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Phase 1 Trial of 4 Thyroid Hormone Regimens for Transient Hypothyroxinemia in Neonates of <28 Weeks' Gestation

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Abstract

Background—Transiently low levels of thyroid hormones occur in ~50% of neonates born 24–28 weeks' gestation and are associated with higher rates of cerebral palsy and cognitive impairment. Raising hormone levels shows promise for improving neurodevelopmental outcome.

Objective—To identify whether any of 4 thyroid hormone supplementation regimens could raise T_4 and FT_4 without suppressing TSH (biochemical euthyroidism).

Methods—Eligible subjects had gestational ages between $24^0/_7$ and $27^6/_7$ weeks and were randomized <24 hours of birth to one of six study arms (n = 20–27 per arm): placebo (vehicle: 5% dextrose), potassium iodide (30 μg/kg/d) and continuous or bolus daily infusions of either 4 or 8 μg/kg/d of T_4 for 42 days. T_4 was accompanied by 1 μg/kg/d T_3 during the first 14 postnatal days and infused with 1 mg/mL albumin to prevent adherence to plastic tubing.

Results—FT_4 was elevated in the first 7 days in all hormone-treated subjects; however, only the continuous 8 μg/kg/d treatment arm showed a significant elevation in all treatment epochs ($P < .002$ versus all other groups). TT_4 remained elevated in the first 7 days in all hormone-treated subjects ($P < .05$ versus placebo or iodine arms). After 14 days, both 8 μg/kg/d arms as well as the continuous 4 μg/kg/d arm produced a sustained elevation of the mean and median TT_4, >7 μg/dL (90 nM/L; $P < .002$ versus placebo). The least suppression of THS was achieved in the 4 μg/kg/d T_4 continuous infusion arm. Although not pre-hypothesized, the duration of mechanical

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During this trial Dr Fisher was an employee of Quest Diagnostics, Nichols Research Institute, San Juan Capistrano, CA. The assays were performed by Quest Diagnostics clinical laboratories in Chantilly, Virginia, as indicated in "Methods." Dr Fisher served as a general consultant in this grant regarding interpretation of laboratory data quality and assay performance. The other authors are all full-time faculty at the universities indicated and have no financial relationships relevant to this article to disclose.

ventilation was significantly lower in the continuous 4 μg/kg/d T_4 arm and in the 8 μg/kg/d T_4 bolus arm ($P < .05$ versus remaining arms). ROP was significantly lower in the combined 4 thyroid hormone treatment arms than in the combined placebo and iodine arms ($P < .04$). NEC was higher in the combined 8 μg/kg/d arms ($P < .05$ versus other arms).

Conclusions—Elevation of TT_4 with only modest suppression of TSH was associated with trends suggesting clinical benefits using a continuous supplement of low-dose thyroid hormone (4 μg/kg/d) for 42 days. Future trials will be needed to assess the long-term neurodevelopmental effects of such supplementation.

Keywords

thyroxine; triiodothyronine; hypothyroxinemia; thyroid hormone; monodeiodinase; extremely low birth weight neonate; transient hypothyroxinemia; nonthyroidal illness; euthyroid sick syndrome; cerebral palsy; prematurity; randomized; controlled trial

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Survival for extremely low gestational age neonates (ELGANs) (24–28 weeks' gestation) was negligible before the 1960s and now exceeds 80%.[1] This extraordinary achievement is tempered by the intractable persistence of cerebral palsy (CP) and its accompanying disabilities affecting nearly 1 in 8 survivors at a prorated lifetime cost of nearly $1 million per handicapped child.[2–4] An important priority in newborn medicine, therefore, is to translate gains in survival into survival without today's current high rates of neurodevelopmental impairments.[5]

Low levels of thyroid hormone are commonly found in the first weeks after birth, a hormone phenomenon referred to as transient hypothyroxinemia of prematurity (THOP). Although the etiology of CP and its underlying substrate of white matter injury is mutilfactorial,[6–10] THOP is a strong independent risk factor for CP, white matter injury, and lower cognitive performance, suggesting an unmet preventable cause of neurologic injury.[11–19]

Low thyroid hormone levels in ELGANs arise from a combination of (1) loss of maternal and placenta-supplied hormones; (2) immaturity of the hypothalamic-pituitary-thyroid axis, including limited thyroidal capacity to increase hormone synthesis; and (3) accelerated inactivation (elevated reverse T_3, sulfated forms, diiodothyronine, and monoiodothyronine).[20–23] Iodine imbalance, medications, and adverse perinatal events (ie, nonthyroidal illness syndrome) all exacerbate the effects of these developmental and conditional limitations on thyroid homeostasis.[20–23]

Several trials have treated THOP in ELGANs by using a variety of dosage regimens. In all cases, intervention lowered plasma thyrotropin levels to values consistent with a significant overshoot in treatment.[16,21,24,25] Because excessive thyroid hormone exposure during fetal brain growth may be as undesirable for normal development as is deficiency,[26–28] it is important to identify how to supplement endogenous production without interfering with the maturing homeostatic control systems.

We used a masked randomized trial to identify a dosing regimen that would first elevate serum levels of free circulating thyroxine (FT_4) and total circulating T_4 (TT_4) to target values (≥1.5 ng/dL [19 pM/L] and ≥6 μg/dL [77 nM/L], respectively) while secondarily minimizing suppression of thyrotropin levels (<0.4 mIU/L) over the period of supplementation (42 days) to achieve the most physiologic pattern of homeostasis.

Methods

Study Design and Intervention

Thyroid hormone (Bedford Pharmaceuticals, Mansfield, MA) was administered in 4 treatment arms within 24 hours of birth as thyroxine (T_4) at 4 or 8 μg/kg per day delivered either as a bolus (1 mL/kg in 5% dextrose solution in water intravenously or per os [PO]) or via continuous infusion (0.5 mL/kg per hour intravenously or PO). The dosage was increased by 25% when converting to oral administration.[29] Triiodothyronine (T_3) was provided to all 4 T_4-treated arms at 1.0 μg/kg per day for the first 14 postnatal days as immediately available active hormone.[20,21] Subjects in the 2 continuous-infusion arms who began feedings every 2 hours had the appropriate amount of study drug added to ingested milk every 4 hours. T_4 and T_3 were infused along with 1 mg/mL albumin to prevent a measured 40% loss to plastic tubing.[30] One arm of the study was provided with iodine (Upsher-Smith, Maple Grove, MN), 30 μg/kg per day in 1 mL of aqueous oral solution. The placebo arm received 5% dextrose solution in water (0.5 mL/kg per hour intravenously or PO).

Study Population and Exclusions

The study was approved by the institutional review board of the 3 clinical enrollment sites and the data center. Neonates of $24^0/_7$ to $27^6/_7$ weeks of gestation were enrolled <24 hours after birth. Exclusions included mothers <18 years of age or those with thyroid disease or reported substance abuse (ie, alcoholism or use of heroin or methadone)[31] and newborns with major congenital malformations or if death was expected within 48 hours. If death or withdrawal of consent occurred in the first week of life, the subject was replaced in its study arm by the next available eligible newborn.

Clinical Definitions and Management Strategies

Gestational age was based on the best estimate of the attending neonatologist using obstetrical parameters and examination. Necrotizing enterocolitis (NEC) was recorded if ≥ Bell's stage 2,[32] retinopathy of prematurity (ROP) as ≥ stage 3 in either eye,[33] and chronic lung disease (CLD) as oxygen requirement at 36 weeks to keep oximeter saturations ≥88% to 90%.[34] Fluids and nutrition were provided according to guidelines.[35–38] Soy-based formulas were excluded because they are associated with prolonged increases in thyrotropin.[39] Vasopressors (ie, dopamine/dobutamine) were avoided because these drugs suppress thyrotropin.[31]

Iodine Precautions

Iodinated skin cleansers (eg, Povidone Iodine, Aplicore, Inc, Meriden CT) were avoided because excess iodine suppresses hormone synthesis.[31] Instead, Chlorhexidine (2% wt/vol 70% vol/vol ethanol; Enturia, Inc, Leawood, KS) was used for skin disinfection for 30 seconds followed by a sterile water rinse.

Data Monitoring

Clinical status was recorded daily for 2 weeks and weekly thereafter. Cranial ultrasounds were conducted on postnatal days 1 to 3, 7 to 10, and ≥4 weeks, and were interpreted by a masked radiologist (Paula Brill, MD, Cornell University Medical Center, New York, NY). Free T_4 was measured by using the equilibrium dialysis technique and the other hormones were measured by standard immunoassay technology (Quest Diagnostics, Chantilly, VA).[40]

Data Safety Monitoring Board

A data safety monitoring board (DSMB) and a separate independent medical monitor reviewed study progress and evaluated potential adverse events on a quarterly basis.

Statistical Considerations

A randomization/minimization program (SAS software [SAS Institute, Inc, Cary, NC]) balanced 2 gestational age strata ($24^0/_7$–$26^0/_7$ and $26^1/_7$–$27^6/_7$ weeks), gender, and center. Multiple births were treated as individual subjects, because ex utero experiences over the first 6 postnatal weeks were considered unique to individuals.

Power calculations were based on a sample size necessary to detect a 25% difference in mean FT_4 levels between each pair of the 6 study arms at a 5% significance level with a power of 0.8 allowing for up to a 20% dropout rate by the date of final assessment. Hormone results were examined as area under the curve over time, normalized to weekly values for comparison (analysis of variance; SAS 9.1). For comparing categorical outcomes (eg, death), we used the χ^2 test. When overall significance was attained, preplanned pairwise comparisons between study arms were conducted.

Results

Enrollment

From April 2005 to March 2007, 168 subjects participated: 46% (n = 77) were enrolled in New York, 31% (n = 52) in Amsterdam, and 23% (n = 39) in Madrid (Fig 1).

Changes in Enrollment During the Trial

Eleven subjects were removed from the randomization/minimization file before 7 days by study design (7 deaths, 4 parental withdrawals). In addition, the DSMB interrupted trial enrollment for 2 reasons: (1) By the time 20 subjects had been entered in the bolus 8 μg/kg per day arm, that arm had experienced 6 deaths (postnatal ages: 10, 16, 25, 27, 28, and 31 days) at a time when no other arm had >3 deaths (not statistically significant); and (2) A pharmacy drug dilution error was discovered that resulted in a doubling of the dosage in the Madrid arm. From the onset of the trial until the error was discovered, infants slated to receive 4 and 8 μg/kg per day instead received 8 and 16 μg/kg per day of T_4. Recipients of both 8 μg/kg per day in the initially designated 4 μg/kg group were retained in the 8 μg/kg per day arms. The 13 recipients of 16 μg/kg per day were excluded from the analysis and replaced by new enrollments. Adjusting the SAS randomization/minimization files and extending the enrollment period ensured that adequate numbers of subjects were assigned to each group.

Baseline Comparison of Study Arms

No mother in the study had abnormal T_4 or FT_4 values, but 8 mothers had serum thyrotropin levels of >5.0 mIU/L, suggesting subclinical hypothyroidism at delivery (Table 1). No arm of the study included infants from >2 of these women. Baseline newborn values of T_4, FT_4, T_3, thyroid-binding globulin (TBG), thyrotropin, or cortisol did not differ across study arms (Tables 1 and 2).

Serum Hormone Results Over Time

Free T_4—The median FT_4 value for the placebo arm was <19 pM/L (1.5 ng/dL) throughout the entire period of observation (not shown), indicating that 50% of the control subjects at any given date had values below our predefined threshold (Fig 2A). Interestingly, 5% to 33% of subjects across treatment arms had at least 1 plasma FT_4 value below the threshold

of 19 pM/L, consistent with the severity of illness.[41–43] Only the continuous 8 μg/kg per day treatment arm showed a significant elevation in free T_4 at all time points during study drug intervention ($P < .002$ versus all other groups); this persisted after cessation of treatment ($P < .01$ versus placebo and bolus 4 μg/kg per day; day 56).

Total T_4—During the first 3 days, an elevation in TT_4 was significant when compared with the iodine arm (Fig 2B; $P < .03$ for all hormone arms). After 14 days, both 8 μg/kg per day arms as well as the continuous 4 μg/kg per day arm produced a sustained elevation of TT_4 above the desired level of 7 μg/dL (90 nM/L; hormone arms versus placebo, $P < .002$). This persisted after study drugs were discontinued in the continuous 4 μg/kg per day arm ($P < .001$ versus placebo control).

Total T_3—Total circulating T_3 (TT_3) in both placebo and iodine arms fell below baseline and remained at ~0.8 nM/L (52 ng/dL) (Fig 2C). In all hormone-supplemented subjects, TT_3 remained significantly elevated relative to either placebo or iodine study arms from birth to day 14 ($P < .001$). After 14 days, all study arms showed a gradual rise in TT_3 levels to above the desired values of 1 nM/L (65 ng/dL), becoming statistically indistinguishable from each other.

Thyrotropin—In all subjects, by the third postnatal day, thyrotropin levels fell below the cohort's mean value at birth (5.2 mIU/L; Fig 3, top) and remained low (<0.4 mIU/L) in all hormone-supplemented arms during the 2-week period of infusion of T_3 ($P < .001$ versus placebo and iodine arms). Thyrotropin values of both 4 μg/kg per day arms were intermediate between both 8 μg/kg per day and placebo/iodine arms during days 15 to 42 ($P < .001$ for both comparisons). By 2 weeks after ending the hormone supplementation, the iodine arm and both 8 μg/kg per day arms had significantly lower thyrotropin levels than the placebo arm ($P < .04$).

Few subjects had thyrotropin levels of <0.4 mIU/L at birth (Fig 3, bottom). In contrast, during combined drug treatments (birth to 14 days) over 80% of hormone-treated subjects experienced low thyrotropin ($P < .001$ versus placebo or iodine). When only T_4 was given (days 15 to 42), abnormally low thyrotropin levels were still observed in >40% of the combined 8 μg/kg per day arms but in only 11% of the combined 4 μg/kg per day arms (Fig 3, bottom; $P < .002$ vs 8 μg/kg per day). Two weeks after completion of drug therapy nearly all subjects had thyrotropin values of >0.4 mIU/L.

Thyroid-Binding Globulin—The values for TBG did not differ significantly across study arms, reaching a nadir at day 7 and then gradually rising as a cohort from 15 mg/L at birth to 20 mg/L by study completion independent of interventions (not shown).

Cortisol—At baseline, average cortisol values ranged between 10 and 20 μg/dL across study arms, reflecting enrollment at all hours of the day of birth. Subsequently, samples were obtained at the diurnal nadir, thus becoming more tightly clustered. Cortisol values did not differ significantly by study arm; all values declined gradually and were 5 to 10 μg/dL by day 56 in all arms.

Neonatal Clinical Outcomes

At enrollment, the bolus 4 μg/kg per day arm had more mothers with fever or antibiotic use before delivery and higher neonatal T_3 levels; the iodine arm had the fewest mothers with fever (both $P < .05$, Table 1). At discharge, the rate of NEC was highest in the continuous 8 μg/kg per day arm ($P < .05$ versus other groups). However, NEC-related mortality did not differ across treatment arms and overall was 66% (10 of 15) for these ELGANs.

The duration of mechanical ventilation was lowest in both the continuous 4 μg/kg per day T_4 arm and the bolus 8 μg/kg per day T_4 arm ($P < .05$ versus remaining groups; Table 3). ROP was lowest in the 8 μg/kg per day bolus arm ($P < .05$ versus other groups) and although not prehypothesized, ROP was considerably lower in the combined 4 thyroid hormone treatment arms than in the combined placebo and iodine arms (5% [5 of 93] vs 18% [9 of 51]; $P < .04$). There were no differences in intraventricular hemorrhage (IVH) across treatment arms, but white matter damage was lowest in the bolus 4 μg/kg per day arm ($P < .05$ versus other arms; Table 3).

Discussion

At birth, ELGANs experience a 50% increase in O_2 consumption, a fall in environmental temperature, increased motor activity, increased metabolic and nutrient demands for ex utero growth, and a range of other organ-level maturational adjustments the transition of which proceeds optimally only in the euthyroid state.[20,21,24,25,27,44] THOP occurs in nearly 50% of ELGANs because of an immature hypothalamic-pituitary-thyroid axis, increased in-activation of T_4 and T_3 hormones, attendant low plasma TT_4, and in some cases of nutritional deprivation, decreased synthesis of TBG.[20,21,24,25,44,45] Moreover, TT_4 levels vary inversely with the severity of neonatal illness.[41–43] Serum FT_4 levels typically re-equilibrate to cord blood values or higher within 1 week after birth, yet TT_4 can be delayed as long as 3 to 4 weeks.[17,20,46] Considering these patterns, defining “normal” thyroid levels is difficult.

Because ELGANs frequently suffer severe systemic illness and experience changing biological requirements during a period of critical brain development,[10,20–25,44,47,48] basing target hormone values on either healthy fetal levels or levels observed in term neonates seems imprudent.[24] We argue that biochemical euthyroidism is the minimum thyroid hormone threshold associated with a reduced risk of neonatal illness or better long-term neurodevelopment.

To address the uncertainty, we targeted hormone values associated with favorable clinical outcomes.[21,24,25] First, several large studies show that neuro-developmental outcome is generally better in ELGANs and other premature neonatal populations without THOP.[11,49] Second, short-term improvement in clinical outcomes is reported after thyroid hormone treatment of sick newborns.[16,18] Third, mortality is lower in neonatal cardiac surgical patients with euthyroid sick syndrome with hormone supplementation.[50–52] Fourth, beneficial effects on IQ have been seen after thyroid hormone supplementation of newborns with other conditions (eg, trisomy 21)[53] and congenital hypothyroidism.[54–56] Thus, we identified our goal for a minimum threshold for FT_4 concentration as ≥1.5 ng/dL (19 pM/L), for TT_4 concentration as ≥6 μg/dL (77 nM/L), and for TT_3 concentration as ≥52 ng/dL (0.8 nM/L).[11,16,18,24,25,49–56]

In addition to defining minimum target values to exceed, we sought to identify a clinical euthyroid state defined biochemically as a dose and mode of thyroid hormone supplementation that simultaneously raised the level of FT_4 and TT_4 without suppressing thyrotropin to nearly undetectable levels (a problem in all previous neonatal clinical trials).[16,24] Each of these benchmarks was achieved by using a continuous infusion of thyroid hormone at 4 μg/kg per day of T_4 for 42 days (Figs 2 and 3).

Supplementation of the prohormone T_4 with the active hormone T_3 for the first 14 postnatal days raised the TT_3 blood level (Fig 2) but was coupled with thyrotropin values at or below the assay's level of detection, which is consistent with overtreatment during the period of dual therapy (Fig 3) suggesting that T_3 supplementation is unnecessary. The fewest cases

with a thyrotropin level of <0.4 mIU/L were seen in the 4 μg/kg per day arms and in untreated subjects (Fig 3, bottom). A reasonable conclusion is that 8 μg/kg per day is overtreatment and that 4 μg/kg per day can produce a biochemically euthyroid state with less frequent suppression of thyrotropin. Moreover, T_3 production was not suppressed by using this lower dose regimen compared with previous reports.[57] The current trial becomes the first to succeed in raising thyroid hormone levels to achieve the predefined threshold values of biochemical euthyroidism without suppressing thyrotropin values to <0.4 mIU/L in the majority of infants.

Although not prehypothesized, the mortality rate in the two 4 μg arms (8% [4 of 48]) was half that of the placebo/iodine arms (16% [8 of 51]) and also less than half that of higher dosage arms (22% [10 of 45]; Table 3). Although the pattern suggests a nadir in mortality when the lower thyroid hormone dose is used, these mortality differences failed to achieve statistical significance in this sample, which is underpowered for mortality analyses (Table 3). In a related analysis, when all hormone groups were combined, a statistically significant reduction in ROP stage ≥3 was found compared with the iodine/placebo arms (Table 3; $P < .04$). This is an intriguing result for future investigation, because thyroid hormone effects on vascular and retinal development in both animals and humans have been described.[58] Although these correlations are clearly of interest to clinicians, future experimentation with an appropriately large sample size will be necessary to confirm the validity of these posthoc associations.

An important issue in our study was the dosage error in the Madrid pharmacy. We note that the ensuing dosage (16 μg/kg per day) is nearly the same as the 10 to 15 μg/kg per day starting dose range routinely used to treat congenital hypothyroidism[55] and that earlier interventional trials used as high as 25 μg/kg per day.[59] The Madrid team is following the 13 infants treated with the 16 μg/kg per day dose as outpatients, and their outcomes will be the subject of a separate report. At present, their initial hospital course did not differ significantly from the other hormone intervention groups. Another issue in the study is that the DSMB closed enrollment to the bolus 8 μg/kg per day group because of a perceived trend toward higher mortality. This interruption occurred after 20 of the intended 24 subjects had been enrolled, and thus did little to harm the power of the study. At completion of the trial, we found that death rates across arms were statistically indistinguishable (Table 3).[55]

Conclusions

The THOP 1 trial accomplished the goal of elevating thyroid hormone blood levels in extremely premature neonates to exceed a predefined target threshold without completely suppressing thyrotropin by using continuous 4 μg/kg of T_4 as replacement therapy. The next step is to undertake a properly powered clinical trial that targets long-term neurodevelopmental outcomes and discerns whether thyroid hormone intervention will do more than simply elevate blood levels to target ranges in developing ELGANs.

What's Known on this Subject

Transient low levels of thryoid hormones in ELGANs are associated with cognitive delay and CP independent of other risk factors. It is not clear whether or not to treat, what target blood levels are desirable, or how to achieve them.

What this Study ADDS

Our study defines chemical euthyroidism and demonstrates a method of therapy to achieve this. A future trial will need to determine the impact on central nervous system outcomes.

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Abbreviations

CP	cerebral palsy
CLD	chronic lung disease
DSMB	data safety monitoring board
D5W	5% dextrose water
ELGAN	extremely low gestational age neonate
FT_4	free circulating thyroxine
GM	germinal Matrix
I2	Iodine
IVH	intraventricular hemorrhage
NEC	necrotizing enterocolitis
PO	per os
PVL	periventricular leukomalacia
ROP	retinopathy of prematurity
T_3	triiodothyronine
TT_3	total circulating T_3
T_4	thyroxine
TT_4	total circulating T_4
TBG	thyroid-binding globulin
THOP	transient hypothyroxinemia of prematurity

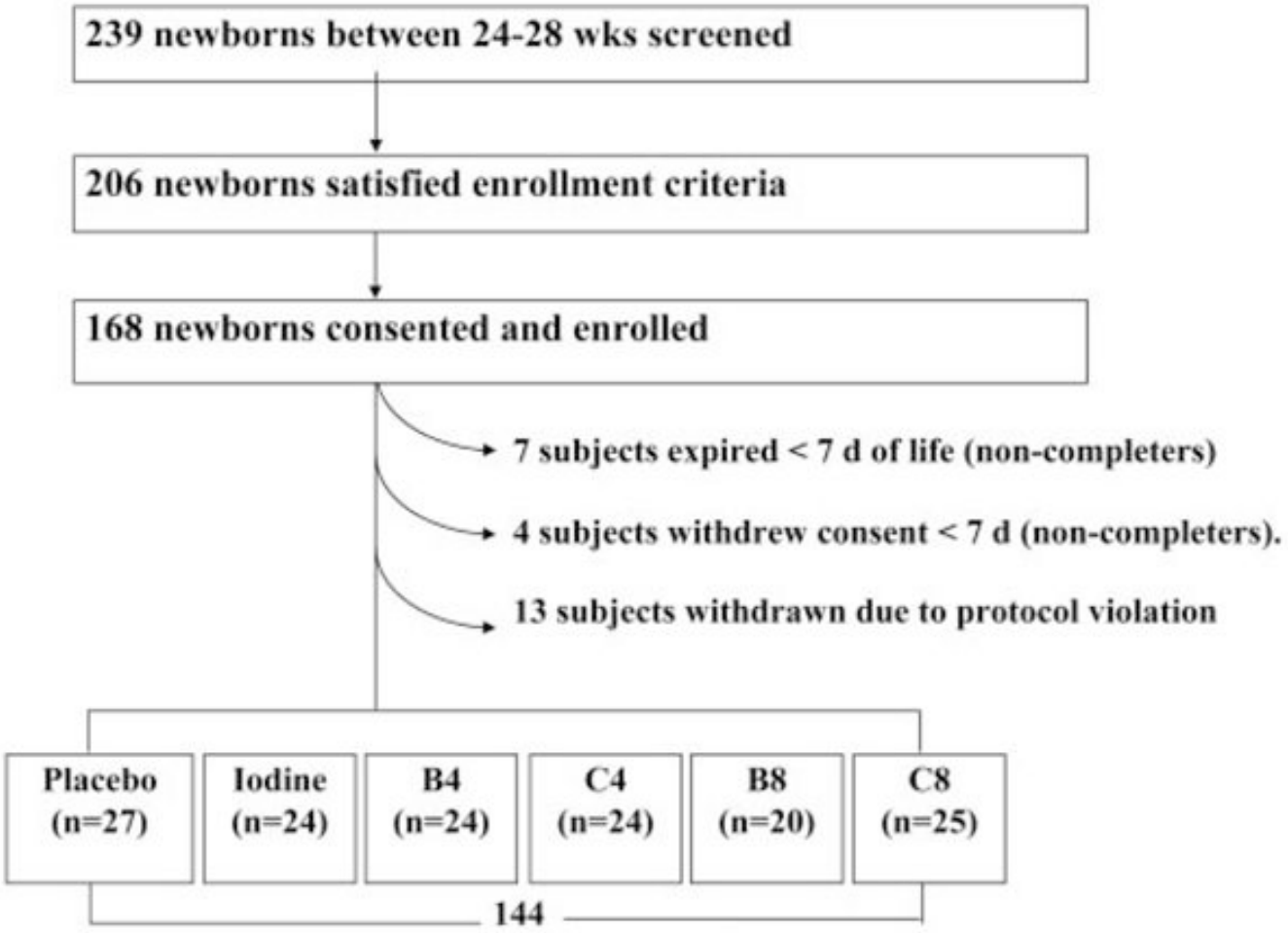

FIGURE 1.

Flowchart of the THOP enrollment and treatment protocol. B4 indicates bolus 4 μg/kg per day; C4, continuous infusion 4 μg/kg per day; B8, bolus 8 μg/kg per day; and C8, continuous infusions 8 μ/kg per day.

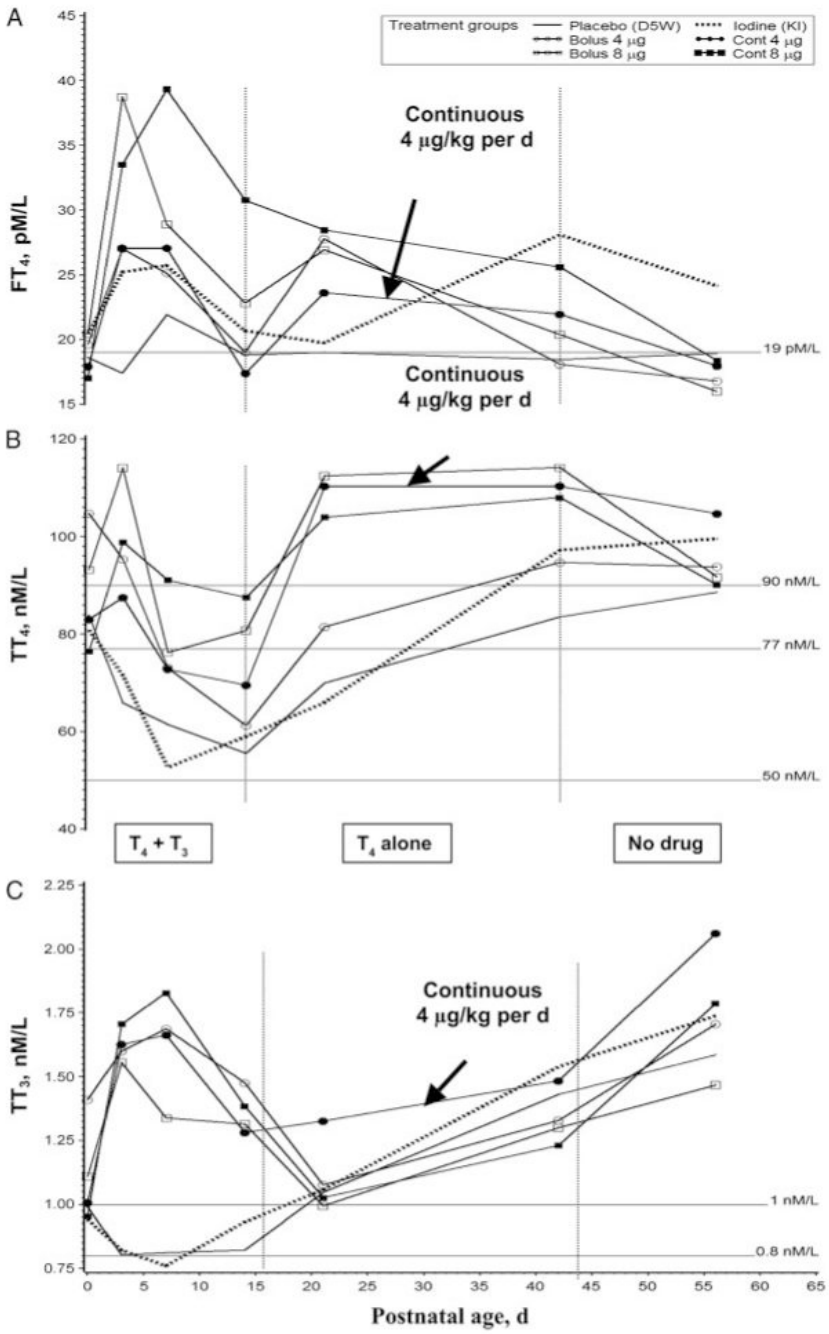

FIGURE 2.

Thyroid hormone levels over time across the 6 study arms. A, Free T_4 results across the 6 study arms Free T_4 was elevated in the first 7 days in all hormone-treated subjects; however, only the continuous 8 μg/kg per day treatment arm showed a significant elevation in all treatment epochs ($P < .002$ versus all other groups), which persisted when off all drugs ($P < .01$ versus placebo and bolus 4 μg/kg per day; day 56). Note: reference line indicates the predefined lower threshold 1.5 ng/dL (19 pM/L); conversion to pM/L: 12.86 × ng/dL = pM/L. B, Total T_4 results across the 6 study arms. Total T_4 remained elevated in the first 7 days in all hormone-treated subjects ($P < .05$ versus placebo or iodine arms). After 14 days, both 8 μg/kg per day arms as well as the continuous 4 μg/kg per day arm produced a sustained

elevation of the mean and median TT_4 above 7 μg/dL (90 nM/L; hormone arms indicated are $P < .002$ versus placebo). Note: reference lines indicate desired level 7 μg/dL (90 nM/L), the predefined lower threshold: 6 μg/dL (77 nM/L), and severely low levels: 3.8 μg/dL (50 nM/L); conversion to nM/L: 12.86 × μg/dL = nM/L. C, Total T_3 results across the 6 study arms. Total T_3 remained significantly elevated relative to either placebo or iodine study arms in all hormone-supplemented subjects during the first 2 weeks' postnatal age while T_3 was being administered ($P < .001$). No other differences were significant compared with either iodine or placebo arms. Note: reference lines indicate desired level 1 nM/L (65 ng/dL) and the predefined lower threshold 0.8 nM/L (52 ng/dL); conversion to nM/L: 65.1 × nM/L = ng/dL. Vertical lines demarcate treatment epochs as indicated in C. Data in each graph are derived from 20 to 27 values per point illustrated; see “Results” and “Discussion” for additional commentary. D5W indicates 5% dextrose in water.

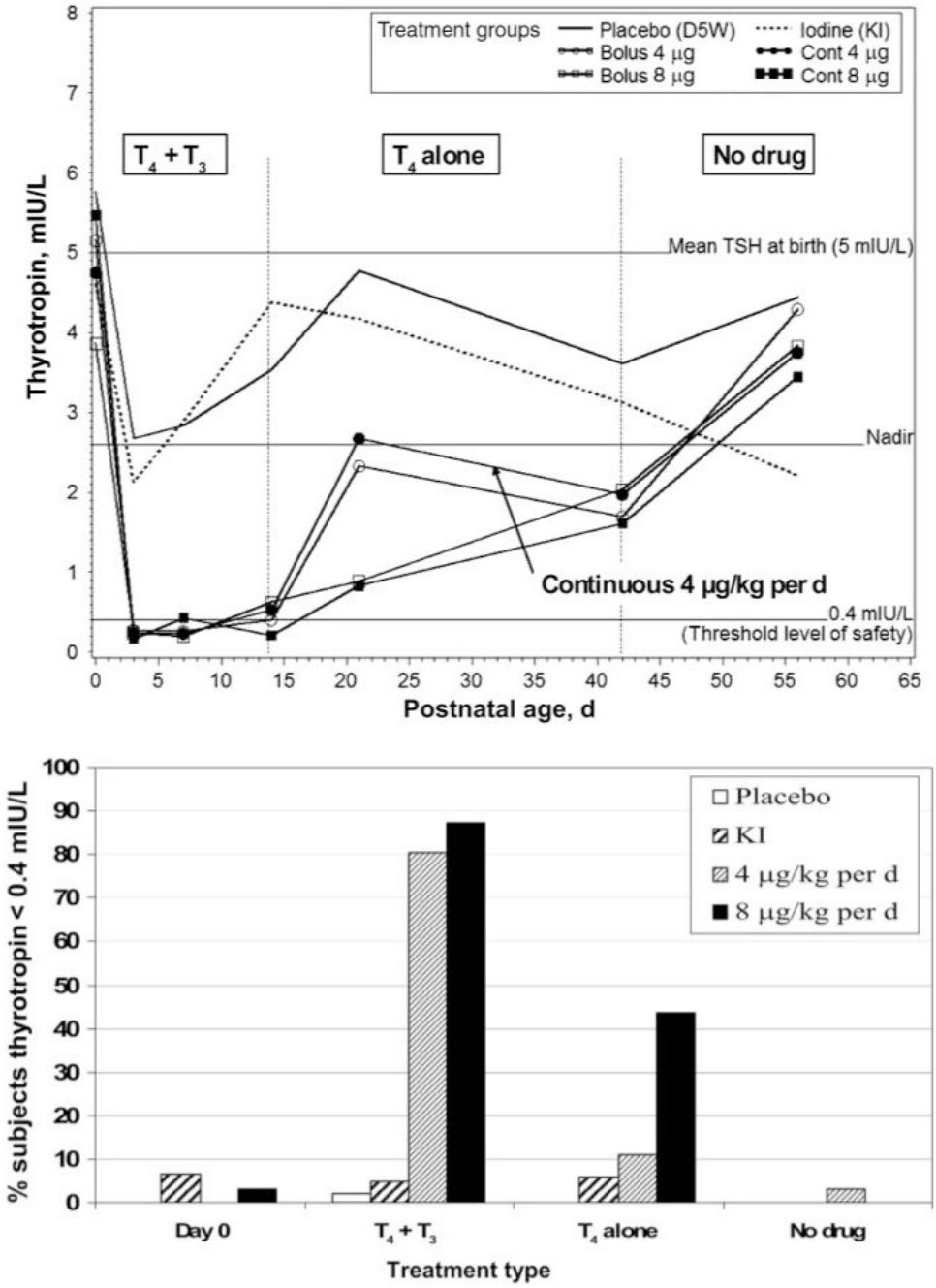

FIGURE 3.

Upper, Thyrotropin results across the 6 study arms. After day 1, all thyrotropin levels fell in the hormone treatment arms to lower values than either placebo or iodine arms ($P < .0001$). Thyrotropin levels of both of the 4 μg/kg per day arms were intermediate between both 8 μg/kg per day and placebo arms during days 15 to 42 ($P < .008$ in either comparison). Similarly, on days 15 to 42, thyrotropin levels in the 8 μg/kg per day arms were both significantly lower than in the placebo and iodine arms ($P < .001$ in either comparison). Note: vertical lines demarcate treatment epochs as indicated. Data from 20 to 27 values per point are illustrated. Lower, Percent of subjects with a thyrotropin level of <0.4 mIU/L. Study arms are combined to illustrate the percentage of enrolled subjects with extremely low

levels of thyrotropin (<0.4 mIU/L). During combined drug treatments (from birth to 14 days), >80% of hormone-treated subjects were affected ($P < .001$ versus placebo or iodine). Subsequently, when supplemented with only T_4 (day 15–42), abnormally low thyrotropin levels were still observed in >40% of the combined 8 μg/kg per day arms but in just 11% of the combined 4 μg/kg per day arms ($P < .002$ vs 8 μg/kg per day). See "Results" and "Discussion" for additional commentary. D5W indicates 5% dextrose in water.

TABLE 1

Maternal Characteristics of THOP Study Subjects According to Treatment Arm

Maternal Characteristic	Placebo (25 Women; 27 Subjects)	Iodine (24 Women; 24 Subjects)	Bolus 4 μg/kg per d (24 Women; 24 Subjects)	Continuous 4 μg/kg per d (14 Women; Subjects)	Bolus 8 μg/kg per d (19 Women; Subjects)	Continuous 8 μg/kg per d (24 Women; 25 Subjects)	Total (129 Women; 144 Subjects)
Maternal age, mean ± SEM, y	31 ± 1	29 ± 1	28 ± 1	30 ± 1	30 ± 1	31 ± 1	30 ± 1
Ethnicity, *n* (%)							
White	18 (67)	15 (63)	12 (50)	13 (54)	15 (75)	15 (60)	88 (61)
Black	7 (26)	6 (25)	7 (29)	8 (33)	4 (20)	4 (16)	36 (25)
Hispanic	2 (7)	2 (8)	2 (8)	3 (12)	1 (5)	4 (16)	14 (10)
Preeclampsia, *n* (%)	5 (19)	1 (4)	3 (12)	6 (25)	1 (5)	3 (12)	19 (13)
Fever ≥ 100.4°F during pregnancy, *n* (%)	3 (11)	0 (0)[a]	9 (38)[a]	2 (8)	1 (5)	1 (4)	16 (11)
Rupture of membrane > 24 h, *n* (%)	4 (15)	7 (30)	10 (45)	6 (29)	6 (30)	4 (19)	37 (28)
Treatment before delivery, *n* (%)							
Antibiotic	11 (41)	8 (33)	18 (75)[a]	13 (54)	8 (40)	10 (40)	68 (47)
Antenatal steroids	23 (85)	21 (88)	23 (96)	21 (88)	13 (65)	20 (80)	121 (84)
Hormone levels after delivery, mean ± SEM							
FT_4, ng/dL	1.7 ± 0.4	1.3 ± 0.1	1.3 ± 0.1	1.3 ± 0.1	1.5 ± 0.1	1.3 ± 0.1	1.4 ± 0.1
TT_4, μg/dL	11.4 ± 0.6	11.5 ± 0.5	11.8 ± 0.6	11.2 ± 0.6	11.2 ± 0.8	11.1 ± 0.5	11.4 ± 0.2
Thyrotropin, mIU/L	2.5 ± 0.4	2.4 ± 0.3	2.7 ± 0.4	2.1 ± 0.4	2.0 ± 0.5	2.0 ± 0.2	2.3 ± 0.1
Thyrotropin > 5.0 mIU/L	2 (10)	2 (9)	1 (5)	1 (5)	2 (12)	0 (0)	8 (7)

The total number of mothers is <144, because 1 mother can appear in up to 3 arms depending on her neonate's treatment assignment as a consequence of multiple gestation.

[a] $P < .05$ for the occurrence of the sign or the mean of the variable in this arm is significantly different from that seen across all study arms.

TABLE 2

Neonatal Characteristics of THOP Study Subjects According to Treatment Arm

Neonatal Characteristic	Placebo (25 Women; 27 Subjects)	Iodine (24 Women; 24 Subjects)	Bolus 4 μg/kg per d (24 Women; 24 Subjects)	Continuous 4 μg/kg per d (24 Women; 24 Subjects)	Bolus 8 μg/kg per d (19 Women; 20 Subjects)	Continuous 8 μg/kg per d (24 Women; 25 Subjects)	Total (129 Women; 144 Subjects)
Birth weight, g							
Mean ± SEM	865 ± 35	870 ± 41	852 ± 44	888 ± 48	860 ± 39	819 ± 31	859 ± 16
Median	870	845	840	825	821	800	835
Range	558–1300	440–1325	460–1340	560–1550	530–1246	499–1190	440–1550
Gestational age, wk							
Mean ± SEM	26 ± 0.2	26 ± 0.2	26 ± 0.2	26 ± 0.2	26 ± 0.2	26 ± 0.2	26 ± 0.1
Median	27	26	26	27	26	26	26
Range	24–28	24–28	24–28	25–28	24–28	24–27	24–28
Hormone levels at birth, mean ± SEM							
FT_4, ng/dL	1.5 ± 0.1	1.6 ± 0.2	1.5 ± 0.1	1.4 ± 0.1	1.6 ± 0.2	1.3 ± 0.1	1.5 ± 0.1
TT_4, μg/dL	6.5 ± 0.5	6.3 ± 0.7	8.1 ± 0.7[a]	6.5 ± 0.4	7.2 ± 0.7	6.0 ± 0.5	6.7 ± 0.2
T_3, ng/dL	64 ± 7	61 ± 7	92 ± 9[a]	65 ± 4	72 ± 10	62 ± 8	69 ± 3
Thyrotropin, mIU/L	5.8 ± 0.7	4.6 ± 0.9	5.2 ± 0.8	4.8 ± 0.5	3.9 ± 0.7	5.5 ± 1.0	5.0 ± 0.3
Male, *n* (%)	18 (67)	13 (54)	13 (54)	10 (42)	12 (60)	16 (64)	82 (57)
Cesarean delivery, *n* (%)	13 (48)	5 (21)	13 (54)	11 (46)	11 (55)	8 (32)	61 (42)
Multiple birth, *n* (%)							
Singleton	20 (74)	20 (83)	18 (75)	18 (75)	16 (80)	18 (72)	110 (76)
Twins or triplets	7 (26)	4 (17)	6 (25)	6 (25)	4 (20)	7 (28)	34 (24)
Apgar score at 5 min of < 7, *n* (%)	4 (15)	2 (8)	6 (25)	5 (21)	6 (30)	6 (24)	29 (20)

The total number of mothers is <144, because 1 mother can appear in up to 3 arms depending on her neonate's treatment assignment as a consequence of multiple gestation.

[a] $P < .05$ for the occurrence of the sign or the mean of the variable in this arm is significantly different from that seen across all study arms.

TABLE 3

Hospital Morbidities at Discharge for the THOP Trial According to Treatment Arm

	Placebo (*N* = 27)	Iodine (*N* = 24)	Bolus 4 μg/kg per d (*N* = 24)	Continuous 4 μg/kg per d (*N* = 24)	Bolus 8 μg/kg per d (*N* = 20)	Continuous 8 μg/kg per d (*N* = 25)	Total (*N* = 144)
Discharge weight or at death, mean ± SEM, g	2973 ± 238	2653 ± 162	2346 ± 93	2596 ± 167	2134 ± 186	2338 ± 167	2521 ± 74
Median	2630	2620	2235	2302	2300	2400	2473
Range	1190–6335	750–4100	1235–3260	910–4600	850–3275	820–3840	750–6335
Duration of ventilator, mean ± SEM, d	38 ± 145	19 ± 5	14 ± 3	9 ± 2[a]	13 ± 3[a]	20 ± 4	19 ± 3
Median	11	9	5	5	10	12	8
Range	0–300	0–95	0–51	0–39	0–35	0–78	0–300
Duration of CPAP, mean ± SEM, d	23 ± 4	19 ± 3	22 ± 3	25 ± 3	24 ± 5	27 ± 4	23 ± 2
Median	18	19	23	27	20	25	23
Range	0–100	0–45	0–52	0–43	0–83	0–56	0–100
Duration of hospital stay, mean ± SEM, d	100 ± 12	88 ± 8	76 ± 6	83 ± 7	67 ± 8	82 ± 6	83 ± 4
Median	84	89	77	82	64	75	82
Range	18–343	15–210	7–116	10–146	10–133	25–132	7–343
Death at >7 d, *n* (%)	4 (15)	4 (17)	2 (8)	2 (8)	6 (30)	4 (16)	22 (15)
ROP ≥ stage 3, *n* (%)	5 (19)	4 (17)	1 (4)	2 (8)	0 (0)[a]	2 (8)	14 (10)
NEC ≥ stage 2, *n* (%)	2 (7)	2 (8)	1 (4)	1 (4)	3 (15)	6 (24)[a]	15 (10)
GM/IVH, *n* (%)	9 (36)	7 (29)	3 (13)	8 (33)	7 (39)	7 (32)	41 (30)
White matter damage, *n* (%)	3 (12)	2 (8)	0 (0)[a]	2 (8)	3 (17)	2 (9)	12 (9)
CLD, *n* (%)	12 (44)	8 (33)	11 (46)	5 (21)	6 (30)	9 (36)	51 (35)
Combined arms: mortality, % (*n*/*N*)	16 (8/51)			8 (4/48)		22 (10/45)	
Combined arms: ROP > stage 3, % (*n*/*N*)	18 (9/51)			6 (3/48)		4 (2/45)	
Combined arms: NEC, % (*n*/*N*)	8 (4/51)			4 (2/48)		20 (9/45)[a]	
Combined arms: GM/IVH, % (*n*/*N*)	31 (16/51)			23 (11/48)		31 (14/45)	
Combined arms: white matter, % (*n*/*N*)	10 (5/51)			4 (2/48)		11 (5/45)	
Combined arms: CLD, % (*n*/*N*)	39 (20/51)			33 (16/48)		33 (15/45)	

CPAP indicates continuous positive airway pressure; GM, germinal matrix.

[a]The occurrence of the sign or the mean of the variable in this arm is significantly different from that across all study arms; $P < .05$.