STUDY PROTOCOL

Introduction

Cardiovascular disease (CVD) is a major health problem worldwide. According to the World Health Organization (WHO), it is estimated that 17.9 million people died from CVD in 2019, representing 32% of all global deaths. Of these incidences, 85% were caused by heart attacks and strokes. More than three-quarters of deaths due to cardiovascular disease occur in low- and middle-income countries (WHO, 2020). In 2007, there were 45 million surgeries in the US, of which 6.9 million were heart surgeries. The number of patients who underwent coronary artery bypass graft (CABG) surgery decreased from 405,000 in 2003 due to an increase in percutaneous angioplasty and stent interventions (PCI) (Hessel et al., 2013).

The Annual Report of Harapan Kita National Hospital 2020, heart surgery procedures included 447 coronary surgeries, 69 coronary artery bypass graft (CABG) and valve surgeries, 404 valve surgeries, 63 congenital surgeries, and 49 vascular surgeries. According to the Performance Report of Dr. Sardjito Hospital 2020, atherosclerotic heart disease was the 9th most common outpatient disease with 7,383 visits and also the most common inpatient disease with 734 visits (Dr. Sardjito Hospital, 2021). Most cases of heart disease that cannot be managed by conventional drug therapy require surgical intervention. Heart surgery procedures carry a high risk, but with advances in surgical techniques, medications, and heart surgery equipment, some complications in heart surgery can be minimized (Boom, 2013).

In recent decades, cardiac surgery has become increasingly common and safe to perform. Based on the type of procedure, cardiac surgery is divided into coronary artery bypass grafting (CABG), valve repair or replacement surgery, and cyanotic and acyanotic congenital heart defect surgery. Cardiac surgery is almost impossible to perform when the heart is still beating and filled with blood, but the CPB machine makes it possible by stopping the heart and providing a clear surgical field. The CPB machine takes over the functions of the heart and lungs to ensure systemic circulation while the heart and lungs are stopped or not functioning. Venous blood from the superior and inferior vena cava is directed to the CPB machine reservoir through cannulation, and the blood is then oxygenated through a membrane oxygenator so that oxygen-rich blood can be pumped back to the body through the aortic cannula. To provide a clear view for the surgeon, the aortic root is cross-clamped, which clears the area of the heart surgery from blood. Based on its use, the cardiopulmonary bypass (CPB) machine is divided into on-pump and off-pump CPB machines (Hessel, Shann, 2015; Hall, Guyton, 2011; Eugene, 2015).

The cardiopulmonary bypass machine requires artificial pipes to flow blood, causing blood to come into contact with the non-physiological surface of the extracorporeal circuit (ECC). This triggers a cascade of coagulation, activating the complement system, and releasing pro-inflammatory cytokines, resulting in systemic inflammatory response syndrome (SIRS) and neutrophil-endothelial adhesion, which activates the process of endothelial dysfunction. This can cause reperfusion disturbances in the heart muscle, lung cells, kidney cells, and postoperative neurological disorders. These disturbances can last for several days and can cause multi-organ dysfunction (Bojar, 2008).

Cardiopulmonary bypass circuit needs priming fluid to fill the tubes, pumps, and reservoirs. The purpose of this fluid is to eliminate air and air bubbles that can be carried into the systemic blood flow, which can cause air embolisms. In addition, hemodilution occurs, reducing blood viscosity, which can reduce shear stress if the circuit is used to pump blood to the patient's entire body. In the early days of cardiopulmonary bypass machine use, donor blood or the patient's own blood was used as priming, but this was impractical, uneconomical, and caused many complications (Cooper and Giesecke, 2015).

Crystalloid priming fluid began to be used in the early 1960s to replace blood, but its use can cause excessive hemodilution, which can damage the blood components. Blood damage can also occur due to pressure that compresses the rotating blood vessel pipes, causing shear stress. The blood flow rate in the cardiopulmonary bypass machine is directly proportional to the density of the pump rotor compressing the pipes (shear rate). Shear stress is the product of shear rate and blood viscosity. It can be extremely hazardous if the viscosity and flow rate of blood are not considered in the use of cardiopulmonary bypass machines. In practice, the flow rate of blood during the use of a cardiopulmonary bypass machine to meet the body's metabolic demands, or the commonly used flow rate in full flow cardiopulmonary bypass machines, is 2.4-3 L/m2/minute. The use of a flow rate lower than 50 ml/kg/minute or 2.0 L/m^2/minute is currently being investigated. Machin and Allsager (2006) suggested that a flow rate of 1.2 L/m^2/minute and hypothermia at 30°C is sufficient for adequate tissue perfusion in patients with a hemoglobin level of 7 g/dL (hematocrit 22%), but if the hemoglobin level is lower, a higher flow rate of >2.2 L/m^2/minute may be necessary.

During the surgery, hypothermia techniques are also used to reduce damage to blood components, metabolic disorders, heart and brain dysfunction. Increased viscosity, decreased blood flow, and increased systemic vascular resistance (SVR) will result in decreased tissue perfusion. This is the adverse effect of using blood priming in the heart-lung bypass machine. Hemodilution technique using crystalloid solution for priming can reduce the adverse effects

of the heart-lung bypass machine. Hemodilution has a direct effect of reducing viscosity and hematocrit, decreasing hematocrit will reduce SVR and increase tissue perfusion. The heart-lung bypass machine during heart surgery ensures the supply of oxygen to the tissues, this oxygen transport depends on the availability of oxygen, cardiac output, hemoglobin, tissue perfusion, and the ability of the tissue to utilize oxygen (Cooper Jr, Giesecke, 2015).

In 1988, W.C. Shoemaker introduced goal-directed oxygen therapy (GDT) for the management of critically ill patients, with DO_2 management being considered successful in improving patient outcomes. GDT aims to restore optimal tissue perfusion using aggressive monitoring parameters including cardiac index (CI), DO_2, mean arterial pressure (MAP), oxygen, inotropic therapy, and vasopressors. This success inspired the use of GDT for perfusion during the use of cardiopulmonary bypass, also known as goal-directed perfusion (GDP).

GDP aims to improve the balance of DO2 and tissue metabolism by optimizing hemodilution, blood flow rate, and vasopressor use. GDP is expected to reduce inflammation, improve blood component damage, and maintain blood oncotic pressure. The ultimate goal is to reduce morbidity and accelerate postoperative cardiac surgery recovery (Dijoy et al., 2015). The use of GDP is still under investigation, but GDT has been proven to improve patient outcomes. Goal-directed therapy (GDT) is performed by closely monitoring the delivery of oxygen, oxygen extraction, and lactate levels as a result of metabolism. GDT has adopted the success of targeting measured hemoglobin and flow rate, leading to adequate oxygen delivery (DO2), which is expected to optimize tissue perfusion. This is expected to reduce hemolysis and SIRS response.

Method

Study design

This study employs a double-blind, randomized clinical trial design to investigate the effect of the difference in the use of cardiopulmonary bypass (CPB) machines between goal-directed perfusion and conventional methods on hemolysis and inflammation in adult patients undergoing heart surgery and using CPB machines at Dr. Sardjito Hospital in Yogyakarta. The study has obtained approval from the Faculty of Medicine, Public Health and Nursing Gadjah Mada University ethics committee and the Education and Training department of RSUP Dr. Sardjito Yogyakarta with approval number KE/FK/0232/EC/2023Sample collection will begin on May 1st, 2023, and data collection will occur simultaneously until approximately August 15th, 2023, or the last cardiac surgery patient is discharged from the ICU.

Participant

Consecutive patient who are 18-65 years old weighing 40-100 kg with NYHA I or II undergoing cardiac surgery using the cardiopulmonary bypass (CPB) machines. Patients are excluded from the trial if they used extra corporeal circulation before surgery: intra-aortic balloon pump (IABP), hemodialysis, renal replacement continuous therapy, and intraventricular assisted device. We also excluded patient with a history of severe hemolysis and inflammation and patients who needs urgent or emergency surgery. The drop-out criteria are heart surgery lasting less than 60 minutes using the heart-lung machine or patient death before heart-lung machine use. Patient will be informed consent before the randomization to get the detail of the surgery and its intervention.

All heart surgeries will use a Sorin type C5 CPB machine with a Terumo Capiox FX 15 RW 20 or Terumo Capiox FX 15 RW 25 oxygenator. The heart surgery team will consist of two cardiac surgeons with the same level of competency and experience, one performing surgery for structural heart abnormalities and the other performing CABG surgery, assisted by two cardiovascular anesthesiologist and two perfusionists with the same level of competency and experience. Sample collection will begin on May 1st, 2023, and data collection will occur simultaneously until approximately August 15th, 2023, or the last cardiac surgery patient is discharged from the ICU

Randomization

Eligible patients were randomly assigned using computerized permutation block randomization. It is computerized based, and each participant will be obtaining random numbers and assigned to chosen treatment condition

Standard Procedure

On the day of surgery, the patient will be prepared in the operating room, fitted with an EKG monitor and pulse oximeter. Continuous arterial blood pressure monitoring will be performed. The patient will then be anesthetized with general anesthesia according to the standardized protocol. Central venous catheter and an arterial catheter were inserted in the operating room. Arterial blood samples of 1 cc will be taken for blood gas analyses, electrolyte, and ACT testing using POCT iStat. Then, a blood sample of 5 cc will be taken from the central vein for plasma-free hemoglobin, haptoglobin, TNF-α, IL-6 testing, and will be placed in an

ice-cold box before the use of the heart-lung machine. A sternotomy will be performed. Heparin at a dose of 3mg/kgBW will be administered, and ACT will be checked.

Subsequently, the preparation for aortic cannulation will be done after ACT is more than 300 and connected to the aortic circuit of the heart-lung machine. The patient will be allocated to either the conventional heart-lung machine group or the goal-directed perfusion heart-lung machine group according to the randomization table. Venous cannulation will be inserted and connected to the heart-lung machine circuit.

If the ACT level is more than 400, the heart-lung machine will be gradually run until all venous blood is circulated to the heart-lung machine (considered as the start of the heart-lung machine). Evaluation of the heart-lung machine will be performed, and if there are no problems, the aorta will be cross-clamped, and cardioplegia will be administered until the heart stops beating (considered as the start of aortic cross-clamping). According to the randomization results, the patient will receive treatment according to the sample allocation.

Then, arterial blood samples were taken sequentially at the pre-cardiopulmonary bypass, 60, 90, and 120 minutes during cardiopulmonary bypass for blood gases analyses, electrolyte, and ACT examination using POCT iStat, and 5 cc of blood samples were taken from the central vein for plasma-free hemoglobin, haptoglobin, TNF-α, and IL-6 examination.

After the surgery is complete, the aortic clamp will be released and the heart will start beating again (counted as the end of cross-clamp aorta). Gradually, the cardiopulmonary bypass support will be reduced until it reaches the minimum (flow rate 1/4 - 1/8 CI) and if hemodynamics is stable, the cardiopulmonary bypass support will be stopped. Then, the heparin reversal (protamine) will be given according to the dose. Blood components will be given as needed. After the surgery is complete, the patient will be transported to the ICU with sufficient sedation and analgesia. During transportation, the patient will be monitored with a transport monitor.

Study Outcome

The planned outcome of the research is to assess the effects of GDP intervention during cardiopulmonary bypass surgery on various markers and parameters. The primary outcome measures are plasma free hemoglobin and haptoglobin, which are markers of hemolysis, as well as interleukin 6 and TNF-alpha as inflammatory markers. These markers will be evaluated at four different time points: T0 (pre-CPB), T1 (60 minutes during CPB), T2 (90 minutes during CPB), and T3 (120 minutes during CPB).

In addition, the researchers will evaluate several secondary outcome measures, including complete blood count, peripheral blood morphology, blood glucose, electrolyte levels urea and creatinine levels, lactate levels, and arterial blood gas analysis. These outcome measures will also be evaluated at the same time points as the primary outcome measures (T0-T3).

Following the surgery, the researchers will conduct follow-up assessments on the patients. Additional outcome measures to be evaluated include the duration of ventilator use (measured in hours), length of stay in the ICU (measured in hours), and other postoperative assessments such as complete blood count, chemistry panel and organ function tests, lactate levels, electrocardiogram, and chest X-ray. These assessments will be conducted at several time points, especially at T4 (upon arrival in the ICU), T5 (24 hours postoperative), T6 (48 hours postoperative), and T7 (72 hours postoperative). If possible, follow-up assessments will continue on subsequent days until the patients are discharged from the hospital.

In addition to the planned outcomes of the research, there are also intraoperative data that will be evaluated during the surgery. The duration of the surgery (measured in minutes), the duration of cardiopulmonary bypass (CPB) (measured in minutes), the duration of aortic cross clamp (measured in minutes), the amount of additional fluid given (measured in cc), the number of vasopressors, inotropic agents, and packed red blood cells transfused will also be assessed.

To measure haptoglobin, interleukin 6, and TNF alpha levels, the ELISA method will be used with the ELISA reader from Bio-Rad iMARK. The normal reference range for haptoglobin is 41 to 165mg/dL. For interleukin 6, the normal reference range is less than 5 pg/mL, and for TNF alpha, it is less than 8.1 pg/mL. In addition, the plasma free hemoglobin levels will be measured using the colorimetric hemoglobin assay kit from Sigma Aldrich with the Bio-Rad iMARK ELISA reader. The normal reference range for plasma free hemoglobin is less than 0.4 mg/dL. These measurements will help assess the primary outcomes of the study and evaluate the level of hemolysis and inflammation during and after cardiopulmonary bypass surgery.