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Neurocognitive Development of Children 4 Years After Critical Illness and Treatment With Tight Glucose Control

A Randomized Controlled Trial

Dieter Mesotten, MD, PhD
Marijke Gielen, MD
Caroline Sterken, MPsych
Kirsten Claessens, MPsych
Greet Hermans, MD, PhD
Dirk Vlasselaers, MD, PhD
Jurgen Lemiere, MPsych, PhD
Lieven Lagae, MD, PhD
Marc Gewillig, MD, PhD
Benedicte Eyskens, MD, PhD
Ilse Vanhorebeek, MEng, PhD
Pieter J. Wouters, MSc
Greet Van den Berghe, MD, PhD

Context A large randomized controlled trial revealed that tight glucose control (TGC) to age-adjusted normoglycemia (50-80 mg/dL at age <1 year and 70-100 mg/dL at age 1-16 years) reduced intensive care morbidity and mortality compared with usual care (UC), but increased hypoglycemia (≤40 mg/dL) (25% vs 1%).

Objective As both hyperglycemia and hypoglycemia may adversely affect the developing brain, long-term follow-up was required to exclude harm and validate short-term benefits of TGC.

Design, Setting, and Patients A prospective, randomized controlled trial of 700 patients aged 16 years or younger who were admitted to the pediatric intensive care unit (ICU) of the University Hospitals in Leuven, Belgium, between October 2004 and December 2007. Follow-up was scheduled after 3 years with infants assessed at 4 years old between August 2008 and January 2012. Assessment was performed blinded for treatment allocation, in-hospital (83%) or at home/school (17%). For comparison, 216 healthy siblings and unrelated children were tested.

Main Outcome Measures Intelligence (full-scale intelligence quotient [IQ]), as assessed with age-adjusted tests (Wechsler IQ scales). Further neurodevelopmental testing encompassed tests for visual-motor integration (Beery-Buktenica Developmental Test of Visual-Motor Integration); attention, motor coordination, and executive functions (Amsterdam Neuropsychological Tasks); memory (Children's Memory Scale); and behavior (Child Behavior Checklist).

Results Sixteen percent of patients declined participation or could not be reached (n=113), resulting in 569 patients being alive and testable at follow-up. At a median (interquartile range [IQR]) of 3.9 (3.8-4.1) years after randomization, TGC in the ICU did not affect full-scale IQ score (median [IQR], 88.0 [74.0-100.0] vs 88.5 [74.3-99.0] for UC; $P=.73$) and had not increased incidence of poor outcomes (death or severe disability precluding neurocognitive testing: 19% [68/349] vs 18% [63/351] with UC; risk-adjusted odds ratio, 0.93; 95% CI, 0.60-1.46; $P=.72$). Other scores for intelligence, visual-motor integration, and memory also did not differ between groups. Tight glucose control improved motor coordination (9% [95% CI, 0%-18%] to 20% [95% CI, 5%-35%] better, all $P\leq.03$) and cognitive flexibility (19% [95% CI, 5%-33%] better, $P=.02$). Brief hypoglycemia evoked by TGC was not associated with worse neurocognitive outcome.

Conclusion At follow-up, children who had been treated with TGC during an ICU admission did not have a worse measure of intelligence than those who had received UC.

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In critically ill patients, adults as well as children, hyperglycemia is associated with adverse outcome.[1-9] In 2009, a randomized controlled trial (RCT) of 700 patients, performed in a tertiary referral pediatric intensive care unit (ICU), revealed that tight glucose control (TGC) with insulin infusion targeting age-adjusted normoglycemia (50-80 mg/dL for infants and 70-100 mg/dL for children) prevented serious ICU morbidity compared with the usual care (UC), which tolerated hyperglycemia up to 215 mg/dL.[10] Specifically, the number of patients with new infections was reduced with TGC, with less inflammation, less myocardial damage, shorter duration of hemodynamic support, and a shorter stay in the ICU (ICU mortality was also reduced by an absolute 3%).

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Author Affiliations: Departments of Intensive Care Medicine (Drs Mesotten, Gielen, Hermans, Vlasselaers, Vanhorebeek, and Van den Berghe and Mss Sterken and Claessens and Mr Wouters), Child and Adolescent Psychiatry (Dr Lemiere), Pediatric Neurology (Dr Lagae), and Pediatric and Congenital Cardiology (Drs Gewillig and Eyskens), Catholic University of Leuven, Leuven, Belgium.

Corresponding Author: Greet Van den Berghe, MD, PhD, Department of Intensive Care Medicine, Catholic University of Leuven, Herestraat 49, B-3000 Leuven, Belgium (greet.vandenberghe@med.kuleuven.be).

Caring for the Critically Ill Patient Section Editor: Derek C. Angus, MD, MPH, Contributing Editor, *JAMA* (angusdc@upmc.edu).

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However, because the targets for blood glucose, the normal fasting levels for age,[11] were much lower in these young children than in adults, the incidence of hypoglycemia of 40 mg/dL or lower increased from 1% with UC to 25% with TGC. The hypoglycemia episodes were not detectably symptomatic and always short-lasting, because they were quickly diagnosed with accurate tools and treated carefully in the setting of the study protocol.[10] Symptomatic hypoglycemia in young children has been associated with variable brain damage comprising diffuse white matter injury, hemorrhage and infarction, basal ganglia/thalamic abnormalities, and commonly cortical lesions.[12] However, hyperglycemia may also deleteriously affect brain integrity and cognition.[13-15] A recent study[16] on brain specimen of human patients and experimental animals showed that hyperglycemia during critical illness causes brain inflammation, impaired astrocyte function, and neuronal damage in hippocampus and frontal cortex. Therefore, the use of TGC in young patients in the ICU may have both beneficial and deleterious effects on various parts of the developing brain, with potentially long-term consequences for neurocognitive development.

To exclude harm and hereby validate the observed short-term ICU benefits of TGC in critically ill infants and children, a longer-term follow-up evaluation, particularly a broad and in-depth assessment of neurocognitive development, was required. We herein report the results of this preplanned long-term follow-up study of the 700 patients originally included in the University Hospitals, Leuven, Belgium, pediatric TGC trial.[10]

METHODS

Patients and Healthy Controls

Between October 2004 and December 2007, 700 patients aged 16 years or younger admitted to the pediatric ICU of the University Hospitals in Leuven, Belgium, had been enrolled in a prospective, randomized controlled study on TGC.[10] For the full study protocol, we refer to the eProtocol (available at http://www.jama.com) and the report of the original acute outcome study.[10] The study protocol and consent forms were approved by the institutional ethical review board (ML2586).

In brief, on admission, patients fulfilling inclusion criteria were randomly assigned to either TGC or UC, after written informed consent from the next-of-kin. Throughout the ICU stay, in the TGC group (n=349), insulin infusions targeting blood glucose concentrations of 50 to 80 mg/dL in infants (aged <1 year) and concentrations of 70 to 100 mg/dL in children (aged 1-16 years) were initiated. In the UC group (n=351), insulin infusion was only initiated when blood glucose exceeded 215 mg/dL twice and stopped when blood glucose concentration decreased below 180 mg/dL. Whole blood glucose was systematically measured in arterial blood at 1-hour to 4-hour intervals with an ABL700 analyzer (Radiometer Medical A/S). To convert blood glucose to mmol/L, multiply by 0.0555.

Follow-up of all patients included in the initial trial was scheduled 3 years after randomization. Patients who were infants at study inclusion were evaluated when they reached the age of 4 years so that intelligence could be uniformly quantified across the age range of the study population. Initial screening for survival status was performed via hospital notes or via contact with the general practitioner or referring pediatrician. When parents could be reached by telephone, they were invited to return to the University Hospitals, Leuven, Belgium, to have their child evaluated by a pediatrician and a psychologist. In case the parents refused to come to University Hospitals, Leuven, Belgium, it was proposed that the pediatrician and the psychologist would examine the child at his/her home or school.

To weigh any eventual difference between the TGC and UC groups against a healthy control population, patients' siblings were invited to participate in the neurocognitive evaluation. In addition, age-matched unrelated healthy children were asked to participate via school recruitment and mouth-by-mouth advertising all over Flanders, during the period required to recruit all patients. Parents of participating children, the few children who had reached 18 years at the time of follow-up, or both provided written informed consent.

The patients who participated in the RCT are further referred to as post-ICU patients to distinguish from healthy control children referred to as controls.

Death and severe disability precluding neurocognitive assessment at follow-up were a priori defined as poor outcomes.

Clinical Neurological Examination

The clinical neurological evaluation was performed by 1 pediatrician (M. Gielen) who had not been involved in the treatment of the patients in the ICU and was strictly blinded for randomization to either TGC or UC group. First, head circumference, body weight, and height were measured. Then, to exclude major neurological abnormalities, a classical neurological examination was performed. The result of the examination was scored normal or abnormal for 8 neurological domains[17,18]: (1) interaction/language skills, (2) gross motor function, (3) involuntary movements, (4) reflexes, (5) coordination and balance, (6) fine motor function, (7) cranial nerves, and (8) special senses (sensory, visual, and auditory function) (eMethods 1). An abnormal result for each of these domains was given 1 point and the sum of these domains gave the total score for neurological abnormalities.

Neurocognitive Testing

All participants were tested by 2 experienced pediatric psychologists (C.S. and K.C.), also strictly blinded for randomization to either TGC or UC group. After an extensive time of working together to guarantee similarity in judging the test results, the psychologists worked independently.

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We aimed at a broad evaluation of neurocognitive functions, as previously performed for patients with type 1 diabetes.[19] The neuropsychological test battery therefore comprised tests measuring general intellectual functioning, visual-motor integration, attention, motor coordination, inhibitory control and cognitive flexibility, verbal and visual-spatial learning and memory, and questionnaires on behavior. General intelligence was assessed with the Wechsler Intelligence Quotient (IQ) scales adapted for the Dutch language. Wechsler Preschool and Primary Scale of Intelligence-Revised[20] was used for children aged 4 years to younger than 6 years, Wechsler Intelligence Scale for Children-3rd Edition[21] was used for children aged 6 years to younger than 17 years, and Wechsler Adult Intelligence Scale-3rd Edition[22] was used for children aged 17 years or older. Total IQ, verbal IQ, and performance IQ were scored. Visual-motor integration (total standard score) was assessed with the Beery-Buktenica Developmental Test of Visual-Motor Integration, 5th Edition (all ages).[23]

Attention, motor coordination, and executive functions were analyzed by computerized tasks of the Amsterdam Neuropsychological Tasks (ANT) system.[24,25] The main advantage of the ANT, compared with paper-and-pencil tasks, is that the measurement of reaction times in combination with accuracy (error rate) contributes to the sensitivity to detect problems in these neurocognitive domains.[26] We a priori selected the 3 ANT tasks that could be performed by all children within the wide age range of our study population.[24,25,27,28] Baseline Speed assesses alertness by measuring simple reaction time to 32 visual stimuli (expressed in milliseconds). Mean reaction time and SD of the reaction time were obtained for the nondominant and dominant hands. The Tapping Task measures motor coordination. The number of taps in 10 seconds was counted for the nondominant hand, dominant hand, bimanual alternating, and bimanual synchronous. The Response Organization Objects test measures inhibitory control and cognitive flexibility by calculating the differences in reaction time and the differences in number of errors between tests of increasing demand.[28,29]

Out of the Children's Memory Scale (CMS) for children aged between 5 years and younger than 17 years, 4 tasks were selected to measure specific verbal-auditory memory and nonverbal, visual-spatial memory functions.[30] The CMS numbers test measures verbal memory span (repeating numbers forward) and verbal working memory (repeating numbers backward). Standard scores for verbal memory span and working memory were analyzed. For CMS pictures, word pairs, and dots tests, with different age versions, proportional scores were analyzed (proportion of correct responses with proportional scores ranging from 0 to 1 [higher scores reflect better performance]). The CMS pictures test assesses visual-spatial memory span (proportion correctly recalled picture locations), and the CMS word pairs and dots tests measure verbal-auditory and nonverbal, visual-spatial learning (proportion correctly completed word pairs or correctly recalled dot locations during 3 learning trials), immediate memory (proportion correctly recalled word pairs or correctly recalled dot locations), delayed memory (proportion correctly recalled word pairs or correctly recalled dot locations after delay of 25-35 minutes), and recognition (proportion correctly recognized word pairs after delay of 25-35 minutes).

The Child Behavior Checklist (CBCL for 1.5-5 years or CBCL for 6-18 years) was filled out by the parents or the child's legal guardian to assess behavioral problems.[31,32] For our study, the CBCL scores for internalizing, externalizing, and total problems were analyzed.

All these tests have been extensively used to quantify neurocognitive development in various pediatric populations.[27-29,33-36]

Statistical Analysis

The primary study goal was to analyze whether TGC caused harm to neurocognitive development, with intelligence (full-scale IQ) as the primary end point, the null hypothesis being no difference between the TGC and UC groups. A mean loss of 4 IQ points in the TGC group was considered to be the minimal effect size (exceeding the SE of the IQ tests), which is assumed to be functionally relevant.[37-40] The sample size of this study (n = 700) was determined for the primary ICU outcomes.[10] The a priori calculated statistical power to detect a loss of 4 IQ points with TGC was 82% taking into account incomplete follow-up.

Poor outcomes (death or severe disability) are reported as numbers and percentages. Significance of differences was analyzed by χ^2 testing for proportions followed by multivariable logistic regression analysis correcting for baseline risk factors (race, geographic and linguistic origin, sex, age group at randomization, history of diabetes mellitus, malignancy, a prerandomization syndrome or illness a priori defined as affecting neurocognitive development [further referred to as syndrome] as well as the diagnostic group, severity of illness, and blood glucose level on ICU admission).

For the children who were tested for neurocognitive function, results are presented as median (interquartile range [IQR]). Initial significance testing was performed with nonparametrical testing (Wilcoxon rank sum test) for continuous or ordinal variables (JMP version 9.0.0 [SAS Institute]). To exclude the possibility that incomplete follow-up induced bias, multiple data imputation using baseline factors was performed.[41] Imputation was performed with IBM SPSS Statistics 19 (SPSS Inc). Data from 10 imputed data sets were subsequently pooled to obtain an intention-to-treat analysis estimate (eMethods 2). Ninety-five percent CIs for the difference of the medians were calculated with the method proposed by Bonett and Price.[42] To further exclude any possible bias evoked by the

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poor outcomes (death or disability), a score inferior to the worst of the tested values was arbitrarily given to these patients followed by multivariable regression analysis.

To assess whether hypoglycemia during intensive care had affected neurocognitive development, patients who had experienced hypoglycemia in the TGC group were compared with patients from the UC group matched by propensity scores for baseline characteristics. Propensity score matching was performed with IBM SPSS Statistics 19 (SPSS Inc) and R statistical software version R2.10.1 (R Foundation for Statistical Computing).[43,44] One-to-one nearest neighbor matching was performed by using a caliper of 0.2 (eMethods 3). In addition, in the total population and using multivariable linear regression analysis, the independent association of hypoglycemia with the studied neurocognitive outcomes was assessed, correcting for all baseline risk factors and for randomization to either TGC or UC group.

Two-sided $P \leq .05$ was considered statistically significant. No corrections were performed for multiple comparisons.

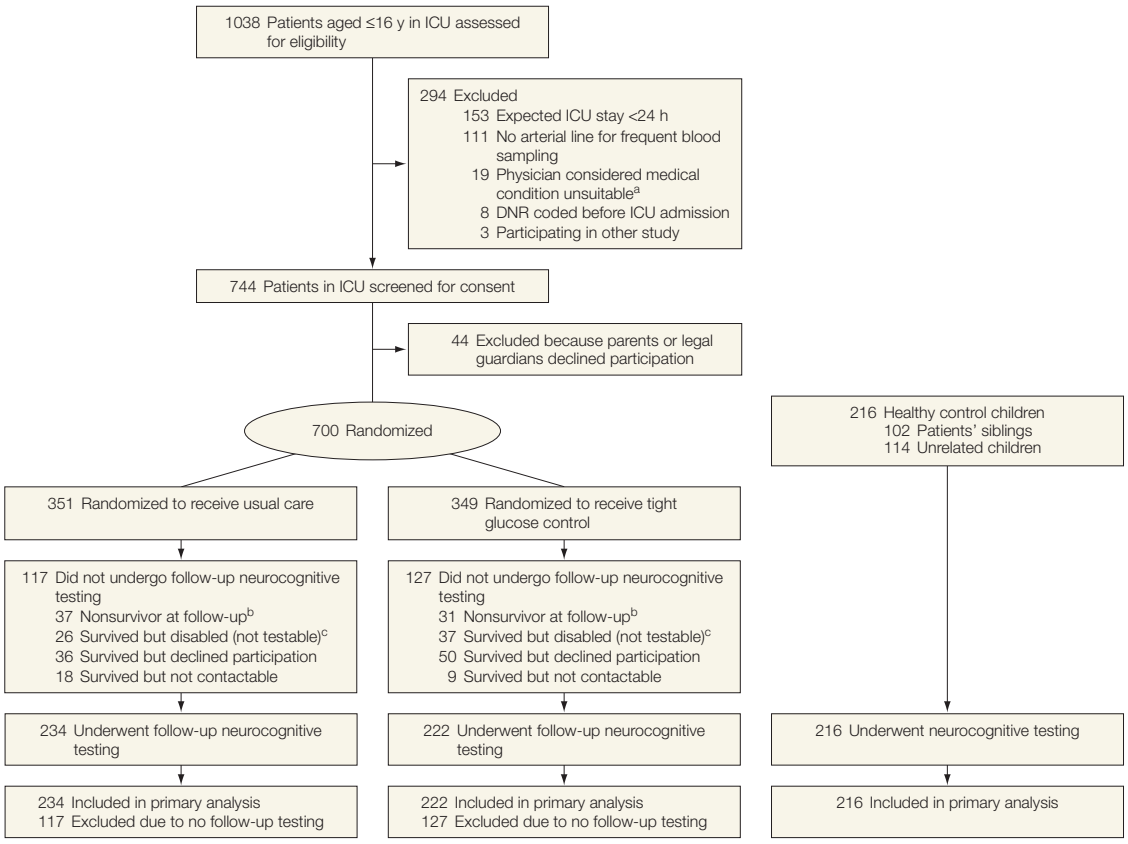
RESULTS

Follow-up was performed between August 2008 and January 2012 at a median (IQR) of 3.9 (3.8-4.1) years after inclusion in the RCT.

Neurocognitive Assessment

Of the total population, 569 patients were alive and testable at follow-up. Twenty-seven children could not be reached and 86 children declined participation (16% of the total population, no difference between TGC and UC groups; $P = .42$) (FIGURE). Demographics of tested patients were comparable except for slight imbalance in race, origin, language, and the presence of a prerandomization syndrome (syndrome or illness that is known to affect neurocognitive development) (TABLE 1). These imbalances were not evoked by biased recruitment to follow-up, because similar small differences were present in the total study population (N = 700)

Figure. Flow Diagram of Study Participants



DNR indicates do not resuscitate; ICU, intensive care unit.
[a] The 19 medical disorders that were considered unsuitable by the treating physician consisted of 2 patients dependent on home ventilation, 6 patients with metabolic disorders, 2 patients for whom it was the personal opinion of the treating physician that it would be inappropriate to participate in a study in view of poor prognosis (although the patients formally did not have a DNR code), and 9 patients who had already been treated with intensive insulin therapy elsewhere before assessment for participation.
[b] Causes of death are shown in eTable 3 (available at http://www.jama.com).
[c] More information on the diagnoses of the severely disabled patients who could not be tested is shown in eTable 4.

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(Table 1). The neurocognitive testing was performed at a median (IQR) age of 5.2 (4.2-8.3) years. Eighty-three percent of the patients were tested in hospital (82.6% in TGC group vs 82.8% in UC group, $P = .96$).

The scores given by the 2 pediatric psychologists were comparable within each study group and scores did not change over the time. The subgroup of patients who were infants at the time of randomization behaved similarly to the older children for all applicable tests (P for all interaction $\geq .20$).

Intelligence. Full-scale IQ, verbal IQ, and performance IQ scores were comparable in patients in the TGC and UC groups (**Table 2**). Full-scale IQ scores were 15 points (95% CI, 12-18; $P < .001$) lower in post-ICU patients than in healthy control children (eTable 1 and eTable 2); a difference that was reduced to 9 points (95% CI, 6-12; $P < .001$) after propensity score matching for baseline risks and biometrics at follow-up.

Visual-Motor Integration. Beery-Buktenica Developmental Test of Visual-Motor Integration scores were comparable in patients in the TGC and UC groups (Table 2). In addition, post-ICU patients scored lower than healthy control children ($P < .001$) (eTable 2).

Attention, Motor Coordination, Inhibitory Control, and Cognitive Flexibility. None of the scores for the ANT tasks were worse in the TGC group than in the UC group. In the TGC group, motor coordination was actually improved (9% [95% CI, 0%-18%] to 20% [95% CI, 5%-35%] better, all $P \leq .03$) and also cognitive flexibility (19% [95% CI, 5%-33%] better, $P = .02$;

Table 1. Demographics and Blood Glucose Control in the Total ICU Population, Tested Post-ICU Population, and Healthy Controls[a]

Characteristics	Total ICU Population: Usual Care (n = 351)	Total ICU Population: Tight Glucose Control (n = 349)	Total ICU Population: P Value	Tested Post-ICU Population: Usual Care (n = 234)	Tested Post-ICU Population: Tight Glucose Control (n = 222)	Tested Post-ICU Population: P Value	Healthy Controls (n = 216)
Caucasian race[b]	327 (93.16)	314 (89.97)	.13	225 (96.15)	201 (90.54)	.02	211 (97.69)
Exclusive European[b]	315 (89.74)	296 (84.81)	.05	217 (92.74)	190 (85.59)	.01	201 (93.06)
Exclusive Dutch language	284 (80.91)	271 (77.65)	.30	196 (83.76)	170 (76.58)	.06	186 (86.11)
Male sex	199 (56.70)	202 (57.88)	.76	135 (57.69)	126 (56.76)	.85	94 (43.52)
Infant (age < 1 y) at randomization	160 (45.58)	157 (44.99)	.87	112 (47.86)	103 (46.40)	.77	NA
Diagnostic groups at randomization							
Cardiac surgery for congenital heart defects	265 (75.50)	261 (74.78)	.93	195 (83.33)	170 (76.57)	.49	NA
Complicated/high-risk surgery or trauma	38 (10.83)	36 (10.32)		19 (8.12)	22 (9.91)		NA
Solid organ transplant surgery	7 (1.99)	6 (1.72)		5 (2.14)	5 (2.25)		NA
Infectious medical disorders	16 (4.56)	16 (4.58)		6 (2.56)	8 (3.60)		NA
Neurological medical disorders	8 (2.28)	13 (3.72)		3 (1.28)	5 (2.25)		NA
Other medical disorders	17 (4.84)	17 (4.87)		6 (2.56)	12 (5.41)		NA
At randomization							
Malignancy	15 (4.27)	21 (6.02)	.31	5 (2.14)	8 (3.60)	.34	0 (0)
Diabetes	3 (0.9)	3 (0.9)	>.99	1 (0.4)	1 (0.4)	>.99	0 (0)
Syndrome[c]	133 (37.89)	151 (43.27)	.16	61 (26.07)	70 (31.53)	.19	16 (7.41)
PELOD first 24 h in ICU, median (IQR)[d]	11 (2-12)	11 (2-12)	.58	11 (2-12)	11 (2-12)	.62	NA
Socioeconomic status score, median (IQR)[e]	NA	NA		35 (24-48)	34 (24-50)	.96	42 (29-54)
At follow-up, median (IQR)							
Height, cm	NA	NA		108 (103-128)	110 (104-134)	.36	122 (108-151)
Weight, kg	NA	NA		19 (16-26)	19 (16-29)	.44	22.6 (18.0-40.7)
Head circumference, cm	NA	NA		50.7 (49.3-52.7)	51.0 (49.4-52.9)	.50	52.0 (50.7-54.0)
Age, y	NA	NA		5.1 (4.2-8.2)	5.3 (4.2-9.2)	.30	6.7 (4.7-11.5)
Patients with hypoglycemia ≤40 mg/dL in ICU	5 (1.42)	87 (24.92)	<.001	3 (1.28)	51 (22.97)	<.001	NA
Blood glucose control during ICU stay, median (IQR), mg/dL							
Admission blood glucose	136 (103-187)	128 (101-164)	.22	137 (103-187)	130 (104-159)	.26	NA
Mean morning blood glucose in ICU	126 (109-146)	89 (77-101)	<.001	128 (109-149)	89 (75-98)	<.001	NA
Lowest blood glucose in ICU	87 (70-104)	51 (40-64)	<.001	87 (70-104)	52 (40-64)	<.001	NA

Abbreviations: ICU, intensive care unit; IQR, interquartile range; NA, not applicable (values only known when the patients were seen at follow-up); PELOD, pediatric logistic organ dysfunction score.

SI conversion: To convert glucose to mmol/L, multiply by 0.0555.

[a] Data are No. (%) unless otherwise specified.

[b] Participants were classified according to race and geographical origin by the investigators. These classifications were performed to capture ethnical and regional differences in the frequency of consanguinity, which may adversely affect cognitive performance.[45]

[c] A priori defined syndrome or illness, which is known to affect neurocognitive development (eTable 4).

[d] Used as a marker for severity of illness.[46] A higher PELOD score (range of possible scores, 0-71) reflects more severe illness.

[e] Socioeconomic status of the patient's parents was calculated with a modified version of the Hollingshead 7-point scale of educational level and the 9-point scale of occupational level.[47,48] More points are given to higher educational or occupational level. Status score of an individual parent is calculated by adding the occupation value × 5, and the education value × 3. The average of the paternal and maternal score is used as the socioeconomic status score of the patient's family. A score of 66 is the highest possible score.

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Table 2. Results of Neurocognitive Test Battery in Tested Post-ICU Population and Healthy Controls[a]

Neurocognitive Tests	Healthy Controls (n = 216)	Tested Post-ICU Population: UC (n = 234)	Tested Post-ICU Population: TGC (n = 222)	*P* Value (TGC vs UC): Tested Population	*P* Value (TGC vs UC): Imputation for Missing Values[b]
Clinical neurological evaluation score (range, 0-8)	0 (0-1)	1 (0-2)	1 (0-2)	.46	.53
Intelligence (range of possible scores, 45-155)					
Full-scale IQ	103 (91-111)	88.5 (74.3-99.0)	88.0 (74.0-100.0)	.73	.75[c,d]
Verbal IQ	102 (91-114)	89.0 (76.5-101.0)	90.0 (74.0-101.0)	.72	.98
Performance IQ	103 (91-112)	88.0 (76.0-101.0)	88.0 (73.0-101.0)	.62	.78
Visual-motor integration (range, 0.9-20)	10 (8-12)	8 (7-10)	8 (6-10)	.60	.41
Attention, motor coordination and executive functions					
Alertness					
Reaction time dominant hand, msec	488 (320-704)	679 (449-938)	641 (383-933)	.18	.22
Within-patient SD of repeated tests	166 (83-385)	379 (144-623)	327 (117-603)	.19	.26
Reaction time nondominant hand, msec	501 (326-729)	647 (458-933)	612 (362-925)	.18	.18
Within-patient SD of repeated tests	193 (87-381)	325 (164-589)	255 (119-567)	.11	.18
Motor coordination (No. of taps in 10 s)					
No. of unimanual taps					
Dominant hand	35 (25-46)	28 (21-37)	30 (23-42)	.08[e]	.03[c,f]
Nondominant hand	29 (21-43)	23 (17-31)	25 (19-36)	.03[e]	.006[c,g]
No. of valid alternating taps	13 (6-30)	8 (2-18)	8 (2-20)	.96	.92
No. of valid synchronous taps	21 (12-31)	15 (8-23)	18 (10-27)	.02[h]	.02[c,i]
Inhibition and flexibility					
Δ Reaction time (inhibition), msec	209 (80-487)	340 (123-549)	259 (105-502)	.20	.12
Δ No. of errors (inhibition)	1 (0-2)	2 (0-3)	1 (0-3)	.82	.96
Δ Reaction time (flexibility), msec	550 (283-798)	679 (400-901)	548 (362-816)	.02[j]	.02[c,k]
Δ No. of errors (flexibility)	1 (0-3)	2 (0-4)	2 (0-4)	.65	.92
Memory	(n = 124)	(n = 100)	(n = 98)		
Verbal-auditory					
Numbers (range, 1-19)					
Memory span (forward)	9 (7-11)	8.0 (6.0-9.0)	7.0 (5.7-9.0)	.28	.63
Working memory (backward)	10 (8-13)	8.5 (6.0-11.0)	9.0 (6.0-10.0)	.39	.37
Word pairs (proportion of correct responses)					
Learning	0.50 (0.39-0.67)	0.43 (0.30-0.53)	0.42 (0.32-0.54)	.75	.09
Immediate memory	0.50 (0.36-0.64)	0.30 (0.20-0.50)	0.40 (0.20-0.50)	.28	.23
Delayed memory	0.40 (0.30-0.50)	0.28 (0.10-0.40)	0.30 (0.20-0.40)	.22	.38
Recognition	1.00 (0.95-1.00)	0.96 (0.87-1.00)	0.97 (0.92-1.00)	.23	.27
Nonverbal, visual-spatial (proportion of correct responses)					
Pictures: Memory span	0.89 (0.80-0.93)	0.83 (0.70-0.87)	0.83 (0.70-0.88)	.88	.44
Dots: Learning	0.89 (0.83-0.94)	0.77 (0.66-0.88)	0.77 (0.66-0.89)	.71	.67
Dots: Immediate memory	1.00 (0.75-1.00)	0.83 (0.50-1.00)	0.83 (0.53-1.00)	.67	.50
Dots: Delayed memory	1.00 (0.75-1.00)	0.83 (0.50-1.00)	0.83 (0.50-1.00)	.74	.60
Learning index (range, 50-150)	101 (90-109)	93 (78-103)	90 (82-99)	.84	.62
Behavior (by proxy), T score	(n = 206)	(n = 227)	(n = 215)		
CBCL–internalizing problems (range, 29-100)	48 (41-57)	52 (45-61)	55 (45-61)	.23	.42
CBCL–externalizing problems (range, 28-100)	46 (40-55)	50 (42-57)	51 (44-56)	.39	.31
CBCL–total problems (range, 24-100)	47 (40-55)	52 (45-59)	53 (45-59)	.44	.59

Abbreviations: CBCL, Child Behavior Checklist; ICU, intensive care unit; IQ, intelligence quotient; TGC, tight glucose control; UC, usual care.

[a] Data are median (interquartile range). For intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness (a response has to be generated between 150 and 4000 ms after the appearance of a target) and within-patient SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For inhibition and flexibility (a response has to be generated between 200 and 6000 ms; the differences in reaction time and the differences in number of errors between tests of increasing demand are calculated), higher scores reflect worse performance. For numbers within verbal-auditory memory, higher scores reflect better performance. For explanation of word pairs, pictures, and dots tests, see "Methods" section. For learning index (learning word pairs and learning dots), higher scores reflect better performance. CBCL–internalizing problems (eg, anxious/depressed behavior) and CBCL–externalizing problems (eg, aggressive behavior). T scores are standardized scores with a mean value of 50 and an SD of 10, with T scores of 60 or higher indicative for the presence of behavioral problems.[31,32]

[b] For details about imputation, see "Methods" section.

[c] Multivariable analysis with value inferior to the worst of the tested values given to nonsurvivors and not testable children.

[d] TGC vs UC, $P = .71$.

[e] UC vs healthy controls, $P < .001$; TGC vs healthy controls, $P = .003$.

[f] TGC vs UC, $P = .12$.

[g] TGC vs UC, $P = .05$.

[h] UC vs healthy controls, $P < .001$; TGC vs healthy controls, $P = .01$.

[i] TGC vs UC, $P = .04$.

[j] UC vs healthy controls, $P = .008$; TGC vs healthy controls, $P = .68$.

[k] TGC vs UC, $P = .02$.

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a posteriori calculated statistical power, 96%-99%) (Table 2). Despite improvement in the TGC group, the motor coordination performances remained inferior to those in the control group (all $P \leq .01$), but the cognitive flexibility score was comparable with that of healthy children in the TGC group ($P = .68$ vs control group) but not in the UC group ($P = .008$ vs control group). Overall, the scores for the ANT tasks, except those for cognitive flexibility, were worse in post-ICU patients than in the control group (all $P \leq .02$), although significance was lost after propensity score matching for baseline risks and biometrics at follow-up (eTable 2).

Memory. Memory could only be assessed in children aged between 5 and 17 years, because tests did not apply outside this age range. Again, no differences were present between the TGC and UC groups (Table 2). Overall, post-ICU patients performed worse than healthy children (*P* values between .05 and <.001 for most tests) (eTable 2).

Behavior. Behavior was assessed via the CBCL questionnaire filled out by the parents. The TGC and UC groups performed similarly (Table 2). Overall, post-ICU patients scored worse than healthy controls (all $P \leq .002$), although significance was lost after propensity score matching for baseline risks and biometrics at follow-up (eTable 2).

Clinical Neurological Evaluation. In the TGC group, scores for neurological abnormalities were not worse than in the UC group (Table 2). Post-ICU patients scored worse than healthy children ($P < .001$), although the significance was lost after propensity score matching for baseline risks and biometrics at follow-up (eTable 2).

Poor Outcomes

The number of patients with a poor outcome (death or disability) at follow-up was similar in the TGC (68/349 [19%]) and UC (63/351 [18%]) groups (risk-adjusted odds ratio [OR], 0.93; 95% CI, 0.60-1.46; $P = .72$) (Figure). Nine percent (31/349) of the children allocated to the TGC group and 11% (37/351) of the children in the UC group had died (risk-adjusted OR, 0.45; 95% CI, 0.21-0.94; $P = .03$) (causes of death are shown in eTable 3). Thirty-seven children in the TGC group (11%) and 26 children in the UC group (7%) were severely disabled (risk-adjusted OR, 1.20; 95% CI, 0.66-2.18; $P = .56$). In 60 of these 63 disabled children, the disability was explained by the prerandomization presence of a syndrome (eTable 4). The dominant independent determinant for severe disability at follow-up was a prerandomization syndrome (risk-adjusted OR, 44.71; 95% CI, 15.51-190.44; $P < .001$).

Association With Hypoglycemia During Intensive Care

Propensity score matching of all patients in the TGC group who experienced hypoglycemia with patients in the UC group resulted in a matched population of 160 patients (eTable 5). In this selection, 15% of patients in the TGC group had died 4 years after inclusion vs 16% of patients in the UC group ($P = .82$) and the proportion of disabled patients was also comparable (15% in the TGC group and 11% in the UC group, $P = .64$). Ninety-one patients were tested for neurocognitive development. Most neurocognitive outcomes revealed no significant differences, whereas patients who experienced TGC-induced hypoglycemia performed better for cognitive flexibility than matched patients in the UC group ($P = .04$) (TABLE 3).

In multivariable regression analysis performed on the total population of 700 patients, hypoglycemia was never a significant independent risk factor for worse neurocognitive outcomes (eTable 6). The severity of hypoglycemia also was not associated with neurocognitive outcome.

COMMENT

Four years after participating in an RCT in the pediatric ICU, treatment with TGC during ICU treatment did not increase the incidence of poor outcomes (death or severe disability) and did not adversely affect any of the tested domains of neurocognitive development. Scores for intelligence, visual-motor integration, and memory were not statistically significantly different, whereas TGC improved motor coordination and cognitive flexibility, the latter up to the level of healthy children. Hypoglycemia during ICU treatment, which often occurred with TGC, was not independently associated with worse neurocognitive outcome.

This follow-up study was performed to exclude harm evoked by TGC during ICU treatment in the pediatric population. Our finding that even minor effects of TGC on intelligence were absent, and that TGC evoked benefit for some of the more subtle domains of cognition, is striking. Indeed, in contrast with a blood glucose target of 80 to 110 mg/dL (normal for adults but not for young children), which showed circulating blood glucose levels virtually unaltered in children after cardiac surgery,[49] targeting the much lower age–normal blood glucose range in our study effectively prevented hyperglycemia but also increased the risk of brief episodes of severe hypoglycemia (from 1% to 25%).[10] Hypoglycemia is traditionally considered to be a potential cause of long-term cognitive impairment in patients with early onset diabetes mellitus.[50] However, in adolescents with type 1 diabetes who participated in the follow-up of the Diabetes Control and Complications Trial, a study that investigated the effect of tight blood glucose control with insulin, cognitive functions did not decline over time despite relatively high rates of severe hypoglycemia.[51] In adult patients who were critically ill, hypoglycemia was associated with subtle disturbances of neurocognitive functions,[52] but causality was never proven. In a large study of patients with cardiac disease,[53] only spontaneous but not insulin-induced hypoglycemia was associated with adverse outcome.

We previously measured circulating markers of neuronal and astrocyte damage in relationship to hypoglycemia during ICU treatment.[54] Although higher levels of these biomarkers were observed in children who developed hy-

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Table 3. Effect of Hypoglycemia[a]

Neurocognitive Tests	Usual Care Propensity Score Matched (n = 44)	Tight Glucose Control–Induced Hypoglycemia (n = 47)	*P* Value
Clinical neurological evaluation score (range, 0-8)	1 (0-2)	0 (0-1)	.09
Intelligence (range, 45-155)			
Full-scale IQ	84 (72-95)	89 (76-100)	.35
Verbal IQ	86 (75-101)	92 (77-101)	.27
Performance IQ	86 (74-100)	88 (73-105)	.69
Visual-motor integration (range, 0.9-20)	8 (7-10)	9 (7-10)	.41
Attention, motor coordination and executive functions			
Alertness			
Reaction time dominant hand, msec	895 (746-1115)	895 (739-1089)	.66
Within-patient SD of repeated tests	613 (408-811)	567 (378-725)	.30
Reaction time nondominant hand, msec	901 (704-1099)	915 (658-1022)	.89
Within-patient SD of repeated tests	570 (308-732)	555 (305-711)	.61
Motor coordination (No. of taps in 10 s)			
No. of unimanual taps			
Dominant hand	20 (17-28)	24 (19-29)	.17
Nondominant hand	19 (14-23)	19 (17-25)	.16
No. of valid alternating taps	5 (1-10)	5 (2-11)	.80
No. of valid synchronous taps	8 (3-14)	13 (5-19)	.17
Inhibition and flexibility			
Δ Reaction time (inhibition), msec	536 (271-905)	414 (223-609)	.11
Δ No. of errors (inhibition)	3 (1-5)	1 (0-4)	.45
Δ Reaction time (flexibility), msec	884 (637-1006)	634 (405-813)	.04
Δ No. of errors (flexibility)	1 (–1 to 4)	1 (–1 to 4)	.82
Memory			
Verbal-auditory			
Numbers (range, 1-19)			
Memory span (forward)	7 (6-9)	5 (5-11)	.67
Working memory (backward)	6 (5-11)	8 (6-10)	.67
Word pairs (proportion of correct responses)			
Learning	0.50 (0.21-0.52)	0.37 (0.30-0.52)	.75
Immediate memory	0.36 (0.10-0.45)	0.40 (0.05-0.55)	.67
Delayed memory	0.29 (0.10-0.40)	0.40 (0.05-0.45)	.75
Recognition	1.00 (0.75-1.00)	0.87 (0.75-1.00)	.41
Nonverbal, visual-spatial (proportion of correct responses)			
Pictures: Memory span	0.67 (0.52-0.91)	0.77 (0.62-0.83)	.91
Dots: Learning	0.72 (0.54-0.81)	0.72 (0.47-0.89)	.75
Dots: Immediate memory	0.83 (0.31-0.83)	0.67 (0.33-0.92)	>.99
Dots: Delayed memory	0.83 (0.31-0.83)	0.67 (0.50-0.92)	.83
Learning index (range, 50-150)	93 (67-96)	87 (84-95)	.91
Behavior (by proxy), T score			
CBCL–internalizing problems (range, 29-100)	55 (44-63)	50 (41-62)	.75
CBCL–externalizing problems (range, 28-100)	52 (43-57)	51 (44-56)	.73
CBCL–total problems (range, 24-100)	53 (44-61)	51 (45-58)	.42

Abbreviations: CBCL, Child Behavior Checklist; ICU, intensive care unit; IQ, intelligence quotient.

[a] Data are median (interquartile range). For intelligence and visual-motor integration, higher scores reflect better performance. For reaction time alertness (a response has to be generated between 150 and 4000 ms after the appearance of a target) and within-patient SD of repeated tests, higher scores reflect worse performance. For motor coordination, higher scores reflect better performance. For inhibition and flexibility (a response has to be generated between 200 and 6000 ms; the differences in reaction time and the differences in number of errors between tests of increasing demand are calculated), higher scores reflect worse performance. For numbers within verbal-auditory memory, higher scores reflect better performance. For explanation of word pairs, pictures, and dots tests, see "Methods" section. For learning index (learning word pairs and learning dots), higher scores reflect better performance. CBCL–internalizing problems (eg, anxious/depressed behavior) and CBCL–externalizing problems (eg, aggressive behavior). CBCL T scores are standardized scores with a mean value of 50 and an SD of 10, with T scores of 60 or higher indicative for the presence of behavioral problems.[31,32]

poglycemia, they were already increased before the hypoglycemic insult and related to the severity of illness. Hypoglycemia, which was always rapidly detected and treated, did not affect these markers. In addition, the current functional neurocognitive follow-up could not attribute a causal damaging role to brief hypoglycemia. This suggests that transient hyperglycemia during critical illness may be more damaging to the brain than brief hypoglycemia, at least in those ICU settings that use accurate tools to monitor blood glucose for titration of insulin.[55-57] Indeed, the use of inaccurate glucose monitoring tools recently was shown to evoke risk of harm associated with hypoglycemia.[58,59] Furthermore, experimental evidence supports the damaging effect of hyperglycemia and of increased glucose levels after hypoglycemia, more so than hypoglycemia per se.[60] Therefore, the mode of correcting hypoglycemia, avoiding large fluctuations of hyperglycemia following hypoglycemia, similar to what was performed in our study,[10] may be important to avoid brain damage. The data by no means argue against all efforts to avoid hypoglycemia. However, when trained nurses and accurate monitoring tools are available, efforts to avoid hyperglycemia in children who are critically ill should not be abandoned solely because of the risk of brief hypoglycemia.

The finding that specifically motor coordination and cognitive flexibility were improved by TGC during ICU treatment suggests that the controlling brain areas may be specifically sensitive to hyperglycemia. These regions comprise the prefrontal cortex, as evidenced in patients with frontal lobe lesions and by neuroimaging studies of executive tasks.[61-63] Deleterious effects of hyperglycemia to the frontal cortical areas are in line with previous observations of children with diabetes mellitus[13] and with results from recent neuropathological studies in critical illness.[16] Imaging studies are required to investigate this further.

Our data also provide evidence that some of the neurocognitive impairment previously reported in children

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who have been critically ill could be beneficially affected by altering medical care.[64-66] This is in line with previous studies showing that the choice of surgical technique for correction of congenital cardiac anomalies affects the cognitive potential of young children.[67-69]

The strength of our study is the documentation of long-term vital status of all 700 patients and the neurocognitive follow-up data (dead, disabled, or quantified by testing) of 84% of this population. The recruitment rate was high and therefore risk of biased conclusions was low. The imputation strategies, performed to correct for missing data, confirmed the results. The sample size was large enough to exclude minimal harm of TGC with a high statistical power. In addition, the exhaustive and meticulous ascertainment of neurocognitive status certainly was a strength.

Some weaknesses of our study should be highlighted. First, the age of the youngest children in the study, who were infants at the time of inclusion, did not allow to assess memory in that subgroup, because tests are only available on children aged 5 years or older. However, all other cognitive functions could be assessed and did not suggest specific vulnerability of this subgroup. Nevertheless, a further follow-up of these children is needed. Second, neuroimaging studies were not performed to further define the most vulnerable areas in the brain. Third, given the high proportion of patients with cardiac surgery, extrapolation to other ICU populations should be performed with caution. Fourth, this was a single-center trial; therefore, the experience of the clinical staff may have weighed heavily on the results. Nevertheless, this is a proof-of-concept study, performed in a well-controlled setting of an RCT, which was able to address the key issue of potential harm to neurocognitive outcome evoked by hyperglycemia vs hypoglycemia during childhood critical illness. Because randomized trials that deliberately induce hypoglycemia in patients are impossible for evident ethical considerations, our study provides high-quality data to fill this gap in clinical knowledge.

In conclusion, 4 years after childhood critical illness, TGC to age-adjusted normoglycemia in an experienced ICU, despite having frequently evoked brief episodes of hypoglycemia, did not cause any detectable harm to intelligence and improved other areas of cognition.

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Study concept and design: Mesotten, Gielen, Sterken, Vlasselaers, Lemiere, Lagae, Vanhorebeek, Wouters, Van den Berghe.

Acquisition of data: Gielen, Sterken, Claessens, Vlasselaers, Gewillig, Eyskens.

Analysis and interpretation of data: Mesotten, Gielen, Sterken, Hermans, Van den Berghe.

Drafting of the manuscript: Mesotten, Gielen, Sterken, Van den Berghe.

Critical revision of the manuscript for important intellectual content: Mesotten, Gielen, Sterken, Claessens, Hermans, Vlasselaers, Lemiere, Lagae, Gewillig, Eyskens, Vanhorebeek, Wouters, Van den Berghe.

Statistical analysis: Mesotten, Gielen, Sterken, Hermans, Van den Berghe.

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Study supervision: Mesotten, Lemiere, Lagae, Gewillig, Eyskens, Vanhorebeek, Van den Berghe.

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