CLINICAL INVESTIGATION

Glycemic Control in Pediatric Patients on Extracorporeal Membrane Oxygenation

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OBJECTIVES To determine whether glycemic control has an effect on outcomes for pediatric patients on extracorporeal membrane oxygenation (ECMO) therapy, while controlling for multiple factors.

METHODS A single-center retrospective chart review was performed on 82 patients who required ECMO from January 1, 2008, to December 31, 2010. All glucose concentrations collected while patients were on ECMO were analyzed; multiple other factors that may have affected mortality were also recorded. Primary outcome was mortality, and secondary outcomes were length of time on ECMO and length of time until death or discharge from the hospital.

RESULTS Of 82 patients, 53 patients survived ECMO (64.6%). Glucose control had no effect on survival of patients on ECMO (p=0.56), even when controlling for multiple factors (p=0.48). Similarly, statistical evaluation showed no differences for hospital mortality in relationship to controlled serum glucose (p=0.50). Patients with controlled glucose spent an average of 31.5% more time on ECMO than non-controlled patients (p=0.048).

CONCLUSIONS In this study, glycemic control, defined as serum glucose concentration between 60 mg/dL and 250 mg/dL for >95% of the time on ECMO, had no statistically significant effect on mortality for patients on ECMO. Future studies could focus on tighter glucose control or specific dextrose/glucose protocols to evaluate whether improved glucose control would have an effect on morbidity and mortality.

INDEX TERMS blood glucose, ECMO, extracorporeal membrane oxygenation, insulin, morbidity, pediatric intensive care

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INTRODUCTION

Hyperglycemia is associated with increased mortality, as well as complications including infection and organ failure in adult patients. Complications from hyperglycemia, such as increased length of stay, increased duration of mechanical ventilation, increased incidence of infection, and death, are also seen in pediatric patients.[1-3] Poor glucose control has detrimental effects on specific subsets of pediatric patients, including those in intensive care units, neonates, patients with severe burns, and postcardiac surgery patients.[4-6] Another potential group of pediatric patients who might benefit from normoglycemia is patients receiving extracorporeal membrane oxygenation (ECMO) therapy. ECMO uses a modified cardiopulmonary bypass machine for longer-term cardiac and pulmonary recovery. One retrospective study examined the clinical outcomes of hyperglycemia in adult patients on ECMO but found no effect on mortality.[7] No studies to date have investigated the effects of glycemic control in the pediatric population on ECMO. Because patients on ECMO are at a higher risk for morbidity or complications including infection, hemorrhage, renal failure, and death, it is important to identify any measure, including glycemic control, which may help improve outcomes for this population.[8] The goal of this study was to examine the effects of serum glucose control on morbidity and mortality for pediatric patients on ECMO.

MATERIALS AND METHODS

A retrospective observational chart review was performed for patients who required ECMO in

the pediatric intensive care unit at a large, free-standing pediatric hospital. The pediatric intensive care unit consists of 72 beds and cares for patients with a variety of diagnoses and disease states, including pre- and post-cardiac surgery, trauma, neurosurgery, infection, and oncology. This institution has been using ECMO since 1986. Both veno-arterial (VA) and veno-venous (VV) ECMO are used, but most patients are placed on VA ECMO. The location of cannulation (e.g., chest vs. neck) is determined according to surgeon preference and patient-specific availability for access. The pilot study was approved by the hospital's Institutional Review Board.

Two individuals collected data for all patients placed on ECMO from January 1, 2008, to December 31, 2010. The ECMO coordinator for the hospital provided a complete list of these patients. Patients known to have diabetes at the time of ECMO cannulation were excluded because of the pre-existing potential for glucose instability. Patients with missing data (unknown glucose values or endpoints) were also excluded from the study. Demographic data were collected for each patient, including age, weight, sex, race, principle diagnosis, and reason for ECMO. Patients were grouped by age: infant (ages 0-1 years), toddler (age 1-3 years), and child (>3 years). Collected clinical data included length of time on ECMO, year when ECMO was performed, circumstances surrounding ECMO initiation (emergent vs. nonemergent cannulation), serum glucose values, amount of time patient was maintained in the target serum glucose range (60–250 mg/dL), amount of time the patient was hyper- or hypoglycemic, treatment (if any) of hyperglycemia, infections, corticosteroid use, mortality, and time until death or discharge from hospital. Infections were measured by positive results from blood, urine, stool, sputum, and wound cultures, but positive cultures that had been clinically determined to be contaminants were not included.

Data for pre-operative antibiotic usage were not collected, as all cardiac surgery patients are given a standard regimen of 1 dose each of ampicillin, 25 mg/kg intravenous, and oxacillin, 25 mg/kg via syringe pump. The glucose range of 60–250 mg/dL was chosen based on previous studies and because of the potential risks associated with hypoglycemia; all recorded glucose values (both laboratory and bedside point-of-care values) were analyzed to determine whether

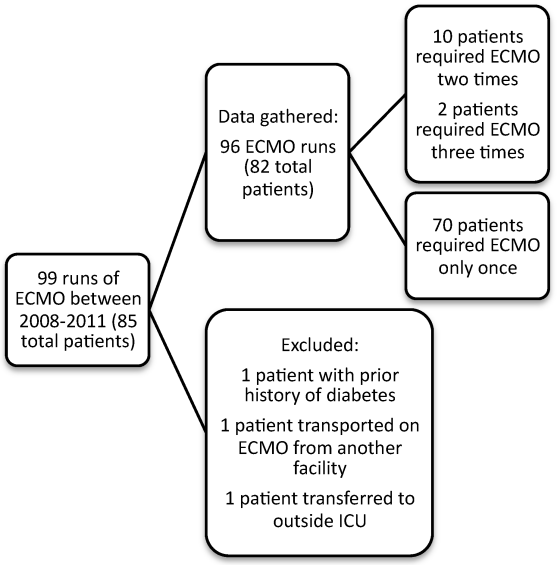

Figure 1. Flowchart Detailing the Patient Inclusion Numbers and Exclusion Reasons

patients fell into this range.[9,10] If ECMO cannulation occurred more than once for an individual patient, analysis included only data from the first ECMO cycle. The primary outcome was mortality; secondary outcomes were length of time on ECMO and length of time to death/discharge from hospital.

Statistical analysis was performed using SAS version 9.2 software (SAS Institute, Cary, NC). The univariate association between mortality and each covariate was analyzed using the Fisher exact test when at least one cell had an expected count of five or less and a chi-square test otherwise. Primary endpoints and statistically significant endpoints were further analyzed using logistic regression analysis. Student *t*-test was used for log-transformed time on ECMO and length of hospital stay. Any p values less than 0.05 were considered statistically significant.

RESULTS

Baseline Characteristics

Patient charts from 2008 to 2010 were reviewed. During that time, 85 patients required ECMO, for a total of 99 ECMO courses. Twelve patients required more than one course of ECMO. Of the 85 patients, 82 patients qualified for study inclusion. Figure 1 further illustrates the process of patient selection. Baseline demographic and

Table 1. Demographic Data for Patients with Controlled and Non-controlled Glucose and Total Time Spent on ECMO for Each Patient Group

Characteristic	Patients with Controlled Glucose [n =36; (43.9%)]	Patients with Uncontrolled Glucose [n=46 (56.1%)]	Mean ± SD Hours on ECMO	Total (n=82)
Age (yr)				
0-1	26 (51)	25 (49)	124.4 ± 97.6	51
1-3	4 (40)	6 (60)	66.2 ± 55.9	10
>3	6 (28.6)	15 (71.4)	122.6 ± 132.2	21
Sex				
Female	12 (35.3)	22 (64.7)	102.7 ± 74.4	34
Male	24 (50)	24 (50)	126.8 ± 121.1	48
Race				
Black	7 (41.2)	10 (58.8)	124.9 ± 105	17
Hispanic	8 (50)	8 (50)	120.8 ± 97.6	16
Other/unknown	2 (25)	6 (75)	141.4 ± 157.8	8
White	19 (46.3)	22 (53.7)	105.4 ± 92.8	41
Weight (kg)				
≤5	15 (41.7)	21 (58.3)	126.9 ± 98.9	36
5-20	14 (51.9)	13 (48.1)	115.4 ± 110.7	27
≥20	7 (36.8)	12 (63.2)	99.9 ± 108.9	19
Principal diagnosis				
Cardiac	27 (44.3)	34 (55.7)	112.3 ± 89	61
Sepsis	5 (41.7)	7 (58.3)	131.6 ± 132.5	12
Other	4 (44.4)	5 (55.6)	128.1 ± 162.1	9

clinical data for study patients are summarized in Tables 1 and 2.

ECMO and Hospital Mortality

Of the 82 patients in the study, fifty-three survived ECMO, and of those, 33 survived to discharge. Only 13 patients (15.9%) used insulin at any time during ECMO, even though 46 patients (56.1%) were found to have controlled serum glucose for less than 95% of the time during ECMO. Only 16 patients (19.5%) were controlled 100% of the time while on ECMO (Figure 2). All patients who received insulin were given regular insulin by continuous infusion via a syringe pump. Insulin doses were started between 0.01 units/kg/hr and 0.05 units/kg/hr, with an average starting rate of 0.033 units/kg/hr. Dosages were titrated to glucose goals, which were patient-specific based on clinical situation and clinician preference.

Controlled serum glucose concentrations (between 60–250 mg/dL for >95% of the time) did not have an effect on ECMO survival (p=0.56) (Table 3). Hospital mortality was similarly unaffected by glucose control (p=0.5) (Table 4). This finding continued to remain true when controlling for all other variables (p=0.48). ECMO mortality was significantly correlated with infection and patient age and weight (p=0.027, 0.003, and 0.005, respectively). Female sex and corticosteroid use were associated with a decreased hospital survival rate (p=0.009 and 0.019, respectively). Patients with a primary cardiac diagnosis had a significantly higher survival rate than patients with non-cardiac diagnoses, even when controlling for multiple factors (p<0.001). Patients with cardiac diagnoses were 5.38 times more likely to survive hospital courses than patients with other diagnoses (95% confidence interval [CI] 1.44–23.8). ECMO survival in 2008 was 17%. Survival improved in the following 2 years (2009 = 45.3%; 2010 = 37.7%; p=0.043). Patients placed on ECMO in 2010 were 11.4 times more likely to survive to discharge than those in 2008 and were 3.3 times more likely to survive than those in 2009. Hospital survival also improved yearly, with a survival rate in 2010 of 51.5% compared to 39.4% in 2009 and 9.1% in 2008 (p=0.002).

Length of ECMO and Hospital Stay

Patients placed emergently on ECMO spent 60.4% less time on ECMO than those placed

Table 2. Clinical Data for Patients with Controlled and Non-controlled Glucose and Average Time on ECMO

Characteristic	Controlled Glucose [n=36 (43.9%)]	Uncontrolled Glucose [n=46 (56.1%)]	Hours on ECMO (Mean ± SD)	Total (n=82)
Insulin use				
No	34 (49.3)	35 (50.7)	114 ± 98.9	69
Yes	2 (15.4)	11 (84.6)	131.8 ± 133.7	13
Steroid use				
No	11 (52.4)	10 (47.6)	97.7± 93.6	21
Yes	25 (41)	36 (59)	123.4 ± 107.8	61
Infection				
No	24 (48)	26 (52)	106 ± 89.1	50
Yes	12 (37.5)	20 (62.5)	133.8 ± 124.3	32
Emergent cannulation				
Yes	9 (27.3)	24 (72.7)	83.9 ± 86.5	33
No	27 (55.1)	22 (44.9)	139 ± 110.3	49
Reason for ECMO				
Arrest	9 (29)	22 (71)	84 ± 87.4	31
RF	7 (63.6)	4 (36.4)	169.4 ± 133.9	11
Low CO	9 (53)	8 (47)	118.7 ± 66.8	17
Bypass	6 (50)	6 (50)	150.4 ± 140.9	12
Other	5 (45.6)	6 (54.5)	117.3 ± 103.9	11

Bypass, failure to wean from bypass; CO, cardiac output; RF, respiratory failure

nonemergently (p=0.0033), despite having no greater risk of death while on ECMO (p=0.56) or in the hospital (p=0.43). Patients with controlled glucose levels spent an average of 31.5% more time on ECMO than non-controlled patients (p=0.0475) (Table 5). Glucose control did not affect length of hospital stay (p=0.73).

DISCUSSION

In this retrospective chart review, controlled glucose levels on ECMO had no effect on survival, either during ECMO or during patients' hospital stay. These findings are disappointing as identifying measures to improve patient outcomes on ECMO is necessary. There may be several reasons for these results.

There was significant variability in glucose control: only 16 patients (19.5%) were controlled 100% of the time. In this institution, blood glucose values are checked once every hour if a patient is receiving an insulin drip. Patients taking intermittent subcutaneous insulin or who are not taking insulin therapy are monitored according to clinician discretion and preference. In addition, patient glucose goals are also determined on an individual patient-by-patient basis according to clinician preference. An institutional protocol for initiating insulin therapy and frequency of glucose level monitoring could lead to less interpatient variability and therefore results that might be more broadly applicable. The frequency of blood glucose monitoring also affects the calculated percentage of time a patient's blood glucose is within the goal range. More frequent monitoring might capture more hyper- or hypoglycemic times and therefore make it more difficult to meet the standard of control 95% of the time. More consistent monitoring would lead to more consistent results when this method is used to analyze blood glucose control.

In addition, the glucose range chosen (60–250 mg/dL) is wide and allows for considerable variability in glucose values. The range of glucose from 60 to 250 mg/dL was chosen based on similar ranges in previous studies[9] and the potential risks associated with hypoglycemia.[10] In order to be considered controlled, patients were required to be within this range >95% of the time to account for the acute stress response and resultant glucose variability that occur ECMO is initiated. However, this range may allow for too much glucose variability; a tighter range might show different effects of normoglycemia on survival.

Twenty-three of the patients in the study were hypoglycemic (glucose, <60 mg/dL) while on ECMO (28%), but overall, patients were hypoglycemic for only 2% of the time they spent on

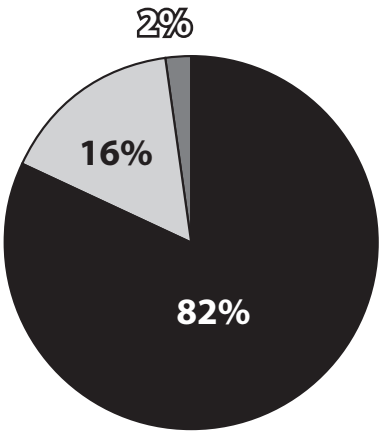

Figure 2. Total Percentage of Time of All patients Spent in Each Glucose Category.
■ % of time normoglycemic; □ % of time hyperglycemic; ■ % of time hypoglycemic

ECMO (Figure 2). For this reason, mortality rates for hypoglycemic patients were not specifically examined; hypoglycemia and hyperglycemia were combined as abnormal glucose values. Hypoglycemia itself may be a predictor of disease severity and has been found to be independently associated with mortality.[10]

Corticosteroid use causes an increase in blood glucose variability; therefore, it was included as a variable. However, patients were considered treated with a corticosteroid regardless of whether it was one dose at initiation of ECMO or many doses throughout the duration of ECMO. Likewise, most pre-cardiac surgeries use preoperative steroids; these doses were not counted because they occurred before the initiation of ECMO. Multiple doses or pre-ECMO doses of steroids might have significantly influenced glucose variability. While the authors recognize that the effect of corticosteroids on blood glucose is dose-related, the goal of the study was to determine the effect of blood glucose on mortality, so the effect of corticosteroid usage was only a secondary variable, and dose was not included in the analysis.

Factors of infection and the emergent nature of ECMO cannulation were included in this study because they can significantly affect blood glucose levels.[11,12] Data for arterial pH, renal replacement therapy, hepatic function, use of inotropes, and chest reexploration were beyond the scope of this study. These factors have been associated with survival outcomes in ECMO patients.[8] Future studies could reexamine blood glucose control while controlling for these factors.

To date, only one study has examined the relationship between glycemic control and outcomes in patients on ECMO.[7] That research on adult patients also found no statistically significant differences in mortality or patient complications with regard to glucose levels. There are several key differences between that previous report and this study. Hyperglycemia was defined as a glucose mean of >170 mg/dL, and only the mean glucose level and not the amount of time a patient was hyper- or hypoglycemic was reviewed. This is a fairly conservative level for pediatric patients in whom hypoglycemia can have negative effects.[13]

Overall, patients who were placed on ECMO in 2010 (51.4%) had improved overall hospital survival compared to patients from 2009 and 2008 (39.4% and 9.1%, respectively). It is possible that as the institution and clinical staff have become more familiar with ECMO, patient outcomes have improved. This improvement is likely to be independent of glycemic control.

Patients placed emergently on ECMO spent an average of 2 fewer days on ECMO than those non-emergently cannulated (p=0.0033). These results could be an anomaly, as they were not the primary outcome of this research and the sample size was small (fewer than 100 patients).
Alternatively, ECMO is sometimes used proactively for respiratory or cardiac recovery for a specific length of time. In contrast, patients placed emergently on ECMO require immediate life-saving measures that could have the potential to be reversed in a shorter length of time. For example, patients unable to wean from cardiopulmonary bypass may be placed on ECMO to allow their heart to recover after cardiac surgery, while a patient with a shunt occlusion may require emergent ECMO only until the occlusion is repaired. Similarly, emergent ECMO may elicit a hyperglycemic response because of stress, and patients placed on ECMO because of a failure to wean from bypass may be hyperglycemic postoperatively. This is a possible explanation for the finding that patients with uncontrolled glucose levels spent less time on ECMO than controlled patients.

All patients who required ECMO were included in this study; however, most patients had a cardiac diagnosis. Patients with cardiac

Table 3. Comparison of Demographic Characteristics and Clinical Features of ECMO In Non- survivors and Survivors

Characteristic	Nonsurvivors [n=29 (35.4%)]	Survivors [n=53 (64.6%)]	p Value
Age (yr)			
0-1	11 (21.6)	40 (78.4)	0.003*
1-3	6 (60)	4 (40)	
>3	12 (57.1)	9 (42.9)	
Sex			
Female	14 (41.2)	20 (58.8)	0.35†
Male	15 (31.3)	33 (68.7)	
Race			
Black	7 (41.2)	10 (58.8)	0.14*
Hispanic	9 (56.3)	7 (43.7)	
Other/unknown	3 (37.5)	5 (62.5)	
White	10 (24.4)	31 (75.6)	
Weight (kg)			
≤5 kg	7 (19.4)	29 (80.6)	0.005†
5-20 kg	10 (37)	17 (63)	
≥20 kg	12 (63.2)	7 (36.8)	
Principal diagnosis			
Cardiac	14 (23)	47 (77)	<0.001*
Sepsis	9 (75)	3 (25)	
Other	6 (66.7)	3 (33.3)	
Insulin use			
No	22 (31.9)	47 (68.1)	0.20*
Yes	7 (53.8)	6 (46.2)	
Steroid Use			
No	5 (23.8)	16 (76.2)	0.20†
Yes	24 (39.3)	37 (60.7)	
Infection			
No	13 (26)	37 (74)	0.03†
Yes	16 (50)	16 (50)	
Controlled glucose level			
Yes	14 (38.9)	22 (61.1)	0.56†
No	15 (32.6)	31 (67.4)	
Emergent cannulation			
Yes	13 (39.4)	20 (60.6)	0.53†
No	16 (32.7)	33 (67.3)	
Reason for ECMO			
Arrest	12 (38.7)	19 (61.3)	0.83*
RF	5 (45.5)	6 (54.5)	
Low CO	6 (35.3)	11 (64.7)	
Bypass	3 (25)	9 (75)	
Other	3 (27.3)	8 (72.7)	
Year			
2008	12 (57.1)	9 (42.9)	0.04†
2009	11 (31.4)	24 (68.6)	
2010	6 (23.1)	20 (76.9)	

Bypass, failure to wean from bypass; CO, cardiac output; RF, respiratory failure

* Fisher exact test

† Chi-square test

Table 4. Comparison of Patients Who Survived to Discharge Versus Those Who Died Prior to Discharge (i.e., Hospital Mortality)

Characteristic	Non-survivors [n=29 (35.4%)]	Survivors [n=53 (64.6%)]	p Value
Age (yr)			
0-1	27 (52.9)	24 (47.1)	0.29*
1-3	7 (70)	3 (30)	
>3	15 (71.4)	6 (28.6)	
Sex			
Female	26 (76.5)	8 (23.5)	0.009†
Male	23 (47.9)	25 (52.1)	
Race			
Black	8 (47.1)	9 (52.9)	0.5*
Hispanic	11 (68.8)	5 (31.2)	
Other/unknown	6 (75)	2 (25)	
White	24 (58.5)	17 (41.5)	
Weight (kg)			
≤5 kg	21 (58.3)	15 (41.7)	0.11†
5-20 kg	13 (48.1)	14 (51.7)	
≥20 kg	15 (78.9)	4 (21.1)	
Principal diagnosis			
Cardiac	31 (50.8)	30 (49.2)	0.01*
Sepsis	11 (91.7)	1 (8.3)	
Other	7 (77.8)	2 (22.2)	
Insulin use			
No	40 (58)	29 (42)	0.45†
Yes	9 (69.2)	4 (30.8)	
Steroid Use			
No	8 (38.1)	13 (61.9)	0.019†
Yes	41 (67.2)	20 (32.8)	
Infection			
No	27 (54)	23 (46)	0.18†
Yes	22 (68.8)	10 (31.2)	
Controlled glucose level			
Yes	23 (63.9)	13 (36.1)	0.5†
No	26 (56.5)	20 (43.5)	
Emergent cannulation			
Yes	18 (54.5)	15 (45.5)	0.43†
No	31 (63.3)	18 (36.7)	
Reason for ECMO			
Arrest	16 (51.6)	15 (48.4)	0.64*
RF	8 (72.7)	3 (27.3)	
Low CO	12 (70.6)	5 (29.4)	
Bypass	7 (58.3)	5 (41.7)	
Other	6 (54.5)	5 (45.5)	
Year			
2008	18 (85.7)	3 (14.3)	0.002†
2009	22 (62.9)	13 (37.1)	
2010	9 (34.6)	17 (65.4)	

Bypass, failure to wean from bypass; CO, cardiac output; RF, respiratory failure.

* Fisher exact test

† Chi-square test

Table 5. Glycemic Control and Time on ECMO.

	Glucose Controlled [n=36 (43.9%)]	Glucose Not Controlled [n= 46 (56.1%)]
Average time on ECMO (hr)	134.5 ± 108.2	103 ± 100.4

diagnoses were more likely to survive ECMO support and hospital stay ($p<0.001$ and $p=0.005$, respectively). This remained true for ECMO support even after controlling for multiple factors ($p=0.0002$). There are several potential explanations for this finding. Cardiac conditions may lead to better outcomes because of the potential for repair. Other conditions that may lead to ECMO support may not have a repairable cause, such as severe poisonings or cancer. In addition, cardiac patients make up the largest population of patients placed on ECMO at the study institution and therefore clinicians have the most expertise in these cases.

Overall, glucose control did not affect patient survival, either while on ECMO or until hospital discharge. Future studies could examine whether tightly controlled glucose has a beneficial effect on survival for pediatric patients on ECMO.

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ABBREVIATIONS ECMO, extracorporeal membrane oxygenation; VA, veno-arterial; VV, veno-venous

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