Clinical Research

Risk factors of sepsis after open congenital cardiac surgery in infants: a pilot study

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ABSTRAK

Latar belakang: *Sepsis pascaoperasi merupakan salah satu penyebab tingginya mortalitas dan morbiditas pascaoperasi pada anak di bawah 1 tahun yang menjalani operasi jantung terbuka. Penelitian ini bertujuan mengevaluasi peran lama teknik pintas jantung paru, timektomi, kompleksitas operasi, dan status gizi terhadap kejadian sepsis pascaoperasi jantung terbuka pada anak di bawah 1 tahun.*

Metode: *Sebanyak 40 orang anak di bawah 1 tahun dengan penyakit jantung bawaan yang menjalani operasi jantung terbuka dengan* Aristotle Basic Score *(ABS) ≥6 diikuti. Analisis dilakukan pada data klinis, labolatorium preoperasi, dan tanda-tanda sepsis pascaoperasi atau sampai maksimal 7 hari pascaoperasi terhadap pasien. Analisis bivariat dilakukan sesuai dengan karakteristik data. Variabel dengan nilai p<0,200 dalam uji bivariat kemudian diikutsertakan dalam model regresi logistik.*

Hasil: *Pasien yang menggunakan pintas jantung paru lebih dari 90 menit kemungkinan untuk mengalami sepsis 5,538 kali bila dibandingkan dengan pasien yang menggunakan teknik pintas jantung paru kurang dari 90 menit (80% vs 25%, RR=5,538, p=0,006). Secara statistik, gizi kurang (86% vs 84%, RR=1,059, p=1,000), timektomi (50% vs 76%, RR=0,481, p=0,157) dan ABS (p=0,870) tidak berhubungan dengan kejadian sepsis pascaoperasi.*

Kesimpulan: *Lama pintas jantung paru memengaruhi kejadian sepsis pascaoperasi jantung terbuka pada anak usia di bawah 1 tahun dengan Aristotle Basic Score ≥6. Diperlukan studi lebih lanjut untuk menilai faktor risiko lainnya yang memengaruhi kejadian sepsis pada populasi ini.*

ABSTRACT

Background: Postsurgical sepsis is one of the main causes of the high mortality and morbidity after open congenital heart surgery in infants. This study aimed to evaluate the role of cardiopulmonary bypass duration, thymectomy, surgical complexity, and nutritional status on postsurgical sepsis after open congenital cardiac surgery in infants.

Methods: A total of 40 patients <1 year of age with congenital heart disease, Aristotle Basic Score (ABS) ≥6 were followed for clinical and laboratory data before and after surgery until the occurrence of signs or symptoms of sepsis or until a maximum of 7 days after surgery. Bivariate analyses were performed. Variables with p≤0.200 were then included for logistic regression.

Results: Duration of cardiopulmonary bypass ≥90 minutes was associated with 5.538 increased risk of postsurgical sepsis in comparison to those ≤90 minutes (80% vs 25%, RR=5.538, p=0.006). No association was observed between the incidence of postsurgical sepsis with poor nutritional status (86% vs 84%, RR=1.059, p=1.000), thymectomy (and 50% vs 76%, RR=0.481, p=0.157), and Aristotle Basic Score (p=0.870).

Conclusion: Cardiopulmonary bypass time influences the incidence of sepsis infants undergoing open congenital cardiac surgery. Further studies are needed to elaborate a number of risk factors associated with the incidence of sepsis in this population.

Keywords: aortic cross-clamp, Aristotle Basic Score, cardiopulmonary bypass, congenital heart disease, nutritional status, sepsis

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Congenital heart disease (CHD) is a type of heart disorders that occurred before delivery. Malformations in structures of the heart or circulatory functions arise as a result of disruptions, or failures of cardiac development at the early stage of foetal growth.[1] In the United States, it is approximated that eight in 1,000 live births suffer from CHD, up to a third of the cases are associated with a complex and fatal cardiac malformation which need urgent surgical correction.[2] In Indonesia, according to data from the Indonesian Ministry of Health Centre of Data and Information (*Pustadin Kementerian Kesehatan*), approximately 36.000 of 4.6 million live births in 2011 were estimated to suffer from CHD. The National Cardiovascular Centre Harapan Kita (NCCHK) could only cover 2.3% of CHD cases in Indonesia annually.

Majority of CHDs are aetiologically unclear. However, gestational diabetes mellitus, infections (i.e. Rubella infection), obesity, smoking, drugs (i.e. retinoic acid, thalidomide, anti-epileptic drugs, antidepressants, and angiotensin-converting enzyme inhibitors), and genetic syndromes (i.e. trisomy 13, trisomy 18, down syndrome, turner syndrome, and other genetic mutations), have been attributed as risk factors.[3–5]

Congenital heart disease manifests in a variety of signs and symptoms; 2–3 from 1,000 live births in CHD do not show any clinical signs during the first year of life. However, complex cardiac malformation often results in cardiac failure, severe hypoxemia, right or left functional cardiac pumping disruption, and pulmonary hypertension, which increeases the risk of mortality without a prompt surgical correction.[3]

Corrective surgery is an invasive approach (i.e. open cardiac surgery) which aims to correct functional and anatomical malformation of the heart. Delay in early corrective cardiac surgery has been resulted in a high mortality and morbidity rate.[6]

A three years study (1991–1994) at the Southampton University Hospital, United Kingdom, demonstrated a 4.4% post cardiac surgery mortality rate (<30 days). This rate was even higher (18%) when the procedure was performed in emergency setting,[7] and 29% when performed in a younger age population (i.e. <1 year of age); the study concluded that younger age with low body weight was one of the risk factors associated with high mortality and morbidity rate after cardiac surgery.[8–12]

In addition to young age, low body weight, and delayed diagnosis and treatment, sepsis has been noted as one of major determinant of the high mortality and morbidity rate after open cardiac surgery. Data from the NCCHK internal database demonstrated a sepsis rate of 15% in patients of older age and low surgical complexity. Further, the overall mortality rate in patients undergoing congenital heart surgery was 8–10%. These numbers may be even higher in children less than one year of age (infants); thus, preventing sepsis will assure a better outcome in these patients.

The present study was conducted to evaluate risk factors [including the effect of cardiopulmonary bypass (CPB) procedure duration (i.e. >90 minutes), nutritional status, surgical complexity as assessed with the Aristotle Basic Score (ABS), and thymectomy associated with the incidence of sepsis after surgery in infants with ABS of six.

METHODS

Forty patients with CHD, aged less than one year old, and ABS ≥6 were observed prospectively for the incidence of sepsis after open cardiac surgery at the Paediatric Congenital Cardiac Surgery Division, NCCHK, were included in the study. Those with prior history of open cardiac surgery, suffered from any associated genetic syndrome and human immunodeficiendy virus (HIV), confirmed with clinical and laboratory assessments, were excluded. Subjects with thymus aplasia, died on surgery, or died less than three days after the surgery were dropped out. Clinical and laboratory analyses were recorded starting at 0 hour (i.e. at the initiation of cardiac surgery) until 192 hours after the surgery. Demographic data including sex, age, weight, height, and nutritional status according to the World Health Organization-National Center for Health Statistics (WHO-NCHS) Z score (age for weight calculation) and clinical data such as blood pressure, heart rate, respiratory rate, temperature, ABS, CPB duration and aortic cross-clamp duration, intubation duration, length of intensive care unit (ICU) stay, and sepsis were recorded. Blood samples were drawn to evaluate serum leukocytes, platelet, C-reactive protein (CRP), lactate, ureum, and creatinine concentration. Congenital cardiac

surgical complexity was evaluated according to the ABS.

Diagnosis of sepsis was confirmed according to the surviving sepsis campaign criteria; however, a number of changes in the criteria were made as the study population including children of less than one year of age. Sepsis was confirmed when two or more systemic inflammatory response syndrome signs and symptoms are present: such as rectal temperature >38.3°C or <36°C, tachycardia (heart rate >189 beat/min) or bradycardia (heart rate <90 beat/min), tachypnoea (respiratory rate >34x/min), leukocytosis >17,500/μL or leukopenia <5,000/μL, CRP >10mg/L, procalcitonin ≥2μg/L, vasopressors (epinephrine or norepinephrine in dose of more than 0.05 μg) with any suspicion of infections confirmed by blood or sputum culture on the third day (>72 hours) after surgery.

Prolonged utilization of CPB and aortic cross-clamp were defined as CPB time of more than 90 minutes and aortic cross-clamp duration of more than 60 minutes. Mechanical ventilation use of more than 24 hours and ICU stay of more than three days were defined as prolonged intubation time and prolonged ICU stay, respectively.

All numerical data were evaluated for its normality by using the Saphiro-Wilk test. Normally distributed data were presented in mean (standard deviation) while median (minimum-maximum) were used when data are not normally distributed. Categorical data were presented in frequency and percentage. Bivariate analyses were conducted using Mann-Whitney, Chi-square, and Fisher Exact test. Logistic regression analysis was performed for multivariate evaluation. All data were assessed using SPSS version 20.

The protocol of this study has been approved by the ethics committee of the National Cardiac Centre, Harapan Kita Hospital, Jakarta (No: LB.05.01.1.4/13/2013).

RESULTS

A total of 40 subjects, 19 (47.5%) male and 21 (52.2%) female, were analyzed. Majority of the subjects suffered from a poor nutritional status (85%); the mean age and median ABS were 158 days and 7.355 respectively (Table 1).

Most of the subjects underwent open cardiac surgery with a median CPB duration of 107 minutes; 13 subjects (32.5%) utilized CPB for more than 90 minutes. The median aortic cross-clamp time was 62 minutes; 20 subjects (50%) experienced aortic cross-clamp time of more than 60 minutes. CPB and aortic cross-clamp procedures were not performed on 22.5% of the subjects. Thymectomy was conducted on 27 subjects (67.5%) (Table 1).

Twenty four subjects (60%) were intubated for more than 24 hours, 25 (62.5%) were treated at the intensive care unit for more than 72 hours. Mortality rate and sepsis were 2.5% and 35%, respectively (Table 2). Surgical diagnosis and procedures are presented in Table 3.

On Fisher Exact test, subjects who were on CPB for more than 90 minutes were 5.538 more likely to experience sepsis compared to those on CPB for less than 90 minutes (80% vs 20%, RR=5.538, p=0.006). Poor nutritional status was insignificantly associated with 1.059 higher risk of sepsis than normal nutrition (85.7% vs 14.3%, RR=1.059, p=1.000). Similarly, sepsis was observed with a risk of 0.481 times in those who

Table 1. Demographic and surgical characteristics

Demographic variables	(n=40)
Age, mean (SD), days	158 (107.11)
Sex, n (%)	
Male	19 (47.5)
Female	21 (52.5)
Nutritional status, n (%)	
Normal	6 (15.0)
Poor	34 (85.0)
CPB time, n (%)	
>90 minutes	13 (32.5)
<90 minutes	18 (45.0)
Without CPB	9 (22.5)
AOX time, n (%)	
<60 minutes	11 (27.5)
>60 minutes	20 (50.0)
Without AOX	9 (22.5)
Thymectomy, n (%)	27 (67.5)
Day 0 VI score, mean (SD)	10.3 (5.1)
ABS Score, median (min-max)	6.3 (6–11)

SD: standard deviation; CPB: cardiopulmonary bypass; AOX: aortic cross-clamp; VI: vasoactive-inotropic; ABS: Aristotle Basic Score

Table 2. Postsurgical parameters

Post-surgical variables	n (%)
Length of ICU stay	
>72 hours	25 (62.5)
<72 hours	15 (37.5)
Length of mechanical ventilation	
<24 hours	16 (40.0)
>24 hours	24 (60.0)
Surgical problems	
Delayed sternal closure	1 (2.5)
SVT	1 (2.5)
Total AV block	1 (2.5)
None	37 (92.5)
Sepsis	14 (35.0)
Mortality	1 (2.5)
Time of sepsis diagnosis	
72nd hour	1 (2.5)
80th hour	3 (7.5)
88th hour	1 (2.5)
96th hour	3 (7.5)
104th hour	2 (5.0)
112th hour	1 (2.5)
120th hour	2 (5.0)
122nd hour	1 (2.5)

SVT: supraventricular tachycardia; AV: atrioventricular

underwent thymectomy than the counterparts (50% vs 50%, RR=0.481, p=0.157); the result, however is not statistically significant. In the study population, there was no statistical significance in the association of ABS and the incidence of sepsis (p=0.870) (Table 4).

Multivariate logistic regression test was performed to analyze the risk factors of sepsis. The analysis concluded that the risk factors were associated with the incidence of sepsis with R^2 of 0.255 and p value of 0.065.

DISCUSSION

Infection is one of the most common problems which occurs after open cardiac surgery. A study by Barker et al[13] and colleagues concluded that small baby, complex heart disease, open cardiac surgery, preoperative treatment of more than one day, mechanical ventilation use before surgery, and genetic disorder were closely associated with major postsurgical infections such as mediastinitis, sepsis, and endocarditis.[13] Our study analyzed patients who had a high risk of major postsurgical infection (i.e. sepsis) as we included infants with complex cardiac disease and underwent open cardiac surgery.

Sepsis has been a major complication of open cardiac surgery with a high rate of morbidity and mortality.[14,15] A number of studies have been conducted to evaluate the outcome of open cardiac surgery in paediatrics however study concerning the incidence of postsurgical sepsis particularly in infants with ABS ≥6 has been limited.

Our pilot study at the NCCHK observed a high rate of sepsis (35%) in infants who underwent open cardiac surgery with ABS ≥6. Postsurgical sepsis has been postulated to be resulted from an imbalance of pro- and anti-inflammatory cytokines release. This inequity further causes a reduction of inflammatory response towards infections. A study by Franke A et al[16] and colleagues demonstrated a biphasic curve of immune response induced by open cardiac surgery. On day one (phase one) of the immune response, the pro-inflammatory and anti-inflammatory reactions were originated from the body innate immune response. Balance of pro- and anti-inflammatory cytokine release on the first phase of immune response occurred on the third day. From the third until the fifth day after the surgery (phase two), adaptive immunity started to react.[16] This response was characterized by the release of anti-inflammatory cytokines. These phenomena serve as the basis of early systemic inflammatory response syndrome after open cardiac surgery and explain the reason of sepsis to arise starting from the third day after the surgery. In our study, all incidence of sepsis was diagnosed on day three (the 72nd hour) until day five (the 122nd hour) after surgery (Table 2).

Cardiopulmonary bypass use in open cardiac surgery induces endotoxemia, hemodilution, and systemic inflammation resulted by direct contact activation, ischemic reperfusion injury, and splanchnic hypoperfusion. infants have been the most vulnerable population to suffer from the reactions as their body immune response is immature. This immaturity of immune system causes an increased risk of sepsis and poor outcome after open congenital cardiac surgery compared to the older aged children.[17–21]

Table 3. Surgical diagnosis and procedures

Diagnosis*	n (%)	Procedures†	n (%)
Patent ductus arteriosus	23 (24.5)	VSD closure	47 (41.2)
Ventricular septal defect	18 (19.1)	PDA ligation	22 (19.2)
Atrial septal defect	9 (9.57)	ASD closure	11 (9.64)
Pulmonary atresia	7 (7.45)	BT shunt	9 (7.89)
Patent foramen ovale	5 (5.3)	Arterial switch operation	5 (4.35)
Double outlet right ventricle	4 (4.2)	Atrial septectomy	3 (2.63)
Coarcation of the aorta	4 (4.2)	BCPS	3 (2.63)
Transposition of the great artery	4 (4.2)	Coarctation of the aorta repair	3 (2.63)
Transposition of the great artery with intact ventricular septum	3 (3.2)	PA banding	2 (1.75)
Total anomalous pulmonary venous connection	3 (3.2)	Damus Kaye Stensel	1 (0.9)
Complete atrioventricular septal defect	2 (2.12)	Rastelli	1 (0.9)
Taussig Bing anomaly	2 (2.12)	AORPA repair	1 (0.9)
Tetralogy of Fallot	2 (2.12)	CAVSD repair	1 (0.9)
Anomalous origin of the right pulmonary artery	1 (1.06)	TOF total correction	1 (0.9)
Pulmonary stenosis	1 (1.06)	MPA ligation	1 (0.9)
Truncus arteriosus	1 (1.06)	Mitral valve repair	1 (0.9)
VSD sub-arterial, doubly-commited	1 (1.06)	Azygous vein ligation	1 (0.9)
Mitral atresia	1 (1.06)		

* in one subject there might be more than 1 surgical diagnosis; † in one subject there might be more than 1 surgical procedures; VSD: ventricular septal defect; PDA: patent ductus arteriosus; ASD: atrial septal defect; BT: Blalock-Taussig; BCPS: Bidirectional Cavo-Pulmonary Shunt; PA: pulmonary atresia; AORPA: anomalous origin of the right pulmonary artery; CAVSD: complete atrioventricular septal defect; TOF: Tetralogy of Fallot; MPA: Main Pulmonary Artery

Table 4. Bivariate analysis of the risk factors of sepsis

Risk Factors	Sepsis		RR (95% CI)	p
	Yes, n (%)	No, n (%)		
CPB time				
CPB >90 minutes	8 (80)	5 (25)	5.538 (1.328–20.604)	0.006*
CPB <90 minutes	2 (20)	15 (75)		
Thymectomy status				
Thymectomy	7 (50)	19 (76)	0.481 (0.223–1.123)	0.157*
Without thymectomy	7 (50)	6 (24)		
Nutritional status				
Normal nutrition	2 (14)	4 (16)	1.059 (0.323–3.689)	1.000*
Poor nutrition	12 (86)	21 (84)		
ABS	6.65 (6–11)	6.30 (6–11)		0,87†

* Data are presented in relative risk (95% CI), p value was acquired from Fisher exact test; † Data are presented in median (min – max), p value was acquired from Mann Whitney test. CPB: cardiopulmonary-bypass; ABS: Aristotle Basic Score

Mortality and mortality after open cardiac surgery were closely associated with CPB duration.[22] This result is supported by a study by Chai et al[23] and associates who demonstrated that patients who underwent CPB for more than 90 minutes resulted in a more severe pulmonary injury compared to those who were less than 90 minutes in CPB. Additionally, a longer CPB time disrupts the normal functioning of kidney, nervous system, and gastrointestinal tract; thus, increases morbidity and mortality after surgery.[23–29] Gastrointestinal tract vascular integrity and perfusion were disrupted (i.e. sphlanchnic hypoperfusion) by a long CPB time (>90 minutes). Further, cardiac malfunctioning alone might cause

damages in the alimentary tract mucosal barrier resulting in bacterial and endotoxins translocation to systemic circulation and sepsis. In accordance to this hypothesis, Klein et al[30] stated that the duration of cardiopulmonary bypass increased the risk of endotoxemia and postsurgical infection.[30] Further, complex congenital cardiac diseases were substantially related with the risk of necrotizing enterocolitis. Even though the enterocolitis was not directly associated with mortality rate, 20% of patients with this inflammatory reaction would die.[31]

In our study, major infection (i.e. sepsis) was observed to be significantly higher in patients with CPB duration of more than 90 minutes compared to those with shorter CPB duration (80% vs 20%, RR=5.538, p=0.005). Inferior postsurgical outcomes were also observed in this study group with prolonged ICU stay (64.6% vs 35.3%, p=0.005) and prolonged mechanical ventilation (68.8% vs 31.2%, p=0.002). These results are in accordance with the previous trials which demonstrated that CPB time was associated with the incidence of sepsis, morbidity, and mortality after open congenital cardiac surgery particularly in younger aged children with complex cardiac malformation. Endotoxemia and necrotising enterocolitis (NEC) might also play a role in the high incidence of sepsis in our study population; unfortunately, we did not elaborate it further.

Thymectomy has been known to influence the population of T lymphocytes, serum CD8 and CD4 concentration after surgery.[32] Decreased in number and function of T lymphocytes has been postulated to be one of the causes of sepsis after open cardiac surgery with thymectomy.[33] Our study, on the contrary, did not observe a significant relation between sepsis rate and thymectomy (RR=0.481, p=0.157). A number of previous studies have been conducted to evaluate the association of thymectomy and outcomes of open cardiac surgery with partial, total, or without thymectomy and resulted in similar answers. There was one study, however, demonstrating a significantly lower thymic recent emigrant cells and lymphocytes subpopulation in patients who were thymectomized compared to the counterparts. The incidence of postsurgical immunodeficiency, recurrent infections, neoplasm, or autoimmune reactions was also not significantly related with thymectomy procedures.[32,34,35] This occurrence might be explain by an incomplete thymectomy, release of mature T cells before the procedure, compensatory increase in the non-specific immune responses such as neutrophils and natural killer cells, and activation of other reticuloendothelial cells.[34]

Failure to thrive and poor nutritional status have been considered as one of the major problems in children with congenital cardiac anomaly. Up to 40% of children with congenital heart problem suffered from failure to thrive and a poor nutritional status. Nutritional status is closely associated with immune response and outcomes of open cardiac surgery.[36–38] A study in paediatric population in Bangladesh demonstrated that a poor birth weight was associated with immunity disruptions manifested in a low CD3 concentration, accelerated peripheral T cells death, and increased turn over cycle of T cells by thymus. All of the processes resulted in decreased immunity towards infection in children. Additionally, a low birth weight increases the risk of infections in later life.[39] A decrease in immune response resulted from poor nutritional status has been one of the most important risk factors of alteration in inflammatory responses after open cardiac surgery. Hassen et al[40] observed an increased risk of systemic inflammatory response syndrome after a major blood vessel surgery in patients with protein energy deficiency.[40] Further, in a population of children after Fontan surgery demonstrated that Z-score of less than -2 was significantly associated with mortality, surgical failure, and length of hospital stay.[41] Nutritional status calculated by weight for age formula and young age were correlated with length of stay and hemodynamic status after a Glenn bidirectional surgery.[42] While accompanied with hypoalbuminemia, a poor nutrition in children with congenital heart disease increased the risk of mortality and postsurgical infections as well as prolonged hospital stay.[43]

In our observation, 85.7% of the subjects who suffered from sepsis had a poor nutritional status; this finding, however, showed no significant finding on bivariate analyses (RR=1.059, p=1.000). Our finding is supported by previous study by Azakie et al[44] in which they concluded that low birth weight or prematurity was related with a poor outcome in children who underwent open cardiac surgery; yet, the finding was not statistically significant.[44] These data might imply a better development of open cardiac surgical approach in premature or low and very low birth weight baby; hence, the

previously significantly related risk factors were no longer found to be essential today.

Aristotle basic score (ABS) is one approach to evaluate complexity in congenital cardiac surgery. ABS consists of three main components: (1) mortality, (2) morbidity (i.e. length of ICU stay), and (3) surgical difficulty.[45,46] Subjects with sepsis in our study had a median ABS of 6.65 (6–11). There was no statistically significant correlation between ABS and sepsis rate. This insignificant finding might be resulted from the fact that ABS is the simplest method to evaluate and project complexity and outcomes after congenital cardiac surgery without considering patients characteristics such as anatomical variations, associated surgical procedures, age, and co-morbidities in the assessment as the Aristotle Comprehensive Score (ACS). A study by Kansy and colleagues analyzed the outcome of open congenital cardiac surgery with surgical complexity evaluated with four different stratification methods: (1) Aristotle Basic Score; (2) Risk Adjustment for Congenital Heart Surgery-1 (RAHCS-1 Categories); (3) The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery Congenital Heart Surgery Mortality Score (STAT Mortality Score); and (4) STAT Mortality Categories.[47] The study observed that STAT Mortality Score had a stronger correlation with mortality outcome. Insignificant result between ABS and sepsis in our analysis might also be resulted from a better management of patients with a complex congenital cardiac disease which in turn significantly reduced the rate of morbidity and mortality after surgery.

In conclusion, the risk factors evaluated in our study could only explain 25.5% variability of sepsis. CPB time of more than 90 minutes was significantly related with sepsis rate after open cardiac surgery in infants with ABS ≥6. Further study is needed to elaborate the role of a number of risk factors associated with sepsis in this population.

Conflicts of interest

The authors affirm no conflict of interest in this study.

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