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Impact of the insulin and glucose content of the postoperative fluid on the outcome after pediatric cardiac surgery

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Abstract: *Introduction:* The aim of this study was to investigate the role of the insulin and glucose content of the maintenance fluid in influencing the outcomes of pediatric patients undergoing heart surgery. *Methods:* A total of 2063 consecutive pediatric patients undergoing cardiac surgery were screened between 2003 and 2008. A dextrose and an insulin propensity-matched group were constructed. In the dextrose model, 5% and 10% dextrose maintenance infusions were compared below 20 kg of weight. *Results:* A total of 171 and 298 pairs of patients were matched in the insulin and glucose model, respectively. Mortality was lower in the insulin group (12.9% vs. 7%, $p = 0.049$). The insulin group had longer intensive care unit (ICU) stay [days, 10.9 (5.8–18.4) vs. 13.7 (8.2–21), $p = 0.003$], hospital stay [days, 19.8 (13.6–26.6) vs. 22.7 (17.6–29.7), $p < 0.01$], duration of mechanical ventilation [hours, 67 (19–140) vs. 107 (45–176), $p = 0.006$], and the incidence of severe infections (18.1% vs. 28.7%, $p = 0.01$) and dialysis (11.7% vs. 24%, $p = 0.001$) was higher. In the dextrose model, the incidence of pulmonary complications (13.09% vs. 22.5%, $p < 0.01$), low cardiac output (17.11% vs. 30.9%, $p < 0.01$), and severe infections (10.07% vs. 20.5%, $p < 0.01$) was higher, and the duration of the hospital stay [days, 16.4 (13.1–21.6) vs. 18.1 (13.8–24.6), $p < 0.01$] was longer in the 10% dextrose group. *Conclusions:* Insulin treatment appeared to decrease mortality, and lower glucose content was associated with lower occurrence of adverse events.

Keywords: cardiac surgery, pediatrics, insulin, glucose, dextrose, maintenance infusion, critical care, heart surgery, children

Introduction

Hyperglycemia and poor glycemic control are major risk factors for increased morbidity and mortality in various clinical settings, including pediatric patients undergoing cardiac surgery. Recent studies have identified associations between critical illness and hyperglycemia (CIH) and adverse outcomes after congenital heart surgery [1–3]. Although tight glycemic control has been shown to improve outcomes in some studies, these results have triggered controversy because of the high incidence of hypoglycemic events in the pediatric population [4, 5]. Approaches with less stringent glycemic targets have been introduced for pediatric intensive care unit patients with low risks of hypoglycemia, but the benefit of this more liberal glycemic control is still questionable. Therefore, the aim of this study was to investigate the effect of liberal management of CIH with insulin use and to evaluate an alternative or complementary path to insulin use (i.e., the reduction of the amount of glucose infusion) in a large retrospective cohort of pediatric patients following cardiac surgery. To assess whether the insulin usage or the glucose infusion reduction improved outcomes, we compared in-hospital mortalities and postoperative morbidities in propensity-matched pediatric cardiac surgery patients.

Methods

Patients and samples

Between January 2003 and December 2008, 2063 consecutive pediatric patients (<18-year old) who underwent cardiac surgery and were admitted to our cardiac intensive care unit were screened after Institutional Review Board approval. The board waived the need for parental informed consent. All the perioperative data were obtained by a prospectively collected institutional database, which collected data for quality control measurements. After deleting the cases with missing data, 1667 (insulin model) and 1401 (dextrose model) patients remained for further analysis. None of the patients who were included in the present analyses had a history of diabetes mellitus. The categorical and continuous predictor variables that were included in the model are shown in *Table I.*

The cardiac surgical procedures were graded by applying the Risk Adjustment for Congenital Heart Surgery (RACHS-1) method. To quantify the amount of cardiac support, we calculated the modified inotropic score, as described by Wernovsky [6]: dopamine + dobutamine + (epinephrine*100) + (norepinephrine*100) + (milrinone*20), using peak infusion rates measured in micrograms/kilogram/min. Dextrose-containing infusions (10% dextrose for patients <20 kg and 5% dextrose for patients >20 kg) had been administered postoperatively before the policy change was implemented (5% for each patient). Insulin infusions of 0.1 IU/kg/h were initiated if the BG (blood glucose) values of the patients exceeded 10 mmol/L at two consecutive measurements. Blood glucose measurements were performed via point-of-care equipment from whole blood samples on the day of surgery (D0), on the first postoperative day (D1), and on the second postoperative day (D2), for an average of six to eight times daily.

Death was defined as the demise from any cause. The combined endpoint of the study was defined as death after arrival at the intensive care unit (ICU) (including patients who died after having been transferred to another hospital) or after development of multiple organ dysfunction, which consisted of any two of the following complications: 1) postoperative low output syndrome (clinical signs: tachycardia, oliguria, cold extremities or cardiac arrest, and an increase in the base deficit of >4 on two consecutive blood gas measurements); 2) pulmonary complication (defined as non-infectious); 3) non-vascular oxygenation problems (atelectasia, pneumothorax, chylothorax, and phrenic paresis); 4) renal failure (peritoneal dialysis, or hemodialysis); 5) infections (catheter-related and deep-sternal wound infections, positive blood cultures, or sepsis); and 6) neurological events (convulsions without a prior history or hemorrhage or infarcts demonstrated by cranial imaging), which were also included in the composite outcome [7].

Statistical analysis

The data were summarized using descriptive statistics, which were expressed as counts and percentages for the categorical variables and as means and standard deviations (SD) for the continuous data. Patients with missing data regarding their baseline covariates and clinical outcomes were excluded from the analysis. Demographic and perioperative differences between the patients were compared using the chi-square and *t*-tests where appropriate. Because the patients were not randomly allocated to the treatment or control groups, they were not comparable with respect to the important covariates. To overcome the bias resulting from the design of this study, we constructed two propensity score models (one for receiving insulin and one for receiving a 10% or 5% dextrose infusion) to adjust for differences in the characteristics between the treated patients and the non-treated patients. The propensity scores were developed using a non-parsimonious multivariable logistic regression model, with treatment considered as the outcome and all the risk factors that potentially confounded the treatment effect considered as the predictor variables. The treated patients were matched to the non-treated patients with similar propensity scores. A 1:1 nearest-neighbor greedy matching without replacement was employed (Stata/PSMATCH2) to form pairs, using calipers with a width equal to 0.25 of the standard deviation of the logit of the propensity score. The 171 and 298 matched pairs were analyzed for differences in their baseline characteristics and in the aforementioned predefined outcome variables. The outcomes and measured covariates were compared between the groups via a paired *t*-test for the continuous variables and McNemar's test for the categorical data. To assess whether the propensity score model had been correctly specified and the balance of the baseline characteristics between the two groups had been achieved, the standardized differences were estimated. Across the 16 baseline covariates, the standardized differences ranged from a low of –0.07 to a high of 0.09 in the insulin model and from a low of –0.07 to a high of 0.06 in the dextrose-delivery model, indicating that the means and prevalence of the variables were very similar between the groups in the different models. The selection of the predictor variables was based on our previous results [8], and a custom Java code generator determined all the possible variations of the confounders that yielded a standardized difference within the range of 10%. All of the tests were two-sided. We considered $p < 0.05$ to be significant. The analyses were conducted using Stata SE 12 (Stata, College Station, TX), the SPSS 16.0 statistical software (SPSS, Inc., Chicago, IL), and STATISTICA (data analysis software system) (StatSoft, Inc. [2007], version 8.0, www.statsoft.com).

Table I Predictor variables before and after matching – insulin model

	Before matching						After matching					
	Control n = 1469		Insulin n = 198				Control n = 171		Insulin n = 171			
	n/med	% (IQR)	n/med	% (IQR)	SD	p value	n/med	% (IQR)	n/med	% (IQR)	SD	p value
Preoperative predictors												
Gender (female)	674	45.88	77	38.88	0.14	0.064	67	39.18	66	38.59	**0.01**	1.00
Acute surgery	163	11.09	41	20.70	–0.29	**<0.01**	30	17.54	27	15.78	**0.04**	0.66
Resternotomy	292	19.87	49	24.74	–0.12	0.11	57	33.33	44	25.73	**0.08**	0.39
Pre-op intensive care stay	250	17.01	83	41.91	–0.64	**<0.01**	68	39.76	62	36.25	**0.07**	0.43
Preoperative cyanosis	436	29.68	95	47.97	–0.40	**<0.01**	75	43.85	81	47.36	**–0.07**	0.49
Preoperative prostaglandin administration	160	10.89	60	30.30	–0.58	**<0.01**	46	26.90	43	25.14	**0.03**	0.69
Preoperative pulmonary hypertension	239	16.26	40	20.20	–0.11	0.16	39	22.80	33	19.29	**0.08**	0.43
Age (years)	1.01	(0.36–4.86)	0.37	(0.03–1.78)			0.39	(0.04–2.34)	0.44	(0.04–2.64)		
Age (years) natural logarithm	0.009	(–1.02–1.58)	–0.99	(–3.5–0.57)	0.57	**<0.01**	–0.94	(–3.21–0.85)	–0.82	(–3.21–0.97)	**–0.05**	0.58
RACHS (points)					–0.74	**<0.01**					**0.03**	1.00
1	234	15.92	11	5.55			15	8.77	9	5.26		
2	705	47.99	64	32.32			51	29.82	62	36.25		
3	445	30.29	74	37.37			66	38.59	68	39.76		
4	71	4.83	36	18.18			32	18.71	25	14.61		
6	14	0.95	13	6.56			7	4.093	7	4.09		
Intra- and postoperative predictors												
Delayed sternal closure	140	9.53	101	51.01	–1.28	**<0.01**	75	43.85	75	43.85	**0.00**	1.00
Intraoperative aprotinin administration	286	19.46	62	31.31	–0.29	**<0.01**	55	32.16	50	29.23	**0.06**	0.54
Post-CPB nitric oxide administration	72	4.90	49	24.74	–0.79	**<0.01**	38	22.22	38	22.22	**0.00**	1.00
Maximum BG on the day of surgery (mmol/L)	7.8	(6.5–9.2)	10.1	(8.2–13.1)	–1.11	**<0.01**	9.4	(8–12)	9.6	(7.9–11.9)	–0.01	0.9
CPB time (min)	64	(41–106)	118	(76–175)	–0.80	**<0.01**	116	(58–167)	112	(71–165)	**–0.01**	0.98
Blood transfusion (mL/kg)	15.78	(0–34.24)	42.38	(13.79–70.17)	–0.95	**<0.01**	35.71	(5.88–68.75)	33.33	(11.11–66.6)	**0.04**	0.63
Post-CPB cumulative inotropic index (points)	4	(0–14)	20	(10–35)	–1.08	**<0.01**	16	(6–30)	19.6	(8–33)	**0.01**	0.91

Data are presented as number and incidence (%) or median and interquartile range (IQR). Significant values are indicated by bold. CPB, cardiopulmonary bypass, RACHS, risk adjustment for congenital heart surgery. Pearson-Chi^2, Student's t-test, paired t-test, and McNemar's test were used for the comparison of variables

Results

The model of insulin treatment

During the 5-year period, 2060 patients underwent operations. The analyzed database (1667 patients) in the insulin model contained the data of 298 (17.8%) neonates, 577 (34.6%) infants, and 792 (47.5%) children. In the study population of 1667 patients, 198 (11.8%) patients were treated with insulin. Sixty patients (3.5%) died. Renal replacement therapy was required in 97 (5.8%) patients. The demographic and perioperative characteristics of the patients, clustered by the insulin treatment, are listed in *Table I*. Compared with the patients who were not subjected to continuous insulin control, the patients who received insulin underwent a more complex surgery with a long duration of the cardiopulmonary bypass procedure, were more likely to exhibit cyanosis, and required mechanical ventilation before surgery. The insulin patients received larger amounts of inotropic drugs and more transfusions, and they required nitric oxide and prostaglandins more frequently. The patients in the insulin group were younger, and one-fifth of them underwent acute surgeries and rethoracotomies. The measured blood glucose levels on the day of surgery and on the first and second postoperative days in the insulin group were higher than in the control patients (data not shown). The propensity score derivation model comprised 16 variables, including the following: gender (male), logarithmic transformation of age, acute surgery, resternotomy, delayed sternal closure, cyanosis, RACHS score, preoperative pulmonary hypertension, preoperative ICU stay (days), cardiopulmonary bypass time (minutes), preoperative prostaglandin administration, maximum blood glucose value (mmol/L) on the day of surgery, post-bypass inotropic score, requirement for nitric oxide, transfusion (mL/kg), and use of aprotinin. These variables were discriminatively quantified by measuring the receiver-operating-characteristic area (c-index, 0.87). Through this model, 171 (of 198) insulin patients were matched to 171 (of 1469) non-insulin (control) patients. *Table II* presents the outcomes of the patients before and after propensity matching. Before propensity matching, the patients who were treated with insulin exhibited a higher mortality and morbidity compared with the non-insulin-treated patients. After propensity-score matching, the standardized differences for all the measured variables were less than 10%, suggesting complete comparability of the preoperative and perioperative characteristics across the groups *(Fig. 1)*. The occurrence of infection (18.1% vs. 28.7%, $p = 0.0143$) and the requirement for dialysis (11.7% vs. 24%, $p < 0.01$) were higher in the insulin group. The duration of the mechanical ventilation (hours) and the length of the ICU (days) and hospital stay (days) were also greater compared with the non-insulin patients. The in-hospital mortality (12.9%

Table II Outcome variables before and after matching – insulin model

	Before matching					After matching				
	Control $n = 1469$		Insulin $n = 198$			Control $n = 171$		Insulin $n = 171$		
	n/med	% (IQR)	*n*/med	% (IQR)	*p* value	*n*/med	% (IQR)	*n*/med	% (IQR)	*p* value
Combined outcome	191	13.0	89	44.94	**<0.01**	66	38.59	71	41.52	0.54
Death	43	2.92	17	8.58	**<0.01**	22	12.86	12	7.01	0.049
Low output syndrome	260	17.69	108	54.54	**<0.01**	75	43.85	89	52.04	0.09
Pulmonary complication	205	13.95	47	23.73	**<0.01**	36	21.05	40	23.39	0.59
Renal failure	43	2.92	54	27.27	**<0.01**	20	11.69	41	23.97	**<0.01**
Severe infection	156	10.61	56	28.2	**<0.01**	31	18.12	49	28.65	0.01
Neurological event	23	1.56	12	6.06	**<0.01**	8	4.67	8	4.67	0.99
Day of death	2	(1–16.5)	10.5	(3–24.25)	**0.04**	2	(1–7.75)	6.5	(2.5–13.5)	0.12
Total hospital LOS (days)	16.5	(13.2–22.1)	23.2	(17.6–30.9)	**<0.01**	19.8	(13.6–26.6)	22.7	(17.6–29.7)	**<0.01**
Mechanical ventilation time (hours)	20	(9–54)	117.5	(56–190)	**<0.01**	67	(19–140)	107,00	(45–176)	**<0.01**
Total ICU LOS (days)	6.3	(4.2–10.8)	14,00	(8.8–22)	**<0.01**	10.9	(5.8–18.4)	13.7	(8.2–21)	**<0.01**

Data are presented as number and incidence (%) or median and interquartile range (IQR). Significant values are indicated by bold. Student's *t*-test, Pearson-Chi^2, McNemar's test, and paired *t*-test were used as appropriate

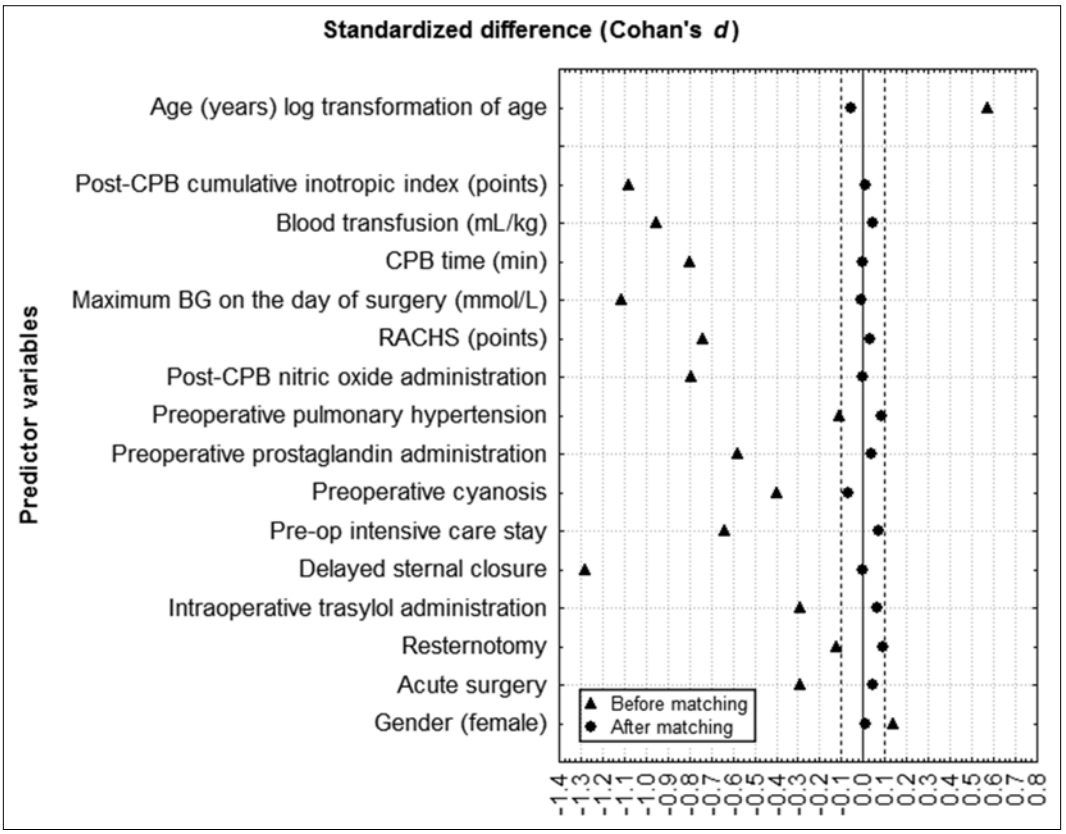

Fig. 1. Standardized differences in the values of the predictor variables – insulin model

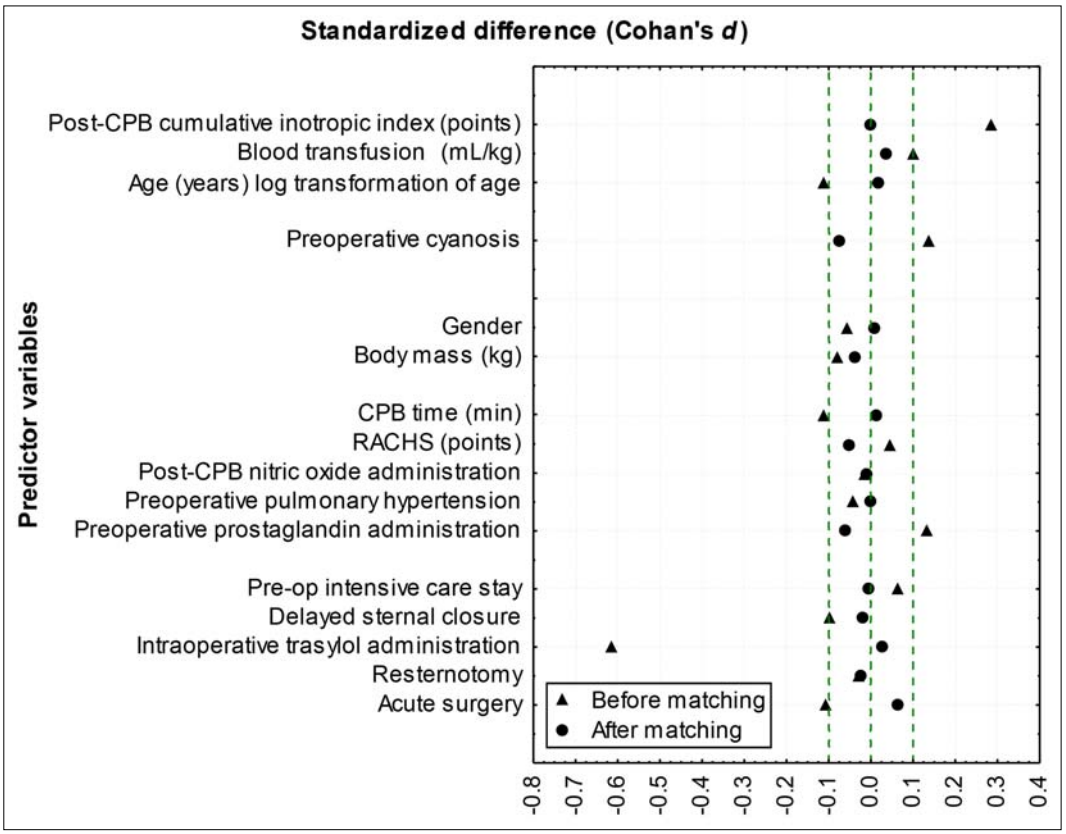

Fig. 2. Standardized differences in the values of the predictor variables – dextrose model

vs. 7%, $p = 0.049$) was lower in the insulin-treated group. No difference was observed in the time of death after surgery between the control and insulin-treated groups [median days: 2 (IQR: 1–7.75) vs. 6.5 (2.5–13.5); $p = 0.12$, respectively].

The model of dextrose delivery

We compared the patients who weighed less than 20 kg and who received 10% dextrose solutions (77.2%) to those who received 5% dextrose infusions (22.7%). The dextrose model contained the data of 308 (21.9%) neonates, 583 (41.6%) infants, and 510 (36.4%) children. In this population of 1401 patients, 319 (22.7%) patients were treated with a 5% dextrose solution (D5). Fifty-six patients (3.9%) died. Renal replacement therapy was required in 92 (6.5%) patients. The demographic and perioperative characteristics of the patients are listed in *Table III*. The D5 patients received higher amounts of inotropic drugs, were more likely to exhibit cyanosis, and required prostaglandins more frequently. The maximum BG levels (mmol/L) on the day of surgery (7.7 vs. 8.7, $p < 0.01$), on the first postoperative day (6.7 vs. 8.2, $p < 0.01$), and on the second postoperative day (6 vs. 7.4, $p < 0.01$) were also higher in the group in which the daily fluid intake was maintained by 10% dextrose infusions. The propensity score model for dextrose delivery included the following 16 variables: gender (male), body mass (kg), logarithmic transformation of age, acute surgery, resternotomy, delayed sternal closure, cyanosis, RACHS score, preoperative pulmonary hypertension, preoperative ICU stay (days), cardiopulmonary bypass time (minutes), preoperative prostaglandin administration, post-bypass inotropic score, requirement for nitric oxide, transfusion (mL/kg), and use of aprotinin. The model was discriminative (c-index, 0.734). Using this model, 298 (of 319) D5 patients were matched to 298 (of 1082) D10 patients. *Table IV* lists the outcomes of the patients before and after propensity matching. The standardized differences for all the measured variables were also less than 10% in this model, suggesting complete comparability of the preoperative and perioperative characteristics across the groups, as in the insulin model *(Fig. 2)*.

Discussion

Using propensity score methods, we successfully matched a relatively large number of patients who were treated with continuous insulin therapy after pediatric cardiac surgery to a group of patients (comparable with respect to every measured covariate) who were not in the insulin model. We also successfully matched patients with a fluid balance maintained by D10 dextrose solutions to patients treated with D5-containing fluids. After matching, we found that insulin treatment was associated with a lower mortality rate but was linked to an increased duration of mechanical ventilation, as well as the hospital and ICU stay, and an increased rate of renal failure and severe infection. We also found that patients who received a reduced carbohydrate calorie intake had a decreased LOS and exhibited lower rates of infection, pulmonary complications, low-output syndrome, and composite outcomes.

Until the early years of the twenty-first century, hyperglycemia was not routinely controlled in the ICU, except among patients with known diabetes mellitus. After several studies demonstrated that the management of glycemic disturbances in patients with DM is a useful practice [9–13], investigators attempted to prove the same benefit of insulin treatment in non-diabetic, critically ill patients. Subsequently, the concept that hyperglycemia in non-DM subjects as an adaptive response to stress is a beneficial condition became outdated, and the previous passive approach to hyperglycemia was no longer optimal for any ICU patients, regardless of whether they had DM [14]. Hyperglycemia occurs frequently, and it is associated with increased morbidity and mortality in critically ill adults and pediatric patients [14–19]. Insulin therapy has become a favored practice in ICUs. However, certain studies of the adult population have demonstrated that tight glycemic control is inferior to liberal control [20], thus raising awareness of the high risk of hypoglycemia. By contrast, a randomized controlled trial in children, conducted by Vlasselaers et al., has revealed associated reductions in mortality and the length of stay (LOS), and tight glycemic control has been determined to cause a severe increase in the risk of hypoglycemia in *pediatric intensive care unit* (PICU) children [5]. According to the latest randomized trial with continuous glucose monitoring, intensive insulin therapy targeting a glucose level of 4.4 to 6.1 mmol/L does not reduce the mortality, infection rates, or LOS compared with standard care in pediatric patients after cardiac surgery [21]. These results contrast with the findings of Vlasselaers et al. because the glycemic target range is different – although this fact might not fully explain the discrepancies between the studies. Apparently, there are various conclusions regarding these results, and it is not surprising that considerable disparity exists among the attitudes toward stress hyperglycemia and its management in the critically ill pediatric population.

The retrospective analysis in the present study revealed that continuous insulin therapy in this large cohort of pediatric cardiac surgery patients was associated with increased rates of infection, renal failure, longer durations of mechanical ventilation and LOS, and fewer occurrences of in-hospital death. Some studies suggest that the beneficial effects of insulin therapy are due more to blood glucose control than to the insulin itself [22].

Table III Predictor variables before and after matching – dextrose model

	Before matching						After matching					
	Dextrose 5% n = 319		Dextrose 10% n = 1082		Standardized difference	p value	Dextrose 5% n = 298		Dextrose 10% n = 298		Standardized difference	p value
	n/med	% (IQR)	n/med	% (IQR)			n/med	% (IQR)	n/med	% (IQR)		
Preoperative predictors												
Body mass (kg)	6.2	(3.8–9)	5.95	(3.8–9.7)	–0.08	0.17	6.3	(3.8–9)	5.5	(3.6–9)	**–0.03**	0.61
Age (years) log transformation of age	–0.49	(–2.4–0.31)	–0.44	(–1.56–0.52)	–0.11	0.08	–0.462	(–1.96–0.31)	–0.579	(–2.2–0.35)	**0.01**	0.84
Gender (female)	140	43.88	505	46.67	–0.05	0.38	135	45.30	134	44.96	0.01	1.01
Acute surgery	37	11.59	167	15.43	–0.10	0.08	36	12.08	30	10.06	0.06	0.41
Resternotomy	59	18.49	212	19.59	–0.02	0.66	52	17.44	55	18.45	–0.02	0.71
Pre-op intensive care stay	85	26.64	259	23.93	0.06	0.32	74	24.83	75	25.16	–0.01	0.92
Preoperative cyanosis	134	42.00	383	35.39	0.13	0.03	113	37.91	124	41.61	–0.07	0.28
Preoperative prostaglandin administration	63	19.74	162	14.97	0.13	**0.04**	53	17.78	60	20.13	–0.05	0.47
Preoperative pulmonary hypertension	60	18.80	222	20.51	–0.04	0.51	59	19.79	59	19.79	0.01	1.01
RACHS (points)					0.04	0.15					–0.05	1.01
1	43	13.47	115	10.62			43	14.42	32	10.73		
2	142	44.51	555	51.29			135	45.30	141	47.31		
3	101	31.66	309	28.55			92	30.87	100	33.55		
4	24	7.52	85	7.85			22	7.38	18	6.04		
6	9	2.82	18	1.66			6	2.01	7	2.34		
Intra- and postoperative predictors												
CPB time (min)	68	(30–111)	69	(43–115)	–0.11	**0.04**	65.5	(28–104)	64.5	(24–106)	**0.01**	0.88
Blood transfusion (mL/kg)	23.8	(11.19–44.44)	23.34	(6.66–42.16)	0.10	0.15	23.43	(10.8–41.6)	22.72	(5.45–40.81)	0.03	0.64
Post-CPB cumulative inotropic index (points)	10	(4–24)	7	(2–18)	0.28	**<0.01**	10	(4–21)	10	(4–20)	**–0.01**	0.98
Intraoperative aprotinin administration	6	1.88	281	25.97	–0.6	**<0.01**	6	2.01	5	1.67	**0.02**	1.01
Delayed sternal closure	44	13.79	189	17.46	–0.09	0.12	37	12.41	39	13.08	–0.02	0.79
Post-CPB nitric oxide administration	25	7.83	90	8.31	–0.01	0.78	21	7.04	22	7.38	–0.01	0.86

Data are presented as number and incidence (%) or median and interquartile range (IQR). Significant values are indicated by bold

Table IV Outcome variables before and after matching – insulin model

	Before matching					After matching				
	Dextrose 5% $n = 319$		Dextrose 10% $n = 1089$			Dextrose 5% $n = 298$		Dextrose 10% $n = 298$		
	n/med	% (IQR)	*n*/med	% (IQR)	*p* value	*n*/med	% (IQR)	*n*/med	% (IQR)	*p* value
Combined outcome	46	14.42	226	20.75	**0.01**	41	13.75	74	24.83	**<0.01**
Death	10	3.13	46	4.22	0.37	10	3.35	11	3.69	1
Low output syndrome	54	16.92	300	27.54	**<0.01**	51	17.11	92	30.87	**<0.01**
Pulmonary complication	43	13.47	207	19.00	**0.02**	39	13.08	67	22.48	**<0.01**
Renal failure	19	5.95	73	6.70	0.61	15	5.03	20	6.71	0.37
Severe infection	34	10.65	174	15.97	**0.01**	30	10.06	61	20.46	**<0.01**
Neurological event	6	1.88	26	2.38	0.58	5	1.67	10	3.35	0.31
Total hospital LOS (days)	16.6	(13.3–22.2)	18.1	(14–24.5)	**<0.01**	16.4	(13.1–21.6)	18.1	(13.8–24.6)	**<0.01**
Mechanical ventillation time (hours)	25	(9–79)	31.5	(12–94)	0.16	24	(9–76)	34	(12–97)	0.12
Total ICU LOS (days)	8	(5.1–14)	7.4	(5.1–14.1)	0.39	7.55	(4.6–1.4)	8.2	(5.3–14)	0.08

Data are presented as number and incidence (%) or median and interquartile range (IQR). Significant values are indicated by bold. Student's *t*-test, Pearson-Chi^2, McNemar's test, and paired *t*-test were used as appropriate

An increased amount of insulin was positively associated with death in the ICU, regardless of the prevailing BG level – which again supports the previous hypothesis that blood glucose control is the dominant factor in improving mortality [23]. It is possible that higher insulin requirements are strong markers of the disease severity, reflected as a higher morbidity and mortality. However, our results contradict these observations by demonstrating a survival benefit in the insulin group despite the fact that these patients exhibited higher BG levels than the control group. Nevertheless, it is difficult, particularly in an observational cohort, to clearly distinguish the contribution of glucose control and the direct effect of insulin on the decrease in mortality and morbidity. In this case, we believe that the insulin therapy acted as a surrogate for other covariates that were associated with the outcome.

Therefore, the increased rates of infection and renal failure in the insulin group even after propensity score matching (although the difference in all the outcomes narrowed after matching) suggest that we could not rule out all bias and that the patients treated with insulin were in worse metabolic condition and were even more severely ill. However, insulin therapy exhibits confirmed anti-apoptotic, anti-inflammatory, endothelium-protective, anti-thrombotic, and anti-fibrinolytic properties, as well as many other reportedly beneficial and direct effects [24–28] that (without knowing the exact mechanism) could have contributed to the improved mortality outcomes in our cohort. These findings contradict the only randomized trial [21] in this particular pediatric population, in which tight glycemic control was compared to standard care with the aid of continuous glucose monitoring that concentrated on preventing hypoglycemia after cardiac surgery.

The other fact to be considered is that, in addition to peripheral and hepatic insulin resistance, stress-induced catecholamine release, commonly used ICU drugs (such as steroids and vasopressors) [29–31], and excessive glucose-containing infusions for fluid maintenance also compound the problem and play an important role in precipitating high blood glucose concentrations [32–37]. Dextrose delivery is considered necessary to prevent hypoglycemia, glycogen breakdown, and the amplification of protein catabolism in the critically ill, fasting child, but not in as high concentrations as has been used in the past. Many studies have reported that a reduced glucose intake can prevent hypoglycemic episodes while maintaining the blood glucose concentration within the normal range [38–41]. Our results confirm these findings. Furthermore, a recent investigation by Verbruggen et al. [42] revealed that lowering the dextrose load in patients may be an alternative or complementary method to insulin therapy for glycemic control. Selecting the glucose concentration is a forced choice between avoiding hypoglycemia and avoiding hyperglycemia. Indeed,

many investigators have found that the delivery of high concentrations of dextrose leads to elevated blood glucose levels, which are associated with higher morbidity rates during the perioperative period [35, 41, 43]. We believe that the beneficial effects are attributable to the significantly lower blood glucose levels, albeit still hyperglycemic, in the D5 group. In this setting, the number of patients who were treated with insulin was relatively low (11.7%, not shown), and 67% of them were in the D10 group. Sixty-five percent of the patients were under 1 year of age. In a recent clinical trial, even 0.9% dextrose was proven to provide a glucose load sufficient for preventing hypoglycemia in infants in intraoperative settings [44]. However, this concentration, as a part of fluid maintenance, might not be adequate for certain clinical situations in which the metabolic rate severely increases. In addition to considering the risk of hypoglycemia due to the low carbohydrate reserves and higher metabolic rates in these patients, avoiding an excessive rate of dextrose administration is beneficial.

Study limitations

This study had several limitations. Because we conducted an observational study, residual confounding is possible. However, we succeeded in balancing the differences between the treatment and control groups based on the standardized differences. The propensity score matching controlled only for the observed covariates, and there might have been unmeasured confounders that we did not consider. Indeed, bias related to improvements in managing congenital heart diseases, preheld beliefs regarding controlling stress hyperglycemia throughout the study period, or unmeasured clinical severity might have also played an important role in undermining our conclusions. The other limitation is that the calorie-intake policy changed during the study period, and this difference was not incorporated into the insulin propensity model; moreover, the choice regarding insulin use was often driven by the preference of the attending physician rather than by the protocol. In this single center study, we observed patients who had markedly heterogeneous congenital heart diseases and baseline characteristics, and we successfully matched 86% of the patients who received insulin therapy. Thus, our results may be interpreted as generalizable, which is one of the strengths of our study – in addition to its large cohort of pediatric cardiac patients, the prospectively collected database, and the well-defined postoperative complications.

Summary

Using the propensity score method, we found that the liberal glycemic control of critical-illness hyperglycemia via continuous insulin administration in the pediatric cardiac-surgical population does not reduce the occurrence of postoperative complications that are believed to be associated with elevated BG levels; however, a survival benefit was observed. Furthermore, the reduction of the carbohydrate caloric intake might be a reasonable supplement to liberal and non-intensive insulin therapy, considering the aforementioned controversies and the latest randomized trial [21] that has addressed the management of critical-illness hyperglycemia in children after cardiac surgery.

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Authors' contribution: Each author participated sufficiently in the work to take public responsibility for the content. AS, PS, and DJL made the conception and designed this study. MG, ZP and ES, AS acquired the data. TS, PS, DJL and AS analyzed and interpreted the data. DJL, PS and AS wrote the manuscript, for which DJL and PS prepared the figures and tables. AS and JG provided expert opinion. All authors read and approved the final manuscript.

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