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RESEARCH

The Correlation Between Syndecan-1 Post Cardiopulmonary Bypass and Duration of Ventilator Use in Open Heart Surgery Patients at Dr. Sardjito General Hospital, Yogyakarta

Fatmi Eka Putri, Meta Restu Synthana, Juni Kurniawaty
Department of Anesthesiology and Intensive Therapy Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University RSUP Dr. Sardjito Yogyakarta, Indonesia
*Coresponden author: Fatmi Eka Putri, Department of Anesthesiology and Intensive Therapy Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University RSUP Dr. Sardjito Yogyakarta, Indonesia (fatmiekaputri@gmail.com)

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ABSTRACT

Background: Open heart surgery involves the use of a cardiopulmonary bypass machine (CPB) to replace the heart and lungs during surgery. The use of CBP can damage the endothelial glycocalyx, which triggers increased levels of syndecan-1, an indicator of endothelial degradation. Elevated syndecan-1 levels are associated with various complications, such as coagulation disorders, edema, and organ dysfunction. In the lungs, endothelial glycocalyx damage can lead to edema and lung parenchymal damage, which can impair overall lung function and lead to a decreased PaO2/FiO2 ratio, requiring prolonged postoperative ventilator use.
Objective: This study aimed to determine the relationship between post-CBP syndecan-1 levels and the duration of ventilator use in open heart surgery patients at Dr. Sardjito General Hospital, Yogyakarta.
Methods: This study was a prospective, analytical, observational cohort study conducted at Dr. Sardjito General Hospital, Yogyakarta. The sample consisted of adult patients undergoing open heart surgery, with the exclusion criteria being patients using preoperative mechanical assist devices. Syndecan-1 levels were measured using the ELISA method using the Elabscience Human SDC1 kit. Data were analyzed using SPSS. Bivariate and multivariate analyses were also performed to evaluate factors influencing ventilator duration.
Results: The study was conducted on 34 subjects with a mean age of 46 ± 13.71 years. The average CPB duration was 92.94 ± 47.57 minutes, with preoperative syndecan-1 levels of 8.86 ± 5.08 ng/ml, while post-CPB levels were 11.74 ± 3.71 ng/ml, with delta syndecan-1 levels of 2.87 ± 4.18 ng/ml. Spearman's correlation test showed no association between increased syndecan-1 levels post-CPB and ventilator duration (p=0.848). Bivariate analysis showed no significant effect on other variables. Multivariate analysis showed that BMI and P/F ratio were significantly associated with ventilator duration
Conclusion: There was no correlation between increased syndecan-1 levels and ventilator duration in open heart surgery patients at Dr. Sardjito General Hospital, Yogyakarta (p = 0.848).

Keywords: Cardiopulmonary bypass (CPB), endothelial glycocalyx, syndecan-1, ventilator

INTRODUCTION

Cardiac surgery is one of the most frequently performed and complex types of surgery. Cardiac surgery is generally classified into two types: open-heart surgery and closed-heart surgery. In open-heart surgery, the heart's function as a blood pump is replaced by a cardiopulmonary bypass machine (CPB) to replace the work of the heart and lungs during the surgery. The cardiopulmonary bypass machine is carefully calibrated, continuously monitored, and operated by a trained perfusionist. After the surgery is complete, the heart is restarted to pump blood throughout the body. Unlike open-heart surgery, closed-heart surgery is performed without the aid of extracorporeal circulation and on a heart that is still beating.[1]

Open-heart surgery can cause endothelial glycocalyx (EG) damage and increase syndecan-1 (SDC-1) levels. Triggers for EG damage can stem from acute inflammatory stimuli during cardiac surgery, such as surgical trauma, ischemia-reperfusion injury, and contact between blood and the artificial surfaces of the CBM circuit. Endothelial cells act as the first barrier to prevent inflammation. Therefore, damage to the endothelial cell (EG), characterized by SDC-1 degradation, leads to increased permeability of the blood vessel wall, increased leukocyte adhesion, and increased perivascular inflammation.[2]

The endothelial glycocalyx (EG) is a layer on the luminal side of blood vessels composed of glycosamoglycans (syndecan, glypican, hyaluronan) and plasma proteins. EG plays a role in preventing mechanical stress from blood flow and producing nitric oxide (NO), anticoagulant factors (protein C, antithrombin), and vascular protective enzymes (superoxide dismutase).[3] EG degradation causes the breakdown of its constituent components, resulting in increased levels of syndecan-1 and heparan sulfate in the plasma, which can trigger damage-associated molecular patterns (DAMPs) and a systemic inflammatory cascade.[3] This can lead to capillary leakage, platelet and leukocyte aggregation, coagulation disorders, systemic and myocardial edema, loss of vascular tone, and heterogeneity in microvascular perfusion. Furthermore, EG degradation can also lead to impaired tissue perfusion and oxygenation, with clinical manifestations of edema, hypotension, hypovolemia, and shock.[3] A study found increased levels of syndecan-1, TNF-α, and IL-18 in patients undergoing cardiac surgery.[4]

After cardiac surgery, approximately 2.6–22.7% of patients have difficulty weaning themselves from ventilators due to cardiac and non-cardiac problems. The duration of CPB, which stimulates endothelial glycocalyx damage, is also a known risk factor for prolonged postoperative ventilator use. Persistent endothelial glycocalyx damage indicates a pathological condition caused not only by the release of endothelial glycocalyx but also by impaired glycocalyx remodeling, thus exacerbating and prolonging the damage to vascular integrity, as evidenced by elevated syndecan-1 levels. Increased syndecan-1 levels are associated with increased blood vessel permeability, resulting in a positive cumulative balance and causing pulmonary edema and loss of lung tissue integrity, which is thought to be related to a low PaO2/FiO2 ratio and increased ventilator requirements.[5] Therefore, this study will examine the relationship between syndecan-1 and the duration of ventilator use

METHODS

This study is an observational analytical study with a prospective cohort design that aims to assess the relationship between postoperative syndecan-1 levels and the duration of ventilator use in open heart surgery patients at Dr. Sardjito General Hospital Yogyakarta during July – August 2025. Samples were obtained by consecutive sampling method from patients who met the inclusion criteria with a total of 34 subjects. Inclusion Criteria: Adult patients (age ≥ 18 years) undergoing open heart surgery. Exclusion Criteria: Patients using preoperative mechanical assist devices. Dropout criteria: Patients who cannot be weaned from the cardiopulmonary bypass machine, patients who received Fresh Frozen Plasma transfusion during the use of the cardiopulmonary bypass machine, patients who experienced Death on the table, patients who underwent redo surgery, and patients who died.

RESULT

This study included 34 subjects (50% male and 50% female). The average age of the subjects was 46 ± 13.71 years. The average Body Mass Index (BMI) was 22.90 ± 3.79 kg/m2. The most common type of surgery undergone by the subjects was valve surgery (61.8%). 14.7% of the subjects had a history of diabetes mellitus and 44.1% had comorbid Congestive Heart Failure (CHF). The subjects' preoperative left ventricular ejection fraction was in the good category with an average of 63.21 ± 8.97% (Table 1).

Spearman's analysis yielded a correlation coefficient of r = -0.034. This indicates that the strength of the relationship between increased Syndecan-1 levels and duration of ventilator

Table 1. Subject Characteristics

	Total Patients (n=34)	
	Mean ± SD	n (%)
Gender		
Male		17 (50,0)
Female		17 (50,0)
Age (Year)	46,00 ± 13,71*	
Body Mass Index (kg/m2)	22,90 ± 3,79*	
Type of Surgery		
CABG		6 (17,6)
Valve		21 (61,8)
Congenital		6 (17,6)
Multiple		1 (2,9)
Comorbidities		
Diabetes Mellitus		5 (14,7)
Congestive Heart Failure		15 (44,1)
Kidney Failure		0 (0,0)
History of previous heart surgery		0 (0,0)
Critical Preoperative State		0 (0,0)
Left ventriclular Function		
Good		32 (94,1)
Reduced		2 (5,9)
Ejection Fraction (%)	63,21 ± 8,97*	
CPB Duration (minutes)	92,94 ± 47,57**	
Ischemic Time (minutes)	65,47 ± 31,93**	
Preoperative Syndecan-1 Level (ng/ml)	8,86 ± 5,08*	
Post CPB Syndecan-1 Level (ng/ml)	11,74 ± 3,71*	
Delta Syndecan-1 (ng/ml)	2,87 ± 4,18*	
Ventilator Duration (hours)	21,32 ± 20,49**	

Abbreviation: CABG = Coronary Artery Bypass Graft; *Data normally distributed (Shapiro-Wilk Test); **Data not normally distributed (Shapiro Wilk Test)

Table 2. Correlation of Delta Syndecan-1 Levels with Duration of Ventilator Use

Delta Syndecan-1	Duration of Ventilator Use	Correlation
2,87 ± 4,18	21,32 ± 20,49	r = -0,034 p = 0,848

Table 3. Bivariate Analysis of Variables Affecting the Duration of Ventilator Use

Variable	Duration of Ventilator Use		
	Median (Min-Maks)	r	p
Age (year)		0.035	0.846
Gender			
Male	19.0 (10.0 – 132.0)		0.226
Female	17,0 (10,0 – 22,0)		
BMI (kg/m2)		-0.333	0.054
Type of Surgery			
CABG	19.5 (10-39)		0.351
Valve	17 (10-36)		
Congenital	18.5 (13-132)		
Multiple	19 (19-19)		
Ejection Fraction (%)		-0.254	0.147
Left Ventricular Function			
Good	17.0 (10.0 – 132.0)		0.462
Reduced	19.5 (17.0 – 22.0)		
Congestive Heart Failure			
Yes	16.0 (10.0 – 39.0)		0.565
No	17.0 (10.0 – 132.0)		
Diabetes Mellitus			
Yes	19.0 (17.0 – 39.0)		0.067
No	17.0 (10.0 -132.0)		
CPB Duration (minutes)		0.030	0.865
Ischemic time (minutes)		0.019	0.914
Preoperative Syndecan-1 Level (ng/ml)		0.065	0.714
Post CPB Syndecan-1 Level (ng/ml)		0.047	0.794
P/F ratio after surgery		-0.162	0.361

* Spearman Correlation Test (numerical variables), Mann Whitney Correlation Test (categorical variables)

Table 4. Multivariate Analysis of Variables Affecting the Duration of Ventilator Use

Variable	Standardized Coefficients	Std. Error	t	p
Intercept	110.3915	42.368	2.606	0.015
Age (year)	-0.0389	0.287	-0.245	0.808
Gender	-7.4965	7.915	-0.947	0.352
BMI (kg/m2)*	1.2301	1.105	-1.113	0.276
Ejection Fraction (%)	-0.6451	0.435	-1.483	0.150
Congestive Heart Failure	1.8434	7.898	0.233	0.817
Diabetes Mellitus	8.3180	11.059	0.752	0.459
CPB Duration	0.0087	0.091	-0.0925	-0.196

Description: *Significant at p<0.05

use is relatively weak, indicating that there is no significant linear relationship between the two variables. The significance test results showed a p-value of 0.848, which is greater than the generally accepted significance value of 0.05. This means that the observed correlation is

not statistically significant, so the trend in the relationship that emerged is most likely caused by random variation and does not reflect a real relationship (Table 2).

Bivariate analysis revealed no significant correlation between these variables and the duration of ventilator use. Gender, BMI, and ejection fraction had a weak correlation with a p-value of <0.25. These variables were then subjected to multivariate analysis (Table 3).

This study used Ordinary Least Squares Regression for multivariate analysis. Multivariate analysis was performed on variables with a p-value <0.25 and variables strongly suspected of influencing the duration of ventilator use. This was used to determine the dominant factors correlated with the duration of ventilator use. The results of the multivariate analysis revealed no significant correlation between these variables and the duration of ventilator use. (Table 4).

DISCUSSION

The endothelial glycocalyx (EG) is a layer on the luminal side of blood vessels composed of glycosaminoglycan chains (syndecan, glypican, hyaluronan) and plasma proteins. At the microcirculatory level, the use of cardiopulmonary bypass (CPB) during cardiac surgery can damage the glycocalyx layer and cause the breakdown of its components. Elevated levels of syndecan-1 and heparan sulfate in plasma can trigger damage-associated molecular patterns (DAMPs) and a systemic inflammatory cascade.[3,6]

Plasma syndecan-1 levels can vary depending on the individual's clinical condition and the testing method used. The normal range of syndecan-1 in plasma of healthy individuals in several studies ranges from less than 15 pg/ml to approximately 41-185 ng/ml, depending on the measurement method, ELISA kit used, population (age, geography, subclinical/comorbid health conditions), and preanalytical factors (sample type, sampling time, and sample treatment/handling).[7,8] In this study, preoperative syndecan-1 levels were recorded at 8.86 ± 5.08 ng/ml, while post-CPB levels were 11.74 ± 3.71 ng/ml, with delta syndecan-1 at 2.87 ± 4.18 ng/ml. This increase in syndecan-1 levels after CPB was 1.89 ± 1.73 times higher than preoperative syndecan-1 levels and was statistically significant. Syndecan-1 measurements in this study used the Elabscience Human SDC1 reagent kit with a detection range of 0.16–10 ng/ml and a sensitivity of 0.1 ng/ml.

The increase in syndecan-1 levels after CPB is caused by several factors, including changes in wall shear stress, ischemia/reperfusion injury, systemic inflammatory reaction syndrome (SIRS), and perioperative fluid management .[9]

Although syndecan-1 levels increased significantly after CPB, syndecan-1 was not a factor that directly influenced the duration of ventilator use in patients undergoing open heart surgery. In this study, a correlation coefficient of r = -0.034 was obtained, and a significance test showed a p value of 0.848, indicating that the observed correlation was not statistically significant (p>0.05).

These results differ from previous research that found syndecan-1 to be a biomarker for endothelial damage associated with post-surgical complications and duration of ventilator use. However, this previous research had not been conducted in post-cardiac surgery patients. A study found an association between syndecan-1 levels and ventilator-free days (VFD), where patients with higher syndecan-1 levels had lower ventilator-free days, indicating that endothelial damage and inflammation are associated with longer duration of ventilator use (p<0.001). However, this study was conducted in a population of patients with septic shock.[5]

Glycocalyx damage, reflected by increased syndecan-1, may contribute to capillary leak syndrome, which worsens breathing in post-cardiac surgery patients and leads to longer ventilation requirements. However, this study did not report ventilator duration directly, but rather ARDS and lung function as the primary indicators. In this study, a significant correlation was found with the incidence of ARDS in the subgroup of patients with non-pulmonary sepsis (p=0.05) compared with the subgroup with pulmonary sepsis (p=0.72). However, overall, syndecan-1 levels were not significantly associated with ARDS incidence. This suggests

that syndecan-1 appears to be more relevant as a biomarker for ARDS in patients with non-pulmonary sepsis.[10]

Another study which examined syndecan-1 as a predictive biomarker in patients with ventilator-acquired pneumonia using bronchoalveolar lavage fluid (BALF) samples, showed that increased syndecan-1 levels correlated with the severity of lung damage, as assessed by the Lung Injury Score (LIS). High syndecan-1 levels indicate alveolar epithelial injury, leading to impaired gas exchange. In this study, syndecan-1 levels in patients with severe lung injury ranged from 1.42 to 9.83 ng/ml, with an average of 5.61 ng/ml. However, this study did not report the duration of ventilator use directly, and the samples taken were bronchoalveolar lavage fluid (BALF), not serum plasma.[6]

The discrepancies in these research findings suggest that while endothelial glycocalyx degradation may contribute to lung damage, it is not a primary predictor of ventilator duration. In cardiac surgery, pulmonary endothelial damage occurs not only through biotrauma but also through mechanical trauma. Biotrauma describes pulmonary and systemic inflammation caused by CPB use, ischemia and reperfusion injury, surgical procedures, and stretch-sensitive mechanoreceptor channels during mechanical ventilation. Meanwhile, mechanical trauma refers to damage caused by volume, pressure, and atelectasis. Mechanotrauma caused by high tidal volumes and surfactant release, as well as atelectasis that disrupt surfactant function, contribute to lung injury, not just pulmonary inflammation.[11]

Postperfusion lung syndrome (PPS) is a condition that occurs after CPB use, characterized by an increased alveolar-arterial (A-a) O2 gradient following CPB use, peaking 18-48 hours postoperatively. This ventilation-perfusion disorder is caused by a multifactorial process that results in increased interstitial pulmonary fluid and hypoxemia. These factors include (1) atelectasis and loss of surfactant; (2) hypoxic lung tissue damage caused by blood hemolysis, protein denaturation, pulmonary embolism, and ischemic-reperfusion injury; (3) accumulation of activated neutrophils in the lung tissue, resulting in pulmonary capillary damage and plasma leakage; and (4) transfusion reactions, such as Transfusion-Related Acute Lung Injury (TRALI).[12]

Systemic endothelial glycocalyx damage may not always directly impact severe clinical lung dysfunction requiring prolonged ventilation. Endothelial glycocalyx damage can be mild or transient. Furthermore, the body also has compensatory mechanisms such as glycocalyx resealing and fluid and hemodynamic control, so the clinical effects are minimal. A literature review on "capillary leak/ endothelial permeability" stated that although biochemical markers (shedding) are available, there are no universal diagnostic criteria linking EG biomarkers to specific clinical outcomes. Therefore, even if syndecan-1 increases, this effect may not be sufficient to influence ventilator requirements, especially if the patient is well managed postoperatively (protective ventilation, fluid control, optimal ICU care).[13]

Another factor that may influence the results of this study is the timing and dynamics of changes in syndecan-1 levels. Numerous studies have found conflicting findings regarding the timing of peak syndecan-1 levels. Some studies suggest that syndecan-1 levels change dynamically, increasing immediately after an insult (in this case, CPB), then decreasing over time. A study on the role of glycocalyx components (syndecan-1) and MMP-9 as predictive factors in patients on CPB and the length of ICU stay indicated that syndecan-1 levels are dynamic. In this study, syndecan-1 levels were measured before induction (T0), after aortic dissection (T1), at sternal closure (T2), 1 hour postoperatively (T3), and 24 hours postoperatively (T4). Syndecan-1 levels increased significantly until sternal closure (T2), then decreased slightly 1 hour postoperatively (T3), and decreased significantly 24 hours postoperatively (T4), but remained higher than before induction (T0). These results underscore the importance of measurement timing in identifying a clearer relationship between syndecan-1 levels and ventilator duration.[14] Another study found that plasma syndecan-1 levels in patients increased after CPB and peaked

15 minutes after aortic clamp release. They then gradually decreased to reach preoperative syndecan-1 levels.[15] Syndecan-1 levels were measured in only one study.

A study on 250 elective valve surgery patients found no significant difference in ventilator use for >24 hours between the high syndecan-1 (≥90 ng/mL) and low syndecan-1 (<90 ng/mL) groups.[16] In this study, syndecan-1 levels were also measured twice: before induction and after protamine administration. However, the differences observed in this study were limited to the valve surgery category, so the results cannot be generalized to all types of cardiac surgery.[16] A cohort study of 459 ICU patients on ventilators examined endotheliopathy biomarkers (Syndecan-1, soluble Thrombomodulin (sTM), and Platelet Endothelial Cell Adhesion Molecule-1 (PECAM) and their association with 30-day ventilator-free days, PaO2/FiO2 ratio at ICU admission, and 30-day mortality. It showed that syndecan-1 was not associated with 30-day ventilator-free days, but was significantly associated with mortality while on ventilator.[17] This study did not consider length of ventilator use as a direct outcome and was conducted in a different population.

Other technical factors, such as large variations in the data, as seen from the relatively high standard deviations for both variables, and significant patient variability, may impact the power of the analysis. Furthermore, the heterogeneity of the study sample, including age, comorbidities, race, inflammatory profile, postoperative care management, and mechanical ventilation management, significantly varied the data distribution. This reduces statistical power to detect associations with the variable duration of ventilator use.[18]

Based on an analysis of the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database (ACSD) and various literature, several predictors increase the risk of prolonged ventilator use, namely, critical preoperative conditions, age, smoking habits, organ dysfunction (renal failure, pulmonary hypertension), complexity and duration of surgical procedures (redo operations, CPB duration, long aortic cross-clamp duration), preoperative cardiac structural parameters, hematologic status, inotropic use, and postoperative complications (such as pulmonary edema, arrhythmias, cardiac dysfunction, and IABP use).[19–21]

In a study conducted perioperative variables were identified that were statistically associated with Prolonged Mechanical Ventilator (PMV) ($p < 0.05$). These preoperative variables included female gender, atrial fibrillation, previous cardiac surgery, congestive heart failure, hemoglobin level, and creatinine clearance. <30 mL/minute/1.73 m2. Intraoperative variables included valve surgery, combined surgery, CPB duration >120 minutes, vasopressor use, inotrope use, inhaled nitrous oxide use, ECMO (venoarterial extracorporeal membrane oxygenation) support, and intra-aortic balloon pump support. Postoperative variables included norepinephrine dose and serum lactate at ICU admission.[22]

This study conducted a bivariate analysis and found no significant association between most of the variables tested and the duration of ventilator use. However, gender, BMI, ejection fraction, and diabetes mellitus had weak correlations with p values <0.25. These variables were then analyzed multivariately, along with age, CHF, and CPB duration, which are theoretically related to the duration of ventilator use. The multivariate analysis showed that no significant association between most of the variables tested and the duration of ventilator use.

This study has several limitations. First, it was not specifically stratified based on surgical complexity and CPB duration. Second, only one type of endothelial biomarker measurement was used to describe the impact of inflammation. Third, the limited time course of the measurements reduced the power to detect correlations and significance

CONCLUSION

There is no correlation between increased syndecan-1 levels and the duration of ventilator use in open heart surgery patients at Dr. Sardjito General Hospital, Yogyakarta.

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RECOMMENDATIONS

Further research is needed, taking into account the complexity of the surgery and the duration of CPB, to hopefully provide a better correlation. Other endothelial biomarkers, such as heparan sulfate levels, should be examined to compare syndecan-1 levels. The sample measurement time should be extended to allow for a more comprehensive understanding of the dynamics of syndecan-1 level changes

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