

Iodine Supplementation for Premature Infants Does Not Improve IQ

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Williams FLR, Ogston S, Hume R, Watson J, Stanbury K, Willatts P, Boelen A, Juszczak E, Brocklehurst P; I2S2 Team. Supplemental iodide for preterm infants and developmental outcomes at 2 years: an RCT. *Pediatrics* 2017;139(5) [Epub April 14, 2017].

SUMMARY

Background

Delivery before 37 weeks of gestation is common, affecting 1 in 10 births in the United States (1). Transient hypothyroxinemia occurs in up to half of infants born before 28 weeks of gestation (2) and has been associated with long-term developmental deficits in some studies (3). Transient hypothyroxinemia of prematurity likely has multiple causes, including nonthyroidal illness and both iodine deficiency and excess. Determining the exact iodine requirements of premature infants has been challenging. These infants have high intrathyroidal iodine turnover, their intrathyroidal iodine stores are low, and they are vulnerable to iodine-induced hypothyroidism because their ability to escape the Wolff-Chaikoff effect is not fully developed. Very preterm infants are initially fed parenterally and may be at risk for iodine deficiency until they are able to transition to enteral nutrition (4). Trials of levothyroxine treatment to improve developmental outcomes of premature infants with hypothyroxinemia have been inconclusive (1). Whether iodine supplementation of preterm infants can improve neurocognitive outcomes had not previously been studied.

Methods

This is a randomized, double-blind clinical trial conducted at 21 neonatal units in U.K. hospitals. Enrollment was completed between 2010 and 2012. Infants less than 42 hours of age, born at less than 31 weeks of gestation, and who were likely to survive were eligible for inclusion. Children of mothers who

were exposed to iodinated contrast media or topical iodinated cleansers during pregnancy or delivery were excluded. Infants were randomly assigned either to treatment with 30 $\mu\text{g}/\text{kg}/\text{day}$ of iodide (administered in solution either enterally or parenterally) or to placebo. Interventions were continued until the equivalent of 34 weeks of gestational age. Blood spots were collected at days 7, 14, and 28 of life as well as at 34 weeks of gestational age for measurement of T_4 , TSH, and thyroxine-binding globulin (TBG). Information about medications, nutrition, and level of hospital care were ascertained until the equivalent of 36 weeks of gestation. Children were assessed at 2 years of age using the Bayley Scales of Infant and Toddler Development III (Bayley-III). Medical and social information up to age 2 was ascertained by caretaker questionnaire.

The primary outcome was the score on the three Bayley-III domains (corrected for prematurity). Secondary outcomes included individual Bayley-III subtests, thyroid-function and TBG values at up to 34 weeks of gestation, types and severity of neonatal illness, and use of prescription medication. The study was powered to detect a mean 6-unit difference in the Bayley-III scores. Differences in scores were assessed using independent-samples t-tests. The study used an intention-to-treat analysis. The minimum possible Bayley-III score was assigned to infants who died or were too disabled for meaningful assessment. Hypothyroxinemia was defined as a T_4 corrected for gestational age at or below the 10th percentile.

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Results

The number of patients enrolled was 1271; 2 were withdrawn because of randomization errors and the parents of 14 subjects withdrew consent. Baseline characteristics were similar between the treatment and placebo groups. A total of 65 iodide-treated and 66 placebo-treated infants died before age 2 years. A total of 498 iodide-treated and 499 placebo-treated infants underwent assessment at age 2 (79% of each group), and a total of 631 iodide-treated and 628 placebo-treated infants were included in intention-to-treat analyses. As neonates, 9 iodide-treated infants and 2 placebo-treated infants were treated with levothyroxine; at the age of 2 years, 8 iodide-treated and 5 placebo-treated children were taking levothyroxine. There was no significant difference between the mean (\pm SD) treatment and placebo groups in the main Bayley-III domains: 88.9 \pm 19.2 versus 89.2 \pm 19.5 ($P = 0.77$) for the cognitive score; 88.2 \pm 21.0 versus

88.0 \pm 21.6 ($P = 0.87$) for the motor composite score; and 85.1 \pm 21.7 versus 85.2 \pm 21.8 ($P = 0.97$) for the language composite score. TSH levels were slightly but significantly higher in the treated group at days 7 and 14 of life, but T_4 and TBG levels did not differ between the groups. Postnatal complications did not differ between groups.

Among the 288 hypothyroxinemic infants, treatment with iodide appeared to improve outcomes such that the treated group, but not the placebo group, had Bayley-III scores similar to those of the euthyroid infants. No serious adverse events were reported during the trial.

Conclusions

Treatment of premature infants with 30 μ g/kg/day of iodine appeared to be safe but did not alter neurodevelopmental outcomes at 2 years of age.

ANALYSIS AND COMMENTARY

This was the first randomized trial to examine whether iodine supplementation of premature infants improves cognitive outcomes. Study strengths include its randomized, blinded design. Treatment groups were well matched in terms of their degree of prematurity and other baseline characteristics. Although there was substantial loss to follow-up (most of it due to child deaths), this appeared to be nondifferential. The Bayley-III is a robust outcome instrument. However, because such cognitive assessments in young children are not very predictive of long-term outcomes (5), continued follow-up of this cohort would be of interest. A limitation of the study is the lack of assessment of infant urinary iodine concentrations and total nutritional iodine intakes. It was assumed, but not actually demonstrated, that these infants were iodine-deficient at baseline.

Why did this trial fail to show a treatment effect? One possibility is that the iodine dose selected may have been too high (or that there were additional, unmeasured, sources of iodine intake that contributed to iodine excess, a possibility that the study authors thought was unlikely), as reflected by the slightly but significantly higher TSH values in treated children at some of the neonatal time points. Another possibility is that the iodine dose selected was too low. Careful iodine balance studies in preterm infants are needed to better understand their requirements. Subgroup analyses suggested that any benefit might have been restricted to preterm infants with baseline hypothyroxinemia; a separate trial is needed to address this possibility.

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