic balloon pumps, or extracorporeal membrane oxygenation. The time has come to revisit and perhaps advance the science of endocrine support in chronic critical illness. A definitive randomized-controlled trial is needed to evaluate clinical effectiveness.

Conflicts of interest None declared.

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Author contributions *Salmaan Kanji* contributed substantially to all aspects of this manuscript, including conception and design; acquisition, analysis, and interpretation of data; and drafting the article. *Jonathan Neilpovitz* and *Benjamin Neilipovitz* contributed substantially to the acquisition of data. *John Kim*, *Wael Haddara*, *Michelle Pittman*, *Hilary Meggison,* and *Rakesh Patel* contributed substantially to the conception and design of the study as well as interpretation of data and the conception and design of the manuscript.

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