Prognostic significance of sICAM-1 and sVCAM-1 molecules for cardiac surgery in pediatric patients with pulmonary hypertension

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Abstract

Objective: To investigate preoperative and postoperative blood levels of soluble intercellular and vascular cell adhesion molecules (sICAM-1, sVCAM-1) in patients with and without pulmonary hypertension (PAH) due to congenital heart disease and left to right (L-R) shunt and to determine whether these molecules can be used as reliable prognostic markers of endothelial activity to predict surgical outcomes.

Methods: In this observational prospective cohort study; 42 patients, operated for L-R shunt were divided into three groups. Group 1: L-R shunt without PAH, Group 2: L-R shunt with PAH, Group 3: L-R shunt with PAH and postoperative low cardiac output syndrome (LCOS). Their sICAM-1 and sVCAM-1 levels were measured preoperatively (sICAM-0, sVCAM-0) and on the first (sICAM-1, sVCAM-1) and fifth postoperative days (sICAM-2, sVCAM-2).ROC curve for various cut-off levels of sICAM-0, sVCAM-0 in differentiating PAH patients with and without LCOS.

Results: In Group 3, sICAM-0 and sVCAM-2 levels were higher than Group 1 and 2. The ROC curve demonstrated a significant association between sICAM-0 in patients with L-R shunt and PAH (Group 2 and 3) and the development of LCOS (area under the curve: 0.98, p<0.01 and 0.97, p<0.01, respectively). At a sICAM-0 concentration >359 ng/mL, there was a sensitivity of 90% and specificity of 95% for identification of LCOS in patients with L-R shunt and PAH (AUC: 0.98, 95% CI: 0.95-1.02, p<0.01).

Conclusion: High preoperative sICAM-1 molecule may be used to predict postoperative dichotomous outcome in patients with PAH associated with L-R shunt. *(Anadolu Kardiyol Derg 2014; 14: 274-9)*

Key words: sICAM-1, sVCAM-1, pulmonary hypertension, cardiac surgery, predictive value

Introduction

Pulmonary arterial hypertension (PAH) is usually associated with congenital heart diseases especially with left to right (L-R) shunt. Increased pulmonary blood flow and pressure may play role in vascular remodeling. Endothelial cell dysfunction, abnormal shear stress, circumferential wall stretch, and an imbalance in vasoactive mediators lead to vasoconstriction, inflammation, thrombosis, cell proliferation, impaired apoptosis, and fibrosis (1). Soluble intercellular and vascular cell adhesion molecules (sICAM-1, sVCAM-1) that mediate vascular inflammation via promoting leukocyte adhesion to activated endothelial cells are glycoproteins from the immunoglobulin super family. Therefore, these adhesion molecules are widely used as early markers of endothelial damage and activation (2-4). Elevation of circulating endothelial adhesion molecules are commonly seen in patients with idiopathic PAH or secondary pulmonary hypertension associated with congenital heart disease and sickle cell disease (2, 5, 6). Cardiac surgery is also associated with increased plasma adhesion molecule levels (7). Recently; increased sICAM-1 levels have been reported in patients with L-R shunt with PAH (8). Cardiac surgery of the patients with PAH carries increased risk of mortality and morbidity which can be reduced by using prognostic markers of endothelial activation and there is no study to investigate prognostic value of ICAM and VCAM in this group of patients. We aimed to investigate the effects of cardiac surgery on ICAM and VCAM values and secondly to evaluate the prognostic significance of their baseline values for the prediction of postoperative low-cardiac output syndrome (LCOS).

Methods

Study design

Study was designed as an observational prospective cohort study.

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Study population

The study was conducted in our pediatric cardiology and pediatric heart surgery clinics between January 2008 and June 2009. Forty two patients operated for atrial septal defect (ASD), ventricular septal defect (VSD) and atrioventricular septal defect (AVSD) were included in the study. All patients received anticongestive therapy (digoxin and/or diuretics and/or angiotensin converting enzyme inhibitor). These patients were divided into three groups according to the presence of PAH and LCOS.

Group 1. L-R shunt without PAH, contained 5 ASD, 7 VSD patients.

Group 2. L-R shunt with PAH, contained 1 ASD, 14 VSD, 4 AVSD patients.

Group 3. L-R shunt with PAH and LCOS, contained 6 VSD, 5 AVSD patients. Seven Down syndrome patients were included in the study (Group 1 contained 1, Group 2 had 3, Group 3 had 3). Patients who received specific PAH therapy were excluded from the study. The study was approved by Local Ethics Review Committee. Informed consent forms were obtained from the parents of the patients.

Study variables and clinical examinations

Physical examination, chest X-ray, electrocardiography and echocardiography were used for the diagnosis and angiography was performed on selected patients. The diagnosis was also confirmed during the surgery. Serum levels of sICAM-1 and sVCAM-1 were obtained preoperatively (ICAM-0, VCAM-0), on the first (ICAM-1 and VCAM-1) and fifth postoperative days (ICAM-2 and VCAM-2). The patients were evaluated for infection by white blood cell, platelet count, erythrocyte sedimentation rate, C-reactive protein, glucose, for hypoxia and acidosis by blood gases (pH, lactate, oxygen and carbon dioxide pressure), for anemia by hemoglobin, for ischemia by troponin I and for renal insufficiency by creatinine and urea. These values were recorded preoperatively and on the first and fifth postoperative days. The aortic pressure and the mean pulmonary arterial pressure (PAP) were recorded invasively at the operating room before and after surgical closure. Duration of cardiopulmonary bypass (CPB) and duration of aortic cross clamp time, length of stay in the intensive care unit, the types of inotropic support and the mortality were recorded. When mean PAP was higher than 25 mm Hg during the surgery was accepted as PAH. LCOS was defined as the need for high inotropic support with dopamine, dobutamine and adrenalin due to low blood pressure and low urinary output in the postoperative period.

Cardiopulmonary bypass protocol

The CPB circuit included a roller pump, a disposable membrane oxygenator, and an arterial filter. It was established by using bicaval cannula or single two-stage venous cannula inserted into the right atrium/inferior vena cava and an arterial cannula. Cooling and rewarming were carried out with a heat exchanger. The priming solution consisted of a crystalloid solution of isotonic sodium chloride (0.9%) and mannitol (3 mL/kg). Packed red blood cells were used to obtain a hematocrit value of 25% before starting CPB. Heparinization was achieved with heparin sulfate. All patients received a continuous infusion of nitroglycerine (0.5-1 µg/kg/min) in the re-warming period. During CPB, a perfusion index of 2.4 to 2.6 L (min/m^2) was used. Deep hypothermia was performed at 22 to 26°C. After cross clamping, blood cardioplegia with addition of potassium chloride, sodium bicarbonate, magnesium sulfate was given at the dose of 30 mL/kg. Intermittent antegrade cold blood cardioplegia (4°C) was used for myocardial protection. Neutralization of heparin was achieved with protamine sulfate in a 1-1.5 ratio. Intravenous administration of vasodilator and inotropic agents were used if necessary to wean the patients from CPB.

sICAM-1 and sVCAM-1 assessment

Clotted blood samples were obtained from a central venous catheter and the serum was separated promptly and stored at -20°C until analysis. The quantitative sandwich enzyme-linked immunosorbent assay technique was used for the determination of sICAM-1 and sVCAM-1 levels (eBioscience, Human sICAM-1 and sVCAM-1; Platinum Elisa, Bender Med System, GmbH, Vienna, Austria). Tests were performed according to the manufacturer's recommendations (9). The results were reported in nanogram per mililiter.

Statistical analysis

SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) was used for the statistical analysis. Quantitative parameters were given as the mean and standard deviation (SD). Qualitative parameters were given as the frequency distribution and percentage. Kolmogorov-Smirnov test were applied to evaluate homogeneity of the variances. Because of the nonhomogeneous variables, Kruskal-Wallis test was used in order to assess the difference between the groups. If p values was found to be <0.05, Mann-Whitney U test was applied. Wilcoxon signed ranks test was used to compare ICAM-0, 1, 2, VCAM-0, 1, 2, mean aortic pressure and mean PAP. Friedman test was used to compare intragroup changes of ICAMs and VCAMs. Positive or negative correlations between adhesion molecules and demographic, operative and laboratory variables found by Pearson tests. A p-value of <0.05 was considered as statistically significant. ROC curve for various cut-off levels of preoperative adhesion molecules (ICAM-0, VCAM-0) in differentiating PAH patients with and without LCOS. A stepwise logistic regression test was performed to analyze the predictors of LCOS development with the different modalities using by ICAM-0, VCAM-0, preoperative mean PAP, age, weight, duration of CPB time, aortic cross-clamp time.

Results

Demographic characteristics

Group 1 consisted of 12 patients (7 girls and 5 boys) with the age 10.1±1.1 (range 4-21) months and mean body weight 7.9±2.6 (range 5-13) kg. Group 2 consisted of 19 patients (11 girls and 8 boys) with the age of 10.8±5.4 (range 5-14) months and body weight of 7.2±2.8 (range 4-11) kg. Group 3 consisted of 11 patients (6 girls and 5 boys). Their mean age was 6.8±1.9 (range 4-11) months and their mean body weight was 4.5±1.2 (range 3-7) kg. There were no significant differences between group 1 and 2 in age and body weights (p>0.05). However, age and body weights of group 3 patients were lower than group 1 and 2 (p<0.05).

Laboratory characteristics

Biochemical analysis of preoperative, first and fifth postoperative days were shown on Table 1. The patients in the group 3 had higher white blood cell counts, erythrocyte sedimentation rates, C reactive protein, urea, creatinine, troponin and lactate and lower hemoglobin levels than the other groups on the fifth postoperative day. The Group 3 patients had also higher troponin and lower platelet levels than the other groups on the first postoperative day (Table 1).

Clinical characteristics

Clinical characteristics of the patients were shown on Table 2. Pre and postoperative mean PAP values of group 1 patients were lower than the other groups (p<0.05). The CBP time of group 3 patients were longer than group 1 (p<0.05). The length of intensive care unit stay of group 3 patients were longer than group 1 and 2 (p<0.05). The group 3 patients required higher dose inotropic support such as adrenaline, dopamine, and dobutamine than the other two groups. Seven patients improved in 72-83 hours while four patients died between postoperative 12-34 days due to sepsis and multible organ failure. The patients who died had high mean PAP (56 mm Hg) and mean sICAM-1 (665 ng/mL) levels.

sICAM and sVCAM values

The adhesion molecule levels of all groups are shown on Table 3. The patients in group 3 had higher ICAM-0 and VCAM-2 levels than group 1 and 2 (p<0.01). There was no significant difference among groups for ICAM-1, 2, VCAM-0, 1 (Table 3). We also evaluated intragroup changes of adhesion molecules. sICAM levels were not found to be statistically different whereas sVCAM levels were statistically lower than preoperative and postoperative 5. days levels (Table 3).

We also investigated the correlation among adhesion molecule levels and other clinical and laboratory parameters. There was a correlation between ICAM-0 and preoperative mean PAP (r=0.43, p<0.01), postoperative mean PAP (r=0.44, p<0.01), CPB (r=0.34, p<0.05), postoperative hemoglobin (r=-0.43, p<0.01), platelet count (r=-0.47, p<0.01), erythrocyte sedimentation rate (r=0.75, p<0.01), C reactive protein (r=0.49, p<0.01), creatinine (r=0.82, p<0.01), urea (r=0.83, p<0.01) and troponin (r=0.59, p<0.01) levels. While high ICAM 0 showed a close relationship with the postoperative parameters, VCAM-0 was not associated with these parameters.

The ROC curve demonstrated a significant association between ICAM-0 levels of the patients with L-R shunt and PAH (group 2 and 3) and the development of LCOS [area under the curve: 0.98, 95% confidence interval (C): 0.95-1.02, p<0.01]. At ICAM-0 concentration >359 ng/mL with the sensitivity 0.90 and the specificity 0.95 (AUC: 0.98) was used for identification of LCOS in the patients with L-R shunt and PAH (Fig.1). VCAM 0 was not found to be associated with LCOS in these patients.

We used stepwise logistic regression model to analyze the predictors of LCOS development. However, no variable was found to be a risk factor in LCOS development in the stepwise

Table 1. Preoperative and postoperative laboratory variables of the study

		Group 1 n=12	Group 2 n=19	Group 3 n=11
Hemoglobin, mmol/L	Preop	11.5±2.1	11.4±1.5	10.8±2.2
	Postop 1 day	10.9±1.5	10.3±1.3	9.3±3.3
	Postop 5 day	10.2±0.9[a]	11.1±0.6[b]	8.1±2.6[a,b]
White blood cell, x 10^{10}/L	Preop	9.9±2.1	10.2±1.1	10.6±2.1
	Postop 1 day	11.7±3.2	14.4±3.7	13.4±3.7
	Postop 5 day	12.2±2.2[a]	12.1±3.2[b]	18.9±1.2[a,b]
Platelet, x10^9/L	Preop	249.7±56.2	279.2±65.2	219.2±73.2
	Postop 1 day	196.4±76.3[a]	176.3±86.3[b]	95.3±23.3[a,b]
	Postop 5 day	188.2±79.3	225.2±67.2	166.2±67.2
Erythrocyte sedimentation rate, mm/h	Preop	4.8±2.7	5.1±1.5	4.3±2.5
	Postop 1 day	5.9±2.2	8.2±8.1	9.2±5.1
	Postop 5 day	6.3±2.2[a]	10.3±5.1[b]	33.8±7.1[a,b]
C-reactive protein, mg/dL	Preop	0.4±0.2	0.5±0.1	0.5±0.1
	Postop 1 day	4.8±2.1	3.9±3.1	5.1±1.6
	Postop 5 day	0.1±1.3[a]	0.3±1.2[b]	7.1±1.8[a,b]
Creatinine, mg/dL	Preop	0.3±0.0	0.3±0.1	0.2±0.0
	Postop 1 day	0.5±0.2	0.4±0.1	0.7±0.4
	Postop 5 day	0.3±0.1[a]	0.4±0.2[b]	1.3±0.5[a,b]
Urea, mg/dL	Preop	20.3±10.4	19.2±4.4	23.2±14.3
	Postop 1 day	32.4±10.6	32.4±6.5	36.4±6.5
	Postop 5 day	27.5±10.3[a]	26.3±3.4[b]	66.3±34.4[a,b]
Troponin I, ng/mL	Preop	0.02±0.00	0.01±0.00	0.01±0.00
	Postop 1 day	14.5±3.2[a]	18.2±4.8[b]	42.2±14.8[a,b]
	Postop 5 day	1.1±0.5[a]	2.6±2.2[b]	22.6±12.2[a,b]
Lactat, mmol/L	Preop	0.8±0.5	0.7±0.4	0.7±0.4
	Postop 1 day	2.1±1.6	2.3±1.1	4.8±3.1
	Postop 5 day	1.1±2.2[a]	1.1±2.2[b]	6.7±2.2[a,b]
Glucose, mg/dL	Preop	123.2±45.3	104.5±23.2	124.5±23.2
	Postop 1 day	223.1±53.2	170.1±33.2	170.1±33.2
	Postop 5 day	134.4±23.5	122.3±47.3	131.3±47.3
Blood gases pH	Preop	7.41±0.6	7.37±0.1	7.36±0.7
	Postop 1 day	7.42±0.1	7.36±0.1	7.35±0.6
	Postop 5 day	7.38±0.2[a]	7.37±0.2[b]	7.32±0.6[a,b]
Blood gases pO_2, mm Hg	Preop	97.5±2.5	98.7±7.4	97.4±2.7
	Postop 1 day	98.2±1.6	97.1±5.1	94.8±3.1
	Postop 5 day	97.1±2.2	98.3±2.2	96.7±2.2
Blood gases pCO_2, mm Hg	Preop	38.9±2.7	37.7±7.2	36.9±6.7
	Postop 1day	38.1±3.2	36.1±3.2	39.2±3.2
	Postop 5 day	38.4±3.5	38.5±7.3	39.3±7.3

Postop 1: postoperative first day, Postop 5: postoperative fifth day, Preop: preoperative, Kruskal-Wallis and Mann-Whitney U tests were used to compare groups [a]: Group 1-3, p<0.05, [b]: Group 2-3, p<0.05

logistic regression models. In chi-square analysis; LCOS developed in 3.2% of patients having sICAM-0 concentration below 359 ng/mL while it developed 90.9% of the patients with sICAM-1 concentration above 359 ng/mL (χ^2: 32.291, p<0.01).

Table 2. Variables and outcomes of patients during and after the cardiac surgery

	Group 1 n=12	Group 2 n=19	Group 3 n=11
mPAP; before surgical closure, mm Hg	21.3±2.9[a,b]	39.2±10.4[a]	44.6±2.7[b]
mPAP; after surgical closure mm Hg	18.8±3.2[a,b]	31.6±8.7[a]	36.5±4.6[b]
AoP; before surgical closure, mm Hg	46.8±2.7	47.2±4.3	45.3±15.1
AoP; after surgical closure, mm Hg	46.2±3.1	49.1±3.1	49.2±13.1
Duration of CPB, min.	75.2±12.2[b]	86.8±15.3	92.1±17.3[b]
Duration of aortic cross-clamping, min.	46.9±19.7	48.9±8.5	54.8±10.4
Intensive care unit stay, day	3.4± 8.0[b]	4.2±1.6[c]	9.7±5.9[b,c]
Inotropic support			
No inotrope	4 (pt)		
Dopamine renal, 3 μg/kg/min	8 (pt)	15 (pt)	
Dopamine and dobutamine		4 (pt)	
Dopamin, dobutamine and adrenaline			11 (pt)
Outcome			
Mortality			4 (pt)
The good progress	12 (pt)	19 (pt)	7 (pt)

AoP - aortic pressure; CPB - cardiopulmonary bypass; mPAP - mean pulmonary arterial pressure; pt - patients
Kruskal-Wallis and Mann-Whitney U tests were used to compare groups, [a]: Group 1-2, p<0.05, [b]: Group 1-3, p<0.05, [c]: Group 2-3, p<0.05

Discussion

The main result of this study is that the high preoperative sICAM-1 level can be used for the prediction of LCOS in the patients, operated for L-R shunt and PAH. When preoperative sICAM-1 concentration is above 359 ng/mL, LCOS may occur with 90% sensitivity and 95% specificity. Therefore, the patients with high sICAM-1 should be closely followed-up. Preoperative sICAM-1 showed also a parallel course with mean PAP and its highest levels were found in patients with LCOS. Therefore, we consider that adhesion molecules especially sICAM-1 level may be used to predict postoperative dichotomous outcome in patients with PAH associated with L-R shunt. Also, preoperative high mean PAP and sICAM-1 levels and those which still high in the first postoperative hours were found to be a risk factor in the development of LCOS. Four patients who died had also high mean PAP and sICAM-1 levels.

In LCOS patients, long CPB time, lactic acidosis, renal insufficiency and anemia are usual to determine. This situation is also extremely common in low weighted young infants.

Pulmonary arterial hypertension, a frequent complication of congenital heart diseases with L-R shunt, is an important cause of morbidity and mortality in infants and young children undergoing cardiac surgery (10). Endothelial damage and vascular inflammation in the pulmonary circulation are considered to play an important role in development of PAH, especially during the cardiac surgery (11). Activation of endothelial cells and the subsequent rise in surface expression of adhesion molecules are the two main steps of inflammatory reaction in endothelial damage (12). It is very difficult to determine the endothelial damage

Table 3. Serum level of adhesion molecule in study patients

	Group 1 n=12	Group 2 n=19	Group 3 n=11	All groups	Significance
sICAM-0	220.2±37.5	241.9±54.6	655.3±328.8	344.0±251.7	p<0.01[a]
	(164-296)	(122-372)	(266-1255)		
sICAM-1	276.2±64.5	321.8±143.9	503.6±319.7	356.4±208.3	NS
	(189-386)	(120-648)	(234-1289)		
sICAM-2	240.1±86.8	355.6±208.2	464.8±272.3	351.2±215.0	NS
	(145-399)	(97-813)	(103-980)		
Chi-square	3.167	3.263	4.909	0.333	
Intragroup significance	NS	NS	NS	NS	
sVCAM-0	1085.4±490.6	1197.8±710.7	1329.3±821.1	1200.1±677.6	NS
	(228-1727)	(318-2737)	(245-2971)		
sVCAM-1	734.7±893.5	662.4±405.0	889.7±523.7	742.6±601.6	NS
	(231-3519)	(140-1910)	(167-1686)		
sVCAM-2	789.0±344.4	907.1±529.6	1943±572	1144.9±685.2	p<0.01[a]
	(398-1379)	(170-1890)	(1504-3161)		
Chi-square	7.167	9.579	11.636	22.619	
Intragroup significance	p<0.05[b]	p<0.01[b,c]	p<0.01[b,c]	p<0.01[b,c]	

sICAM - soluble intercellular adhesion molecules; sVCAM-1- soluble vascular cell adhesion molecules; [a]Group 1-3, Kruskal-Wallis and Mann-Whitney U tests were used to compare groups. [b]sVCAM-1-sVCAM-0 [c]sVCAM-1-sVCAM-2, nonparametric Friedman test were used to compare intragroup changes before and after operations. ICAM and VCAM values determined as ng/mL

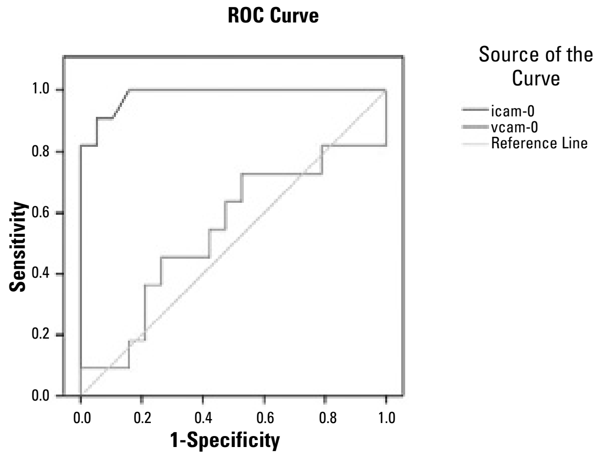

Figure 1. The ROC curve demonstrated a significant association between ICAM 0 levels in patients with L-R shunt and PAH (group 2 and 3) and the development of LCOS

in patients with L-R shunt with PAH preoperatively. However, it is crucial to make this determination preoperatively for postoperative successful management of these patients. Persevering PAH and associated high adhesion molecules may cause LCOS and death. Unfortunately, this issue has not been satisfactorily elucidated, yet. Therefore, we aimed to determine the mean PAP and the adhesion molecule levels before and after the surgical closure and investigated their relations with various operative and postoperative variables in 42 patients with PAH due to L-R shunt.

Previous studies have demonstrated that by the effect of CPB, the circulating adhesion molecule levels may vary at each postoperative hour. In the study of Boldt et al. (13) the sICAM-I levels decreased after CPB and increased on the postoperative first and second days. However postoperative serum levels of both adhesion molecules did not reach preoperative levels. Hambsch et al. (14) found that the sICAM-1 levels increased 4 hours after CPB and returned to baseline level on the postoperative first day. However, in those studies the effects of various congenital heart diseases and PAH on the endothelial activity were neglected (13, 14). In our study, sICAM-1 levels were slightly affected by CPB and surgery, whereas sVCAM-1 levels decreased on the first postoperative day (Table 3). sVCAM-1 returned to preoperative values on the fifth postoperative days. This variability may be due to the clinical diversity of the patients. Duration of CPB also affects the endothelial cell function. Blume et al. (15) showed that the infants and children undergoing CPB with longer pump time had higher levels of soluble adhesion molecules. We also found a positive correlation between the CPB and sICAM-1 levels.

Elevated adhesion molecules have also been reported in patients with systemic inflammatory response syndrome, sepsis, and multiple organ failure (16-19). These clinic syndromes and LCOS are inseparable parameters especially in critically ill patients. Therefore we found the highest pre-postoperative adhesion molecule levels in the patients with postoperative LCOS with PAH.

PAH as a result of increased pulmonary blood flow is a well known complication of congenital heart disease. Increased pulmonary blood flow from the L-R shunt causes both vascular endothelial and endothelial barrier dysfunction (1, 12). Recently, Bakouboula et al. (2) found that there was a positive correlation between endothelial stimulation, mean PAP, and sVCAM-1 in adult patients. Another study of children with congenital heart diseases showed that sICAM-1 levels were significantly higher in PAH group (8). Like these studies, we also found a strong association between mean PAP and preoperative sICAM-1 level. Therefore, we concluded that increased PAP was highly associated with elevated preoperative sICAM-1 level.

Study limitations

The aim of this study was to determine mean PAP and the adhesion molecule levels before and after the surgical closure of L-R shunt and to investigate their relation with various operative and postoperative variables. However, the number of patients in the study was not adequate much to make definite comments.

Conclusion

These data showed that elevated preoperative sICAM-1 molecule may help us to predict the cardiovascular outcome of the patients operated for L-R shunt with PAH. To reduce postoperative complications of these patients, sICAM-1 level should be determined. If sICAM-1 is >359 ng/mL, PAP and Qp/Qs have to be measured and cardiac operation should be reevaluated. PAP should be reduced by medical drugs such as nitric oxide, iloprost etc. Future studies are needed to show whether anti-inflammatory treatment which normalize adhesion molecule level is helpful to reduce the morbidity and mortality in the patients with high sICAM 1 levels.

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