Correlation between serum lactate levels and outcome in pediatric patients undergoing congenital heart surgery

Doğuştan kalp cerrahisi geçiren pediatrik hastalarda serum laktat düzeyleri ile sonuç ilişkisi

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ABSTRACT

Background: This study aimed to investigate the correlation between perioperative arterial lactate levels and morbidity and mortality in children undergoing cardiac surgery.

Methods: A total of 236 patients who underwent open heart surgery due to congenital heart disease (121 males, 115 females; mean age 56.4 month (median: 42 month): range, 1 day to 204 month) between June 2014 and May 2016 were retrospectively analyzed. The arterial blood gas analysis results at baseline (after insertion of arterial cannula), during the cooling and warming-up phases in cardiopulmonary bypass, during the sternal closure, and at 0, 6, 12, and 24 hours in the postoperative intensive care unit stay were recorded. The patients were divided into two groups according to their lactate levels: Group 1 (lactate level <4.5 mmol/L, n=183) and Group 2 (lactate level ≥4.5 mmol/L, n=53). Correlation between the lactate groups and demographic data, intraoperative and postoperative variables, postoperative complications, and mortality were investigated.

Results: Sixty-nine patients (29.2%) had cyanotic heart disease. A total of 53 patients (22.5%) had lactate levels of ≥4.5 mmol/L. At least one complication occurred in 41% of the patients. Development of at least one complication (p=0.027) and mortality rate (p<0.001) were significantly higher in the patients with lactate levels of ≥4.5 mmol/L. Seventeen patients (7.2%) died in the postoperative period, and 15 of them had lactate levels of ≥4.5 mmol/L at least once within the first 24 hours. In terms of mortality, lactate levels of ≥4.5 mmol/L at any time, prolonged mechanical ventilation (>48 hours), and undergoing complex surgery (high the Risk-adjusted Classification for Congenital Heart Surgery-1 score, category 4-6) were the independent risk factors for mortality.

Conclusion: Blood arterial lactate level of ≥4.5 mmol/L was found to be a risk factor for postoperative morbidity and mortality in pediatric patients undergoing congenital heart surgery.

Keywords: Cardiac surgery; congenital; heart defects; lactate; mortality; postoperative complications.

ÖZ

Amaç: Bu çalışmada doğuştan kalp cerrahisi geçiren pediatrik hastalarda perioperatif arteriyal laktat düzeyleri ile mortalite ve morbidite arasında ilişki olup olmadığı araştırıldı.

Çalışma planı: Haziran 2014-Mayıs 2016 tarihleri arasında doğuştan kalp cerrahisi geçiren 236 hasta (121 erkek, 115 kadın; ort. yaş 56.4 ay (median: 42 ay): dağılım, 1 gün-204 ay) retrospektif olarak değerlendirildi. Başlangıçta (arter kanülü uygulandıktan sonra), kardiyopulmoner baypas soğuma ve ısınma fazında, sternum kapatılması aşamasında ve ameliyat sonrası yoğun bakım kalış süresi 0, 6, 12. ve 24. saatlerdeki arteriyel kan gazı analizleri kaydedildi. Hastalar laktat düzeylerine göre iki gruba ayrıldı: (Grup 1 laktat düzeyi <4.5 mmol/L, n=183; Grup 2 laktat düzeyi ≥4.5 mmol/L, n=53). Gruplar ile hastaların demografik verileri, ameliyat sırası ve ameliyat sonrası değişkenler, komplikasyonlar ve mortalite arasındaki ilişki araştırıldı.

Bulgular: Altmış dokuz hastada (%29.2) siyanotik kalp hastalığı vardı. Toplamda 53 hastada (%22.5) laktat düzeyi 4.5 mmol/L ve üzerinde idi. Hastaların %41'inde en az bir komplikasyon gelişti. Laktat düzeyi ≥4.5 mmol/L grupta en az bir komplikasyon gelişimi (p=0.027) ve mortalite oranı (p<0.001) anlamlı olarak daha yüksekti. On yedi hasta (%7.2) ameliyat sonrası dönemde kaybedildi ve bu hastaların 15'inde laktat düzeyi ilk 24 saatte en az bir kez ≥4.5 mmol/L idi. Herhangi bir dönemde laktat düzeylerinin ≥4.5 mmol/L olması, uzamış mekanik ventilasyon (>48 saat) ve hastanın kompleks cerrahi geçirmesi (yüksek Risk-adjusted Classification for Congenital Heart Surgery-1 skoru, kategori 4-6) mortalite için bağımsız risk faktörü olarak tespit edildi.

Sonuç: Doğuştan kalp cerrahisi uygulanan çocuk hastalarda, arteriyel laktat düzeyinin 4.5 mmol/L veya üzerinde olmasının ameliyat sonrası morbidite ve mortalite için bağımsız risk faktörü olduğu saptandı.

Anahtar sözcükler: Kardiyak cerrahi; doğuştan; kalp kusurları; laktat; ölüm oranı; ameliyat sonrası komplikasyonlar

Lactate is used as a marker for oxygen deficiency in anaerobic metabolism at the tissue level. Increase in tissue lactate concentration is associated with cellular dysfunction due to the depletion of high-energy phosphate compounds.[1] Lactate is produced by erythrocytes, perivenous hepatocytes, skeletal muscle myocytes, and skin and is cleansed by the liver and kidneys. Elevated blood lactate levels indicate increased lactate production, decreased lactate clearance, or both occurring simultaneously.[2] Systemic hypoperfusion, hemodilution, and tissue hypoxia are believed to increase lactate levels in patients undergoing cardiopulmonary bypass (CPB). It has also been shown that cytokine response against CPB and various metabolic conditions such as β2 agonist agents used for hemodynamic stabilization and diabetes increase lactate levels.[1-6] High lactate levels following open heart surgery are often associated with increased postoperative mortality and morbidity rates.[7] High lactate levels have also been shown to correlate with duration of CPB, duration of aortic cross-clamp, inotropic scores, and the Risk-adjusted Classification for Congenital Heart Surgery-1 (RACHS-1) subgroups.[8] Lactate elevation is also a risk factor for prolonged intensive care unit (ICU) stay and increased severe postoperative adverse events.[5]

However, the methods used in these studies (such as change of lactate level) differ from lactate cut-off values and vary according to surgical procedures. Therefore, the correlation between increased serum lactate levels, complications, and mortality still remains unclear.[8,9]

In this study, we aimed to investigate the correlation between lactate levels within the first 24 hours, complications, and mortality in pediatric patients with congenital heart disease undergoing open heart surgery.

PATIENTS AND METHODS

This retrospective study was approved by the review board of Clinical Research Ethics Committee of Ege University School of Medicine (Decision Number: 16-2.1/7, date: 07/03/2016) and was conducted in accordance with the principles of the Declaration of Helsinki.

A total of 243 patients were included in the study. Seven patients died during the intraoperative period due to heart failure and were excluded from the study to avoid data loss; two patients had truncus arteriosus, two had great arterial transposition, one patients had double outlet right ventricle, one patient had tricuspid

Table 1. Diagnosis of patients

	Group 1		Group 2	
	n	%	n	%
Non-cyanotic				
Atrial septal defect	47	25.7	5	9.4
Ventricular septal defect	37	20.2	5	9.4
Atrial septal defect + ventricular septal defect	12	6.6	1	1.9
Atrioventricular canal defect	9	4.9	2	3.8
Pulmonary stenosis	12	6.6	5	11.3
Pulmonary regurgitation	4	2.2	4	7.5
Systemic valve stenosis	11	6	5	9.4
Left ventricular outflow obstruction	5	2.7	1	1.19
Coronary anomalies (ALCAPA)	2	1.1	0	0
Cyanotic				
Tetralogy of Fallot	23	12.5	3	5.7
Single ventricle	4	2.2	4	5.7
Anomalous pulmonary venous return	4	2.2	1	1.9
Truncus arteriosus	0	0	2	3.8
Transposition of the great arteries	4	2.2	11	20.7
Double outlet right ventricle	7	3.8	1	1.9
Ebstein anomaly	2	1.1	1	1.9
Hypoplastic left heart	0	0	2	3.8
Total (%)	183	100	83	100

ALCAPA: Anomalous left coronary artery from the pulmonary artery.

stenosis and hypoplastic right heart, and one patient had tetralogy of Fallot and hypoplastic right heart. Extracorporeal membrane oxygenation (ECMO) was not considered due to the complexity of the pathology and the lack of life expectancy, and no patients died within the first 24-hour postoperative period. A total of 236 pediatric patients (121 males, 115 females; mean age 56.4 months (median: 42 months); range, 1 day to 204 month) who underwent open heart surgery due to congenital heart disease between June 2014 and May 2016 were retrospectively analyzed. The data was obtained from patient records and anesthesia follow-up records. Emergency cases, patients not requiring CPB, preoperatively intubated patients, and those who survived less than 24 hours were excluded from the study.

The primary endpoint was the correlation between elevated lactate levels, complications, and mortality. The secondary endpoint was to determine risk factors for the first 30-day mortality.

The patients' preoperative parameters (age, gender, weight, height, body mass index, RACHS-1 scores,[6] and preoperative diagnosis), intraoperative data (duration of anesthesia, duration of surgery, CPB time, aortic cross-clamp time), and postoperative data (inotropic score at postoperative first hour, use of postoperative blood products within the first 24 hours, duration of mechanical ventilation, intensive care unit (ICU) stay, length of hospital stay, postoperative complications, and 30-day mortality) were recorded. The arterial blood gas analysis results (PH, $PaCO_2$, PaO_2, blood

glucose, lactate, hematocrit) and hemodynamic parameters (mean arterial pressure, heart rate, central venous pressure, SpO_2) were recorded at baseline (after the arterial cannula was administered), during cooling and warming-up phases of CPB, in the course of sternal closure, and at postoperative 0, 6, 12, and 24 hours in the ICU stay. The RACHS-1 consists of six categories (category 1-3 low risk group, category 4-6 high risk group).[10] The vasoactive-inotrope score (VIS) was calculated with the formula: Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 100 × Epinephrine dose (mcg/kg/min) + 100 × Norepinephrine dose (mcg/kg/min 10 × Milrinone dose (mcg/kg/min). Inotropic score within the first hour of ≥20 was categorized as high VIS.[11] High lactate level was defined as lactate levels of ≥4.5 mmol/L at least once within the intraoperative period and postoperative first 24 hours. The patients were divided into two groups according to lactate levels measured in arterial blood gas. Group 1 (n=183) included the patients with a lactate level <4.5 mmol/L, while Group 2 (n=53) included those with a lactate level of ≥4.5 mmol/L. The correlation between the demographic data of the patients, their intraoperative and postoperative variables, postoperative complications, and mortality was evaluated in both groups. The following complications were investigated in the study: cardiac complications (right or left heart failure, arrhythmias requiring treatment, ECMO requirement), respiratory complications (pneumonia, re-intubation, acute respiratory distress syndrome, prolonged mechanical ventilation [>48 hours]), renal dysfunction (0.3 mg/dL

Table 2. Patient characteristics

Characteristic variables	Group 1 (n=183)				Group 2 (n=53)				*p*
	n	%	Median	Min-Max	n	%	Median	Min-Max	
Age (month)			42	1 day-204 month			30	2 day-180 month	0.256
Gender									0.160
Male	89				32				
Female	94				21				
BSA (kg/m²)			0.58	0.22-2			0.56	0.14-1.58	0.337
Cyanotic	45	24.6			24	45.3			**0.006**
RACHS-1									**<0.001**
I	47	25.7			5	9.4			
II	83	45.4			21	39.6			
III	48	26.2			12	22.6			
IV	4	2.2			11	20.8			
V	1	0.5			2	3.8			
VI	0	0			2	3.8			

Min: Minimum; Max: Maximum; BSA: Body surface area; RACHS-1: Risk-adjusted Classification for Congenital Heart Surgery.

Table 3. Intraoperative hemodynamic parameters and arterial blood gases

	Baseline Mean±SD	Baseline Median	Baseline Min-Max	CPB cooling Mean±SD	CPB cooling Median	CPB cooling Min-Max	CPB warming Mean±SD	CPB warming Median	CPB warming Min-Max	Sternal closure Mean±SD	Sternal closure Median	Sternal closure Min-Max
Lactate (mmol/L)												
Group 1		0.94	0.07-3.94	2.6±1.0			2.3±0.8				1.9	0.67-4.5
Group 2		1.58	0.7-4.01	4.0±1.1			4.6±1.6				4.45	1.1-10.4
p		<0.001	<0.001	<0.001			<0.001				<0.001	<0.001
Mean arterial pressure (mmHg)												
Group 1	80±16			52±10				65	30-80	66±10		
Group 2	72±21			54±12				66	40-80	66±13		
p	0.007			0.127				0.681	0.681	0.768		
Heart rate (bpm)												
Group 1	126±24									115±19		
Group 2	128±29									117±20		
p	0.685									0.964		
Central venous pressure (mmHg)												
Group 1		10	0-18							11±3.8		
Group 2		9	1-16							11±4.1		
p		0.242	0.242							0.389		
SpO₂ (%)												
Group 1		99	74-100							97±3		
Group 2		99	74-100							95±5		
p		0.54	0.54							0.265		
Arterial PH												
Group 1		7.42	7.11-7.58	7.3±0.1			7.4±0.1			7.4±0.1		
Group 2		7.42	7.2-7.52	7.4±0.1			7.4±0.1			7.4±0.1		
p		0.210	0.210	0.121			0.086			0.093		
PaCO₂ (mmHg)												
Group 1		28	18-73	36±7			36±9				32	24-57
Group 2		29	21-55	35±9			33±11				32	18-58
p		0.221	0.221	0.165			0.062				0.969	0.969
PaO₂ (mmHg)												
Group 1		223	28-596	196±78			228±82			238±136		
Group 2		173	25-576	213±66			223±63			228±145		
p		0.151	0.151	0.116			0.706			0.752		
Hematocrit (%)												
Group 1		34	22-57		26	17-44		26	18-40		29	20-43
Group 2		35	27-53		25	19-40		25	19-37		30	18-41
p		0.210	0.210		0.535	0.535		0.783	0.783		0.887	0.887
Arterial glucose (mg/dL)												
Group 1	92±25				198	62-366	224±55				198	94-359
Group 2	96±30				203	127-395	230±31				198	132-404
p	0.380				0.282	0.282	0.262				0.432	0.432

SD: Standard deviation; Min: Minimum; Max: Maximum; CPB: Cardiopulmonary bypass; SpO₂: Saturation of arterial blood with oxygen as measured by pulse oximetry; PaCO₂: Partial pressure of carbon dioxide in arterial blood; PaO₂: Partial pressure of oxygen in arterial blood.

Table 4. Postoperative hemodynamic parameters and arterial blood gases

	Postoperative 0th hour			6th hour			12th hour			24th hour		
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max
Lactate (mmol/L)												
Group 1		1.85	0.49-5.42		2.2	0.82-7.5		1.43	0.63-4.16		1.17	0.1-3.65
Group 2		5.15	1.1-14.6		6.13	1.5-19.7		3.45	1-16.4		2.48	0.92-7.1
p		<0.01	<0.01		<0.01	<0.01		<0.01	<0.01		<0.01	<0.01
Mean arterial pressure (mmHg)												
Group 1	76±12			80±10			80±10			80±11		
Group 2	71±17			71±15			73±21			73±19		
p	0.027			<0.001			0.013			0.026		
Heart rate (bpm)												
Group 1		122	63-174	127±27			121±26				118	72-221
Group 2		120	75-178	134±30			127±29				12	90-194
p		0.651		0.154			0.111				0.175	
Central venous pressure (mmHg)												
Group 1	8±4				9	1-20		10	0-20	10±4		
Group 2	9±5				9	0-25		10	3-25	11±5		
p	0.442				0.650			0.376		0.203		
SpO₂ (%)												
Group 1	98±3				99	80-100		99	85-100		98	81-100
Group 2	98±4				99	86-100		99	87-100		99	89-100
p	0.710				0.402			0.161			0.783	
Arterial PH												
Group 1		7.43	7.1-7.66		7.41	7.09-7.55		7.43	7.27-7.66		7.44	7.15-7.67
Group 2		7.41	7.1-7.64		7.38	7.06-7.56		7.39	7.11-7.62		7.43	7.17-7.58
p		0.201			0.001			<0.001			0.078	0.078
PaCO₂ (mmHg)												
Group 1	28±7				30	17-80		30	17-49		29	16-61
Group 2	27±7				28	14-62		31	16-67		32	20-55
p	0.528				0.369			0.218			0.210	
PaO₂ (mmHg)												
Group 1	268±122			180±62			159±58			137±51		
Group 2	235±123			192±71			168±62			138±55		
p	0.77			0.483			0.702			0.914		
Hematocrit (%)												
Group 1		32	18-43	32±5			33±5			32±5		
Group 2		32	17-41	33±6			32±5			32±5		
p		0.680		0.756			0.916			0.909		
Arterial glucose (mg/dL)												
Group 1	169±51			175±58			132±35			128±53		
Group 2	187±62			197±67			153±53			138±50		
p	0.056			0.039			0.010			0.111		

SD: Standard deviation; Min: Minimum; Max: Maximum; CPB: Cardiopulmonary bypass; SpO₂: Saturation of arterial blood with oxygen as measured by pulse oximetry; PaCO₂: Partial pressure of carbon dioxide in arterial blood; PaO₂: Partial pressure of oxygen in arterial blood.

increase in creatinine compared to baseline values, and the need for renal replacement treatment/hemodialysis), cerebrovascular complications (convulsion, cerebral hemorrhage, and cerebral infarct), gastrointestinal complications (ileus, mesenteric ischemia), hematologic complications (massive blood transfusion, hemolysis, and disseminated intravascular coagulation), sepsis, multiple organ dysfunction (MODS), revision, and mortality.

Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA). The variables were expressed in mean ± standard deviation (SD), percentage (%), and median (min-max) values. The Kolmogorov-Smirnov test was used to determine whether the variables distributed normally or not. The chi-square and Fisher's exact tests were used for categorical variables, the Independent samples t-test was used to analyze quantitative variables, and the Mann-Whitney U test was used when independent samples t-test was not appropriate. Univariate and multivariate analyses were carried out to examine the mortality-related factors. Significant factors in the univariate analysis were included in the multivariate analysis. Lactate levels of ≥4.5 mmol/L showed the area under the receiver-operating characteristic (ROC) curve to predict 30-day mortality (ROC area: 0.854; 95% confidence interval: 0.761-0.948), with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and test validity of 88.2%, 82.6%, 28.3%, 98.9% and 83%, respectively. A *p* value of <0.05 value was considered statistically significant.

RESULTS

Sixty-nine patients (29.2%) had cyanotic heart disease (Table 1 and 2). Four patients (1.7%) underwent operation under total circulatory arrest, while three patients (1.3%) required ECMO (two patients underwent the Norwood procedure and one patient underwent the Jaten procedure). Three patients were discontinued from ECMO, but died due to MODS. The baseline mean arterial pressure (after arterial cannulation) and mean arterial pressure within the first 24 hours postoperatively were lower in Group 2 compared to Group 1, while the intraoperative and postoperative values of heart rate, central venous pressure, blood glucose level (excluding postoperative 6th hour and 12th hour), hematocrit, and arterial blood gas analyses (excluding PH postoperative sixth hour and PH postoperative 12th hour) were similar in both

groups (p>0.05) (Table 3 and Table 4). A total of 22.5% of the patients (n=53) had lactate levels of ≥4.5 mmol/L. The intraoperative and postoperative mean lactate levels were higher in Group 2 than Group 1 (Table 3, Table 4, and Figure 1). Eleven percent and 4% of the patients had lactate levels of ≥4.5 mmol/L at postoperative 12 and 24 hours, respectively. In addition, lactate levels returned to less than 1.5 mmol/L at the postoperative 24 hours in 58.4% of the patients (Figure 1). The VIS in 11% of the patients was more than or equal to 20, and there was a statistically significant correlation between the increased VIS and increased lactate levels. The VIS was 5 (range: 0 to 40) in the group with a lactate level less than 4.5 mmol/L, while the VIS was calculated as 7.5 (0-70) in the group with a lactate level of ≥4.5 mmol/L (p=0.004). In all patients, the median red blood cells, fresh-frozen plasma, and platelet use were 147.5 mL (0-845), 200 mL (0-1005), and 20 mL (0-644), respectively within intra- and postoperative first 24 hours, and there were no statistically significant difference between both groups (Table 5).

A total of 275 complications occurred in 41% of the patients. The development of at least one complication (Group 1: 37.1% vs Group 2: 54.7%, p=0.027) and mortality rate (Group 1: 1.1% vs Group 2: 28.3%, p<0.001) was significantly higher in the patients with lactate levels of ≥4.5 mmol/L. Seventeen patients (7.2%) died in the postoperative period, while lactate levels in 15 of these patients were ≥4.5 mmol/L within
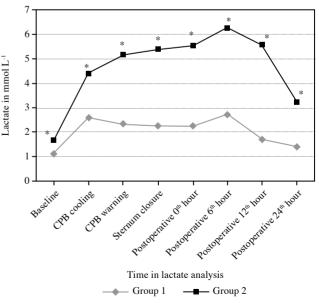

Figure 1. The progress of lactate levels of the group within intraoperative and postoperative first 24 hours.
CPB: Cardiovascular bypass; * p<0.001.

Table 5. Intraoperative and postoperative variables of the patients

	Group 1 (n=183)			Group 2 (n=53)			
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	p
Duration of surgery (min)	219±52.4			255±52.8			**<0.001**
Duration of anesthesia (min)	269±58			315±58			**<0.001**
CPB time (min)		65.5	19-198		90	27-162	**<0.001**
Aortic cross-clamp time (min)		51	0-181		73	0-160	**<0.001**
Vasoactive-inotropic score		5	0-40		7.5	0-70	**0.004**
Duration of MV (hour)		4.5	1.5-1080		6.5	1.5-792	**0.008**
Duration of ICU stay (hour)		23	16-1968		29	12-1680	0.064
Length of stay in hospital (day)		7	4-91		8	2-92	**0.019**
Use of ES (mL)		135	0-715		175	0-845	0.114
Use of FFP (mL)		192	0-960		300	0-1005	0.053
Use of thrombocyte (mL)		20	0-340		30	0-644	0.097

SD: Standard deviation; Min: Minimum; Max: Maximum; CPB: Cardiopulmanary bypass; MV: Mechanical ventilation; ICU: Intensive care unit; ES: Erythrocyte suspension; FFP: Fresh frozen plasma.

the first 24 hours (Table 6). Of the 17 patients that died, six patients had transposition of the great arteries, two had single ventricle, two had hypoplastic left heart, two had tetralogy of Fallot, two had atrioventricular canal defect, one had double outlet right ventricle, one had atrial septal defect and ventricular septal defect, and one patient had total anomalous pulmonary venous return. Among them, 13 patients died from MODS, two patients died from cardiac complications, and one patient died from respiratory complications. In terms of mortality, lactate levels of ≥4.5 mmol/L at any time, prolonged mechanical ventilation, and undergoing complex surgery (high RACHS-1 scores) were found

to be independent risk factors for mortality (Table 7). The lactate levels ranged from 0.1 to 15.9 mmol/L in survivors and from 0.7 to 19.9 mmol/L in non-survivors.

DISCUSSION

In our study, we found that high levels of arterial lactate (≥4.5 mmol/L), complex surgery (high RACHS-1 scores, category 4-6) and prolonged mechanical ventilation duration (>48 hours) were associated with increased mortality in pediatric patients undergoing congenital heart surgery.

Table 6. Distribution of postoperative complications

	Group 1		Group 2		
Types of complications	n	%	n	%	p
At least one complication	68	37.2	29	54.7	**0.027**
Respiratory	29	15.8	22	41.5	**<0.001**
Cardiac	43	23.5	27	50.9	**<0.001**
Neurological	6	3.3	11	20.8	**<0.001**
Renal	11	6	15	28.3	**<0.001**
Gastrointestinal	9	5	6	11.3	0.110
Hematologic	12	6.6	15	28.3	**<0.001**
Multiple organ dysfunction syndrome	6	3.3	14	26.4	**<0.001**
Sepsis	9	5	7	13.2	0.057
Revision	6	3.3	9	17	**0.001**
Mortality	2	1.1	15	28.3	**<0.001**

Table 7. Logistic regression analysis of risk factors associated with mortality

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (per month)	0.947 (0.912-0.984)	**0.005**		
Weight (increase per kg)	0.760 (0.649-0.890)	**0.001**		
Cyanotic (yes)	13.915 (3.854–50.238)	**< 0.001**		
High RACHS-1 (yes)	15.333 (5.022-46.812)	**< 0.001**	14.73 (1.078-201.267)	**0.044**
Baseline MAP (mmHg)	0.930 (0.899-0.963)	**< 0.001**		
Baseline HR (pbm)	1.029 (1.007-1.052)	**0.010**		
SpO₂ (%)	0.916 (0.857-0.978)	**0.009**		
VIS ≥20	18.125 (6.083-54.004)	**<0.001**		
Duration of anesthesia (min)	1.014 (1.006–1.023)	**0.001**		
Duration of surgery (min)	1,013 (1.004–1.022)	**0.003**		
CPB time (minute)	1.031 (1.017-1.045)	**<0.001**	1.025 (0.999-1.053)	0.062
Cross-clamp time (min)	1.024 (1.009-1.038)	**0.001**		
Duration of MV (hour)	1.007 (1.003-1.010)	**<0.001**	1.014 (1.005-1.022)	**0.001**
ICU stay (hour)	1.003 (1.001-1.004)	**0.007**	0.996 (0.992-1.0)	0.077
Lactate ≥4.5 mmol/L	35.724 (7.842-162.732)	**<0.001**	25.252 (2.318-275.093)	**0.008**
ES (any quantity)	1.006 (1.001-1.010)	**0.010**		
FFP (any quantity)	1.004 (1.001-1.007)	**0.018**		

OR; Odds ratio; CI: Confidence interval; RACHS-1: Risk-adjusted Classification for Congenital Heart Surgery (category 4-6); MAP: Mean arterial pressure (increase per a value); HR: Heart rate (increase per beat); SpO₂; peripheral capillary oxygen saturation (increase per a value); VIS: Vasoactive-inotropic score; CPB: Cardiopulmonary bypass (increase per minute); Cross-clamp time: Aortic cross-clamp time (increase per minute); MV: Mechanical ventilation (increase per hour); ICU: Intensive care unit (increase per hour); ES: Erythrocyte suspension; FFP: Fresh frozen plasma.

Postoperative elevation of lactate levels is expected, and lactate levels of 3-4 mmol/L were not considered to be low in previous studies. However, the design of these studies was different, as the cut-off lactate levels were calculated as 3-6 mmol/L.[8,12-14] Molina Hazan et al.[8] found that maximum lactate levels (within postoperative first 12 hours) were correlated with the duration of CPB, duration of aortic cross-clamp, the RACHS-1 subgroups, and inotropic scores. Maarslet et al.[12] reported that young age, low weight, high RACHS-1 scores, prolonged duration of CPB, and inotropic use were risk factors for elevated lactate. In addition, a lactate level of ≥4.5 mmol/L led to an increased risk of dialysis (16.9 fold) and mortality (8.4 fold). However, they were unable to find a correlation between increased lactate levels and duration of intubation and ICU stay. Hatherill et al.[13] showed that lactate levels >6 mmol/L were weak positive predictive values for mortality on admission to the ICU. Another study reported that increased lactate levels were correlated with the stage of hypothermia in CPB, duration of cardioplegic arrest, duration of mechanical ventilation, and the ICU stay.[14]

In our study, a cut-off value of 4.5 mmol/L was chosen based on previous studies, but the lactate levels were in a wide range. Mortality was seen in only 32.1% of the patients with lactate levels of ≥4.5 mmol/L. This result led to a very weak positive predictive value (28.3%). We also found a correlation between the increased lactate levels and high RACHS-1 category, high inotropic scores, being in the cyanotic patient group, long CPB duration, aortic cross-clamp time, duration of operation, and duration of anesthesia.

There are a number of studies that investigate the correlation between lactate and incidence of morbidity and mortality in congenital heart surgery.[14-16] Shemie[14] reported that major complications occurred in 32 of 109 patients, and that lactate levels were higher in patients with complications (8.6±6.1 mmol/L vs 3.2±1.9 mmol/L). Duke et al.[15] reported 12 serious complications in 90 pediatric patients. Blood lactate levels (>4.5 mmol/L),

mean arterial pressure (hypotension), and duration of CPB (>150 minute) were independent risk factors for adverse events when measured at the time of admission to the ICU. When lactate levels were >4.5 mmol/L, the odds ratio was 2.3 (0.5-9.8) for major adverse events. Cardiac output within the first 24 hours, oxygen delivery, mixed venous oxygen saturation, heart rate, and the difference of peripheral-central temperature did not have an effect on major adverse events. Munoz et al.[16] investigated the arterial lactate levels before, during (cooling and warming-up), and after CPB, and upon ICU admission. Serious complications were defined as transfer to the intensive care unit with open sternum, development of renal failure, cardiac arrest, and requirement of resuscitation, requirement for ECMO, and death. High lactate levels were detected in patients who were under total circulatory arrest and in patients who died. A change of over 3 mmol/L in lactate level during CPB had a sensitivity of 82% and specificity of 80%. A total of 142 of all patients did not have any complications, while 18 patients developed at least one complication.

In our study, at least one complication developed in 97 patients (41.1%). Lactate level of ≥4.5 mmol/L was found to be a significant risk factor for complications. Increased complications developed in the high-lactate group which led to an increase in the duration of mechanical ventilation, and length of hospital stay. Because of the fact that some complications (such as pneumonia, increase in creatinine, and renal replacement therapy) may be treated without requiring ICU, no statistically significant difference between increased lactate levels and duration of ICU stay were found.

Mortality after congenital heart surgery is between 8% and 12.5%.[3-5,8,17-19] Cheifetz et al.[3] reported that six of 48 patients who underwent high risk open-heart surgery died. The patients in the group in which the patients died had significantly higher lactate levels in the postoperative period than that of survivors. All patients with an initial lactate level of less than 7 mmol/L, a maximum lactate level of less than 9 mmol/L or 4-6 hour period lactate level of less than 4 mmol/L were discharged from the hospital. In another study, Ghaffari and Malaki[4] found that there was an increase in the arterial lactate levels (1.5-4 mmol/L) for 80% of 31 patients included in the study, while the arterial lactate levels returned to normal (<1.5 mmol/L) in 75% of the patients at postoperative 12 hours. In addition, the persistance of increased lactate levels (>4 mmol/L) at postoperative 24 hours was associated with poor prognosis.

Schumacher et al.[5] reported a mortality rate of 8.2% (n=19) in their study involving 231 infants. The increase of 0.6 mmol/L per hour in lactate levels was a good predictor for mortality (AUC: 0.89, sensitivity: 90%, specificity: 84%, positive predictive value: 34% and negative predictive value: 99%). Similar results were found in subgroups of single or double ventricular heart disease and in different groups of RACHS-1. In a retrospective study involving 255 patients, Molina Hazan et al.[8] investigated the lactate levels at the end of the operation, at ICU admission, and at postoperative 6 and 12 hours. When the Norwood operations were included, the authors reported that the mortality was 10.16% (n=27). The initial lactate level was 4.22±3.2 mmol/L in survivor patients, while it was 8.54±5.4 mmol/L in non-survivors (p<0.01). In the postoperative period, the serial mean lactate levels were significantly lower in survivor patients than those who died. In addition, the lactate levels in the RACHS-1 subgroups were significantly different between the surviving and non-surviving patients.

Charpie et al.[17] investigated the lactate levels of 46 patients who underwent complex heart surgery for three days. In the aforementioned study, mortality was seen in five patients and four patients required ECMO. The mean lactate level was 9.4±3.8 mmol/L in non-survivors and those requiring ECMO, while it was 5.6±2.1 mmol/L in surviving patients (p=0.03). In addition, the positive predictive value of the initial lactate levels higher than 6 mmol/L was 38% for mortality. In contrast, an increase in the lactate levels with 0.75 mmol/L/h was associated with poor outcomes (p<0.001, positive predictive value: 100%). Ladha et al.[18] found that lactate clearance was higher in survivors than non-survivors. Patients with higher lactate clearance (>10%) within the first six hours were found to have improved postoperative outcomes and were found to be associated with decreased mortality rates. In another study, Basaran et al.[19] found that 26 of 60 patients (43.3%) had a mean serum lactate >4.8 mmol/L. Six patients died in the postoperative period, and all of these patients were in the high lactate group. Mortality was also increased in the group with lactate level >4.8 mmol/L (19.0% vs 2.9%; p=0.037). In multivariate analysis; inotrope score, intubation time, and the ICU stay were found to increase the postoperative lactate levels.

High lactate levels (≥4.5 mmol/L) were found in 22.5% (n=53) of our patients within any intraoperative and postoperative period (only two patients had a

baseline lactate level of ≥4.5 mmol/L). In addition, 28.3% of the patients in Group 2 (n=15) died. The lactate levels of the patients reached their peak levels at postoperative 6th hour, and then started to fall off afterwards. Both postoperative high glucose level and low oxygen delivery may contribute to the lactate elevation in the period. Moreover, increased lactate levels may cause increased metabolic acidosis. The mortality in the high-lactate group was 32.1%, while it was 1.1% in the low-lactate group. Multiple factors were related to mortality in the univariate analysis, whereas multivariate analysis revealed that lactate levels with ≥4.5 mmol/L alone, high RACHS-1 score (category 4-6), and the duration of mechanical ventilation (>48 hour) were significant risk factors for mortality.

Study limitations

First, this study was retrospectively designed for a wide range of age and disease, which led to a wide range of lactate levels. Second, lactate levels were obtained from routine analyses, and a blind measurement was unable to be performed. Third, since treatment was not independent from the lactate levels of any individual patient, this may have changed the treatment approach of the intensive care specialist.

In conclusion, lactate levels in congenital heart surgery play a critical role in the morbidity and mortality of patients. High Risk-adjusted Classification for Congenital Heart Surgery-1 category, high inotropic scores, being in the cyanotic patient group, prolonged cardiopulmonary bypass duration and aortic cross-clamp time, and prolonged duration of operation and anesthesia may increase lactate levels. In the present study, lactate levels of ≥4.5 mmol/L, high Risk-adjusted Classification for Congenital Heart Surgery-1 score (category 4-6), and duration of mechanical ventilation (>48 hours) were found to be independent risk factors for mortality. Although high Risk-adjusted Classification for Congenital Heart Surgery-1 category, and cyanotic condition are unmodifiable risk factors, attention should be paid to the use of inotropic agents and duration of operation should be shortened to reduce the mortality and morbidity rates.

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