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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]

[1]Cardiac Neurodevelopmental Program, Boston Children's Hospital and Harvard Medical School, Boston, MA

[2]Department of Psychiatry, Boston Children's Hospital and Harvard Medical School, Boston, MA

[3]Department of Cardiology, Boston Children's Hospital and Harvard Medical School, Boston, MA

[4]Division of Cardiology, C.S. Mott Children's Hospital and University of Michigan Medical School, Ann Arbor, MI

[5]Department of Pediatrics and Communicable Diseases, C.S. Mott Children's Hospital and University of Michigan Medical School, Ann Arbor, MI

[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

[8]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA

Abstract

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.

Reprint requests: Anjali Sadhwani, PhD, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. anjali.sadhwani@childrens.harvard.edu.

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Trial registration ClinicalTrials.gov: NCT00443599.

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.

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.[-] These studies predominantly focused on short-term indices of perioperative morbidity and mortality.[,,] 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.[,] 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.[,] 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. Hyper-glycemia is also associated with neuropathologic abnormalities, including increased microglial activation and neuronal damage in the hippocampus and frontal cortex, but not necessarily with worse neurodevelopmental outcomes in infants with congenital heart disease.[,]

Mesotten et al 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. 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 neuro-developmental 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.[,]

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.[7] 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). 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 and age. Composite scores (mean ± SD, 100 ± 15) 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), the Ages and Stages Questionnaire, Third Edition (ASQ-3), and the Brief Infant Toddler Social-Emotional Assessment (BITSEA). 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,[,] 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. These factors included age at surgery of 60 days or younger, Risk Adjustment in Congenital Heart Surgery (RACHS-1) category of ≥3 (or not assignable), single ventricle physiology, premature birth, maternal education (high school diploma or lower vs associate's degree or higher), prolonged cardio-pulmonary bypass (≥150 minutes), deep hypothermic circulatory arrest, delayed sternal closure, and cardiac ICU duration of stay tertile (<2, 2-4.99, or ≥5 days). Analyses were performed using SAS (version 9.4, SAS Institute, Cary, North Carolina).

Results

Of 619 survivors eligible for neurodevelopmental follow-up at 1 year of age, 237 patients (121 with tight glycemic control and 116 with standard care) participated in the current study from March 1, 2009 to October 3, 2013 for a follow-up rate of 38% (Figure; available at www.jpeds.com). This included 201 patients who returned for in-person neurodevelopmental assessment and 36 patients whose parents completed only questionnaires. Patients who participated in any follow-up (either in person or by mail) were comparable with those who did not participate on most patient characteristics (Table I; available at www.jpeds.com). However, significant differences in participation rates existed by site (Boston 27% vs Michigan 57%; $P < .001$). There was a marginally significant difference in participation by hypoglycemia status (moderate to severe 30% vs no to mild hypoglycemia 39%; $P = .09$).

Among subjects who participated in the neurodevelopmental assessment, there were no treatment group differences in patient or intraoperative characteristics including age at surgery, prematurity, presence of genetic anomalies, maternal education, and duration of cardiopulmonary bypass (Table II). As expected, children in the tight glycemic control group were more likely to receive insulin therapy ($P < .001$) and had significantly lower time-weighted blood glucose averages ($P < .001$) than the standard care group. Seven percent of the tight glycemic control follow-up group and 2% of the standard care follow-up group experienced moderate to severe hypoglycemia ($P = .10$).

The mean age at developmental testing was 13.2 ± 1.8 months. The median interval from age at surgery to age at testing was 302 days (IQR, 230-357). On the Bayley-III measure, mean composite scores for the cognitive, language, and motor domains were comparable across the tight glycemic control and standard care groups (Table III). All mean composite and subscale scores fell in the average range for both groups with the exception of the mean gross motor subscale scores, which fell in the low average range (mean of 6.9 for both treatment groups). There was no difference in adaptive functioning, as measured through the ABAS-II, between the 2 treatment groups. Although the overall global adaptive functioning mean score for both treatment groups fell in the average range (tight glycemic control = 90.2; standard care = 88.3), both groups demonstrated low average mean scores on the self-care subscale (tight glycemic control = 7.4; standard care = 7.0). On the ASQ-3 and the BITSEA, the tight glycemic control and standard care groups were comparable in terms of percentage at-risk for concerns across the different domains. There were also no differences in the percentage at risk for concerns on the ASQ-3 and BITSEA between patients who returned for in-person testing (n = 167) and those whose parents mailed in questionnaires (n = 36). In addition, there were no differences between the tight glycemic control and standard care groups in terms of the percentage of patients who received early intervention services (tight glycemic control = 63%; standard care = 56%; $P = .28$).

After excluding children with a genetic anomaly who had in-person testing (n = 34), children who experienced moderate to severe hypoglycemia (tight glycemic control n = 7 and standard care n = 1) had lower scores on the Bayley-III than children with no to mild hypoglycemia (n = 159; Table IV). Adjusting for site, children with moderate to severe hypoglycemia scored 9.6 points lower on the Bayley-III cognitive composite ($P = .02$), 11.4 points lower on the language composite ($P = .009$), and 10.6 points lower on the motor composite ($P = .03$) compared with children with no to mild hypoglycemia. No differences were found on the ABAS-II composite and subscale scores and the at-risk percentages on the ASQ-3 and BITSEA between children with moderate to severe hypoglycemia and no to mild hypoglycemia, with one exception. On the ASQ-3 personal-social domain, patients with moderate to severe hypoglycemia were more likely to be at risk for concerns than patients with no to mild hypoglycemia (50% vs 17%; $P = .04$).

Patients with moderate to severe hypoglycemia had more medical complications, such as prematurity, complicated cardiac physiology, and longer durations of cardiac ICU stay than patients with no to mild hypoglycemia (Table IV). These factors are all known to be associated with worse neurocognitive performance. After controlling for these and other factors in stepwise multivariable regression analyses, patients with moderate to severe hypoglycemia continued to score lower on the Bayley-III cognitive, language, and motor composites than children with no to mild hypoglycemia (Table V). In addition to hypoglycemia status, lower maternal education and longer duration of cardiac ICU stay were associated with lower language scores; older age at surgery, higher RACHS-1 category, and delayed sternal closure were associated with lower motor scores.

Discussion

In this 2-center prospective randomized trial of infants undergoing cardiac surgery with cardiopulmonary bypass, we found that tight glycemic control did not impact neurodevelopmental outcomes at 1 year of age compared with standard care. Results on indices of cognitive, language, and motor development, adaptive functioning, and personal-social functioning were similar across the 2 groups, consistent with prior research. Contrary to previous work, we observed that moderate to severe hypoglycemia was associated with worse functioning in the cognitive, language, and motor domains, even after controlling for important potential confounders such as complexity of cardiac physiology, and duration of cardiac ICU stay.

Our findings related to hypoglycemia are consistent with studies of preterm children, which noted that neonatal hypoglycemia significantly increased the risk of developmental delays.[7] The results of our study support the theory that the developing brain is exquisitely sensitive to hypoglycemia in the postoperative period, and highlight the need for close glucose monitoring to avoid hypoglycemia when tight glycemic control is administered. Comparing our tight glycemic control protocol (SPECS) with that of the Leuven group,[7] it is notable that our protocol achieved a substantially lower incidence and duration of hypoglycemia. SPECS incorporated continuous glucose monitoring, which proactively alerts providers to pending hypoglycemia so that it could be avoided and to prolonged ongoing hypoglycemia, thus enabling rapid recognition and treatment. Although there is no definitive explanation for the different findings in the Leuven study, a possibility is that less frequent glucose monitoring in the Leuven trial led to incomplete recognition of patients with hypoglycemia, thereby obscuring potential differences between the tight glycemic control and standard care groups. Alternatively, there may be an early negative neurodevelop-mental impact of hypoglycemia that was captured in our study as seen in the lowered scores on the cognitive, language, and motor domains on the Bayley-III, whereas a longer term follow-up study may not show the same findings.

Consistent with other studies, our findings suggest that the etiology of neurodevelopmental delays is multifactorial. In addition to hypoglycemia, patient and perioperative factors such as lower maternal education, longer duration of cardiac ICU stay, older age at surgery, higher RACHS-1 category, and delayed sternal closure were associated with worse neurodevelopmental outcomes. It is, thus, imperative to consider all of these risk factors and their impact on neuro-developmental outcomes as one continues to examine and monitor the use of glycemic control, and in overall patient care in critical care medicine.

Our study should be viewed in light of certain limitations, most notably in subject attrition. Many patients eligible for follow-up did not return for neurodevelopmental assessment owing to distance from the 2 study centers. Moreover, a limited number of the returning sample (8 patients) experienced moderate or severe hypoglycemia. A larger sample size of patients with moderate to severe hypoglycemia, although undesirable, would likely be needed to produce more robust findings. In addition, duration of stay was used as a marker to indicate the severity of postoperative illness in the multivariate analysis rather than individual postoperative factors such as cardiac arrest, low cardiac output, and reoperation.

We also recognize that neurodevelopmental testing at a young age has limited predictive validity for later test performance, suggesting the need for longer term follow-up to assess the effect of tight glycemic control on later neurodevelopmental outcomes. We are in the process of completing a 3-year follow-up of these patients and plan to examine developmental outcomes in this cohort over time.

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Glossary

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

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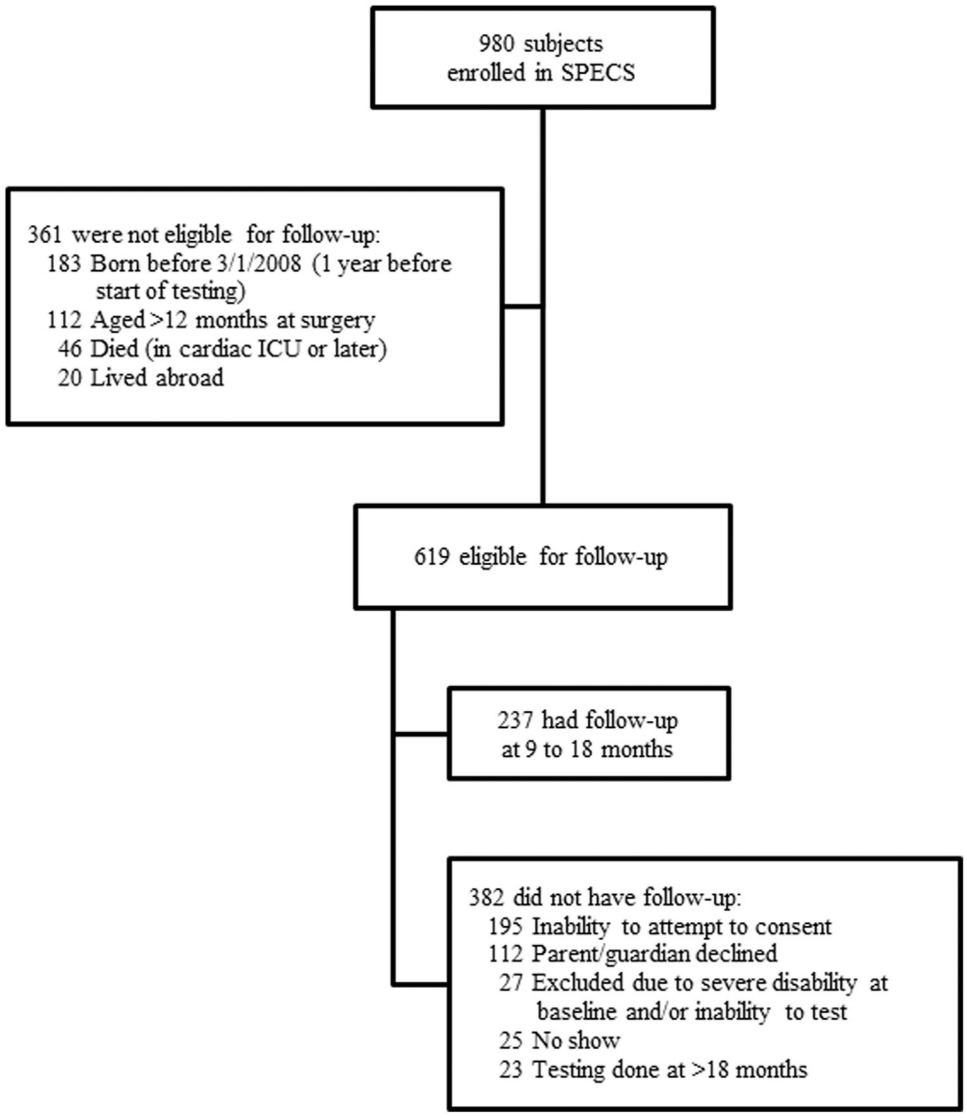

Figure.
Flow diagram of patients enrolled in SPECS.

Table I

Patient characteristics by follow-up status*

	Follow-up (n = 237)	No follow-up (n = 382)	*P* value†
Prerandomization characteristics			
Enrolled in Boston	103 (43)	279 (73)	<.001
Age at surgery, mo	3.3 ± 2.8	3.8 ± 2.9	.06
≤60 d	90 (38)	110 (29)	.12
Female sex	101 (43)	172 (45)	.79
RACHS-1 category ≥3 or not assignable	128 (54)	194 (51)	.60
Single ventricle physiology	50 (21)	72 (19)	1.0
Premature birth (<37 wk)	31 (13)	62 (16)	.23
Genetic anomaly	44 (19)	67 (18)	.65
Intraoperative characteristics			
Duration of cardiopulmonary bypass ≥150 min	42 (18)	96 (25)	.34
Deep hypothermic circulatory arrest	44 (19)	71 (19)	1.0
Delayed sternal closure	31 (13)	51 (13)	.61
Postoperative characteristics			
Treated with insulin therapy in the cardiac ICU	117 (49)	190 (50)	.86
Time-weighted blood glucose average, mg/dL	118 ± 18	122 ± 22	.06
Moderate to severe hypoglycemia (<50 mg/dL)	10 (4)	23 (6)	.09
Cardiac ICU duration of stay, d			.18
<2	60 (25)	111 (29)	
2-4.99	101 (43)	147 (38)	
≥5	76 (32)	124 (32)	

*Values are mean ± SD or n (%).

†*P* values for the comparison between groups were calculated with the use of linear regression or stratified exact tests with adjustment for site, as appropriate.

Table II

Patient characteristics by treatment group [*]

	Tight glycemic control (n = 121)	Standard care (n = 116)	*P* value [†]
Prerandomization characteristics			
Enrolled in Boston	51 (42)	52 (45)	.70
Age at surgery, mo	3.5 ± 2.9	3.1 ± 2.6	.25
≤60 d	43 (36)	47 (41)	.42
Female sex	53 (44)	48 (41)	.79
RACHS-1 category ≥3 or not assignable	65 (54)	63 (54)	1.0
Single ventricle physiology	26 (21)	24 (21)	1.0
Premature birth (<37 weeks)	17 (14)	14 (12)	.70
Genetic anomaly [‡]	23 (19)	21 (18)	.87
Maternal education: high school diploma or lower [§]	35 (29)	34 (30)	1.0
Intraoperative characteristics			
Duration of cardiopulmonary bypass ≥150 min	19 (16)	23 (20)	.49
Deep hypothermic circulatory arrest	20 (17)	24 (21)	.41
Delayed sternal closure	11 (9)	20 (17)	.08
Postoperative characteristics			
Treated with insulin therapy in the cardiac ICU	115 (95)	2 (2)	<.001
Time-weighted blood glucose average, mg/dL	114 ± 14	122 ± 21	<.001
Moderate to severe hypoglycemia (<50 mg/dL)	8 (7)	2 (2)	.10
Cardiac ICU duration of stay, d			.25
<2	33 (27)	27 (23)	
2-4.99	53 (44)	48 (41)	
≥5	35 (29)	41 (35)	

[*] Values are mean ± SD or n (%).

[†] *P* values for the comparison between treatment groups were calculated with the use of linear regression or stratified exact tests with adjustment for site, as appropriate.

[‡] Genetic anomalies include trisomy 21 (n = 35), 22q11 (n = 5), 10q24.32 (n = 1), Holt-Oram syndrome (n = 1), Noonan syndrome (n = 1), and trisomy 18 (n = 1).

[§] Maternal education not available for 2 tight glycemic control and 3 standard care patients.

Table III

Neurodevelopmental outcomes by treatment group*

	Tight glycemic control	Standard care	*P* value†
Bayley-III scores	(n = 100)	(n = 101)	
Age at testing, mo	13.2 ± 1.8	13.3 ± 1.8	.99
Composite scores			
Cognitive	100.2 ± 13.3	100.8 ± 15.6	.75
Language‡	94.7 ± 13.0	94.7 ± 13.1	.99
Motor	87.2 ± 15.8	88.9 ± 16.9	.44
Subscale scores			
Cognitive	10.0 ± 2.7	10.2 ± 3.1	.75
Receptive communication‡	9.4 ± 2.5	9.3 ± 2.4	.74
Expressive communication‡	8.8 ± 2.3	8.9 ± 2.6	.72
Fine motor	8.8 ± 2.7	9.3 ± 3.0	.14
Gross motor	6.9 ± 3.4	6.9 ± 3.5	.98
ABAS-II Composite scores	(n = 77)	(n = 77)	
General Adaptive Composite	90.2 ± 15.8	88.3 ± 13.8	.41
Conceptual	93.9 ± 16.0	91.6 ± 13.5	.35
Social	97.0 ± 14.9	95.3 ± 13.9	.45
Practical	87.2 ± 12.8	86.2 ± 12.5	.58
ASQ-3, at risk	(n = 101)	(n = 102)	
Communication	11 (11)	15 (15)	.53
Gross motor	46 (46)	48 (47)	.89
Fine motor	19 (19)	24 (24)	.49
Problem solving	25 (25)	31 (30)	.43
Personal-social	25 (25)	29 (28)	.64
BITSEA, at risk§	(n = 66)	(n = 71)	
Problem	7 (11)	11 (15)	.46
Competence	20 (30)	26 (37)	.46

*Values are mean ± SD or n (%).

†*P* values for the comparison between treatment groups were calculated with the use of linear regression or stratified exact tests with adjustment for site, as appropriate.

‡Bayley-III language composite score and receptive and expressive communication subscale scores were not available for 1 patient with tight glycemic control.

§BITSEA calculated for patients 12 months and older.

Table IV

Patient characteristics and neurodevelopmental outcomes for patients without a genetic anomaly by hypoglycemia status*

	Moderate to severe hypoglycemia (N = 8)	No to mild hypoglycemia (N = 159)	*P* value†
Patient characteristics			
Age at surgery, mo	1.7 ± 3.7	3.1 ± 2.8	.18
≤60 days	7 (88)	67 (42)	.02
RACHS-1 category ≥3 or not assignable	8 (100)	84 (53)	.009
Single ventricle physiology	1 (13)	37 (23)	.68
Premature birth (<37 weeks)	3 (38)	15 (9)	.04
Maternal education: high school diploma or lower‡	1 (13)	50 (32)	.44
Duration of cardiopulmonary bypass ≥ 150 minutes	2 (25)	29 (18)	.63
Deep hypothermic circulatory arrest	1 (13)	35 (22)	.69
Delayed sternal closure	1 (13)	22 (14)	1.0
Tight glycemic control group	7 (88)	74 (47)	.03
Cardiac ICU duration of stay, d			.02
<2	0	45 (28)	
2-4.99	2 (25)	62 (39)	
≥5	6 (75)	52 (33)	
Bayley-III scores			
Age at testing, mo	14.2 ± 2.7	13.3 ± 1.8	.04
Composite scores			
Cognitive	95.0 ± 10.7	104.7 ± 11.5	.02
Language§	86.5 ± 16.5	97.7 ± 11.6	.009
Motor	82.4 ± 14.4	92.8 ± 13.3	.03
Subscale scores			
Cognitive	9.0 ± 2.1	10.9 ± 2.3	.02
Receptive communication§	7.9 ± 3.2	9.9 ± 2.2	.01
Expressive communication§	7.4 ± 2.5	9.3 ± 2.3	.02
Fine motor	7.9 ± 1.8	9.8 ± 2.4	.02
Gross motor	6.3 ± 3.5	7.7 ± 3.0	.17

*Values are mean ± SD or n (%).

†*P* values for the comparison between groups were calculated with the use of linear regression or stratified exact tests with adjustment for site, as appropriate.

‡Maternal education not available for 3 patients with no to mild hypoglycemia.

§Bayley-III language composite score and receptive and expressive communication subscale scores were not available for 1 patient with no to mild hypoglycemia.

Table V

Multivariable regression to evaluate the impact of hypoglycemia status and other factors on neurodevelopmental outcomes in patients without a genetic anomaly (N = 167)

Bayley-III composite score	Covariates	Beta coefficient (95% CI)	*P* value*
Cognitive	Moderate to severe hypoglycemia	–9.6 (–17.8 to –1.3)	.02
Language†	Moderate to severe hypoglycemia	–9.3 (–17.7 to –1.0)	.03
	Maternal education: high school diploma or lower	–4.0 (–7.9 to –0.2)	.04
	Cardiac ICU duration of stay, d		
	<2	Reference	
	2-4.99	–2.6 (–7.0 to 1.9)	.26
	≥5	–7.8 (–12.5 to –3.0)	.002
Motor	Moderate to severe hypoglycemia	–11.8 (–21.0 to –2.6)	.01
	Age ≤60 days	11.5 (6.7 to 16.3)	<.001
	RACHS-1 category ≥3 or not assignable	–8.6 (–13.3 to –3.9)	<.001
	Delayed sternal closure	–7.3 (–13.2 to –1.3)	.02

**P* values were calculated with the use of multivariable linear regression with adjustment for site. Coefficients for intercept and site are not reported.

†N = 164. Maternal education was not available for 3 patients with no to mild hypoglycemia, including one patient for whom the Bayley-III language composite score was not available.