TOPICAL APPLICATION EFFECT OF TRANEXAMIC ACID IN POSTOPERATIVE BLEEDING AND BLOOD PRODUCTS TRANSFUSION AFTER CARDIAC SURGERY

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CHAPTER 1
INTRODUCTION

1.1. Background

Coronary heart disease is the highest cause of mortality in the world, contributing to 16.6% of deaths in 2016.[1] In Indonesia, 35% of mortality is due to cardiovascular disease, including coronary heart disease.[2] Coronary artery revascularization plays an essential role in managing coronary heart disease by improving antegrade blood flow to reduce chest pain (angina). Cardiopulmonary bypass machine (CPB) has been used in coronary artery bypass grafting (CABG) surgery for over three decades. CPB machines allow for an adequate operating field without being disturbed by cardiac motion when performing coronary artery anastomosis, making intracardiac and extracardiac procedures easier to perform and potentially improving cardiac surgical services.[3] However, CPB machines have many pathological effects, including fluid retention, coagulopathy, the release of inflammatory mediators, pulmonary dysfunction, stroke, and neurocognitive changes. In 2020, coronary artery bypass surgery was one of the most frequently performed procedures at Harapan Kita Heart and Vascular Hospital, with 419 cases. However, some experienced several postoperative complications, such as postoperative bleeding requiring reoperation (24 cases), cardiac arrest (14 cases), atrial fibrillation (11 cases), and stroke within the first 72 hours (5 cases).

The choice of CABG therapy is based on the patient's clinical characteristics, SYNTAX score and the complexity of the coronary anatomy.[4] One of the CABG techniques, off-pump coronary artery bypass (OPCAB), was the first revascularisation procedure performed on a beating heart in 1960. The OPCAB technique was abandoned until the invention of stabilisation aids and positioning aids that facilitate anastomosis. The OPCAB technique when performed by highly skilled surgical specialists can result in complete revascularisation and better outcomes in patients at high risk, including the elderly, low ejection fraction, high

neurological risk, women, and end-stage organ failure.[5]

The surgical technique with OPCAB can be considered in high risk patients to reduce perioperative transfusion requirements. This statement is supported by a *randomised controlled trial* (RCT) study in 2359 patients >75 years old at 12 German institutions with funding from the German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients (GOPCABE) which states that the OPCAB surgical technique significantly reduces blood transfusion requirements.[3] OPCAB is not completely free from the risk of postoperative bleeding, as blood loss in the OPCAB technique can occur due to mechanisms of activation of the fibrinolysis pathway caused by sternotomy, pericardiotomy, excision of vein and artery grafts, residual heparin, platelet disorders and surgical bleeding.[6]

Management of valvular heart disease includes non-surgical and surgical interventions. Both are classified as class II and III recommendations respectively based on the 2017 *European Society of Cardiology* guidelines due to the limited number of studies involving large numbers of subjects related to valvular heart disease.[9,12] Surgical intervention is performed in severe, symptomatic cases, and or there is a decrease in left ventricular ejection fraction <50% which can be done openly or transcatheter.[8] Harapan Kita Heart and Vascular Hospital in 2020 reported 521 patients undergoing heart valve replacement surgery. A total of 158 patients experienced postoperative complications, with the most common complication being bleeding, which was 43 patients.

Massive blood loss is the leading cause of death in cardiovascular surgery. Bleeding from cardiac surgery can be assessed by the volume of *chest tube drainage bleeding* and the need for transfusion of blood components. Based on the guidelines of the Society of Thoracic Surgeons (2011), the use of intravenous tranexamic acid is recommended in cardiac surgery as a strategy to reduce the risk of bleeding (class I recommendation).[9] Tranexamic acid has an antifibrinolytic profile that could

theoretically increase the risk of thromboembolic events such as early closure of coronary vessels, deep vein thrombosis, myocardial and cerebral infarction, and pulmonary embolism. In addition, several post-cardiac coronary artery bypass grafting seizures have been reported in patients receiving high doses of intravenous tranexamic acid.[9,10] According to Pačarić et al., although not statistically significant, post-cardiac surgery adverse events practically impose a cost burden, prolong the hospital stay, and affect the overall quality of life of patients.[11]

Topical application of tranexamic acid (intrapericardial in open heart surgery) is expected to work locally and minimize the systemic effects that occur.[12] The use of tranexamic acid topically has been widely studied in other fields of surgery and is beneficial in reducing bleeding.[13] However, studies studying topical tranexamic acid in cardiac surgery, are limited and generally show results that are not significantly different from intravenous administration, although there is a trend towards less postoperative bleeding in the group that received topical tranexamic acid.[12,13] In addition, the existing studies also used subjects from overseas populations, and there has never been a similar study in Indonesia.

1.2. Problem identification

Topical administration of tranexamic acid in similar patients has been used in other surgical fields and is known to reduce bleeding and blood transfusion. However, similar studies in adult cardiac surgery are controversial, and its use in clinical practice has not been conducted in Indonesia.

1.3. Research question

1. What is the effect of topical tranexamic acid application on bleeding in patients undergoing coronary artery bypass surgery (CABG)?
2. What is the effect of topical tranexamic acid application on bleeding in patients undergoing off-pump coronary artery bypass (OPCAB)?
3. What is the effect of topical tranexamic acid application on bleeding in patients

undergoing heart valve surgery?

4. What is the effect of topical tranexamic acid application on postoperative blood transfusion requirements in patients undergoing coronary artery bypass surgery (CABG)?
5. What is the effect of topical tranexamic acid application on postoperative blood transfusion requirements in patients undergoing off-pump coronary artery bypass (OPCAB)?
6. What is the effect of topical tranexamic acid application on postoperative blood transfusion requirements in patients undergoing heart valve surgery?

1.4. Hypothesis

1. There was a difference in mean bleeding volume between patients given topical tranexamic acid versus placebo in patients after coronary artery bypass surgery (CABG).
2. There was a difference in mean bleeding volume between patients given topical tranexamic acid versus placebo in patients after off-pump coronary artery bypass (OPCAB).
3. There was a difference in mean bleeding volume between patients given topical tranexamic acid versus placebo in patients after heart valve surgery.
4. There was a difference in mean blood product transfusion requirements between patients given topical tranexamic acid versus placebo in patients after coronary artery bypass surgery (CABG).
5. There was a difference in mean blood product transfusion requirements between patients given topical tranexamic acid versus placebo in patients after off-pump coronary artery bypass (OPCAB).
6. There was a difference in mean blood product transfusion requirements between patients given topical tranexamic acid versus placebo in patients after heart valve surgery.

1.5. Research objectives

1.5.1. General objectives

The superiority of topical use of tranexamic acid in patients undergoing adult cardiac surgery was investigated.

1.5.2. Specific objectives

1. The amount of postoperative bleeding in patients undergoing adult cardiac surgery with topical tranexamic acid application was determined.
2. Postoperative blood product transfusion requirements in patients undergoing adult cardiac surgery with topical tranexamic acid application were determined.

1.6. Research benefits

1.6.1. Benefits in the field of science/knowledge

1. To provide a knowledge base regarding the effect of topical tranexamic acid application on post adult cardiac surgery outcomes, including the amount of bleeding and blood products transfusion after cardiac surgery.
2. Encourage further studies on the effects of topical tranexamic acid application on a larger scale or other post adult cardiac surgery outcomes.
3. Increase the number of studies on the effect of topical tranexamic acid application on adult cardiac surgery outcomes

1.6.2. Benefits in the field of health services

1. To inform the management of patients undergoing adult cardiac surgery to reduce postoperative bleeding.
2. Reduce the cost burden and duration of hospitalization due to post-surgical outcomes of adulut cardiac surgery related to post-surgical bleeding.
3. To serve as a reference for future clinical trials on topical tranexamic acid administration.

1.6.3. Benefits for research subjects

Avoid the possibility of undesirable post-surgical outcomes in patients undergoing adult cardiac surgery.

1.6.4. Patient benefits

The improved general quality of life in patients undergoing adult cardiac surgery.

CHAPTER 2
LITERATURE REVIEW

6.1. Coronary heart disease

Coronary heart disease (CHD) is a narrowing of the coronary arteries caused by the thickening and reduced elasticity of the coronary artery walls (arteriosclerosis), which, if severe enough, will cause reduced blood flow to the myocardium. In the early stages, the disease will only reduce coronary blood flow reserve (the average increase in blood flow that follows an increase in myocardial oxygen demand), but in advanced stages, CHD can reduce blood flow in the coronary arteries at rest. In its most severe stage, atherosclerosis in CHD can block blood flow in the coronary arteries.[14]

6.1.1. Management of coronary heart disease revascularization

Intervention in the form of coronary vessel revascularization is currently agreed to be the definitive therapy for coronary heart disease in both acute and chronic coronary syndromes. Based on several studies, it is known that revascularization by percutaneous coronary intervention or coronary artery bypass surgery in patients with coronary heart disease effectively reduces angina and the use of antianginal drugs and improves physical capacity and quality of life compared to the use of medical therapy with short or long term control. However, revascularization is performed on indications that are divided according to clinical appearance and prognostic factors (**Table 2.1**).[21]

Table 2.1 Indications for revascularization in patients with coronary heart disease.[16]

Parameters	Recommended Class	Level of Evidence	
Clinical appearance	Hemodynamically significant coronary vessel stenosis with angina, inadequate response to optimal medical therapy	I	A
Prognostic factors	Stenosis >50% of the left main coronary vessel	I	A
	Stenosis >50% at proximal left anterior descending coronary artery (LAD)	I	A
	Stenosis >50% in two- or three-vessel coronary disease with impaired left ventricular function (ejection fraction ≤35%)	I	A
	The large area of ischemia (>10% left ventricle)	I	B
	Only one remaining patent coronary artery with >50% stenosis	I	C

Description:
Recommendation class: I = recommended.
Level of evidence: A = meta-analysis and multiple randomized clinical trials, B = one randomized clinical trial or sizeable non-randomized study, C = registry, retrospective studies, and/or consensus of expert opinion.

The choice of revascularization method with percutaneous coronary intervention or coronary artery bypass surgery is determined by considering some aspects, such as clinical characteristics, technical and anatomical aspects, and whether or not contemporary interventions are necessary (**Table 2.2**).[21]

Table 2.2 Considerations for choosing the method of coronary artery revascularization by percutaneous coronary intervention or coronary artery bypass surgery.[21]

Aspects	Percutaneous coronary intervention	Coronary artery bypass surgery
Clinical characteristics	• Presence of severe comorbidities • Advanced age, vulnerability, or low life expectancy • Condition and mobility limitations that affect rehabilitation	• Diabetes mellitus • Decreased left ventricular function (ejection fraction ≤35%) • Contraindications to *dual antiplatelet* therapy • Occurrence of post-stent restenosis
Anatomical and technical aspects	• Multiple vessel disease with SYNTAX score 0-22 • Anatomy that allows inadequate revascularization by coronary artery bypass surgery (absence of pathways) • Severe chest deformity, scoliosis	• Multiple vessel disease with SYNTAX score ≥23 • Anatomy that allows inadequate revascularization by percutaneous coronary intervention • A coronary artery with severe calcification
Need for other interventions	None	• Pathology of the ascending aorta requiring surgery • Need for another heart surgery

*SYNTAX score: Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery - to assess the complexity of CHD.

6.2. Coronary artery bypass surgery

Coronary artery bypass graft (CABG) surgery is an open-heart surgical procedure in which a segment of the blood vessel is grafted to create an anastomosis from the aorta to the coronary artery to bypass the blood flow to feed the heart in place of the blocked coronary vessel. This procedure became more feasible after the invention of

the heart-lung machine to perform a heart-lung bypass during surgery. The first successful myocardial vascular graft procedure was performed in 1950 by Vineburg and Buller of McGill University, Canada using an implant from the left internal mammary artery.[22,23]

Subsequently, in 1955, Sidney Smith successfully performed a similar procedure using an implant from the saphenous vein.[17] Both vessels are currently recommended as implants for coronary artery bypass surgery, with the internal mammary artery as the first choice due to the lower incidence of decreased lumen patency, embolization, and perforation post-surgery compared to the saphenous vein. Perforation compared to the saphenous vein. In addition, implants from the radial artery and gastroepiploic artery can also be used.[21,22]

6.2.1. Outcomes after coronary artery bypass surgery

Several complications may occur after coronary artery bypass surgery. The possible complications are not limited to the cardiovascular system but also involve other systems, including respiratory failure, stroke, urinary tract infection, renal impairment, coagulopathy, limb ischemia, failure of wound edge union, pleural effusion, and hematological abnormalities. Frequent postoperative complications include bleeding, infection, congestive heart failure, and chest discomfort.[3,11]

1.1.1 Definition off-pump coronary artery bypass grafting

Coronary bypass artery *graft* (CABG) surgery is the most effective standard treatment for *coronary* heart disease. *Off-pump CABG* (OPCAB) is one of the CABG surgical techniques performed on a beating heart without the aid of a *cardiopulmonary bypass* (CPB) device, requiring high skills to perform this technique so it is not practised as widely as conventional CABG techniques.[54] In the OPCAB technique, the heart is still allowed to beat so stabilisation aids are required with *octopus* and *suction* aids *starfish* to facilitate position transfer during surgery. The OPCAB technique is an option because it can reduce the incidence of

postoperative complications caused by the use of CPB machines, these complications occur due to the effects of systemic inflammation due to the interaction of blood components with foreign objects, namely the surface of the *bypass* circuit. Complications include post surgical haemorrhage, neurocognitive dysfunction, thromboembolism, fluid retention and organ dysfunction.[7] In high risk patients OPCAB has lower morbidity and mortality rates, this is due to improved organ perfusion, protection of the myocardium due to minimal manipulation of the aorta, and avoidance of systemic inflammation due to the use of CPB.[8] Various studies have shown the advantages of OPCAB in reducing transfusion requirements, shorter hospital stay, reduced ICU and ventilator requirements, and more affordable costs.[55]

1.1.2 Indication and contraindication of off-pump coronary artery bypass grafting

The OPCAB technique is recommended for the management of revascularisation surgery alternatif conventional CABG by various guidelines. Indications for revascularisation with CABG are based on the patient's clinical characteristics, SYNTAX score and coronary anatomy complexity. CABG is indicated in patients with diabetes, decreased left ventricular function (EF<30%), patients contraindicated with antithrombotic drugs, diffuse in-stent recurrent restenosis, three vessel lesions with SYNTAX score >23, risk of incomplete revascularisation with percutaneous coronary intervention (IKP), coronary artery lesions with severe calcification, indications of concomitant cardiac surgery.[4] In the chest pain management guidelines issued by the American College of Cardiology/American Heart Association (ACC/AHA) 2021, OPCAB performed by experienced surgical specialists is recommended as the surgical technique of choice for revascularisation in patients with severe pulmonary disease (class IIb, level B-R) and in patients with aortic calcification to reduce the incidence of perioperative stroke (Class IIa, Level B-R).[56] The 2018 European Society of Cardiology/European Association of Cardio-Thoracic Surgery (ESC/EACT) coronary artery revascularisation guidelines recommend the use of the OPCAB

technique by experienced surgeons in patients with a high-risk profile (Class IIA, Level B) and in patients with atherosclerosis of the ascending aorta (Class I, Level B). Patients at high risk are women, patients with left ventricular dysfunction, ST-elevation myocardial infarct (STEMI) patients, patients with a history of stroke, old age, renal insufficiency, history of previous cardiac surgery, cirrhosis, extreme body mass index (BMI) (<25 or >35) and patients with high-risk Society of Thoracic Surgeons (STS) scores. The guideline also recommends the routine use of intraoperative graft flow measurement devices in OPCAB technique procedures (Class IIa, Level C).[21] The 2017 European Association for Cardio-Thoracic Surgery/European Association of Cardiothoracic Anaesthesiology (EACTS/EACTA) bleeding management guidelines for cardiac surgery recommend the OPCAB technique to reduce the need for blood transfusion in anemic patients with low body surface area, patients undergoing surgery with dual antiplatelet therapy (DAPT) treatment and in dialysis-dependent patients (Class IIb, Level B).[56] (3) The main contraindications for OPCAB are performed by inexperienced cardiac surgeons, intracavitary thrombus such as a left ventricular clot, intramyocardial vasculature, malignant arrhythmias, combined valve or ventricular repair, very small (<1mm) or calcified coronary arteries, poor vascular channels, hemodynamically unstable and cardiogenic shock.[55]

1.2 Heart valve surgery

Heart valve surgery is an open-heart surgery that aims to replace the mitral valve or aortic valve that has abnormalities, either stenosis or regurgitation. Current heart valve surgery procedures are also associated with good short-term and long-term outcomes.[58] In valve replacement surgery, the choice of valve replacement can come from bioprosthetics or mechanical prosthetics. The choice of prosthetic is based on the availability of the prosthetic, surgeon's expertise, preference, patient's age, presence of comorbidities, and contraindications to the use of anticoagulants. [59,60]

1.2.1 2.2.1 Procedure

The initial stages of a heart valve surgery procedure are positioning, sternotomy, and insertion of a cardiopulmonary bypass (CPB) machine. The patient is positioned supine, then monitor leads such as radial artery or pulmonary artery catheters are placed and sedation is performed. The patient's chest, abdomen, perineum and extremities are prepared sterile, followed by sternotomy. The mediana sternotomy method is the classic way to access the heart, but minimally invasive strategies such as upper/lower hemisternotomy, minitoracotomy, and right parasternotomy can be performed in order to rotate the ventricles of the heart to access the aortic root. Heparinization is then administered and a heart-lung bypass machine is inserted, before which cardioplegia agents such as low-temperature blood (32^{o} C) are administered anterograd (through the aortic root) and retrograd (through the sinus coronarius). [58,60]

Mitral valve surgery

The initial step for mitral valve surgery starts with accessing the mitral valve site. The best approach to access the mitral valve is to perform a left lateral atriotomy just anterior to the pulmonary veins. Another approach to access the mitral valve is through an incision in the right atrial appendage near the inferior vena cava that continues up to the fossa ovalis on the inferior side. [58,59]

In mitral valve replacement with a prosthesis, partial excision of the native mitral valve is performed while retaining the part of the valve around the annulus and the part attached to the tendinea cord, then suturing with pledgeted horizontal mattress circumferentially around the annulus with a prosthetic valve. Care is taken not to injure structures such as the sinistra circumflex artery, sinus coronarius, left atrial appendage, atrioventricular node, and aortic valve, and not to interfere with the left ventricular outflow tract. After suturing is completed, re-warming and suturing of the access hole to the mitral valve can be performed.[58,59]

After mitral valve replacement surgery is performed, anticoagulant therapy using warfarin

is administered until the target international normalized ratio (INR) of 2.5 to 3.5 is reached if the patient has a mechanical prosthetic valve. The use of warfarin is controversial when the patient has a bioprosthetic replacement valve. Some suggest using it for three months postoperatively and some state that warfarin is given when there are indications such as atrial fibrillation, previous history of thromboembolism, left ventricular dysfunction and hypercoagulable conditions.[59]

Aortic valve surgery

The first step in aortic valve surgery is to perform an aortotomy. This procedure can be performed obliquely or near transection. The oblique aortotomy starts from the anterior side at the midline of the ascending aorta, then proceeds to the right inferoposterior side until it reaches the sinus coronarius. The near-transection aortotomy is performed 4-6 mm above the aortic valve and a circular incision is made that almost cuts the aorta. However, there is a risk of massive bleeding on the posterior side when a near-transection aortotomy is performed so an oblique aortotomy is generally preferred.[58,60]

After aortotomy, inspection of the aortic valve and identification of the coronary ostium site is performed. The aortic valve is then excised starting at the ostium in the center, then moving through the commissure and valve leaflets and circumferentially. This procedure is done carefully so as not to injure the connection between the aortic valve and the mitral valve. Debridement of th*e* calcific material and irrigation with cold saline solution may be performed during the valve excision. Next, suturing of the replacement prosthetic valve at the aortic valve site is performed. The suturing technique can be interrupted, noneverting mattressed pledgets, everting mattressed pledgets, or continuous. After suturing is completed, rewarming and closure of the aortotomy is performed using polypropylene sutures. [58,60]

After aortic valve replacement surgery is completed, hypertension is controlled if present (intravenous sodium nitropruside or nicardipine is usually used) and adequate filling pressures are maintained (central venous pressure 10 - 15 mmHg and pulmonary capillary

pressure 15 - 18 mmHg). Temporary pacing is performed in patients with conduction block which usually resolves within one to two days. In addition, patients with mechanical prosthetic valves received oral warfarin anticoagulation and aspirin on postoperative day 2 to maintain an INR of 2.0 to 2.5 to minimize long-term bleeding and thrombotic events. Patients with bioprosthetic valves can receive aspirin without warfarin.[60]

1.2.2 2.2.2 Postoperative outcomes

The postoperative outcomes of heart valve surgery that need to be considered are similar to those of open heart surgery in general. In-hospital morbidity and mortality in patients undergoing heart valve surgery depends on the patient's demographics, risk factors, previous cardiovascular history, preoperative condition, and operative status (first or reoperative). Causes of early postoperative mortality include bleeding (commonly associated with anticoagulation), stroke, myocardial infarction, respiratory failure, multiorgan failure and infection, while persistent heart failure may be a cause of late mortality.[58,60]

In cases of mitral valve surgery, left ventricular rupture can be one of the fatal complications (occurring in approximately 0.8% of patients). Cerebral small vessel disease (SVD) can occur five years after surgery and the incidence increases significantly after ten years. Valve thrombosis in the absence of infection with obstruction of blood flow through the valve occurs in approximately 0.5% of patients. Patients undergoing mitral valve surgery are also at risk of prosthetic valve endocarditis, with a higher incidence in patients receiving mechanical prosthetic valves than bioprosthetics. The risk of endocarditis in the first year is 1% and the risk decreases to 0.2-0.35% per year. Bacteremia or contaminants causing endocarditis may be acquired intraoperatively or from the use of intravenous catheters, urinary catheters, and surgical wound infections.[58,59]

In cases of aortic valve surgery, mediastinal and perivalvular bleeding requiring reoperation have been reported in 5% and 1-2% of cases, respectively. Cardiac conduction

block is experienced in about 1-2% of patients, while atrial fibrillation is experienced in about one-third of patients with no previous history. In addition, there are some thromboembolic events such as strokes that account for 1-2% of the total cases**.** [58,60]

2.3. Tranexamic acid

6.3.1. Tranexamic acid pharmacology

Tranexamic acid is a synthetic compound derived from the amino acid lysine that is an analog of aminocaproic acid and acts as a fibrinolysis inhibitor. Tranexamic acid works by binding to the five binding sites of the amino acid lysine on plasminogen to inhibit its activation into plasmin which plays a role in fibrinolysis. To inhibit its activation into plasmin which plays a role in fibrinolysis. In addition, tranexamic acid also has an anti-inflammatory profile by inhibiting plasmin-mediated activation of complement, monocytes, and neutrophils. This drug has good absorption with oral administration, an initial dose of 15 mg/kg and a follow-up dose of 30 mg/kg every 6 hours, and is eliminated through the kidneys. Tranexamic acid can also be given intravenously at a dose of 0.5-1 gram three times per day with a dose restriction of 5-10 mg/kg in patients with renal failure.[29] The minimum concentration required to inhibit fibrinolysis in vitro is 10 mcg/ml in adults.[35] A meta-analysis conducted in 2020 said that tranexamic acid administration did not affect blood clotting time but significantly reduced post-surgical bleeding and transfusion requirements in patients with cardiac surgery.[36]

This compound is widely used as a prophylactic and therapeutic agent for bleeding, for example, in surgical interventions and severe trauma, thus reducing the amount of perioperative bleeding and the blood products transfusion after cardiac surgery. Early administration of tranexamic acid, primarily via the intravenous route, is known to increase the chances of survival in emergency cases of massive bleeding. Due to its significant role,

the World Health Organization (WHO) included tranexamic acid in the list of essential drugs.[37] However, it is contraindicated in patients with disseminated intravascular coagulation and upper genitourinary tract bleeding (kidney and ureter) due to its potential to cause excessive blood clot formation.[34]

6.3.2. Effect of tranexamic acid on post-open heart surgery outcomes

Tranexamic acid has been widely used in open-heart surgery to reduce bleeding and the need for post-surgical blood transfusions. Guidelines from the Society of Thoracic Surgeons have recommended using tranexamic acid to reduce bleeding from cardiac surgery (class I recommendation).[9] The anti-inflammatory profile of tranexamic acid also plays a role in addressing the inflammatory response after cardiac surgery, especially for those using cardiopulmonary bypass. This is because cardiopulmonary bypass carries the risk of coagulopathy, including activation of intrinsic and extrinsic coagulation pathways, platelet dysfunction, and systemic inflammatory response.[38] Studies show that low-dose tranexamic acid (10 mg/kg intravenously) is the optimal dose for cardiac surgery.[39]

Despite its benefits in reducing bleeding and inflammation, several unexpected post-surgical side effects have been reported with tranexamic acid as surgical prophylaxis. The antifibrinolytic profile of tranexamic acid theoretically allows for an increased risk of thromboembolic events such as deep vein thrombosis, early occlusion of vascular implants, cerebral and myocardial infarction, and pulmonary embolism.[9,10] This is in line with Ross and Salman's meta-analysis, which showed that some patients receiving tranexamic acid prophylaxis and aprotinin (a tranexamic acid analog) experienced thromboembolic events at 1.9% (95% confidence interval 1.1-2.9) and 3.0% (95% confidence interval 1.8-4.6), respectively. However, these events occurred in patients undergoing surgery for subarachnoid

hemorrhage.[39]

Tranexamic acid can cross the blood-brain barrier, with cerebrospinal fluid concentrations reaching about 10% of plasma concentrations. A concentration of as much as 15 micrograms per milliliter has been said to be the threshold for potential excitation effects.[35] There have been reported cases of patients experiencing seizures after open heart surgery, especially those receiving high doses of intravenous tranexamic acid.[14] Study by Kalavrouziotis et al. showed that tranexamic acid at doses ≥100 mg/kg intravenously was associated with an increased risk of early postoperative seizures in patients undergoing cardiac surgery with cardiopulmonary bypass.[40] Meta-analysis by Takagi et al. and Guo et al. also showed that adult patients who underwent cardiac surgery and received tranexamic acid therapy had a fourfold risk of seizures.[41,42] This is thought to be because the molecular structure of tranexamic acid is similar to that of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, and thus has an antagonistic effect on its receptors in the central nervous system.[9]

Nonetheless, other studies have looked at this issue and provided different results. Saracoglu et al. presented the results of a retrospective cohort study on 172 subjects who underwent open-heart surgery, received a regimen of 50 mg/kg intravenous tranexamic acid as bleeding prophylaxis, and showed no cases of thrombosis, stroke, or seizure. The number of post-heart surgery reoperations was similar to the group that did not receive tranexamic acid prophylaxis. Reoperation was similar to the group that did not receive tranexamic acid prophylaxis (4.1%).[44] In addition, a retrospective cohort study In addition, a retrospective cohort study conducted by Maeda et al. also explained that discontinuing tranexamic acid for cardiac surgery did not make a significant difference in the incidence of thromboembolism and postoperative mortality. However, there was a decrease in seizures and

increased postoperative bleeding when tranexamic acid was not given.[45]

Although studies to date have shown controversial results regarding the adverse effects of tranexamic acid post-open heart surgery, such outcomes clinically affect the cost and duration of hospitalization and the quality of life for patients who experience adverse events.[11] As these events are primarily reported in patients receiving tranexamic acid intravenously, it was thought that the route of administration might influence the risk of postoperative adverse events. Topical administration (intrapericardial in cardiac surgery) is considered a safer alternative as it works locally but is still effective in reducing bleeding and inflammation.[12]

Several studies have compared post-cardiac surgery outcomes on tranexamic acid administration via topical, intravenous, and/or placebo routes, albeit with differing results. Vaněk and Straka's meta-analysis of four randomized controlled clinical trials comparing topical and placebo administration of tranexamic acid in cardiac surgery showed a trend towards decreased bleeding in the group receiving topical tranexamic acid, although not statistically significant.[46] Randomized controlled clinical trials conducted by Hosseini et al., Shah et al., and Chaudhary et al. showed a statistically significant reduction in the amount of bleeding after open heart surgery in the group receiving topical tranexamic acid compared to placebo.[47–49] Similar results were also obtained in the meta-analysis of Montroy et al. and Habbab et al., with no significant difference in the incidence of post-heart surgery seizures and thromboembolism between the topical tranexamic acid and placebo groups.[13,50] Habbab et al. randomized controlled clinical trial was the first to compare post-cardiac surgery outcomes between topical and intravenous tranexamic acid groups, showing a trend toward decreased bleeding, blood products transfusion after cardiac surgery, reoperation, and incidence of post-surgical seizures in the topical tranexamic acid group.[12]

6.3.3. Comparison of systemic and topical tranexamic acid

Intravenous administration of tranexamic acid has been associated with an increased risk of thromboembolism and early *graft* closure in coronary artery bypass surgery. Reported cases of thromboembolism include cerebral, pulmonary, mesenteric, and retinal thromboembolism. Due to the significant systemic side effects of intravenous administration, topical administration of tranexamic acid has become increasingly popular. This is because the local antifibrinolytic effect facilitated by the topical application of tranexamic acid has proven effective in preventing bleeding in several other disease cases, such as post-oral surgery of patients with hemophilia, epistaxis, bladder surgery, and gynecological bleeding.[51]

Topical administration can provide adequate concentrations at the wound site while providing low systemic concentrations.[35] Other studies show that topical tranexamic acid in surgery can significantly reduce bleeding and transfusion requirements without increased side effects.[52,53] This condition may be due to the shallow degree of systemic absorption after topical application compared to intravenous bolus administration. The study stated that topical application of tranexamic acid gave a mean peak serum concentration of 4.9 mcg/mL in the group treated with fluid bolus in the wound cavity and 5.2 mcg/mL in the group treated with moisturizing the wound surface. These levels are lower than the minimum levels required for systemic effects. In addition, at 5 mcg/mL, only 0.5 mcg/mL will cross the blood-brain barrier, making it very unlikely to cause seizures. In contrast, after administration of 1 g of intravenous tranexamic acid, the serum concentration is above 10 mcg/mL for about 2.5 hours.[35]

Topical administration of tranexamic acid in surgery is generally given as a bolus to the cavity or added to irrigation fluid.[35] In a study by De Bonis et al.

100 mL of tranexamic acid solution (1 g in 100 mL of 0.9% NaCl) or room-temperature placebo was poured into the pericardial cavity and mediastinal tissue of patients before sternal closure. The bleeding was measured every hour, every 24 hours, and before discharge. The results showed that 1% tranexamic acid solution applied topically into the pericardial cavity after coronary artery bypass surgery can significantly reduce bleeding in the first 3 hours, with a reduction of 36% in the first 3 hours and 25% in the first 24 hours when compared with placebo. In addition, the study also showed that tranexamic acid could not be detected in blood samples taken 2 hours after the chest tube was opened, indicating that topically applied tranexamic acid can have a topical impact on the pericardial cavity without causing systemic effects, thus preventing the occurrence of feared systemic side effects.[51] However, tranexamic acid should not be applied topically to the central nervous system as it may cause seizures. In addition, topical application of high doses of tranexamic acid may also inhibit glutamate receptors in various tissues. Prolonged exposure to high-dose topical tranexamic acid may prevent nontoxic epithelial reepithelialization and shed in *vivo* human skin wound models.[52]

There is no literature stating the ideal minimum effective dose of tranexamic acid. However, a meta-analysis study from Ausen et al. explained that a tissue concentration of tranexamic acid of at least 10 μg/mL is required to inhibit fibrinolysis significantly. No study has yet described the topical effect of tranexamic acid determined by the concentration of the drug, the total dose, and/or the combination of concentration and contact time of tranexamic acid with the surrounding tissue.[52]

6.4. Theoretical framework

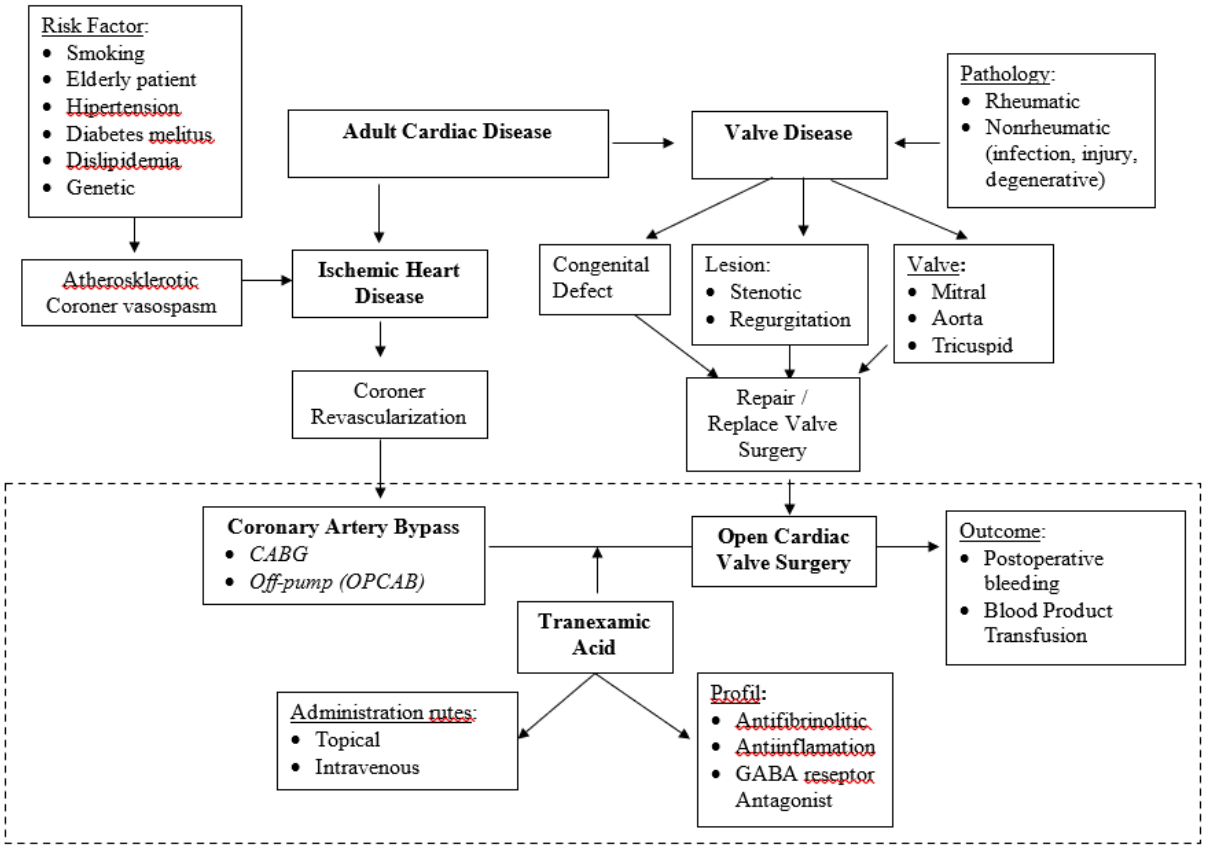

Figure 2.2. Theoretical framework

6.5 Conceptual framework

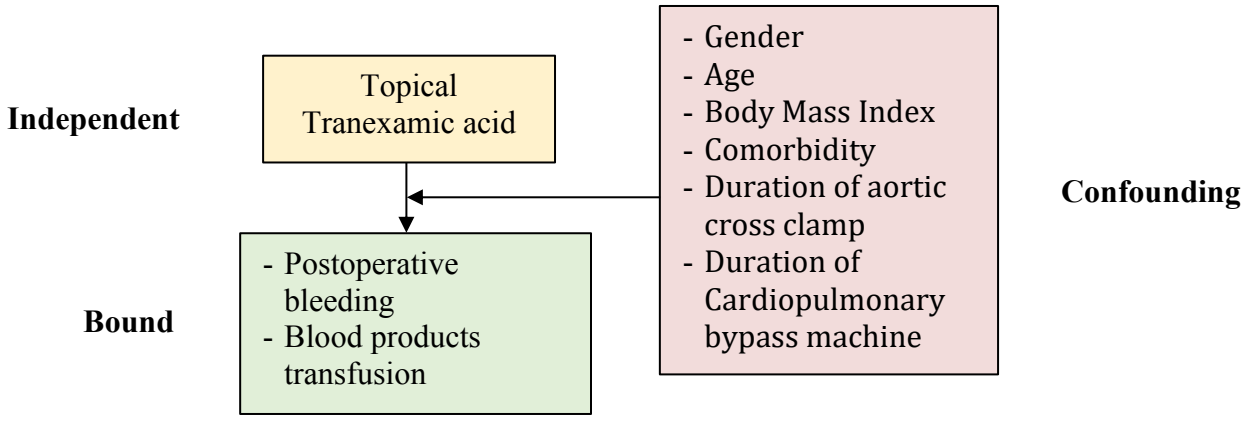

Figure 2.3. Conceptual framework

CHAPTER 3
RESEARCH METHODS

3.1. Research design

This study used a randomized clinical trial, placebo-controlled and double-blinded.

3.2. Time and place of research

This study occurred from October to December 2022 at the Division of Adult Cardiac Surgery, Harapan Kita National Heart Center Hospital (RSPJNHK).

3.3. Research population

The target population in this study were: (1) patients with coronary heart disease who indicated coronary artery bypass surgery (CABG) and off pump coronary artery bypass (OPCAB), (2) patients who had heart valve disease indicated by open-valve heart surgery. The target population was patients who underwent adult cardiac surgery at the Division of Adult Cardiac Surgery, RSPJNHK, from October to Desember 2022.

3.4. Sample selection method

Sampling in this study was conducted consecutively, including all patients who underwent cardiac surgery in the Division of Adult Cardiac Surgery, RSPJNHK, until reaching the target sample size.

3.5. Inclusion, exclusion, and dropout criteria

3.5.1. Inclusion criteria

1. Adult patients aged ≥18 years
2. Coronary heart disease patients indicated for coronary artery bypass surgery and off-pump coronary artery bypass (OPCAB)
3. Patients with heart valve disease are indicated for aortic or mitral valve repair and replacement through open heart surgery.

4. The patient underwent open heart valve surgery with tricuspid valve repair.
5. Patients undergoing open heart surgery at the Adult Cardiac Surgery Division, RSPJNHK.

3.7.1. Exclusion criteria

1. Patients who expressed unwillingness to become research subjects.
2. Patients who have an allergy to tranexamic acid.
3. Patients were undergoing urgent/emergency surgery and minimally invasive surgery
4. The patient underwent a double procedure of simultaneous aortic and mitral valve surgery.
5. Patients with a history of bleeding disorders (coagulopathy) such as clotting factor deficiency and heparin-induced thrombocytopenia or use of intravenous anticoagulants other than heparin at the time of surgery.
6. Patients with a history of thromboembolic disease.
7. Patients with active Infective endocarditis
8. Patients with a history of previous cardiac surgery
9. Patients with a estimated glomerular filtration rate <30 mL/min or on dialysis
10. Patients who receiving oral therapy with clopidogrel, aspirin, dabigatran, or rivaroxaban in the last five days
11. Patients who receiving chronic warfarin therapy who have not stopped their medication and have an international normalized ratio (INR) >1.5 before surgery
12. Patients with pre-operative thrombocytopenia (<50,000 platelets per μL)
13. Pregnancy or breast feeding patients
14. Patients who refusal of blood products
15. Patients with a pericarditis

5.5.2. Dropout criteria

1. Patients are discharged from the operating room with a heart-lung bypass machine or extracorporeal membrane oxygenation (ECMO).
2. History of intraoperative internal or external heart-lung resuscitation.

5.6. Estimated sample size

The number of samples in this study was calculated twice because the dependent variables observed were the amount of bleeding and the need for postoperative blood transfusion, all of which were numerical variables. From the overall calculation results, the largest sample size for this study was taken, then 10% was added to accommodate the possibility of *dropping out*. The formula used in the sample calculation for both variables is the hypothesis test formula for the mean of two independent groups. The literature used as a reference for calculating the sample of this study is a study by Chaudhary et al. (2018).[44] The following are the sample calculation results for each research variable.

- **A variable amount of bleeding**

$$n_1 = n_2 = 2\left[\frac{(z_\alpha + z_\beta)s}{(x_1 - x_2)}\right]^2$$

$$n_1 = n_2 = 2\left[\frac{(1{,}96 + 0{,}842)339{,}021}{300}\right]^2$$

$$n_1 = n_2 = 20{,}05 \sim 20\ sample$$

Description:

= normal standard deviation for type I error with α is 0.05 (1.96)

= normal standard deviation for type II error with β is 0.2 (0.842)

= standard deviation between placebo and treatment groups according to the study (placebo = 445.941 mL and treatment = 232.101 mL, so that the mean value taken = 339.021 mL)[44]

= expected clinical difference (taken 300 mL)

- **Variable blood transfusion needs**

$$n_1 = n_2 = 2\left[\frac{(z_\alpha + z_\beta)s}{(x_1 - x_2)}\right]^2$$

$$n_1 = n_2 = 2\left[\frac{(1{,}96 + 0{,}842)1{,}072}{1}\right]^2$$

$$n_1 = n_2 = 18{,}04 \sim 18\ sample$$

Description:

= average standard deviation for type I error with α is 0.05 (1.96)

= average standard deviation for type II error with β is 0.2 (0.842)

= standard deviation between placebo and treatment groups according to the study (placebo = 1.225 units and treatment = 0.918 units so that the mean value taken = 1.072 units)[44]

= expected clinical difference (taken as 1 unit)

Based on the above calculation results, 20 patients were taken as the minimum sample size for each placebo and treatment group. With the addition of 10% to anticipate dropouts (2 patients per group), the total sample for each group was 22 samples. The total sample for both groups was 44 patients. In this study, there are three arms group (CABG group, OPCAB group, and Valve Surgery group). The total sample for both arms group was 132 patients.

5.7. Data collection and retrieval steps

3.7.1. Before surgery

Patients with coronary heart disease and heart valve disesase who were indicated for cardiac surgery were determined to be eligible for the study based on the inclusion and exclusion criteria through history taking, physical examination, and the results of supporting examinations (electrocardiography, cardiac enzymes, and laboratory) obtained from the

patient's medical record at RSPJNHK. Furthermore, researchers conducted *informed consent* to patients who were eligible to become research subjects and asked for written consent from patients. Patients who agreed to the *informed consent were* randomized into treatment or control (placebo) groups. A research assistant carried out randomization using the "randomizer.org" site. The treatment group in this study received 5 g of tranexamic acid in 50 mL of 0.9% NaCl solution administered topically to the pericardial cavity after protamine administration and before sternotomy closure. In contrast, the control group (placebo) received 100 mL of 0.9% NaCl solution without tranexamic acid administered in the same way as the treatment group. The pharmacy department prepared the preparations in the study so that neither the researchers nor the patients were aware of the preparations used intraoperatively.

3.7.2. Perioperative

Patients who became research subjects underwent coronary artery bypass surgery according to standard operating procedures at RSPJNHK. After inducing anesthesia, undergoing sternotomy, and installing a heart-lung bypass machine (*on-pump*), the patient underwent the primary procedure. Then the research protocol was carried out with either treatment or control (placebo) after the heart-lung bypass machine stopped and before the sternum was closed by previously clamping the chest tube. After skin closure was completed, the chest tube clamps were reopened, and internal suction was performed, followed by connecting the chest tube with a *water-sealed drainage* system to accommodate post-surgical intrathoracic bleeding. The sternal closure to skin suturing process is done within 30-45 minutes.

In OPCAB group, after the graft anastomosis with OPCAB technique was completed, before sternal closure, the patient was given an intervention in

the form of topical tranexamic acid (5g/50mL) or placebo (50mL normal saline) dissolved in 100mL normal warm saline (37^{o} C) which was inserted into the pericardial cavity including mediastinal tissue and allowed to stand for five minutes. It was then cleaned and sternal closure was performed.

The study subjects then underwent heart valve surgery according to the standard operating procedures of RSJPDHK, which began with induction of anesthesia, sternotomy, and CPB insertion. After the heart-lung bypass machine stopped, the chest tube was installed and clamped, the Subject then received one of the placebo or treatment fluids which were divided into two administrations, 50 mL of the first liquid was given to the intrapericardium and 50 mL of the second liquid was given to the sternum. The sternum was closed to the skin with an estimated completion of 30-45 minutes. Chest tube clamps were opened and connected to a water-sealed drainage (WSD) system to remove residual bleeding in the thorax after surgery.

3.7.3. Post-surgery

Patients were intensively treated in the intensive care unit (ICU), intermediate room, and standard room according to clinical conditions. The researcher observed and recorded the amount of bleeding accumulated until chest tube removal and blood products transfusion units of blood components during treatment. Transfusion will be given when there is an indication for transfusion. The indication for *packed red cell* (PRC) transfusion was Hb <10 g/dL, with a target of Hb >10 g/dL. The indication for platelet transfusion was platelets <100,000 U/μL, with a target of platelets >100. The indication for fresh frozen plasma (FFP) transfusion is if APTT > 1.5 times the control, the transfusion target is activated partial thromboplastin clotting time (APTT) < 1.5 times the control. Cryoprecipitate was given if fibrinogen < 100 mg/dL, and the transfusion target was fibrinogen > 100 mg. Observation of bleeding was recorded from initial

bleeding, 6 hours, 24 hours, and 48 hours, or until chest tube removal if the bleeding was <200 mL/24 hours.

Bleeding management protocols were performed if there was excessive or massive bleeding post-surgery. A single researcher conducted all observations to maintain data reliability which was then recorded for further processing.

3.8. Instruments used

This study used a form instrument to record the results of observations of research subjects. The form includes informed consent, preoperative assessment results (history taking, physical examination, supporting examination, and tolerance of the study subject's surgery), and postoperative observations (including the amount of bleeding and the blood products transfusion units).

3.9. Research Variables

Table 3.1 Variables in the study.

Variable Type	Variables
Free	Topical administration of tranexamic acid
Bound	● Number of postoperative hemorrhages o Initial bleeding o Bleeding 6 hours o 24-hour bleeding o 48-hour bleeding ● Need for postoperative blood transfusion o *Packed red cell* (PRC) transfusion o Platelet transfusion o Transfusion of *fresh frozen plasma* (FFP) o Cryoprecipitate transfusion
Confounding[8]	● Gender ● Age ● Body mass index ● Concomitant conditions (diabetes mellitus, hypertension) ● Aortic cross-clamp ● Heart-lung bypass machine

3.10. Operational Definition

Table 3.2 Operational definitions-

Variables	Definition	Measurement	Variable Scale	Variable Value
Administration of topical tranexamic acid	Intrapericardial administration of 5 g tranexamic acid in 50 mL 0.9% NaCl after protamine administration and before sternotomy closure in cardiac surgery	-	Nominal	• Treatment (tranexamic acid) • Control (NaCl 0.9%)
Amount of bleeding				
Initial bleeding	Amount of blood accumulated in the patient's water-sealed drainage (WSD) system shortly after cardiac surgery	Observation of the volume of blood collected in the WSD system	Numerical	mL
6-hour bleeding	Amount of blood accumulated in *the water-sealed drainage* (WSD) system of a patient 6-hour post cardiac surgery	Observation of the volume of blood collected in the WSD system	Numerical	mL
24-hour bleeding	Amount of blood accumulated in *the water-sealed drainage* (WSD) system of a patient 24 hour-post cardiac surgery	Observation of the volume of blood collected in the WSD system	Numerical	mL
48-hour bleeding	Amount of blood accumulated in *the water-sealed drainage* (WSD) system of a patient 48 hours- post cardiac surgery	Observation of the volume of blood collected in the WSD system	Numerical	mL
Blood Transfusion Requirements				
Packed red cell (PRC) transfusion	Amount of PRC transfusions received in post cardiac surgery patients with Hb levels <10 g/dL to reach Hb levels >10 g/dL before discharge.	Observation of the volume of PRC received by the patient	Numerical	mL
Platelet transfusion[49]	Amount of blood platelet transfusions received in post cardiac surgery patients with platelets <100,000 U/µL to reach levels of 100,000 U/µL or in platelet dysfunction.	Observation of the volume of Platelet transfusion received by the patient	Numerical	mL
Fresh Frozen plasma (FFP)Transfusion[49]	Amount of blood FFP transfusions received by post cardiac surgery patients with international normalized ratio (INR) >1.5 to reach 1.5	Observation of the volume of FFP received by the patient	Numerical	mL

Variables	Definition	Measurement	Variable Scale	Variable Value
Cryoprecipitate transfusion[49]	Amount of cryoprecipitate transfusions received by post cardiac surgery patients with fibrinogen levels <100 mg/dL to reach levels of 100 mg/dL	Observation of the volume of cryoprecipitate received by the patient	Numerical	mL
Gender	Patient gender	Data obtained from patient medical records	Nominal	• Male (0) • Female (1)
Age	Age of the patient at the time of the procedure	Data obtained from patient medical records	Numerical	year
Aortic cross-clamp	Length of use of aortic cross-clamp during surgery	Data obtained from patient medical records	Numerical	minutes
Cardiopulmonary Bypass machine (CPB)	Length of time the CPB replaces the patient's circulation during surgery	Data obtained from patient medical records	Numerical	minutes
Body Mass Index (BMI)	(Patient's weight in kilograms) squared divided by (Patient's height in meters) at the time of the procedure.	Data obtained from patient medical records	Numerical	kg/m^2
Comorbidity	Presence of hypertension and/or diabetes mellitus as comorbidities at the time of the procedure	Data obtained from patient medical records	Nominal	• Hypertension (1) • Diabetes Mellitus (2)

Table description:

WSD: *water-sealed drainage*

PRC: *packed red cell*

FFP: *fresh frozen plasma*

INR: *international normalized ratio*

BMI: Body Mass Index

3.11. Research ethics

The study was approved by the ethics committee at Harapan Kita National Heart Center Hospital, number LB.02.01/VII/040/KEP040/2022, and has received research permit approval with number LB.02.01/XX.2/8186/2022.

3.12. Data processing flow

The data of the research subjects collected using the forms were verified and compiled using SPSS software for Microsoft Windows version 20.0 in the form of descriptive tables. Data normality and statistical analysis for each variable were performed using the same software. The tests used to analyze the two dependent variables (amount of bleeding and blood products transfusion after cardiac surgery) were the independent T-test (for normal data distribution) and the Mann-Whitney test (for abnormal data distribution).

3.13. Research flow

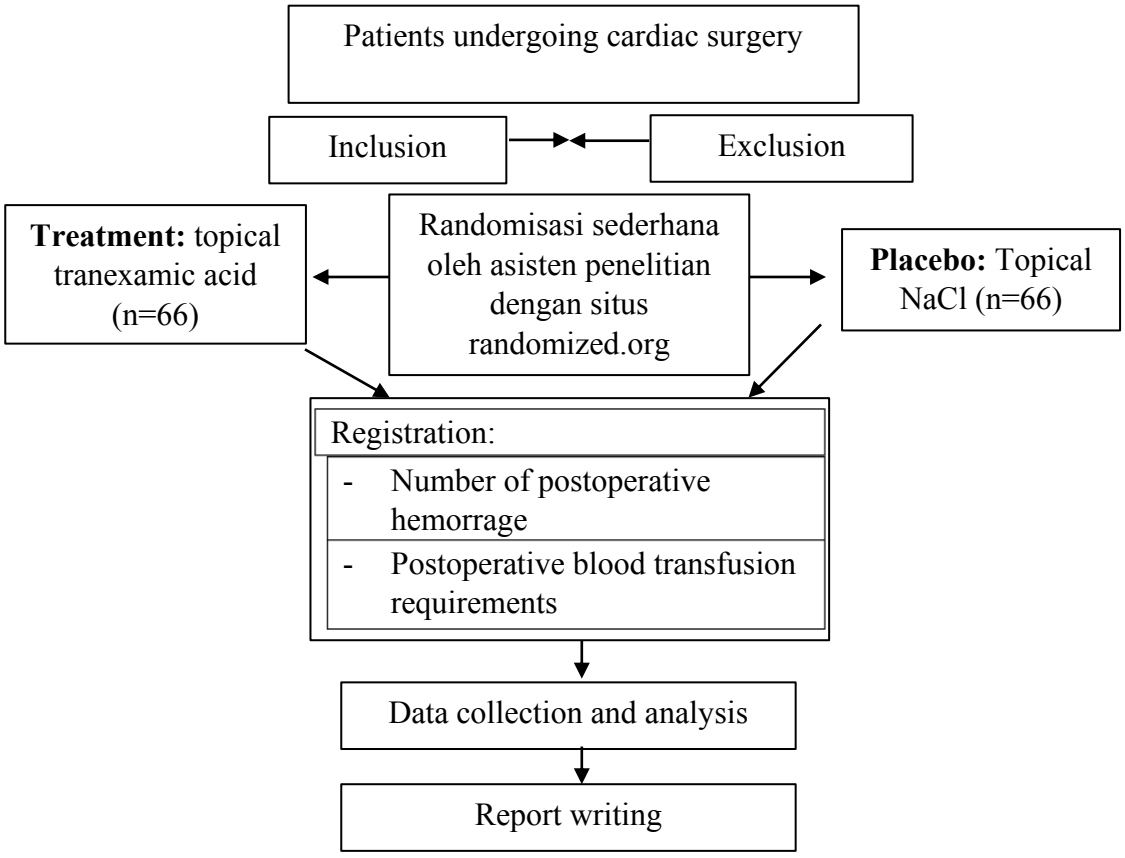

Table 3.3 Research protocol

TIME	LOCATION	ACTION
D-1	Preoperative	1. Patient's informed consent, signature on a consent form 2. Put a green research sticker on the patient's status 3. Ensure **STOP ACE inhibitors** (Captopril, Ramipril, Lisinopril) and **ARBs** (Candesartan, Valsartan) 24 hours preoperatively. 4. Make sure to STOP antiplatelet drugs 3-7 days preoperatively 5. Make sure to STOP Warfarin 4-5 days preoperatively 6. Ensure Heparin STOP 4-6 hours preoperatively 7. Ensure STOP LMWH 12-48 hours preoperatively 8. Record all required patient data on the questionnaire
D+0	Operating Room	1. Induction, intubation 2. Standard operating procedures 3. The surgeon administers topical tranexamic acid (5 g in 50 mL NS) or placebo in 100 mL, 50 mL after protamine administration, and 50 mL before closing the sternum. 4. Chest tube clamps should not be opened until the skin closure process is complete.
D+0	ICU	1. Calculate the initial bleeding when the patient arrives at the intensive care unit 2. Collect blood coagulation examination data (blood, hematocrit, PT/APTT, INR) 3. Count the amount of bleeding from the chest tube in the first 6 hours and 24 hours 4. Disconnect the chest tube if the amount of bleeding is <200 mL in 24 hours
D+1	ICU	1. Count the amount of bleeding from the chest tube in the second 24 hours (if the chest tube is still in place) 2. Chest tube removal when the amount of bleeding is <200 mL in the second 24 hours

TIME	LOCATION	ACTION
		3. Calculate the use of blood component transfusion (PRC, FFP, TC, Cryoprecipitate)
D+2 – hospital discharge	ICU - Wardroom	1. Record clinical output results according to the questionnaire (total amount of drain production and transfusion use of blood components)

1.3 Research schedule

Activities	2022		
	October	November	Desember
Submission of research ethics approval	X		
Data collection and retrieval		X	
Data processing and hypothesis testing			X
Preparation of research report			X

1.4 Detailed cost plan

Proposal drafting (printing and photocopying costs)	Rp600.000,00
Submission of ethics and research permits	Rp900.000,00
Data collection (observation, consumables)	Rp15.000.000,00
Preparation of research report (printing and photocopying costs)	Rp1.500.000,00
Journal publication	Rp5.000.000,00
Total	**Rp23.000.000,00**

1.5 *Dummy table*

Tabel Error! No text of specified style in document..1 Sample table of experimental and control group characteristics

Variables	Experimental Group	Control Group (Placebo)	P-value
Age (years)	Rerata ± SD	Rerata ± SD	
Gender			
Male	n (%)	n (%)	
Women	n (%)	n (%)	
Body surface area (m^2)	Mean ± SD	Mean ± SD	
Comorbidities			
Hypertension	n (%)	n (%)	
Diabetes mellitus	n (%)	n (%)	
Preoperative hemoglobin	Mean ± SD	Mean ± SD	
Preoperative hematocrit	Mean ± SD	Mean ± SD	
Preoperative APTT	Mean ± SD	Mean ± SD	
Preoperative INR	Mean ± SD	Mean ± SD	
Preoperative creatinine	Mean ± SD	Mean ± SD	
Postoperative hemoglobin	Mean ± SD	Mean ± SD	
Duration of aortic cross clamp	Mean ± SD	Mean ± SD	
Duration of use of heart-lung machine	Mean ± SD	Mean ± SD	

Tabel Error! No text of specified style in document..2 Sample output table of CABG results in experimental and control groups

Primary outcome output	Control group (n=22)	Experimental group with TXA (n = 22)	P-value
Volume of chest drain bleeding			
Initial bleeding (mL)	Mean ± SD	Mean ± SD	
6-hour bleeding (mL)	Mean ± SD	Mean ± SD	
24-hour bleeding (mL)	Mean ± SD	Mean ± SD	
48-hour bleeding (mL)	Mean ± SD	Mean ± SD	
Blood Transfusion			
PRC transfusion (mL)	Mean ± SD	Mean ± SD	
FFP transfusion (mL)	Mean ± SD	Mean ± SD	
TC transfusion (mL)	Mean ± SD	Mean ± SD	
Cryoprecipitate transfusion (mL)	Mean ± SD	Mean ± SD	

Tabel Error! No text of specified style in document..3 Sample output table of OPCAB results in experimental and control groups

Primary outcome output	Control group (n=22)	Experimental group with TXA (n = 22)	P-value
Volume of chest drain bleeding			
Initial bleeding (mL)	Mean ± SD	Mean ± SD	
6-hour bleeding (mL)	Mean ± SD	Mean ± SD	
24-hour bleeding (mL)	Mean ± SD	Mean ± SD	
48-hour bleeding (mL)	Mean ± SD	Mean ± SD	
Blood Transfusion			
PRC transfusion (mL)	Mean ± SD	Mean ± SD	
FFP transfusion (mL)	Mean ± SD	Mean ± SD	
TC transfusion (mL)	Mean ± SD	Mean ± SD	
Cryoprecipitate transfusion (mL)	Mean ± SD	Mean ± SD	

Tabel Error! No text of specified style in document..4 Sample output table of valve surgery results in experimental and control groups

Primary outcome output	Control group (n=22)	Experimental group with TXA (n = 22)	P-value
Volume of chest drain bleeding			
Initial bleeding (mL)	Mean ± SD	Mean ± SD	
6-hour bleeding (mL)	Mean ± SD	Mean ± SD	
24-hour bleeding (mL)	Mean ± SD	Mean ± SD	
48-hour bleeding (mL)	Mean ± SD	Mean ± SD	
Blood Transfusion			
PRC transfusion (mL)	Mean ± SD	Mean ± SD	
FFP transfusion (mL)	Mean ± SD	Mean ± SD	
TC transfusion (mL)	Mean ± SD	Mean ± SD	
Cryoprecipitate transfusion (mL)	Mean ± SD	Mean ± SD	

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