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Tight Glycemic Control After Pediatric Cardiac Surgery in High-Risk Patient Populations

Abstract

Background—Our previous randomized, clinical trial showed that postoperative tight glycemic control (TGC) for children undergoing cardiac surgery did not reduce the rate of health care–associated infections compared with standard care (STD). Heterogeneity of treatment effect may exist within this population.

Methods and Results—We performed a post hoc exploratory analysis of 980 children from birth to 36 months of age at the time of cardiac surgery who were randomized to postoperative TGC or STD in the intensive care unit. Significant interactions were observed between treatment group and both neonate (age ≤30 days; P=0.03) and intraoperative glucocorticoid exposure (P=0.03) on the risk of infection. The rate and incidence of infections in subjects ≤60 days old were significantly increased in the TGC compared with the STD group (rate: 13.5 versus 3.7 infections per 1000 cardiac intensive care unit days, P=0.01; incidence: 13% versus 4%, P=0.02), whereas infections among those >60 days of age were significantly reduced in the TGC compared with the STD group (rate: 5.0 versus 14.1 infections per 1000 cardiac intensive care unit days, P=0.02; incidence: 2% versus 5%, P=0.03); the interaction of treatment group by age subgroup was highly significant (P=0.001). Multivariable logistic regression controlling for the main effects revealed that previous cardiac surgery, chromosomal anomaly, and delayed sternal closure were independently associated with increased risk of infection.

Conclusions—This exploratory analysis demonstrated that TGC may lower the risk of infection in children >60 days of age at the time of cardiac surgery compared with children receiving STD. Meta-analyses of past and ongoing clinical trials are necessary to confirm these findings before clinical practice is altered.

Keywords

blood glucose, critical care, heart diseases, hyperglycemia, pediatrics

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Tight Glycemic Control after Pediatric Cardiac Surgery in High-Risk Patient Populations: A Secondary Analysis of the Safe Pediatric Euglycemia after Cardiac Surgery Trial

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Abstract

Background—Our previous randomized clinical trial showed that post-operative tight glycemic control (TGC) for children undergoing cardiac surgery did not reduce the rate of healthcare-associated infections compared to standard care (STD). Heterogeneity of treatment effect may exist within this population.

Methods and Results—We performed a post-hoc exploratory analysis on 980 children from birth to 36 months at the time of cardiac surgery who were randomized to post-operative TGC or STD in the intensive care unit. Significant interactions were observed between treatment group and both neonate (age ≤30 days, P=0.03) and intraoperative glucocorticoid exposure (P=0.03) on the risk of infection. The rate and incidence of infections in subjects ≤60 days old were significantly increased in the TGC group compared to the STD group (rate 13.5 vs. 3.7 infections/1,000 CICU days, P=0.01; incidence 13% vs. 4%, P=0.02), while infections among those >60 days of age was significantly reduced in TGC compared to STD (rate 5.0 vs. 14.1 infections/1,000 CICU days, P=0.02; incidence 2% vs. 5%, P=0.03); the treatment group by age subgroup interaction was highly significant (P=0.001). Multivariable logistic regression controlling for the main effects revealed that previous cardiac surgery, chromosomal anomaly, and delayed sternal closure were independently associated with increased risk of infection.

Conclusions—This exploratory analysis demonstrated that TGC may lower the risk of infection in children >60 days old at the time of cardiac surgery compared to children receiving STD. Meta-

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analyses of past and ongoing clinical trials are necessary to confirm these findings before altering clinical practice.

Keywords

tight glycemic control; hyperglycemia; pediatrics; critical care; congenital heart disease

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Pediatric patients with critical illness experience high rates of hyperglycemia while hospitalized in the intensive care unit. Almost 90% of children undergoing cardiac surgery develop hyperglycemia in the post-operative period. [1-4] Previous observational studies provide conflicting evidence about the association between hyperglycemia and morbidity and mortality in these patients. [3, 5-7] Data from adult cardiac surgical populations [8] suggested the need for an experimental trial to determine whether post-operative tight glycemic control (TGC) with insulin therapy provided benefit over standard blood glucose management. We previously reported the results of the Safe Pediatric Euglycemia after Cardiac Surgery (SPECS) trial [9] where we compared TGC to standard care (STD) in patients from birth to 36 months undergoing cardiac surgery with cardiopulmonary bypass, and showed that TGC did not reduce the incidence of post-operative healthcare-associated infections or mortality.

Though we found no differences between the treatment and standard care groups in the SPECS trial, it remains possible that heterogeneity of treatment effect exists across the study population; both the effectiveness and safety of the treatment can vary between patients with different risks for the primary outcome and treatment harm. [10] Therefore, we aimed to investigate whether there were differential effects of TGC on outcomes in certain identifiable subgroups within the SPECS trial cohort. We focused this analysis on subgroups believed *a priori* to be at higher risk for infections and other morbidities. The results of this exploratory analysis are meant to inform subsequent research on TGC in critically ill children so that conflicting evidence and remaining knowledge gaps can be specifically addressed in future experimental trials and meta-analyses.

Methods

The present study is a post-hoc analysis of the SPECS study database: the SPECS trial methods, statistical analysis plan, and results have been published previously. [9, 11] The SPECS trial (ClinicalTrials.gov number NCT00443599) was a two-center, randomized, controlled trial that enrolled 980 children from birth to 36 months at the time of surgery with cardiopulmonary bypass who received post-operative care in the cardiac intensive care unit (CICU) at either Boston Children's Hospital or the University of Michigan C.S. Mott Children's Hospital. Patients were randomized to receive either TGC (targeting normoglycemia; 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or STD during their recovery in the CICU. Insulin infusions were used to maintain blood glucose levels in the TGC group and doses were titrated according to a proportional-integral-derivative algorithm, which is modeled on beta cell physiology. [12, 13] Both treatment groups were monitored with subcutaneous continuous glucose monitors to assist in glucose control and avoidance of hypoglycemia.

The primary outcome for the trial was incidence of 30-day healthcare-associated infections, which included pneumonia, bloodstream, urinary tract, and surgical site infections, as defined by Centers for Disease Control and Prevention (CDC), per 1,000 CICU days. [14] Secondary outcomes included mortality, cardiac index, duration of vasoactive support and mechanical ventilation, and CICU length of stay. Cardiac index was determined on postoperative day 2 in patients who were mechanically ventilated, sedated, and had a superior vena cava or pulmonary artery catheter in situ. We calculated cardiac index by the Fick principle using oxygen consumption (VO_2) measured by indirect calorimetry, hemoglobin concentration, and the difference between arterial and mixed venous oxygen saturation, as previously validated. [15] In the overall cohort, there was no treatment effect identified in any of the primary or secondary outcomes. [9]

To compare infection rates of SPECS subjects to historical trends we compiled infection data for children less than 3 years of age who were admitted to the Boston Children's Hospital CICU after cardiopulmonary bypass surgery but who did not participate in SPECS. All patients meeting these criteria between 1/1/2005 and 12/31/2012 were included. Infections in non-study patients were defined according to the same CDC criteria used in SPECS and were adjudicated by the same individuals.

The study was approved by the institutional review boards at both Boston Children's Hospital and the University of Michigan CS Mott Children's Hospital. Parents and/or guardians of the patients gave written informed consent.

Statistical analysis

We previously reported pre-specified, high-risk subgroup analyses for patients with a Risk Adjustment in Congenital Heart Surgery (RACHS-1) category [16] of 3 or higher (or not assignable), or a length of stay in the CICU of 3 days or longer; the latter analysis was based on a post-randomization factor. [9] We subsequently performed several stratified post-hoc analyses to determine whether TGC had a differential effect on infection incidence in seven other specific subgroups of the patient cohort. Based on chance alone, we would expect that 0.35 tests out of 7 tests for interaction would be statistically significant at the $P<0.05$ level. The variables used for stratification were those that identified certain subgroups at greater risk of infection and other post-operative morbidities. Seven risk factors present prior to protocol initiation were considered: 1) age at surgery (≤30 vs. >30 days), 2) previous cardiac surgery, 3) chromosomal anomaly, 4) intraoperative glucocorticoid therapy, 5) non-biologic surgical implant used for repair, 6) delayed sternal closure, and 7) first post-operative blood glucose (≥110 vs. <110 mg/dL). Some of these variables – for example, surgical complexity and delayed sternal closure – have been associated with increased risk of healthcare-associated infection in prior analyses, [17- 19] whereas others (e.g., chromosomal anomalies and age) have been known to be associated with mortality and morbidity generally, but not specifically with infection.

Within a subgroup, the effect of tight glycemic control on infection was assessed with the use of odds ratios and exact 95% confidence intervals derived from conditional logistic regression. Potential differential effects of TGC on infection across subgroups were analyzed with the use of exact logistic regression that included the interaction between

treatment group and risk factor after including both as main effects. Given the observed heterogeneity of treatment effect by age at surgery, we explored logistic regression models that included the effects of treatment group, age subgroup, and their interaction, using different age cutoffs. We then used maximum likelihood and a likelihood ratio test-based confidence interval to select an optimal age cutoff. Using this optimal age cutoff we then assessed the potential differential effects of TGC on other outcomes across age subgroups using exact logistic regression for binary outcomes, exact Poisson regression for count outcomes or rates, Cox proportional hazards regression for time-to-event outcomes, and linear regression for continuous outcomes. To explore other potential predictors of infection, multivariable stepwise logistic regression was used. Infections rates in non-study patients ≤60 days old were compared to rates in non-study patients >60 days old using exact Poisson regression. All reported P values are two-sided. Statistical analyses were performed with the use of SAS software, version 9.3. The reporting of results below follows the "Guidelines for Reporting Subgroup Analysis". [20]

Results

All 980 subjects from the original SPECS trial were included in the analyses. Table 1 displays the proportion of subjects with any 30-day healthcare-associated infection and the odds ratio (OR) for infection by treatment arm (TGC vs. STD) within each of the subgroups and the results of the associated tests for interaction. Exact logistic regression analyses demonstrated significant interactions between treatment group and both neonate (age ≤30 days, P=0.03) and intraoperative glucocorticoid use (P=0.03) on the risk of infection (Table 1). Though the point estimates suggested a possible harmful effect of TGC in neonates (age ≤30 days at surgery) and a possible benefit of TGC in patients who did not receive intraoperative glucocorticoids, neither effect was statistically significant at the 0.05 level (P=0.07 and P=0.09, respectively).

Given the observed heterogeneity of treatment effect by age at surgery, we next sought to determine empirically an optimal age cutoff. We explored this by running logistic regression models that included the main effects of treatment group and age subgroup and the interaction term as covariates, where age subgroup was defined using different cutoffs from 30 days to 12 months (Figure 1). Plotting the log likelihood from these models versus age cutoff demonstrated that an age cutoff of 59 days (95% confidence interval 55-71 days via the likelihood ratio test) best discriminated two age subgroups with differential risk of infection based on treatment arm. The difference in model characteristics was negligible when comparing models using an age cutoff of ≤59 days vs. ≤60 days, so for subsequent analyses and ease of reporting we defined the age subgroups as those ≤60 days or >60 days at the time of surgery.

The comparison of the infection outcome between treatment groups within the empirically derived age subgroups is shown in Table 2. The rate and incidence of healthcare-associated infections in subjects ≤60 days of age were significantly increased among those in the TGC group compared to the STD group (rate 13.5 vs. 3.7 infections/1,000 CICU days, P=0.01; incidence 13% vs. 4%, P=0.02), while the rate and incidence of infections among those >60 days of age were significantly reduced in the TGC group compared to the STD group (rate

5.0 vs. 14.1 infections/1,000 CICU days, P=0.02; incidence 2% vs. 5%, P=0.03). The treatment group by age subgroup interactions were highly significant (P=0.001 for each). These analyses did not appreciably change with adjustment for site. There was a differential treatment group by age subgroup effect across the four CDC-defined infection types.

In light of the opposing effects of treatment on infection in the two age subgroups, ≤60 days and 60 days to 3 years, we did not find any statistically significant differences in the baseline characteristics between treatment groups across the age subgroups, as detailed in Supplemental Table 1. Our analysis of the historical Boston Children's Hospital CICU cohort demonstrated that younger patients had a significantly lower overall infection rate compared to older patients (8.0 infections/1,000 CICU days in 1,061 patients ≤60 days of age vs. 12.7 infections/1,000 CICU days in 2,035 patients >60 days; P<0.001).

Blood glucose management differed slightly across the two age subgroups with the percentage of subjects receiving insulin being slightly higher in the younger subgroup (age ≤60 days: TGC 95% vs. STD 6%; age >60 days: TGC 89% vs. STD <1%; interaction P=0.048) but was otherwise not distinguishable. Rates of any hypoglycemia (blood glucose <60 mg/dL) were similarly (interaction P=0.84) elevated in the TGC arm compared with the STD arm in both the younger cohort (TGC 35% vs. STD 18%) and the older cohort (TGC 13% vs. STD 7%). The overall time-weighted glucose average (TWGA) was significantly different (P<0.001) between treatment groups in both age subgroups [age ≤60 days: TGC median 107 (interquartile range 100-115) vs. STD 112 (104-125) mg/dL; age >60 days: TGC 114 (106-122) vs. STD 124 (111-140) mg/dL]. Examination of daily TWGA revealed that TWGA in the TGC group was significantly lower on days 1 and 2 compared to the STD group for patients ≤60 days, while in the older cohort the TWGA difference between treatment arms extended to 3 days, increasing the duration of exposure to treatment differences from TGC within the >60 days subgroup (Figure 2).

Secondary study outcomes were largely similar between treatment groups across the age subgroups with the exceptions of cardiac index and red blood cell transfusions, as shown in Table 3. In the younger cohort (≤60 days) there was no benefit of TGC on cardiac index on postoperative day 2 (TGC 0.9 vs. STD 1.3 L/min/m^2; P=0.12), while in the older cohort there appeared to be a 26% increase with TGC (TGC 2.4 vs. STD 1.9 L/min/m^2; P=0.03). The interaction between treatment group and age subgroup for this analysis was not significant (P=0.15). Further, in all subjects potentially eligible for cardiac index measurement (those intubated on post-operative day 2), there were no differences between treatment groups in mortality, length of CICU or hospital stay, length of vasoactive support, or transfusions in the >60 days subgroup.

There was an increased incidence of transfusion amongst those ≤60 days randomized to TGC (TGC 76% vs. STD 63%; P=0.04), while there was no difference between treatment groups in the >60 days subgroup. The frequency of blood glucose sampling in the overall TGC cohort was greater than in the STD cohort (TGC mean 17 times per CICU day vs. STD 4 times per CICU day). The interaction between treatment group and age subgroup for this analysis was not significant at the 0.05 level (P=0.058).

To explore the potential effects of other factors present prior to protocol initiation on infection, we performed multivariable stepwise logistic regression adjusting for treatment group, age subgroup, and their interaction. Other factors significantly associated with infection included previous cardiac surgery [OR (95% CI) 3.08 (1.41-6.72); P=0.003], chromosomal anomaly [3.05 (1.39-6.51); P=0.005], and delayed sternal closure [4.32 (1.83-10.19); P<0.001]. Although intraoperative glucocorticoid use differed by age (71% subjects ≤60 days received glucocorticoids vs. 45% subjects >60 days; P<0.001), further adjustment for intraoperative glucocorticoid use did not appreciably affect these results. Similarly, further adjustment for site did not appreciably affect the results.

Discussion

In this exploratory analysis of our study cohort from a large randomized controlled trial of tight glycemic control we found differential response to the intervention among patients ≤60 days versus those >60 days of age at the time of surgery. Our analysis suggests that younger patients had an increased rate of healthcare-associated infections with TGC compared to STD while the older patients had a lower rate with TGC compared to STD. There is a history of younger children having increased mortality with insulin therapy in the NIRTURE trial. [21] The NIRTURE study was ongoing at the time of the design of our trial and was subsequently halted early due to potential for harm in the treatment group. Other TGC trials in children [22-24] have not reported analyses of the interaction of treatment group with age subgroups.

To our knowledge, there are no other data suggesting a 60-day age cutoff for differential response to TGC. It is conceivable that TGC confers benefits that have more relevance to the older child whose maternally-acquired, antibody-mediated immunity has waned, [25, 26] as opposed to the infant who also may be more susceptible to protocol-associated hypoglycemia and anemia.[27, 28] These theories will remain speculative, however, until further data can be analyzed confirming the presence of a differential effect above and below 60 days of age in other TGC trial populations.

Upon initial examination of our data, there appeared to be a low rate of infection in the patients randomized to the STD arm in the younger age subgroup. These patients typically have more complex surgery, higher rates of delayed sternal closure, greater exposure to intravenous catheters, and longer CICU stays, and thus might be expected to have a higher infection rate than older infants and children. In order to determine whether the low rate of infection observed in STD subjects ≤60 days old was related to the study procedures used, we evaluated historical data from non-study patients treated in the Boston Children's Hospital CICU. These rates, assessed over the years 2005 to 2012 and previously unpublished, showed similar trends to the rates seen in SPECS. We concluded that the relationship between infection rates in younger (≤60 days) compared to older patients observed in the STD arm of the SPECS trial was consistent with historical trends.

The striking interaction between treatment group and age subgroup on infection rates led us to investigate other clinical outcomes to further explore the benefits of TGC in the older patients. We observed that patients >60 days treated with TGC had significantly higher

cardiac index on post-operative day 2 compared to those in the STD arm, though the interaction between treatment group and age subgroup on this outcome was not statistically significant. This analysis was limited to those in the Boston Children's Hospital CICU with a central venous catheter in the superior vena caval circulation, and who remained intubated on the second post-operative day, as the measurement of oxygen consumption was conducted via the ventilator exhalation valve. Though it is a smaller subset of the overall cohort (N=191), this group of patients, due to higher illness severity, may be most likely to derive benefit from TGC if benefit exists. Both *in vitro* studies and prior clinical reports [29-32] demonstrate the potential benefits to the myocardium of controlling blood glucose with insulin infusion, specifically in mitigating the effects of ischemia-reperfusion injury. Improved myocardial recovery should lead to other important outcome differences, but we observed similar durations of mechanical ventilation, vasoactive support, and CICU and hospital length of stay between treatment arms in the >60 days subgroup. However, these outcomes were calculated for the entire >60 days subgroup, so it may be that only those patients with greater post-operative organ dysfunction (e.g., those mechanically ventilated greater than 48 hours) reap the benefits of TGC. Further analysis of past and ongoing pediatric TGC clinical trials, focusing on patients with the greatest illness severity, may elucidate the possible benefits of TGC to cardiopulmonary recovery.

Younger patients in the TGC arm also had a higher transfusion rate compared to the STD arm, and there was a trend toward a significant interaction between treatment group and age subgroup on transfusion (P=0.058). The increased transfusion rate in the TGC subjects in the ≤60 days cohort is likely a reflection of the increased frequency of blood glucose sampling in the overall TGC cohort compared with STD. Given the smaller body mass and circulating blood volume in the ≤60 days cohort, a similar volume of blood drawn would represent a greater relative amount of blood loss, possibly leading to an increased transfusion rate. This would explain why the same difference in number of blood draws was not associated with increased transfusion rate in the older cohort. We attempted to mitigate this effect in the trial design by using a blood conservation device as well as a bedside glucose meter that required small amounts of blood. There are important limitations to the findings reported in this manuscript. Most importantly, these are exploratory findings based on our initial observation that statistically significant interactions existed between treatment group and age subgroup on rate and incidence of infection. Although there is biologic plausibility for differential immune function at 60 days of age, the age cutoff we report here has not been suggested before in the critical care or TGC clinical literature. Some strengths of our analysis, however, are that this secondary analysis showed a statistically significant treatment group with age subgroup interaction on our primary outcome variable, the 95% confidence interval for the optimal age cutoff was fairly tight (55-71 days), and the characteristics of our STD cohort are consistent with a historical CICU population. We have conducted our analysis and reported the findings in accordance with guidelines recommended by other authors for subgroup analyses of randomized clinical trials. [20, 33] To remain consistent with these recommendations, the findings herein should be interpreted conservatively. The results are appropriately considered hypothesis-generating, rather than confirmatory. It will be crucial to evaluate whether patients greater than 60 days of age demonstrate benefit from TGC in analyses of recent and ongoing clinical trials in the context of a planned meta-analysis.

However, based on the overall null finding in the trial, and the results of this analysis, we would not recommend post-operative TGC for patients ≤60 days of age who undergo cardiac surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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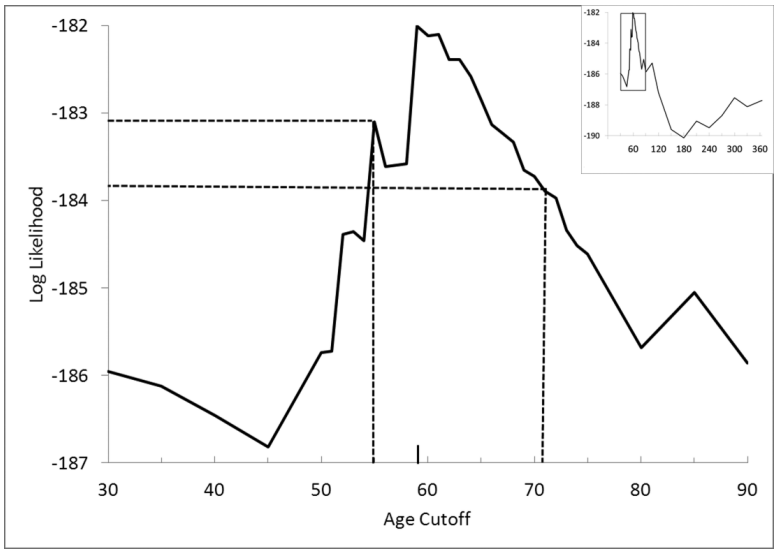

Figure 1.

Exploring the age cutoff. Plot of the log likelihood from logistic regression models, which included the main effects of treatment group and age subgroup (as defined using different age cutoffs) and the interaction term as covariates, versus age cutoff. The maximum likelihood estimate (MLE) is 59 days (confidence interval 55-71 days).

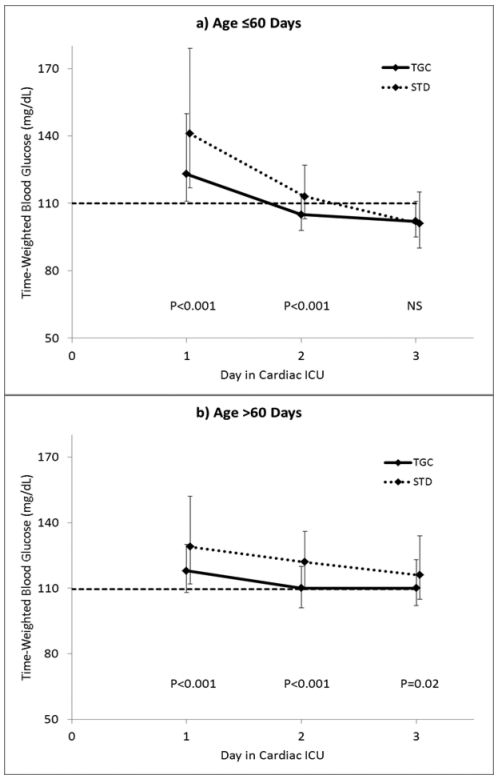

Figure 2.

Time-weighted Blood Glucose Average by Day, According to Treatment Group and Age Subgroup. The panels show time-weighted blood glucose averages (TWBA) calculated from all blood glucose samples on the day of post-operative admission to the cardiac intensive care unit (CICU) (day 1) and the subsequent two days (7 a.m. to 6:59 a.m.). Panel A shows the TWGA by day for subjects ≤60 days old at the time of surgery, while Panel B shows the TWGA by day for subjects >60 days old. The points represent the medians, while the error bars extend to the 25th and 75th percentiles. NS denotes not significant.

Table 1

Effect of Tight Glycemic Control on Healthcare-Associated Infections in Subgroups

Subgroup	Patients, No.		Patients with Infection[a], No. (%)		Odds Ratio (Exact 95% CI)	Exact *P* Value for Interaction[b]
	TGC	STD	TGC	STD		
Overall	490	490	24 (5)	24 (5)	1.00 (0.54-1.87)	-
RACHS-1 category[c]						0.09
≥3 or Not assignable	263	250	21 (8)	15 (6)	1.36 (0.65-2.91)	
1-2	227	240	3 (1)	9 (4)	0.34 (0.06-1.40)	
Age at surgery						0.03
≤30 days	99	99	12 (12)	4 (4)	2.95 (0.85-13.05)	
>30 days	391	400	12 (3)	20 (5)	0.60 (0.26-1.31)	
Previous cardiac surgery						0.37
Yes	119	118	7 (6)	10 (8)	0.68 (0.21-2.05)	
No	371	372	17 (5)	14 (4)	1.23 (0.56-2.74)	
Chromosomal anomaly						0.33
Yes	94	98	5 (5)	9 (9)	0.56 (0.14-1.94)	
No	396	392	19 (5)	15 (4)	1.27 (0.60-2.72)	
Intraoperative glucocorticoid therapy						0.03
Yes	255	247	19 (7)	11 (4)	1.73 (0.76-4.11)	
No	235	243	5 (2)	13 (5)	0.39 (0.11-1.18)	
Implant left during surgery						1.0
Yes	317	320	18 (6)	19 (6)	0.95 (0.46-1.96)	
No	173	170	6 (3)	5 (3)	1.19 (0.30-5.01)	
Delayed sternal closure						0.53
Yes	63	58	10 (16)	7 (12)	1.37 (0.43-4.59)	
No	427	432	14 (3)	17 (4)	0.83 (0.37-1.81)	
First post-operative blood glucose						1.0
>110 mg/dL	352	356	19 (5)	19 (5)	1.01 (0.50-2.06)	
≤110 mg/dL	138	134	5 (4)	5 (4)	0.97 (0.22-4.32)	

TGC denotes Tight Glycemic Control, STD Standard Care, CI confidence interval, RACHS-1 Risk Adjustment in Congenital Heart Surgery, and CICU cardiac intensive care unit.

[a] Healthcare-associated infections include pneumonia, bloodstream, and urinary tract infections, which were tracked for up to 30 days in the CICU or until 48 hours after discharge from the CICU, and surgical site infections, which were tracked for 30 days after the index procedure. For patients who remained in the CICU for more than 30 days, the number of patient-days in the CICU was considered to be 30.

[b] The *P* values for the interaction between treatment group and risk factor were calculated from logistic regression models including the main effects and interaction term as covariates.

[c] The scale for RACHS-1 categories ranges from 1 to 6, with higher categories indicating greater risk.

Table 2

Healthcare-Associated Infections, According to Treatment Group and Age Subgroup

Infections Outcome	Age ≤60 Days		Relative Risk or Odds Ratio (Exact 95% CI)	Age >60 Days		Relative Risk or Odds Ratio (Exact 95%)	Exact *P* Value for Interaction[a]
	TGC (n=128)	STD (n=113)		TGC (n=362)	STD (n=377)		
Infections[b], no. of patients (%)							
Any infections							
Yes	16 (13)	4 (4)	3.87 (1.20-16.43)	8 (2)	20 (5)	0.40 (0.15-0.97)	0.001
No	112 (88)	109 (96)		354 (98)	357 (95)		
No. of infections							
0	112 (88)	109 (96)		354 (98)	357 (95)		0.001
1	16 (13)	4 (4)		8 (2)	18 (5)		
2	0	0		0	2 (<1)		
30-day rate of healthcare-associated infections, no. of infections/1,000 days in CICU	13.5	3.7	3.68 (1.19-15.11)	5.0	14.1	0.39 (0.15-0.92)	0.001
Type of infection, no.							
Pneumonia	1	0		2	3		
Bloodstream	3	0		0	4		
Urinary tract	1	0		1	6		
Surgical site	11	4		5	9		

TGC denotes Tight Glycemic Control, STD Standard Care, CI confidence interval, and CICU cardiac intensive care unit.

[a]The *P* values for the interaction between treatment group and age subgroup were calculated from logistic regression models for the proportion of subjects with any infection or exact Poisson regression models for the number of infections and 30-day infection rate. These models included the main effects and interaction term as covariates.

[b]Healthcare-associated infections include pneumonia, bloodstream, and urinary tract infections, which were tracked for up to 30 days in the CICU or until 48 hours after discharge from the CICU, and surgical site infections, which were tracked for 30 days after the index procedure. For patients who remained in the CICU for more than 30 days, the number of patient-days in the CICU was considered to be 30.

Table 3

Study Outcomes, According to Treatment Group and Age Subgroup

Outcome	Age ≤60 Days		Age >60 Days		*P* Value for Interaction[a]
	TGC (n=128)	STD (n=113)	TGC (n=362)	STD (n=377)	
30-day mortality, no./total no. (%)[b]	2/128 (2)	5/112 (4)	3/360 (<1)	1/372 (<1)	0.22
Length of stay in the CICU, days[c]					0.46
Median	6.7	6.5	2.1	2.1	
IQR	4.3-12.0	4.0-12.8	1.7-4.8	1.6-4.6	
Length of stay in the hospital, days[c]					0.42
Median	14.5	15	7	6	
IQR	9-26.5	9-29	5-11	5-10	
Mechanical ventilation, days[c]					0.50
Median	5	5	2	2	
IQR	4-8	3-10	1-3	1-3	
Cardiac index on day 2, L/min/m$^{2.}$[d]					0.15
Median	0.9	1.3	2.4	1.9	
IQR	0.7-1.5	1.0-1.9	1.8-3.2	1.5-2.7	
Vasoactive support, days					0.99
Median	5	5	2	2	
IQR	3-8.5	3-9	0-3	0-3	
Red-cell transfusion, no. (%)	97 (76)	71 (63)	173 (48)	181 (48)	0.058

TGC denotes Tight Glycemic Control, STD Standard Care, CICU cardiac intensive care unit, and IQR interquartile range.

[a] The *P* values for the interaction between treatment group and age subgroup were calculated from logistic regression models for binary outcomes, Cox proportional hazards regression models for time-to-event outcomes, or a linear regression model for cardiac index. These models included the main effects and interaction term as covariates.

[b] Eight patients were lost to follow-up between hospital discharge and study day 30.

[c] The duration of the stay in the CICU, the stay in the hospital, and mechanical ventilation were considered to be 30 days for patients with duration of more than 30 days and for the 11 patients who died in the CICU by the 30th day.

[d] The cardiac index on day 2 was measured in 191 patients at Boston Children's Hospital.