Long-Term Outcomes of Hyperglycemic Preterm Infants Randomized to Tight Glycemic Control

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Objective To determine whether tight glycemic control of neonatal hyperglycemia changes neurodevelopment, growth, and metabolism at school age.

Study design Children born very low birth weight and randomized as hyperglycemic neonates to a trial of tight vs standard glycemic control were assessed at 7 years corrected age, including Wechsler Intelligence Scale for Children Fourth Edition, Movement Assessment Battery for Children 2, visual and neurologic examinations, growth measures, dual X-ray absorptiometry, and frequently sampled intravenous glucose tolerance test. The primary outcome was survival without neurodevelopmental impairment at age 7 years. Outcomes were compared using linear regression, adjusted for sex, small for gestational age, birth plurality, and the clustering of twins. Data are reported as number (%) or mean (SD).

Results Of the 88 infants randomized, 11 (13%) had died and 57 (74% of eligible children) were assessed at corrected age 7 years. Survival without neurodevelopmental impairment occurred in 25 of 68 children (37%), with no significant difference between tight (14 of 35; 40%) and standard (11 of 33; 33%) glycemic control groups ($P = .60$). Children in the tight group were shorter than those in the standard group (121.3 [6.3] cm vs 125.1 [5.4] cm; $P < .05$), but had similar weight and head circumference. Children in the tight group had greater height-adjusted lean mass (18.7 [0.3] vs 17.6 [0.2] kg; $P < .01$) and lower fasting glucose concentrations (84.6 [6.30] vs 90.0 [5.6] mg·dL^{-1}; $P < .05$), but no other differences in measures of body composition or insulin-glucose metabolism.

Conclusion Tight glycemic control for neonatal hyperglycemia does not change survival without neurodevelopmental impairment, but reduces height, increases height-adjusted lean mass, and reduces fasting blood glucose concentrations at school age. *(J Pediatr 2017;■■:■■-■■).*

Trial registration ACTRN: 12606000270516.

Hyperglycemia is common in infants born very preterm or at very low birth weight,[1] and is associated with increased risks of mortality and neonatal morbidities.[2-5] In critically unwell adults, hyperglycemia is commonly controlled by restricting glucose intake or administration of insulin[6]; however, in preterm infants, restriction of caloric intake may result in faltering growth, and insulin infusion increases the risk of hypoglycemia,[7] both of which are associated with poor neurodevelopmental outcomes.[8,9] Exposure to neonatal hyperglycemia or exogenous insulin during critical developmental periods also may affect pancreatic development,[10,11] increasing the risk of glucose intolerance in later life—a risk already increased in children[12] and adults[13] born preterm, possibly due to loss of β-cell mass.[14]

In a previous randomized trial,[15] we found that infants randomized to tight glycemic control for neonatal hyperglycemia were more likely to be treated with insulin at higher doses and for longer durations compared with those randomized to standard treatment. However, the 2 groups had similar carbohydrate intake, and there were no between-group differences in the rates of common neonatal morbidities or mortality. Tight glycemic control resulted in improved weight gain and head circumference growth, but not linear growth, by 36 weeks postmenstrual age (PMA). Greater head circumference growth is associated with increased brain volume and may be associated with improved neurodevelopmental outcome.[16] However, infants randomized to tight glycemic control also had a 3-fold higher incidence of hypoglycemia.[15] Thus, with tight glycemic control in preterm infants, there may be a trade-off between reduced morbidity from reduced hyperglycemia and brain injury caused by hypoglycemia. The finding of increased weight gain without

BRIEF	Behavior Rating Inventory of Executive Function
HINT	Hyperglycemia in Neonates Trial
MABC-2	Movement Assessment Battery for Children 2
PMA	Postmenstrual age

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Supported by the Health Research Council of New Zealand programme grant (12-095) and the A+ trust project grant (5486). A.T. received research support from the University of Auckland Senior Health Researcher Scholarship and a Gravida: National Centre for Growth and Development doctoral scholarship. The authors declare no conflicts of interest.

https://doi.org10.1016/j.jpeds.2017.09.081

associated linear growth suggests that tight glycemic control also may alter neonatal body composition, potentially increasing the long-term risks of glucose intolerance and metabolic syndrome in these children.

Methods

In the Hyperglycemia in Neonates Trial (HINT) (anzctr.org.au: ACTRN12614000492651), conducted in 2005-2008, a total of 88 hyperglycemic preterm infants (<1500 g birth weight or <30 weeks' gestation) were randomized to standard glycemic control (blood glucose concentration maintained <180 mg·dL^{-1} [<10.0 mM]) or tight glycemic control (blood glucose concentration maintained <155 mg·dL^{-1} [<8.6 mM], or 72-108 mg•dL^{-1} [4-6 mM] if on insulin).[15] The primary outcome was linear growth rate to 36 weeks PMA. All surviving children randomized in the HINT were eligible to participate in the present follow-up study. Families were traced and invited to attend an assessment at 7 years ± 6 months corrected age.

Data on birth weight, sex, birth plurality, gestational age, survival, blood glucose concentration, insulin dosing, and fluid and nutritional intake were obtained from the electronic neonatal medical record. Maternal ethnicity was prioritized,[17] and *z*-scores for measurements at birth, 28 days postnatal age, and 36 weeks PMA were calculated.[18] Socioeconomic deprivation (New Zealand Deprivation Index) at birth was derived from the maternal pregnancy booking address.[19] Macronutrient intake for the first 28 postnatal days was calculated. The Clinical Risk Index in Babies, Version 2 score was used as a measure of neonatal illness severity.[20] The neonatal morbidities of intraventricular hemorrhage, periventricular leukomalacia, necrotizing enterocolitis, retinopathy of prematurity, early- and late-onset sepsis, major neonatal surgery, chronic lung disease, and discharge with home oxygen were defined in accordance with Australia and New Zealand Neonatal Network criteria.[21]

Assessments were conducted at the Liggins Institute research clinic, University of Auckland, or at a location convenient for the participant. Caregivers gave written consent and children gave verbal assent to assessment. All assessors were blind to the neonatal randomization status of participants. Ethical approval was obtained from the Northern B Ethics Committee (NTY/12/05/035).

Weight, height, sitting height, head circumference, and abdominal circumference were measured and used to generate *z*-scores.[22] Leg length was calculated from standing and sitting heights.

Body composition was assessed using dual energy X-ray absorptiometry (Lunar Prodigy using enCORE software; GE Healthcare, Chicago, Illinois). Bone mineral density, fat mass, and lean mass were adjusted for height.

A modified frequently sampled glucose tolerance test was performed.[23] Glucose concentrations were measured with an enzymatic colorimetric assay (902 Autoanalyzer; Hitachi, Tokyo, Japan), and insulin concentrations using electrochemiluminescence immunoassay (Eclysis 2010 immunology analyzer; Hitachi). Fasting insulin and glucose concentrations were taken as the average of 3 baseline samples. Bergman's minimal model (MinMod; Millennium Software, Los Angeles, California) was used to calculate insulin sensitivity, acute insulin response to glucose, glucose effectiveness, and disposition index. The glucose disappearance constant was calculated as well.[24]

Trained assessors administered the following standardized developmental tests: the Wechsler Intelligence Scale for Children, Fourth Edition, Australian; the Beery-Buktenica Developmental Test of Visual Motor Outcomes; the Movement Assessment Battery for Children, 2nd Edition (MABC-2); and the Test of Everyday Attention in Children, using the Sky search, Score!, Creature counting, and Sky search DT subtests only. Raw scores were transformed to age-scaled or standard scores as appropriate.

Caregivers were asked to complete the Behavior Rating Inventory of Executive Function (BRIEF), Child Health Questionnaire, Modified Health Utilities Index 2 scale, Achenbach System of Empirically Based Assessment child behavior checklist, and a demographic questionnaire. The child's teacher was asked to complete the BRIEF and Achenbach System of Empirically Based Assessment teacher forms. Global executive composite T scores ≥60 on the parent- and teacher-completed BRIEF forms were defined as impaired home function and impaired classroom function, respectively.

Children were examined by a pediatrician. Cerebral palsy was categorized using the Gross Motor Function Classification Scale.[25] Presenting visual acuity was assessed by an optometrist using a crowded logMAR chart and scored by letter.[26] Blood pressure was measured using oscillometric methods with the child semireclined. The average of 3 measures was taken and converted to *z*-scores.[27] Average systolic or diastolic blood pressure ≥95th percentile for sex, age, and height was defined as hypertension, and ≥90th percentile was defined as prehypertension.[27]

Statistical Analyses

Statistical analyses were performed using SAS version 9.4 and JMP version 11.2.0 (SAS Institute, Cary, North Carolina). The primary outcome was survival without neurodevelopmental impairment, defined a priori as any of the following: full-scale IQ standard score >1 SD below the mean, MABC-2 total score ≤5th percentile, cerebral palsy, visual acuity of 6/60 (1.0 logMAR) or worse in the best eye, or hearing impairment requiring hearing aids. Secondary outcomes included individual components of the primary outcome, executive function, growth, glucose metabolism, blood pressure, body composition, health, and quality of life outcomes.

Descriptive data are presented as number (%), mean (SD), or median (IQR). Continuous variables were compared between groups using the 2-sample *t* test, or the Wilcoxon test if not normally distributed. Categorical data were compared using exact methods. Primary and secondary outcomes were compared between treatment groups using unadjusted and adjusted linear regression models, and are presented as OR or mean difference between groups, with 95% CI and *P* value.

FLA 5.5.0 DTD ■ YMPD9508_proof ■ November 30, 2017