Impact of Tight Glycemic Control on Neurodevelopmental Outcomes at 1 Year of Age for Children with Congenital Heart Disease: A Randomized Controlled Trial

Anjali Sadhwani, PhD[1,2], Lisa A. Asaro, MS[3], Caren Goldberg, MD, MS[4,5], Janice Ware, PhD[1,2], Jennifer Butcher, PhD[5,6], Michael Gaies, MD, MPH, MSc[4,5], Cynthia Smith, RN, BSN[4,5], Jamin L. Alexander, BA[7], David Wypij, PhD[3,8], and Michael S. D. Agus, MD[7]

Objective To assess the association of postoperative tight glycemic control and hypoglycemia in children undergoing cardiac surgery with neurodevelopmental outcomes at 1 year of age.

Study design A 2-center, prospective, randomized trial of postoperative tight glycemic control vs standard care was conducted in 980 children undergoing cardiac surgery. Neurodevelopmental outcomes were assessed at nine to 18 months using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), the Adaptive Behavior Assessment System, Second Edition, the Ages and Stages Questionnaire, Third Edition, and the Brief Infant Toddler Social-Emotional Assessment.

Results Neurodevelopmental follow-up was performed on 237 patients with a mean age of 13 months. No significant treatment group differences were found in the Bayley-III and Adaptive Behavior Assessment System, Second Edition composite scores or percentage at risk based on the Ages and Stages Questionnaire, Third Edition and the Brief Infant Toddler Social-Emotional Assessment. Patients who experienced moderate to severe hypoglycemia (n = 8) had lower Bayley-III composite scores compared with patients with no to mild hypoglycemia, even after controlling for factors known to be associated with poorer neurodevelopmental outcomes.

Conclusion For infants undergoing cardiac surgery, tight glycemic control did not impact neurodevelopmental outcomes compared with standard care. These data suggest a possible association between moderate to severe hypoglycemia and poorer neurodevelopmental outcomes at 1 year of age. *(J Pediatr 2016;174:193-8)*.

Trial registration ClinicalTrials.gov: NCT00443599.

Several investigations have examined the benefits and risks of using tight glycemic control to maintain normoglycemia (blood sugar levels between 80-110 mg/dL) in postoperative critically ill adults and children.[1-4] These studies predominantly focused on short-term indices of perioperative morbidity and mortality.[3,5,6] Although evidence for the effects of tight glycemic control on the number of infections and duration of intensive care unit (ICU) stay have been contradictory, studies in pediatric critical care have consistently been complicated by an increase in hypoglycemia.[3,7] The relationships between tight glycemic control, hypoglycemia, and later neurodevelopmental outcomes in this population have not been fully explored.

Both hypoglycemia and hyperglycemia may impact brain development after pediatric cardiac surgery. Neonates exposed to hypoglycemia demonstrate persistent neurodevelopmental and physical deficits.[8,9] Neuroimaging data reveal white matter abnormalities, including cortical abnormalities, white matter hemorrhage, and basal ganglia/thalamic lesions. The more severe the white matter injury, the greater the degree of neurodevelopmental impairment.[10] Hyperglycemia is also associated with neuropathologic abnormalities, including increased microglial activation and neuronal damage in the hippocampus and frontal cortex,[11] but not necessarily with worse neurodevelopmental outcomes in infants with congenital heart disease.[12,13]

ABAS-II	Adaptive Behavior Assessment System, Second Edition
ASQ-3	Ages and Stages Questionnaire, Third Edition
Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
BITSEA	Brief Infant Toddler Social-Emotional Assessment
ICU	Intensive care unit
RACHS-1	Risk Adjustment in Congenital Heart Surgery
SPECS	Safe Pediatric Euglycemia after Cardiac Surgery

From the [1]Cardiac Neurodevelopmental Program, Departments of [2]Psychiatry and [3]Cardiology, Boston Children's Hospital and Harvard Medical School, Boston, MA; [4]Division of Cardiology, [5]Department of Pediatrics and Communicable Diseases, [6]Division of Pediatric Psychology, C.S. Mott Children's Hospital and University of Michigan Medical School, Ann Arbor, MI; [7]Division of Medicine Critical Care, Boston Children's Hospital and Harvard Medical School, Boston, MA; and [8]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

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Mesotten et al[14] investigated neurodevelopmental follow-up in a cohort of critically ill children from the Leuven randomized trial of tight glycemic control vs standard care. Neurodevelopmental assessment was conducted 4 years after enrollment in the study when children were between 4-8 years of age. Results indicated no harm from hypoglycemia and possible benefits of tight glycemic control on developmental outcomes despite a high incidence of severe hypoglycemia (≤40 mg/dL, 25%) in the tight glycemic control group.[14] The impact of tight glycemic control on development at younger ages, closer to the time of randomization, has not been reported to date.

In this context, we sought to examine whether postoperative tight glycemic control and hypoglycemia impact neurodevelopmental outcomes at approximately 1 year of age in infants undergoing cardiac surgery with cardiopulmonary bypass. This prospective follow-up evaluation includes participants from the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial.[5,15]

Methods

The SPECS study is a 2-center (Boston Children's Hospital and the University of Michigan C. S. Mott Children's Hospital) randomized controlled trial (ClinicalTrials.gov: NCT00443599). A detailed description of the study methodology and results of the main study have been published previously.[5,15] Nine hundred eighty infants and children between the ages of 0-36 months who were undergoing surgery with cardiopulmonary bypass were randomly assigned either to tight glycemic control using an insulin dosing algorithm to maintain target glucose level between 80-110 mg/dL or standard care in the cardiac ICU to assess the impact of tight glycemic control on morbidity and rates of health care-associated infections. Subcutaneous continuous glucose monitoring was used to determine levels of glucose and alert regarding hypoglycemia. Hypoglycemia was defined as mild (50-59 mg/dL), moderate (40-49 mg/dL), or severe (<40 mg/dL). Moderate and severe hypoglycemia were combined in this analysis owing to the low incidence of severe hypoglycemia. The study was approved by the institutional review board at each institution.

Neurodevelopmental follow-up was added as a secondary outcome on December 1, 2008, after 159 patients had been enrolled at Boston. Patients were eligible for 1-year follow-up if they were <1 year of age when enrolled in the trial, were born after March 1, 2008 (1 year before the start of testing), lived in the US, and were 9-18 months old at the time of follow-up. Patients were invited back for neurodevelopmental assessment that included the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III).[16] Assessments were conducted by 2 experienced child psychologists blinded to group assignment and hypoglycemia status. The Bayley-III is a standardized measure used to evaluate the current development of infants and children ≤42 months of age. Composite scores (mean ± SD, 100 ± 15) and subscale scores (10 ± 3) are reported for the cognitive, language, and motor domains.

Parents also completed the Adaptive Behavior Assessment System, Second Edition (ABAS-II),[17] the Ages and Stages Questionnaire, Third Edition (ASQ-3),[18] and the Brief Infant Toddler Social-Emotional Assessment (BITSEA).[19] The ABAS-II is a standardized questionnaire for children from birth to 18 years of age that assesses adaptive functioning. Composite scores for overall adaptive functioning, conceptual, social, and practical domains (100 ± 15) and subscale scores (10 ± 3) are reported. The ASQ-3 is a developmental screener for children 1 month to 5 years of age that assesses risk of developmental delay in the domains of communication, gross and fine motor development, problem solving, and personal-social skills using pre-established score thresholds. The BITSEA assesses social-emotional problems and competencies of children aged 12-36 months and identifies at-risk children based on age-specific score thresholds. The percentage of patients who meet ASQ-3 and BITSEA risk thresholds are reported. If patients were unable to come to the clinic for neurodevelopmental assessment and families agreed to participate, parents were mailed the ASQ-3 and BITSEA.

Potential risk factors for poor neurodevelopmental outcomes were obtained from the study database, including surgical procedure complexity, age at surgery, time-weighted blood glucose average, and cardiac ICU duration of stay. Additional risk factors related to the child's demographic, medical, and developmental history were obtained through an intake form completed by the parent, including prematurity, maternal education, and receipt of early intervention services. Presence of a genetic anomaly was based on medical record review to assess whether genetic testing was conducted and a genetic diagnosis was noted.

Statistical Analyses

Descriptive statistics were calculated, including mean values and SDs for continuous variables and frequency counts and percentages for categorical variables. Group comparisons were made using linear regression for continuous variables or stratified exact tests for categorical variables, with adjustment for site. Excluding patients with genetic anomalies that have established patterns of associated developmental disabilities,[20,21] we used stepwise multivariable linear regression with adjustment for site to further evaluate the impact of moderate to severe hypoglycemia on neurodevelopmental outcomes after controlling for other factors known to be associated with poorer neurodevelopmental outcomes.[22] These factors included age at surgery of 60 days or younger,[23] Risk Adjustment in Congenital Heart Surgery (RACHS-1) category[24] of ≥3 (or not assignable), single ventricle physiology, premature birth, maternal education (high school diploma or lower vs associate's degree or higher), prolonged cardiopulmonary bypass (≥150 minutes), deep hypothermic circulatory arrest, delayed sternal closure, and cardiac ICU