**An-Najah National University**

**Faculty of Graduate Studies**

# THE EFFICACY OF ADMINISTRATION OF TRANEXAMIC ACID PRE AND POST CARDIOPULMONARY BYPASS VERSUS PLACEBO IN REDUCING BLOOD LOSS TRANSFUSION IN CARDIAC SURGERY: A PROSPECTIVE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND TRIAL

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**This Thesis is Submitted in Partial Fulfillment of the Requirements for the Master Degree of Nurse Anesthesia, Faculty of Graduate Studies, An-Najah National University, Nablus - Palestine.**

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# Dedication

This study is wholeheartedly dedicated to Almighty God, for His guidance, and protection and forgiving me good health to carry out this research.

It is also dedicated to my beloved parents for inspiration and prayers during the completion of this research, to my husband, the love of my life, to my sons Quis &Ghaith for their continuous oral, spiritual and emotional support in completion of this thesis and to my sisters Asma, Duaa, and Aya ,and brother Mohammad, Abd Al-Rahman and Nasser Aldeen for their encouragement.

# Acknowledgment

First and foremost, I would like to praise Almighty Allah, the Most Gracious, and the Most Merciful for His blessings during my study and completion of this thesis. May Allah's blessings and prayers go to His final Prophet Muhammad (peace be upon him), his family and his companions.

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My ultimate thanks go to my beloved family for their endless support, love, prayers and generous help and support during the completion of this thesis. Also, my thanks go to my classmates in the graduate program for every single moment of joy and sorrow we cherished together since the first time we stepped into university campus. Moreover, I would like to express my thanks to all my friends who have helped me in completing this thesis.

Finally, I have a great expectation that my study will be beneficial and useful and will make a difference in the lives of many patients.

# Declaration

I, the undersigned, declare that I submitted the thesis entitled:

**THE EFFICACY OF ADMINISTRATION OF TRANEXAMIC ACID PRE AND POST CARDIOPULMONARY BYPASS VERSUS PLACEBO IN REDUCING BLOOD LOSS TRANSFUSION IN CARDIAC SURGERY: A PROSPECTIVE, RANDOMIZED, PLACEBO- CONTROLLED, DOUBLE-BLIND TRIAL**

I declare that the work provided in this thesis, unless otherwise referenced, is the researcher's own work, and has not been submitted elsewhere for any other degree or qualification.

**Student's Name:** _____

**Signature:** _____

**Date:** _____

# List of Contents

# List of Tables

# List of Figures

# List of Appendices

**THE EFFICACY OF ADMINISTRATION OF TRANEXAMIC ACID PRE AND POST CARDIOPULMONARY BYPASS VERSUS PLACEBO IN REDUCING BLOOD LOSS TRANSFUSION IN CARDIAC SURGERY: A PROSPECTIVE, RANDOMIZED, PLACEBO- CONTROLLED, DOUBLE-BLIND TRIAL**

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## ABSTRACT

Cardiopulmonary Bypass (CBP) provides a blood–free field surgery, but it has complications. One of these complications is blood loss and bleeding. Therefore, to save blood in cardiac surgery, antifibrinolytics, agent, like Tranexamic Acid (TXA), can be used.

The Study aim to assess TXA clinical efficacy and safety to reduce blood loss, and the need for blood transfusions of the patient during Coronary Artery Bypass Grafting (CABG), using CPB.

A sample of Ninety -nine patient was included in this study. A prospective, randomized, placebo–controlled, double-blind study of patients received placebo (n= 33) or TXA 15 mg/ kg before CPB, then was infused 1 mg\kg\h and stopped after termination of CBP and reversal of heparin. This was followed by a TXA infusion of 1 mg /kg / h for 5 hours (n = 33) or TXA 15 mg\kg after CPB, and by infusion TXA 1mg\kg\h for 5 h.

The results showed that the mean of the RBC units in control group (Mean=1.42) was significantly higher than both the means of the RBC units in Pre –CPB TXA group (Mean=0.61) and Post- CPB TXA group (Mean=0.64), $p<0.001$. Pertaining to the 48 h. post-op (Mediastinal chest drainage (MCTD)).

The results showed that the mean of the 48 h. post-op (MCTD) in the control group (Mean=209.45) was only significantly higher than the mean of the 48 h. post-op (MCTD) in Post-CPB TXA group (Mean=110.52), P= 0.005. Concerning 72 h. post-op MCTD), the results showed that the mean of the 72 h. post-op (MCTD), in control

group, (Mean=41.67) was only significantly higher than the mean of the 72 h. post-op (MCTD) in Post-CPB TXA group (Mean=14.87), P= 0.006.

In patients undergoing cardiac surgery and at risk for postoperative bleeding, the study has demonstrated that post-CPB TXA has profoundly favorable hemostatic and blood conservation benefits. Giving TXA post CPB has the best hemostatic effects. When compared to placebo, it reduces both blood loss over the course of 48 and 72 hours and the need for blood product administration. Pre-CPB TXA's positive impact, however, is less obvious.

**Keywords**: Cardiopulmonary Bypass; Coronary Artery Bypass Grafting; Tranexamic Acid; bleeding; blood transfusion.

# Chapter one

# Introduction

## 1.1 Background

Valvular open-heart procedures and Coronary Artery Bypass Grafting (CABG) have grown more commonplace since the introduction of Cardiopulmonary Bypass (CPB). There are major problems associated with CPB use even though its use has greatly improved heart surgery's effectiveness. CPB was developed at the outset of the 1950s, enabling the surgeons to treat life-threatening cardiac abnormalities by stopping heart contraction and emptying it from blood while keeping the rest of the body operating normally. A heart-lung machine temporarily replaces the heart and lungs during surgery in cardiac surgery, using CPB. Sadly, the heart-lung machine destroys blood cells during CPB, resulting in a wide range of negative effects in the body (Diodato & Chedrawy, 2014). There has been a long history of surgical teams monitoring the morbidity and fatality rates of CPB procedures. For example, in the Society of Thoracic Surgery national database, most analyses of outcomes in cardiac surgery with CPB focused on post-operative morbidity and death (Ahmed et al., 2014). For CABG and valvular open-heart operations, the perioperative mortality rate was 3.4%; 15.0% of these deaths occurred within the first 24 hours after surgery. Approximately 62.1 percent of these deaths occurred during the first 24 hours due to cardiac problems. Infections accounted for 7.7 percent of the perioperative mortality, whereas respiratory difficulties accounted for 11.8 percent (Abuelkasem et al., 2019).

Procedures requiring cardiac stillness typically involve CPB, a technique widely used in the medical community. In addition, cardiac surgery cannot be performed without the use of CPB. Postoperative hemorrhage is one of the most common surgical complications, and when blood comes into contact with the CPB machine's non-endothelial surface, cellular and humoral pathways, such as the coagulation and fibrinolytic systems, are activated. This increases the procedure's risk of complications. Cells, such as leukocytes and platelets, are stimulated as a result. The occurrence and significance of tissue and organ damage, hyperfibrinolysis, and bleeding are on the rise. Homologous blood transfusions are frequently used to replace blood loss in surgical patients although they increase the risk of infections and viral transmissions, fluid

overload, and the length of hospital stay (Sarkar & Prabhu, 2017).

After cardiac surgery involving CPB, diffuse micro-vascular bleeding (MVB) is a common complication. Platelet dysfunction and fibrinolysis are both present in diffuse MVB, making it a multifactorial condition (Despotis et al., 2007). Many techniques have been developed in order to reduce the amount of blood transfusion required following cardiac surgery (Yousuf et al., 2022). Intra - operative cell-salvage device and improved surgical technique thresholds are among these techniques (Yousuf et al., 2022). Blood transfusions have been linked to poor clinical outcomes in previous studies (Dhir & Tempe, 2018; LaPar et al., 2018). Anti-fibrinolytic therapy is the primary method used to reduce the frequency of transfusions and the use of blood components (Henry et al., 2011). There are anti-fibrinolytic agents which act as hemostatic agents by preserving blood and preventing post or intraoperative bleeding through a variety of mechanisms (Bisbe & Moltó, 2013).

Allogeneic blood transfusions have become more common in recent years, with significant data collected on the percentage of patients who received allogeneic blood products and the number of allogeneic units transferred. Reducing plasma generation and preserving platelet function are two possible mechanisms for reducing bleeding with these drugs (Yao et al., 2020). The lysine binding site on plasmin and plasminogen is inhibited by TXA, a synthetic antifibrinolytic (Niego et al., 2008). When TXA is given prior to CPB, blood loss following CABG is reduced. When administered after CPB in a randomized, control group, or without comparing post-CPB blood loss, when given before bypass, the studies that evaluated the effect of TXA administration after CPB were insufficient. In systematic review, TXA administered after CPB reduced Mediastinal Chest Tube Drainage (MCTD). Before CPB, rather than after CPB, TXA reduced mediastinal blood loss in patients without any control group (Ker, 2018).

Allogeneic blood product transfusions may also be reduced if TXA is delivered prior to CPB. Study of Ker (2018) found that the number of allogeneic blood products transported decreased significantly (n= 419). However, in other studies, the percentage of patients receiving allogeneic blood products decreased without affecting the overall number or did not change at all. When administering TXA to prevent post-cardiopulmonary blood loss and the need for allogeneic transfusions was the goal of this

randomized, blind, placebo-controlled research. Clinical efficacy and safety of TXA in reducing blood loss, blood transfusions, and the coagulation profile during CPB and CABG were evaluated in this study.

### 1.1.1 Coronary Artery Bypass Graft (CABG)

In the United States, more than 200,000CABG surgeries are performed each year (Nawata et al., 2020). The death rate for CABG surgery is reported to be approximately 2% (LaPar et al., 2018). Hemorrhagic shock is a risk associated with CABG because of the open-chest surgery and tissue manipulation that occurs during the procedure. An allogenic blood transfusion is frequently used during cardiac surgery to control bleeding and post-operative anemia. The United States uses about 20% of its annual blood supply for cardiac surgery (LaPar et al., 2018).

Allogenic blood transfusions are frequently used in CABG, but they have been linked to increased postoperative morbidity and mortality. There is a wide range of percentages of patients who are transfused in isolated CABGs, the most common procedure performed by cardiac surgeons. They are between 10% and 90%. To avoid the need for a blood transfusion, doctors can identify patients who are most likely to need one, and treat their conditions before surgery. They have developed intra-operative measures in order to reduce transfusion requirements during the cardiac surgical procedure such as shorter CPB time, smaller incision sites and minimally invasive locations. Despite this, blood transfusion is a common post- and during-surgery treatment (Williams et al., 2013).

Red blood cell transfusions are used to restore or maintain perfusion and oxygenation of tissue, and to maintain a circulating volume of red blood cells and blood. Red blood cell transfusions are linked to tissue ischemia (Murphy et al., 2007). However, transfusion-associated sepsis, stroke and myocardial infarction risk factors include elevated levels of pro-inflammatory cytokines and increased blood cell agreeability (Karamnov et al., 2018).

Blood transfusion in cardiac surgery patients has been linked to post-operative complications such as renal dysfunction, postoperative pneumonia, sternal wound infection, multiple organ failure, and postoperative impairment of pulmonary function.

Complications like these could result in a longer hospital stay (Karamnov et al., 2018). Crawford et al. (2018) observed that one unit of postoperative blood transfusion was most significantly related with the risk of postoperative death and an increase in hospitalization, compared to patients who received the same treatment but did not receive transfusion. (Crawford et al., 2018).

Increased intubation times from transfusions have been linked to adverse surgical outcomes, such as sepsis and pneumonia, as well as post-operative renal failure (Craver et al., 2018). Patients who refused blood transfusion for religious reasons (n= 322) experienced fewer acute problems, shorter hospital stays, and higher overall survival at one year when compared to a larger sample of patients undergoing identical cardiac operations (n=87,453) than those who did receive transfusion. Compounded patients, such as those with cirrhosis, heart failure, sepsis, pulmonary illness and cancer had significantly worse post-operative outcomes after blood transfusions (Biro, 2013), Increased postoperative mortality was associated with an OR of 1.77, CI 1.67-1.87, increase of risk of renal failure (OR 1.77, CI 1.67-1.87) (OR 2.06, CI 1.87-2%)(Perrault et al., 2018).

Blood transfusions should be carefully weighed against the potential risks and benefits of CABG surgery due to the high prevalence of allogenic blood transfusions. These include increased infection risk and a longer hospital stay and correspondingly higher costs (LaPar et al., 2018). Prior to surgery, patients who are more likely to require blood transfusions should be identified so that post-operative care can be tailored to reduce the number of transfusions they require (LaPar et al., 2018).

According to LaPar et al., (2018) and Williams et al., (2013), age, gender, and presence of comorbidities were all predictive factors for transfusion use. Women were found to have lower hematocrit and lower body surface area, thus leading to higher transfusion needs. Despite previous research in this area, there are still questions about the best predictors of the need for blood transfusion.

### 1.1.2 Cardio Pulmonary Bypass (CPB)

Since the development of CPB, cardiac surgery has progressed. A sort of extracorporeal circulation, CBP serves to maintain circulation and respiration while also controlling temperature to ease heart and major vascular surgeries.

#### 1.1.2.1 CPB Circuit

An arterial line filter and heat exchangers are part of the CPB circuit, as are pumps, needles, tubes, and containers. Pressure, temperature, and oxygen saturation are all monitored by modern CPB machines. Safety features, such as oxygen sensors and low-level detector warnings, are also part of the hemoglobin testing process. During CPB, a container is used to collect venous blood while gravity is used to drain it. An oxygen medium heat exchanger then transfers blood from a container to the circulatory system. To provide forward flow, the roller pump uses two rollers mounted on a rotating arm. An increasing number of people are suffering from hemolysis and tubular waste because of this procedure. The use of roller pumps for longer procedures is, therefore, discouraged. Centrifugal pump impellers / stacking cones are housed within the pump's casing. Negative pressure is established at one inlet while positive pressure is induced at the other, resulting in blood flow being accelerated. The produced cardiac output will be decreased unless the flow through the pump increases if the patient's systemic vascular resistance (SVR) increases. The use of centrifugal pumps can increase the preservation of platelets, kidney function, and neurological outcomes in long-term patients (Sarkar & Prabhu, 2017).

#### 1.1.2.2 Cannula

Needles are used to link the patient to the CPB machine and to the electrical circuit. The polyvinyl chloride catheter (PVC) is strengthened with wire to prevent kinking obstructions. Most open-heart surgeries employ single-stage cannula, but most closed-heart procedures use two cannulas injected into the superior and inferior vena cava and linked by a Y-piece double-stage needle. The right atrium is inserted with a single cannula. Gravity is responsible for drainage. Smaller needles and hoses can be used in the circuit because of the vacuum applied to the reservoir. In minimally invasive or repeat procedures, a lengthy cannula is set up to the right atrium through transesophageal echocardiography (TOE) in order to ensure its proper insertion. In order

for blood to flow via the bronchial and thebesian veins, the left side of the heart must be drained through ventilation. The ascending aorta is the most common location for an arterial cannula to be placed (Sarkar & Prabhu, 2017).

#### 1.1.2.3 Oxygenator

It's hard to overstate the historical significance of the bubble oxygen generator in the era of membrane oxygenators. As blood travels outside the fiber, gases pass through the fiber, creating a separation between the blood and gas phases, which is necessary for membrane oxygenation. Air embolisms and gas phases are less likely to occur with these devices. In terms of blood gas regulation, they are less susceptible to air embolism. Emboli filtering is now included into the architecture of newer models, eliminating the need for separate artery filters. As a result of temperature fluctuations in saturated blood, gaseous emboli can be reduced by placing a heat exchanger near the oxygenator (Sarkar & Prabhu, 2017).

#### 1.1.2.4 Tubing

Tubing is usually made of PVC due to its durability and acceptable hemolysis rate. Plasticizers such as di ( 2- ethyl hexyl ) phthalate that are added to provide flexibility are potentially toxic and shown to leach from the tubing(Sarkar & Prabhu, 2017).

#### 1.1.2.5 Reservoir

Open reservoirs collect blood that has been drained from the heart and are more commonly utilized because they allow passive removal of venous air and the application of suction to facilitate drainage. Separate cardiotomy and foaming systems are used to process blood drawn from the heart. To prevent air from entering the arterial circuit, a safe blood level must be maintained in the container when it is utilized.

Closed containers have a reduced blood contact area with artificial surfaces, but they can hold less volume. As a result, there is less inflammation and less post-operative transfusion. In order to process the blood that is suctioned, they need a separate circuit(Sarkar & Prabhu, 2017).

### 1.1.2.6 Cardioplegia System

Aortic cross-clamping is necessary for heart healing, resulting in ischemia conditions. Myocardial infarction's acid intake can be reduced by a procedure known as cardioplegia, in which a solution is perfused into the heart to produce electromechanical obstruction. Aortic cannula is placed distal to clamp, whereas cardioplegia cannula is placed next to it. It is possible to administer cardioplegia to the aortic root or the coronary artery, using a separate pump. With the help of the TOE, the retrograde cannula can be positioned in the coronary sinus. The right ventricle is not adequately protected by retrograde cardioplegia alone. In cases of severe aortic regurgitation, ostial cardioplegia is administered. Continuous or intermittent administration of a crystalloid (cold) or blood-based (hot or cold) cardioplegia is possible. It is common practice to utilize potassium-based solutions. Various substances such as bicarbonate, mannitol, magnesium, calcium, adenosine, procaine, glucose, and glutamate can be added to oxygenated blood in order to achieve blood cardioplegia in a ratio ranging from 1:1 to 8:1. Additionally, the gas line and the mixer, which feed fresh gas to the oxygenator in a predetermined composition, are other circuit components. Total flow determines PaCO2 on the bypass, whereas set Fio2 determines PaO2. In order to remove particles larger than 20 – 40 m in diameter, the arterial line filter is situated distal to the pump. It has been attempted to increase biocompatibility by coating the circuit with various materials. Inflammation and blood clots should be kept to a minimum. Poly-2 methoxyethyl acrylate, phosphorylcholine and trillium are some of the newer coatings that have been shown to reduce inflammation and platelet activation, resulting in minor bleeding and transfusions. The advantages of one coating over another in terms of health benefits are still up for debate (Sarkar & Prabhu, 2017).

### 1.1.2.7 Initiation of CPB

Pre-arterial cannulation, heparin 300 U/kg IV is given to patients with an activated coagulation time (ACT) of more than 480 S (measured after 3 minutes). Aortic dissection is less likely to occur when arterial cannulation pressure is between 90 and 100 millimeters Hg. When venous cannulation causes hypotension, the aortic cannulation is the initial step in reviving the patient's blood pressure. Line pressure is measured when the aortic cannula is linked to tubing to rule out dissection. The venous

clamp is slowly relaxed after venous cannulation to ensure complete CPB, and ventilation is subsequently terminated(Hasegawa et al., 2022).

### 1.1.3 Anticoagulation

It's extremely dangerous to have CPB coagulate. The ACT is a preventative test used to determine if heparinization is enough. Hemodilution and hypothermia can influence the normal range of ACT, which is between 80 and 120. During bypass, the ACT should be checked every 30-40 minutes. The hemochron® and hemoTec® devices are automated ACT measurement instruments. An alternative way of anticoagulation adjustment is to use dose-response curves and the Hepcon device to measure the plasma concentration of the anticoagulant. Some patients may experience an altered heparin response with a failure to attain goal ACT, with subsequent doses of heparin eventually achieving ACT target. Despite high dosages of heparin (800–1000 U / kg), heparin resistance fails to meet the ACT goal. A number of factors can contribute to the development of this condition, such as advanced age, recent exposure to the blood thinner heparin or nitroglycerin infusion, thrombocytosis, or an underlying genetic or acquired antithrombin III deficiency (Li et al., 2021).

### 1.1.4 Tranexamic Acid

By inhibiting the disintegration of hemostatic fibrin, TX is a synthetic amino acid derivative. In cardiology, neurosurgery, and OB/GYN, TXA is frequently utilized as a hemostatic agent and (fibrin sealant) in a variety of procedures (Colferai et al., 2019). Menorrhagia, gastrointestinal bleeding, post-tonsillectomy, genitourinary hemorrhage, and hemophilia, for example. The serum half-life is about 1-2 hours, although the inhibitory action lasts for about 7-8 hours. Plasminogen binding sites on plasminogen are reversibly blocked by antifibrinolytic agents, preventing plasmin from interfering with fibrin polymer lysine residues and resulting in fibrin breakdown (Calapai et al., 2015).

The high affinity for the lysine binding sites on the surface of the native human plasminogen has between 4 and 5 binding sites for lysine (KD =750 M Mmol/L). The plasminogen lysine binding site has a strong affinity for fibrin. Plasminogen is displaced from fibrin's surface when TXA binds to the high affinity-binding location. Although plasminogen conformational changes may lead to the generation of plasmin, fibrin

matrix binding and dissolution are prevented. When compared to the earlier antifibrinolytic agent, epsilon amino-caproic acid, TXA is seven to ten times more effective. Intracellular and extracellular distribution of TXA is widespread and essentially unaltered in the urine. Oral or intravenous administration are also options for this medication (George, 2016). TXA is typically deemed safe and well-tolerated at the recommended dosage. The most common adverse effects include nausea, diarrhea, and abdominal pain (Dunn & Goa, 1999).

### 1.1.5 Haemostasias

The basic homeostatic mechanism necessary to sustain life is the maintenance of circulating blood volume (Landsberg & Krieger, 2014). Vascular damage causes bleeding, which results in decreased hemoglobin levels and decreased blood volume (hypovolemia), all of which can lead to organ failure and death if unchecked (Varenhorst et al., 2012). A set of compensatory mechanisms are activated by the body in response to blood loss in order to allow low levels of blood loss to be tolerated without resulting in significant health consequences. Small amounts of blood loss can be dangerous for people whose bodies can't compensate for it, like the elderly, anemic people, and people with pre-existing cardio-respiratory or hepatic disorders (Varenhorst et al., 2012).

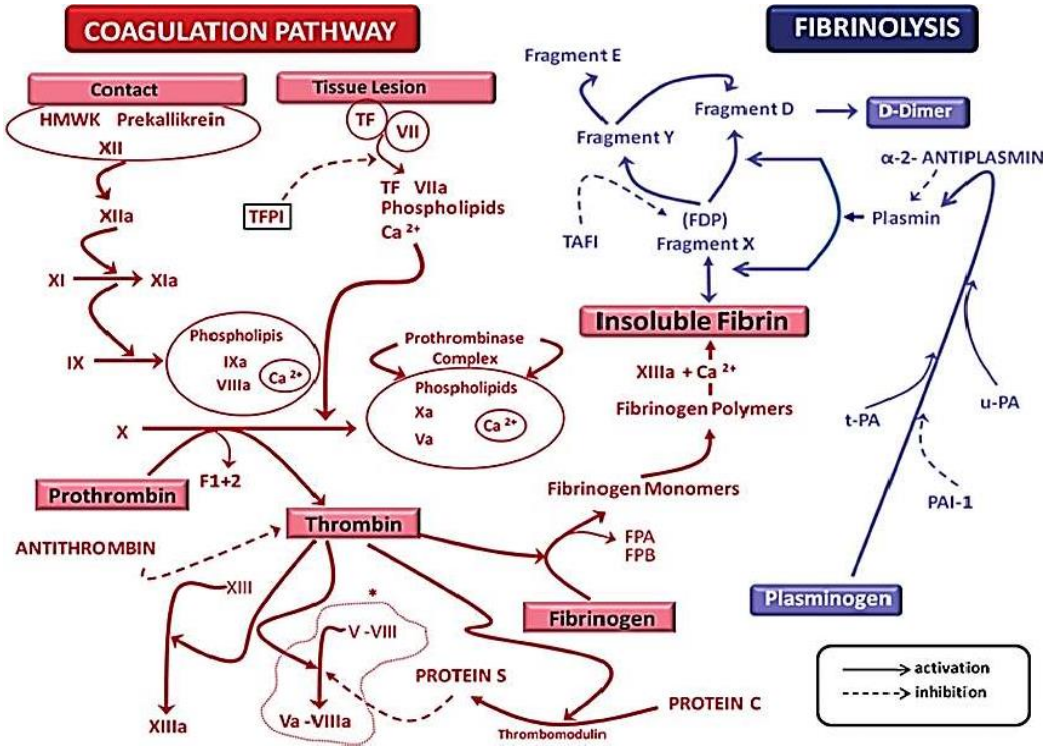
Acute hemorrhage is most commonly caused by trauma, surgery, or childbirth, and the resulting consequences cause significant global death and morbidity. A common hemostatic reaction is triggered by any type of vascular injury, regardless of the underlying cause. Hematological therapy recommendations for large bleeding are frequent in all therapeutic settings. This has resulted in the utilization of surgical evidence by those looking to enhance the management of bleeding in trauma and obstetric patients (Blaudszun et al., 2018).

### 1.1.6 Coagulation and Fibrinolysis

Regardless of the origin of a vascular injury, the body responds with a series of physiological responses aimed at protecting the circulatory system, the coagulation cascade and the fibrinolytic response are both involved in the production and destruction of clots. Figure 1.1 summarizes the coagulation and fibrinolysis cascades(Nesheim, 2003).

**Figure 1.1**

*The coagulation and fibrinolysis pathways*




Localized vasoconstriction and blood migration into the surrounding tissues are the first steps in the homeostatic response to vascular injury. Platelets begin to stick together and deposit at the site of the lesion. Fibrin is formed when thrombin is activated and interacts with the platelet plug to form a seal that is resistant to breakdown at the site of injury (Nesheim, 2003).

The fibrin mesh is broken down as a result of the coagulation response, which is accompanied by a fibrinolytic response. The endothelial cells secrete tissue plasminogen activator (t-PA), which transforms plasminogen trapped in the clot into plasmin. Plasmin adheres to fibrin and digests it, causing the clot to dissolve. Both uncontrolled bleeding and uncontrolled clotting can lead to mortality if these regulatory reactions are out of balance (Huang et al., 2003).

Major blood loss, on the other hand, puts this delicate balance at risk due to the accompanying physiological stressors, including an overactive t-PA that could result in hyperfibrinolysis (a state of excessive fibrinolysis and uncontrolled bleeding). Traumatic, surgical, and obstetric hemorrhage are all linked to hyperfibrinolysis. This can lead to excessive or repeated bleeding, and in turn this can lead to mortality,

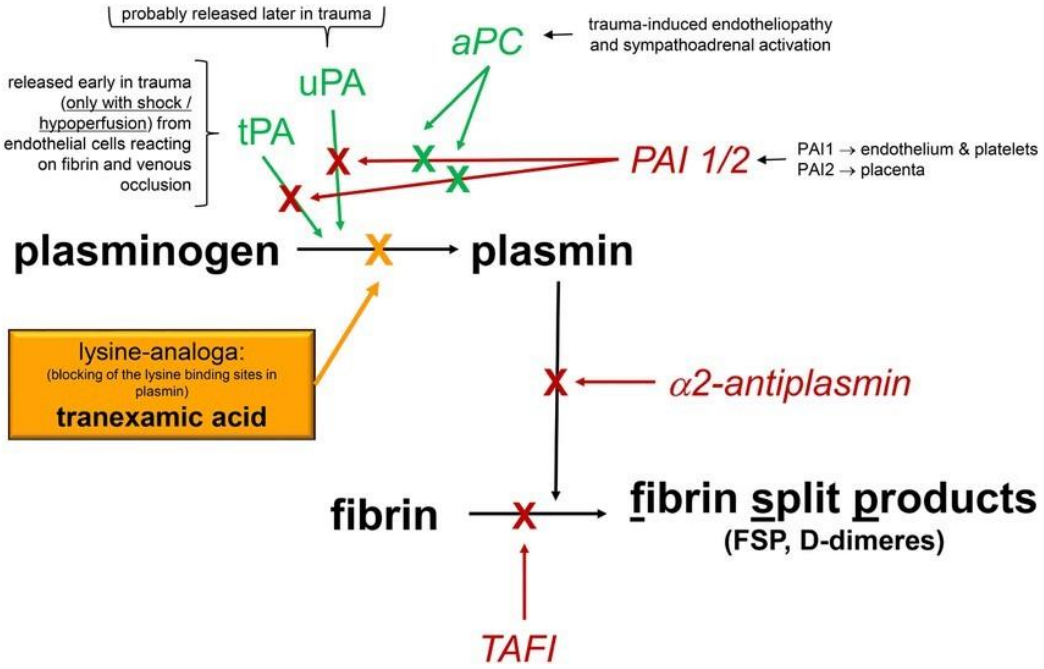
organ dysfunction, multiple organ failure, and sepsis. Blood transfusion-induced immunologic stress exacerbates this second complication (Moore & Moore, 2020).

### 1.1.7 Tranexamic Acid and Its Effect on Bleeding

Fibrinolysis is prevented by TXA, a synthetic lysine amino acid derivative that prevents plasmin from interacting with fibrin (Figure 1.2) (Dunn & Goa, 1999).

**Figure 1.2**

*Mechanism of action of TXA*




There has been an interest in the use of TXA as a fibrinolysis inhibitor since it was initially described in 1962 by husband-and-wife pair Shosuke and Utako Okamoto. Despite the fact that studies on TXA have been published in the medical literature for decades, the number of publications has increased rapidly in the last decade or two. The LSHTM CTU keeps a list of publications on TXA in the form of a bibliographic database(Dunn & Goa, 1999).

For a full comprehension of TXA's anti-fibrinolytic effects, one must first gain a working knowledge of the fibrinolytic system. Platelet activation and fibrin synthesis begin the clotting process after tissue damage in order to prevent bleeding (Cesarman-Maus & Hajjar, 2005). A cascade of serine proteases degrades fibrin in order to prevent clotting. In order to complete the process of fibrinolysis, tissue-type plasminogen

activator converts the zymogen plasminogen into its active form, plasmin (Lijnen 2001). For example, the binding of both fibrinogen and plasminogen activator to their respective lysine binding sites considerably enhances the synthesis of the enzyme, which in turn increases plasmin generation (Cesarman-Maus & Hajjar, 2005). By increasing the number of places on fibrin where the amino acid lysine may attach to the protein, the enzyme plasmin can better attach to its substrate which leads to increased synthesis of the enzyme (Draxler et al., 2019). An analogue of the amino acid lysine, TXA binds to plasminogen's lysine-binding sites and inhibits the conversion of plasminogen to plasmin by competing with the binding of plasminogen to TXA. Using a non-competitive method, TXA can also disrupt the function of plasmin at high concentrations. TXA inhibits fibrin clot breakdown by plasmin by interfering with the conversion of plasminogen to plasmin (Draxler et al., 2019).

Lysine analogue Eaminoacaproic Acid (EACA) has a similar mode of action as TXA, which is also a lysine analogue. EACA, on the other hand, has a potency that is anywhere from 6 to 10 times lower than TXA. Both the strong and the weak plasminogen receptor sites are more strongly bound by TXA than by EACA, which correlates to the difference in their potency. TXA and EACA, on the other hand, are trypsin inhibitors produced from bovine lung tissue, and they have been shown to be ineffective against plasmin. Anti-inflammatory and vasodilatory effects of aprotinin may be due to its action on protease-activated receptor serine protease-sensitive receptors (Slattery et al., 2019).

Antifibrinolytic agent TXA has been shown to be efficacious by an abundance of research and clinical trials alike. According to recent meta-analyses, more than 10,000 surgical patients in 129 randomized controlled trials were evaluated to compare the effects of TXA and placebo. The study found that patients in the TXA group had a 38% reduced risk of blood transfusion and a 35% lower risk of death (Ker et al., 2012). A Cochrane review indicated that TXA reduced blood transfusions by 39 percent with an absolute risk reduction of 19 percent. TXA reduced post-operative blood loss by approximately 248 milliliters per patient and peri-operative blood loss by approximately 444 milliliters per patient, according to the study. TXA and EACA both reduced blood loss and the need for transfusions in a head-to-head study. A comparison of the antifibrinolytics TXA and aprotinin showed no statistical difference in their ability

to reduce postoperative blood loss and allogeneic blood transfusions, as do head-to-head tests (Lee et al., 2013).

Open-heart, orthopedic, menorrhagia, gastrointestinal, liver transplantation, transurethral resection of the prostate (TURP), and craniofacial surgery have all employed TXA to minimize operative hemorrhage (Dunn & Goa, 1999). Continuous intravenous antifibrinolytic therapy throughout the peri-operative period is recommended because of the reported half-life of TXA, which is around 1-1.5 hours. TXA was shown to be distributed in the body in an open, two-compartment model in healthy volunteers, with glomerular filtration serving as the predominant elimination pathway following a single intravenous dosage (Vance, 2018).

More research has shown that approximately 95% of each dose is excreted in the urine in its natural state. As a result, individuals who have been diagnosed with renal insufficiency should have their dosages reevaluated. A single intravenous dose of 10mg/kg TXA or 1g of TXA is suggested for systemic fibrinolysis (Dunn & Goa, 1999). There is no consensus on when to provide the medication. The majority of the literature, on the other hand, recommends that TXA be administered preoperatively, with the clinician having ultimate authority over whether or not to administer it continuously (Choi et al., 2009). Numerous investigations have raised the possibility that anti- fibrinolytic therapy could increase the risk of thromboembolic events. TXA has been shown to stabilize blood clots by reducing the rate at which fibrinolysis occurs, and it has not been shown to have prothrombotic effects. TXA doesn't appear to contribute to the risk of peri-operative thrombosis. Therefore, this is a good finding (Slaughter & Greenberg, 1997). Between 2009 and 2013, a secondary examination of 35,478 pediatric children who had received TXA in the course of a single hospital visit was done. Children's Hospital Association-affiliated 36-hospital Pediatric Health Information System (PHIS) was used to compile data for this study. TXA was used for craniofacial surgery on 1,275 of the participants in this study. Results also showed that tranexamic usage in the pediatric population could be used for a wide range of conditions (Nishijima et al., 2016). The Facial Defects Awareness Center of the Fernando Figueira Internal Medicine Institute (CADEFI) in Brazil conducted a randomized, double-blind trial on 66 patients who underwent palatoplasties from January to December of 2014. Following a 10mg/kg TXA injection, patients in the

trial group had a 1mg/kg continuous infusion for the length of their procedure. Patients in the control group were given a sugar pill as a treatment alternative. Patients estimated total blood volume was used to calculate the intraoperative blood loss in this clinical research. In comparison to the control group, the study group showed an 11.9% reduction in intraoperative hemorrhage (Arantes et al., 2017).

According to Choi, Irwin and Samman (2009), 73 orthognathic surgeries were scheduled for such patients. Preoperative TXA and intraoperative blood loss were the primary objectives of the clinical investigation. Mild hypotensive techniques were used in the anesthesia strategy for all patients. Pre-surgical TXA was administered to the intervention group, while 0.9 percent normal saline was given to control patients. The treatment group lost an average of 878.6 ml of blood, while the control group lost an average of 1257.2 ml of blood - a 422 ml difference. TXA's ability to reduce intraoperative blood loss was demonstrated by these results, which were deemed statistically significant (Choi et al., 2009). Three-blinded studies, using isolated Le Fort I osteotomies, were conducted in 2013 in Chennai, India. In this trial, hypertensive anesthesia was also used. A total of 49 patients ranging in age from 18 to 34 years were enrolled in the study. Group 1 (the control) received a saline placebo 30 minutes before induction, while Group 2 (the intervention) received 10mg/kg TXA at that time. Compared to Group 1, operating time and total blood loss in Group 2 were dramatically reduced. When compared to the control group, the intervention group's total blood loss was 45 percent lower. In addition, preoperative and postoperative hemoglobin and packed cell volume were significantly different. TXA preoperative intravenous injection may reduce the requirement for postoperative blood transfusions, according to these data (Christabel et al., 2014).

Research from that year examined the usefulness of local application of tranexamic acid to lessen blood loss during CABG with randomized, double-blind, prospective, placebo-controlled trials. For 38 patients, main isolated CABG was on the schedule. Patients in the TXA group (nineteen of them) were given 100 milliliters of normal saline to dilute one gram of TXA. The 19 patients in the placebo group received merely 100ml of normal saline. Pericardial and mediastinal cavities were filled with the solution. As a consequence of the study, the two groups were found to be comparable in terms of demographics and surgery. There was a significant difference between the TXA

and placebo groups in the amount of blood lost in the first 24 hours after surgery (p=0.04). The post-op PRBCs transfusion did not differ significantly across groups. TXA in median zero unit required significantly less platelet transfusion than placebo group in a prospective, randomized, placebo-controlled, double-blind research of adult patients undergoing primary coronary bypass surgery, the effects of TXA delivered before and after CPB were assessed. It reduced postoperative blood loss significantly without increasing the patient's risk (Bansal & Arora, 2017).

Retrospective trials were conducted in 2015 in another study. The authors studied the hemostatic effects of TXA in high-risk patients following transapical aortic valve implantation in order to reduce the risk of bleeding and the need for blood transfusions. For the overall study population of 146 patients, early postoperative (24-hour) blood loss was considerably lower in the TXA group than non-TXA group (327ml) Vs (481V318.8ml). It was found that 53.7 percent of those in the TXA group received allogeneic blood products during their stay, compared to 72.8 percent of those in the non-TXA group (2.1 V1.9VS. 2.9 V3.5 units). According to the results of this trial, low- dose intraoperative TXA administration may be useful in minimizing post-operative bleeding and the requirement for allogeneic blood products during transapical valve replacement surgery (Madershahian et al., 2015).

### 1.1.8 Previous Studies on Tranexamic Acid and Cardiac Surgery

In a prospective, randomized, double-blinded clinical trial, Banihashem et al. (2019) conducted a study about transfusion and post-operative blood loss post CABG in patients who were treated with clopidogrel less than five days prior to surgery. If patients had taken their last dosage of clopidogrel and aspirin less than five days before surgery, they were randomly allocated to receive TXA (10 mg/kg prior to actually surgical intervention and 10 mg/kg after protamine neutralization) or a volume of saline solution. Red blood cell transfusion and blood loss for 48 hours after surgery have been logged. Patients having clopidogrel exposure within 48 hours of surgery were found to have an average blood loss of 776.92mL for the TXA group and 1075.00mL for the control group (P=0.03). Patients who had taken clopidogrel within the five days prior to surgery had the same average blood loss and transfusion rate in both groups. TXA reduced blood loss in patients with clopidogrel exposure within 48 hours prior to surgery, according to the findings of this study. As a result, it is preferable that all

patients get TXA prior to surgery (Banihashem et al., 2019).

Topical TXA was tested in a randomized control trial by Rostami, et al. (2020) to see if it may reduce bleeding following coronary artery CABG surgery. TXA and control groups were randomized to 62 patients. TXA (2 g) was injected into the mediastinum by the surgeon following surgery and the removal of the cardiac pump. Both groups were given 100 cc of standard saline in the control group. SPSS 19 software was used to conduct the t-test and Fisher's test on the data. According to the findings, postoperative bleeding, packed cell volume, platelet transfusion, operation duration, and FFP received were all significantly lower in the TXA group than the placebo group ($P = 0.0001$; $P = 0.01$; $P = 0.0001$; $P = 0.0001$; $P = 0.0001$). Age, gender, number of visits to the operating room, and time spent in recovery were all similar. Postoperative bleeding and packed cell volume, platelet transfusion and FFP were all considerably reduced in the study's GABC participants who used topical TXA after surgery. It also had no effect on the patient's return to the operation room or mortality (Rostami et al., 2020).

TXA was administered to Chinese pediatric patients undergoing heart surgery in a meta- analysis conducted by Zou et al. (2022). After May 4, 2021, the databases PUBMED, Cochrane, EMBASE, China National Knowledge Infrastructure (CNKI), Wanfang Data, and VIP Data can be searched. Postoperative hemorrhage, allogeneic transfusion, and reoperation for bleeding were the primary outcomes of interest. Secondary outcomes of focus included recovery following surgery. Treatment effects were calculated using the weighted mean difference (WMD)/odds ratio and a 95% confidence range for continuous/dichotomous variables. Some 15 randomized controlled trials were found in the database, with eight studies in the non-cyanotic congenital group, five in CYP group, and two in CYP/Non-CYP group. According to the results of this meta- analysis, TXA administration can reduce postoperative blood loss for 24 hours in patients who aren't blue, blue, and blue/non-cyanotic, and red blood cell and fresh frozen plasma transfusions for blue/non-cyanotic and blue/non-cyanotic patients who aren't blue. TXA is highly efficient in lowering blood loss in Chinese pediatric heart surgery; however, it is ineffective when it comes to reducing the need for blood transfusion (Zou et al., 2022). TXA's exposure–response association in cardiac surgery was studied by Zufferey, et al., in a meta-analysis in 2021. Patients who underwent CPB were sought for randomized, controlled studies of intravenous

TXA. Seizure assessment now includes additional observational studies. It was estimated in each trial, using a population-based pharmacokinetic model. Analyses were conducted using nonlinear mixed-effects models to examine the exposure–response connection. Data from 64 clinical trials, 18 observational studies, and 49,817 people were compiled. TXA was delivered in 73 different regimens, with the total dose ranging from 5.5mg/kg to 20 g. Postoperative blood loss reduction with TXA was reduced by 40% (95 percent credible interval, 34% to 47%) and the EC50 was 5.6mg/l (95 percent credible interval, 0.07 to 11mg/l). Low- dose regimens had exposure values close to the 80 percent effective concentration, but high-dose regimens had exposure values close to the 90 percent effective concentration. Each of the two regimens had an estimated cumulative blood loss of 58%, and there was an overall two percent difference in transfusion rates. To put it another way, low-dose and high-dose tranexamic acid regimens both doubled the risk of seizures. It was only in this context that the absolute risk increase was clinically important. Low-dose tranexamic acid appeared to be a suitable regimen for minimizing bleeding during CPB surgery, according to a recent study. However, one must proceed with extreme caution when interpreting the findings of this meta-analysis, as they are observational in nature and rely on the accuracy of the estimates of TXA exposure and the study quality to which they were administered (Zufferey et al., 2021).

TXA may increase the risk of death and thrombotic complications in patients following coronary artery surgery, according to Myles, et al. (2017). Aspirin or placebo and TXA or placebo were randomly assigned to individuals who were scheduled to have coronary artery surgery and were at risk for perioperative problems. Death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure or intestinal infarction) after 30 days of surgery were considered the primary outcome for this study. More than 460 of the 4,662 patients who signed the consent form and had surgery were randomized to the TXA group and 2,320 were assigned to the placebo group. Only 386 patients in the TXA group and 420 patients in the placebo group (relative risk, 0.92; 95% confidence range, 0.81 to 1.05; P=0.22) experienced the primary endpoint event (relative risk, 0.92; 95% confidence interval, 0.81 to 1.05). TXA recipients received 4331 units of blood while placebo recipients received 7,994 units (P0.001) during their hospital stay. In the TXA group, major bleeding or cardiac tamponade leading to reoperation happened in 1.4%

of the patients, compared to 2.8% in the placebo group (P=0.001). In the placebo group, seizures occurred in 0.7% of the patients (P=0.002). There was no increased risk of death or thrombotic problems within 30 days of coronary-artery surgery in individuals given TXA compared to placebo, according to one study. Postoperative seizures were more likely to occur in patients who had taken TXA before surgery (Myles et al., 2017).

Intravenous TXA administration in CABG was the subject of a meta-analysis by Zhang et al. (2019). CENTRAL, PUBMED, and EMBASE were used to find randomized controlled trials that addressed this issue. PRISMA-compliant summaries and reports were provided for the findings in this study. Twenty-eight studies matched our inclusion criteria. TXA decreased the need for any allogeneic transfusions (RR: 0.64; 95 percent CI: 0.52–0.78), postoperative reoperational bleeding (RR: 0.46; 95 percent CI: 0.31–0.68), and postoperative chest tube drainage by 206 ml (95 percent CI: 248.23 to 164.15 ml) in the first 24 hours after surgery. After surgery, there was no difference in the risk of postoperative cerebrovascular accident (RR, 0.93; 95% CI, 0.62–1.39), death (RR 0,82; 95% of CI, 0.53–1.28) or heart attack (RR, 0.90; 95% of CI, 0.78–1.05) or acute renal failure (RR, 1.01; 95% of CI, 0.77–1.32). Despite this, postoperative seizures (RR, 6.67; 95% CI, 1.77–25.20) may be more likely to occur. In addition, subgroup analyses in CABG on and off-pump, sensitivity analysis in trials with randomization of more than 99 people, and sensitivity analyses that removed the study with the greatest number of participants strengthened the conclusions above. TXA reduced reoperations for bleeding, blood loss, and the requirement for allogeneic blood products in patients following CABG without worsening prothrombotic complications, according to a recent study. However, the risk of postoperative seizures may be increased (Zhang et al., 2019).

Doukan et al. (2020) examined the effect of TXA on patients receiving low molecular weight heparin treatment during CABG operations. They found that TXA reduced bleeding. A six-month case-control study included 82 patients, 60 of whom underwent CABG with CPB. Patients were separated into two groups on the first postoperative day, according to whether or not TXA had been used during the operation. A dose of 10 mg/kg TXA was administered intravenously to the study group (n=30) while no TXA was given to the patients in the control group (n=30).

Before and 24 hours after a patient's surgery, coagulation variables, such as D-Dimer concentrations, fibrinogen, PT, aPtt, and International Normalized Ratios (INR), were measured. The total amount of packed red blood cells and fresh frozen plasma transfusions, as well as the estimated blood loss and drainage, were all documented. Statistical significance was defined as a P-value 0.05. According to the findings, a total of 39 males and 21 females participated in the trial. There was a 61.6-year-old median age for all patients. Fresh frozen plasma use, age, height, and weight were not statistically different between the two groups (P=0.268, P=0.586, P=0.787, P=0.641). Packets of red blood cells transfused postoperatively in the study group were significantly lower than in the control group (P=0.04). The study group's total mediastinal drainage was lower in the fourth, eighth, and twelfth hours, as well as overall (P=0.016, P=0.006, P=0.013, P=0.04). According to the findings of this study, TXA was found to be a safe medicine that lowered postoperative bleeding in DMAH-using patients undergoing CABG surgeries without causing any negative effects (Doğukan et al., 2020).

According to Verma, et al., (2020), the primary outcome was post-operative bleeding at 4 and 24 hours, and the rate of postoperative transfusion, re-operations, complication rates and serum fibrinogen levels were secondary outcomes. During the period from June 2017 to June 2018, a tertiary-level hospital was used for the study. A prospective, randomized, and double-blind study was carried out. During off-pump CABG procedures, 80 patients were randomly assigned to receive the anesthetics tranexamic acid or the anticoagulant epsilon-amino-caproic acid. After surgery, the patients were monitored and their primary and secondary outcomes were evaluated. At four hours, there was no significant difference in bleeding volume between the two groups: 180 ml (80–250 ml) vs 200 ml (100–310 ml). In the TXA group, the amount of bleeding at 24 hours was much lower than in the epsilon-amino-caproic acid group, with 350 ml (130– 520) vs. 430 ml (160–730) A significant difference between the groups was not found in the frequency of transfusion, re-operations, seizures, renal failure, fibrinogen levels, or D-dimer levels. TXA was found to minimize postoperative bleeding in off-pump CABG much more than epsilon amino caproic acid did after 24 hours (Verma et al., 2020).

Tumer, et al. (2020) assessed the impact of desmopressin and TXA on blood product use and postoperative bleeding in patients who had undergone emergency CABG surgery and had been pretreated with P2Y12 inhibitors by cardiologists. Sixty-two adult patients who underwent emergent CABG surgery and were pre-treated with P2Y12 inhibitors by cardiologists were retrospectively analyzed. Patients' peri-operative data comprised demographics, laboratory findings, blood loss from chest tubes, blood product use, re-thoracotomy requirements, morbidity, and mortality. Two groups of patients were identified: those who got TXA and DDAVP pre-operatively (n=26) and those who received only TXA (n=36). Results showed that the two groups of patients were similar at the beginning of the study. In terms of postoperative blood loss through chest tubes, re-thoracotomy, red blood cell and thrombocyte transfusions, a statistically significant difference was found between Groups I and II (p0.05). Fresh frozen plasma transfusion, inotrope support, and death did not differ statistically and significantly between the two groups. Adding desmopressin to the TXA lowers bleeding and blood product consumption in patients requiring emergency isolated CABG surgery (TÜMER et al., 2020).

Off-pump CABG surgery was evaluated using a single-center historical record review undertaken by Weingarten, et al. (2021). As the study primary endpoint, it measured how much blood was in a chest tube 12 hours after surgery, as well as how long the patient spent in the ICU and hospital after the procedure (days). Some 176 patients were given TXA while others received no treatment. TXA was administered at a dose of 2.1 (1.5) g, with a standard variation of 1.5 g. There were substantial differences in the amount of post-operative chest tube drainage between the TXA and non-TXA groups. Neither the number of transfusions administered nor the number of days spent in the ICU or hospital were significantly different (Weingarten et al., 2021).

Yanartas, et al. (2015) investigated the effects of TXA and a 6% hydroxyethyl starch (HES) solution (130/0.4) in CABG surgery postoperative hemorrhage in a prospective, randomized clinical research. A total of 132 patients were divided into two groups: those given 20 ml/kg of Ringer priming solution with or without intravenous TXA (Group RS-TXA, n=34, and those given Group RS-no TXA, n=32) or those given 10% HES and 10% RS priming solution with or without TXA. The amount of blood

products, hemoglobin, hematocrit, platelet, and coagulation parameters, as well as estimated blood loss and chest tube drainage, were all assessed before and 24 hours after operation. There was a significant decrease in estimated blood loss, postoperative 24-hour drainage losses and blood product transfusions in the TXA-treated Group HES group compared to the other groups (P = 0.023, 0.034, 0.004, 0.001), as well as an increase in hemoglobin and hematocrit values at 12- and 24-hours following surgery (P = 0.041, 0.034, 0.004, 0.001). Both groups had equal levels of platelets (P>0.05). There were, however, no differences between patients receiving Ringer prime solution with or without TXA postoperatively and those who received TXA in the HES 130/0.4 prime solution trial group in terms of estimated blood loss and chest tube drainage (Yanartas et al., 2015).

IV delivery of TXA in off-pump CABG situations was studied by Sun et al. (2020) in a meta-analysis. In order to find RCTs comparing IV TXA use with placebo in the reduction of postoperative 24-hour blood transfusion, as well as postoperative death and thrombotic events, a comprehensive literature search was conducted. A fixed-effects model was used to build the combined estimates, or a random-effects model was used if there was heterogeneity. Egger's test and funnel plots were used to look for evidence of publication bias in the data. Analysis of subgroups was done to identify plausible sources of variation. Search yielded 12 randomized controlled trials. Intravenous treatment of TXA reduced the risk of Packed Red Blood Cell (PRBC) transfusion considerably within the first 24 hours following surgery [risk ratio (RR) = 0.61, 95 percent confidence interval (CI) 0.503 to 0.756, P .001, I2 = 0.0 percent]. While the platelet (RR = 0.613, 95% CI: 0.11 to 3.348, P =.572, I2 = 0%) and total fresh frozen plasma (FFP) transfusions had no statistical significance. The two other types of transfusions did. As for serious adverse events (death or thrombotic problems), there was no statistically significant difference (RR = 0.917, 95 percent CI 0.532-2.581, p =.756, I2 = 0.0 percent) between the groups. Intravenous TXA was found to lower PT and INR-guided FFP transfusion risk in a subgroup analysis (RR = 0.462, 95 per cent confidence interval [CI] = 0.296-0.721; P=.001; I2 = 0%]). After analyzing the results, researchers found that TXA reduced allogeneic blood component transfusions (PRBCs and PT/INR guided FFP transfusions) in off-pump CABG operation without increasing mortality or thrombotic problems (Sun et al., 2020).

A clinical prospective and randomized trial by Altun et al. (2017) examined the hemostatic effects of TXA and Desmopressin acetate (Des) in patients undergoing CABG. A total of 54 patients were enrolled and divided into four distinct groups for further analysis. In terms of numerous bleeding and transfusion parameters, they were compared. According to the findings, in terms of before and post-operative data, there were no significant changes between the groups. It was found that TXA and control groups had higher levels of the Plasmin/-2 antiplasmin complex at the end of postoperative medication infusion. Both the Des and control groups had significantly longer mean durations for all postoperative measures, including the first three hours and total amounts of drainage, volumes of erythrocyte suspension/fresh frozen plasma supplied and costs of blood products. Des had no significant impact on bleeding control and even delayed the hemostatic efficacy of TXA. The hemostasis-related results improved when TXA infusion was used alone in these patient groups (Altun et al., 2017).

### 1.2 Statement of the Problem

In both developing and developed countries, coronary heart disease (CHD) is a primary cause of illness and mortality. Surgical techniques, a form of technology treatment, are frequently used in the management of cardiac disease. An extended recovery period and numerous technical and clinical hurdles are common after CABG surgery. Despite this, cardiothoracic surgeons still conduct it routinely (Gaziano et al., 2006).

Patients undergoing cardiac surgery on CPB are at an increased risk of bleeding both during and after operation. Large foreign surfaces and materials, as well as flow conditions not seen in the circulation, are exposed to bleeding during CPB (Shaw et al., 2013).

Heparinization and reversal, using protamine, as well as the use of homologous blood and pump prime fluids, all affect hemostasis in different ways. Platelet function, coagulation, and the fibrinolytic system are all affected by these variables (Suelzu et al., 2015).

Some of the most common hemostatic alterations, such as abnormal platelet function, activation of blood-clotting processes, and clotting- factor inhibition, have been documented. Hyperfibrinolysis, due to an increased release of tissue-type plasminogen activator, has also been described. Many blood-saving measures have been implemented in these patients due to the fact that excessive bleeding and the requirement for perioperative transfusions are associated with poorer results (Jin & Gopinath, 2016).

Acute normovolemic hemodilution and prophylactic intravenous administration of concentrated fibrinogen or tranexamic acid immediately before and after myocardial revascularization have been shown in previous studies to reduce the need for blood transfusions in high-risk populations by reducing the frequency of postoperative bleeding and fibrinolysis (Ker, 2018; Mohib et al., 2015).

CPB has also been shown to release inflammatory mediators, causing a variety of hemostasis-related alterations in the blood. Thrombocytopenia, disseminated intravascular coagulation, and liver failure can all contribute to the development of acute anemia, which must be treated urgently (Squiccimarro et al., 2021).

In the United States, nearly one in five blood product transfusions happens after heart surgery. During and after heart surgery, blood transfusions are kept to a minimum thanks to blood conservation procedures. Intraoperative cell-salvage devices, better surgery, a hemostatic drug, and conservative transfusion thresholds are all examples of these treatments. It is common practice to use anti-fibrinolytic drugs in conjunction with other medications in order to keep clots stable and prevent excessive blood loss. The use of allogeneic RBCs, following cardiac surgery, is becoming increasingly recognized as a dangerous issue. Transfusions that aren't absolutely necessary can lead to increased morbidity and more direct and indirect hospital expenses. Indirect costs are also substantial(Callum et al., 2019).

People in both developed and developing countries are having their cardiac operated on more frequently than ever before, but little is known about the impact of anti-fibrinolytic medications on postoperative bleeding or the dangers of renal, cardiac, or cerebral problems.

### 1.3 Significance of the Study

CPB-induced fibrinolysis (CPB) can produce excessive bleeding during and after CS, which is one of the most common consequences of CS. CS with CPB uses antifibrinolytic medications to reduce transfusion needs and minimize blood loss during and after surgery. Aprotinin and two lysine analogues, TXA and aminapyric acid have both been utilized as antifibrinolytic medicines. It was shown that one of these medications reduced blood loss by around 300 milliliters despite the fact that fewer patients needed to be transfused. Lysine derivative TXA has an antifibrinolytic action via reversible blocking. Plasminogen molecules have lysine binding sites. Several cases have been documented in the literature and in clinical practice: Prior to initiating CPB, TXA can be delivered either in the form of a bolus immediately upon an anesthesia induction or as a continuous infusion via the CPB bypass; the amount of TXA provided ranges from 10 to 100 mg/kg and is not necessarily adjusted for body weight. A 1968 in -vitro study claimed that the effective antifibrinolytics TXA plasma concentration should be steady and more than 10g/ml (64m) in the last four years of research. To prevent fibrinolysis, tissue analysis extracts reveal that concentrations, as high as 100 g/ml, may be necessary.

Given the lack of conclusive information on how best to provide TXA during CPB and CS, a plan was made to undertake a randomized clinical trial and evaluate the effectiveness of TXA administered prior to or following initiation. Despite this, there is still discussion about the best way to administer the TXA

### 1.4 Aims of the Study

To assess the TXA clinical efficacy and safety to reduce blood loss, the need for blood transfusions, and other complications and to investigate the coagulation profile of the patients during CABG, using CPB.

#### 1.4.1 Objectives

- To assess volume blood loss for patients undergoing CABS, using CPB.
- To compare volume blood loss & blood transfusion between control group, TXA pre-CPB group and TXA after –CPB group.
- To evaluate the amount of blood given through and after a24-hour operation in all groups.

### 1.5 Hypotheses

TXA, administered prior to CPB initiation, significantly reduces bleeding at 0.05 level in patients undergoing CABG compared to the control group.

1. TXA, administered after initiation of CPB, significantly reduces bleeding at 0.05 level in patients undergoing CABG compared to the control group.

2. TXA administered prior to CPB initiation, significantly reduces blood transfusion requirements at 0.05 level in patients undergoing CABG compared to the control group.
3. TXA administered, after initiation of CPB, significantly reduces blood transfusion requirements at 0.05 level in patients CABG compared to the control group.

# Chapter Two

# Methodology

## 2.1 Introduction

An-Najah National University's Institutional Review Board has approved the study, and 99 patients who were scheduled for elective CABG were given written informed consent form to participate in the study.

## 2.2 Study Design

Prospective, randomized, double-bind study, placebo controlled. Random numbers were produced by a computer and used to distribute patients. Once in the operating room, 99 patients were randomly divided into three groups of 33 each.

## 2.3 Participants

Patients who underwent elective CABG

## 2.4 Site and Setting

The experiments were conducted at Ramallah-based Palestine Medical Complex. The medical facility has five wings and 453 beds for patients. This study concentrated on two units: ICU and cardiac operation room.

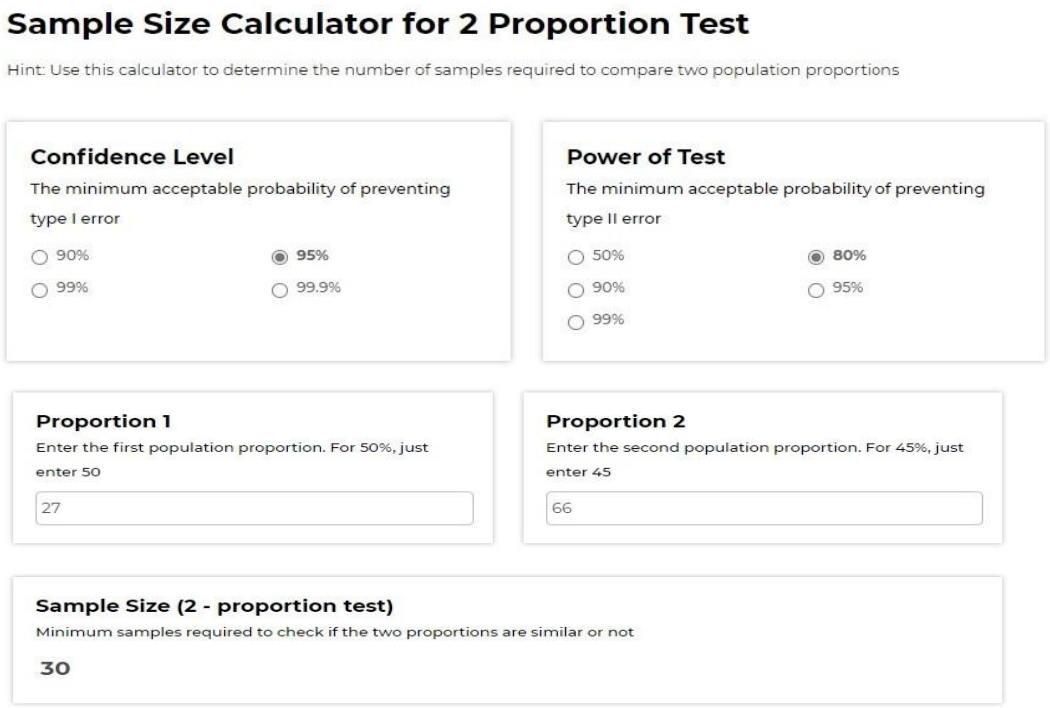
## 2.5 Sample and Sampling

Sample size was calculated based on an existing study performed by Robert et al (1997) which showed that the median number of blood products transferred was 0 units, and the proportion of patients (27% versus 33%), who received any blood products, was not statistically different. There was a statistically significant difference in the percentage of patients receiving blood products between the control group and the other groups (p0.05). Sample size calculation was performed, using the Bench Six Sigma calculator. There were 30 patients in each group, and a total of 90 patients. Three patients were added to each group to cover the dropout rate (10% of the total sample). The final number of sample sizes was 99 patients. Patients would be sufficient to give 80% effect to be found with an -error of 5%. In addition, this study considered prior effectiveness analysis on the control patients, which received both MCTD and transfusion therapies. It was found that the sample of 90 people had 80 percent

power to detect a 50 percent reduction in bleeding and transfusions with a 5-percent error. This suggested that a sample size of 90 patients would be appropriate. Adding the anticipated dropout made it 99 patients.

**Figure 2.1**

*Sample Size Calculator for 2 Proportion Test*




## 2.6 Pre-Enrollment Assessment

All study participants were evaluated clinically by the physician the day before surgery to identify any chronic and acute illnesses that may impair the patient's survival. Each patient must have undergone heart surgery, completed blood count (CBC)and Prothrombin time (PT), Activated partial Thromboplastin Clotting time (APtt), International Normalized Ratio (INR), to examine hemoglobin, platelets & coagulation factor to exclude the patient’s exposure to high risk of bleeding. In addition, all patients should have undergone chest ray, Echocardiogram (Echo) and cardiac catheterization.

## 2.7 Inclusion Criteria

Any patient who was scheduled to undergo primary CABG was eligible to participate in the study as long as they met the inclusion criteria (CABG). He/she also had no known or suspected allergy to TXA and history of prior sternotomies.

## 2.8 Exclusion Criteria

If the patient had any of the following he/she would be excluded: presence of pre-existing renal impairment (serum creatinine of more than 1.36 mg/dl),aspirin consumption within the previous five days ,pre-operative coagulation abnormalities (PT>18 s or APTT>50),a coagulopathy or a platelet count below 100,000 per microliter, anticoagulant treatment (heparin <4h preoperatively or warfarin < 3 days preoperatively),Thrombolytic therapy (streptokinase < 1day preoperatively ), Clopidogrel consumption within the previous five days, autologous pre-donation of blood, and a history of thrombotic events in the previous six months, such as deep vein thrombosis, disseminated intravascular coagulation, or a cerebral thromboembolic accident and pump duration of more than 120 minutes.

## 2.9 Study Period

Data collection began in November 2020 and ended in January 2022.

## 2.10 Study Variables

### a) Dependent Variables:

Demographic, Mediastinal chest tube drainage blood loss, transfusion needing PRBCs, FFP, Platelets, cryoprecipitate, time of operation, hemodynamic parameters (blood pressure, mean arterial blood pressure, peripheral capillary oxygen saturation, ASA, total heparin dose, total protamine dose, laboratory test (CBC, INR, PT, APTT, ACT), drowsiness, agitation, focal neurological deficit, seizures and coma.

### b) Independent Variables:

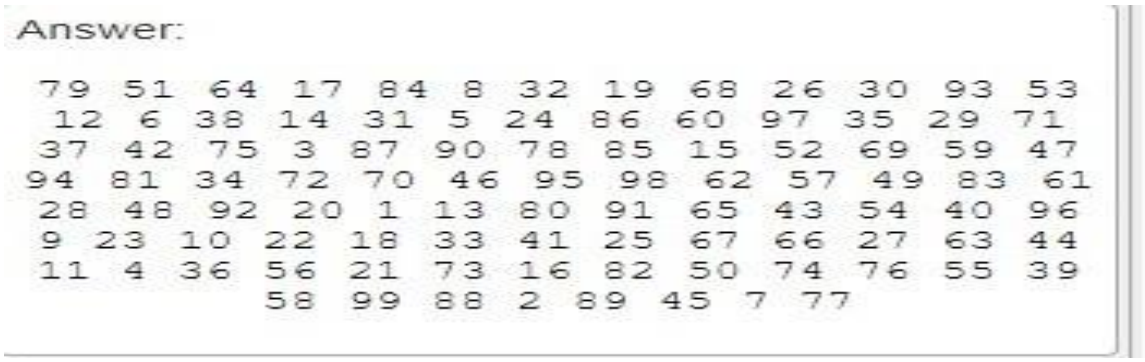
There were two variables: TXA and CPB

## 2.11 Randomization

A computer-generated random number sequence was used to assign patients. After arriving in the operating room and establishing routine monitoring measures, 99 patients were randomly divided into three groups (33 patients in each group). To rule out TXA hypersensitivity, all patients received a 1 ml test dose of trial drugs intravenously 10 minutes before the initial loading dosage.

**Figure 2.2**

*Random Number Generator*




## 2.12 Blindness

Patients and caregivers participating in patient care, the individual who gathered and evaluated data, and outcome assessors were unaware of the treatment group distribution.

## 2.13 Laboratory Testing

Laboratory tests performed prior to surgery included Prothrombin Time (PT), activated partial Thromboplastin Clotting time (APtt), CBC). After the cessation of CPB and neutralization of remaining heparin with protamine, laboratory tests were done in the operating room: PT, APtt, and INR. On admission to the CCU, a CBC, PT, APtt, and INR were repeated. APtt, PT and CBC were conducted every 6 hours for the first 24 hours after CCU admission.

## 2.14 Anesthetic Protocol

All patient in the three groups received the same anesthesia technique and ventilation in Operation Room (OR). When patient arrives in the OR, he/she gets connected with cardiac monitoring, and vital sings (non -invasive blood pressure, heart rate, saturation by pulse oximeter) are taken. Sedation with midazolam 1 mg and fentanyl 50 meq are given by intravenous cannula. Face mask oxygen applied with fresh gas flow 100% oxygen of 5liter\minute, 2 large bore intravenous cannula applied mainly gauge 16 or 14, local anesthetic injected in radial artery area for invasive radial artery line application and immediately connected to the monitor, standard induction of anesthesia started by propofol 1mg \kg and by titration according to blood pressure, vecuronium 0.1mg\kg to facilitate intubation. Fentanyl 5meq \kg was given and then Isoflurane inhalation by 0.6vol% was initiated. Capnography was connected to monitor after intubation. Central line (right internal jugular) was administered and connected to the monitor, Foley catheter was also administered. Anesthesia was maintained with isoflurane 1.2 vol. % in 50 % oxygen and 50 % air. Neuromuscular blockade was vecuronium with this equation 0.3(dose)\kg every 40 minutes. Fentanyl was used to give interoperation analgesia with this equation 2 mcg (dose)\kg every 40minutes. Patient was then given intravenous Cefazolin 1g over 30 min (vancomycin 1 gram in case of a high risk for infection and for admitted patients more than one week). Dexamethasone 8 mg in all operations was given. Heparin 350 units\ kg was administered to reach the desired active clotting time (ACT)480 sec for bypass facilitation. Adrenaline infusion (2mg in 50 cc normal saline), Nitroglycerine (50mg in 50cc normal saline) were prepared as standby according to blood pressure. Insulin infusion (100-unit act rapid in 50 cc normal saline) was prepared according to Random Blood Sugar (RBS). Patient, after operation completion, was transferred to CCU ward intubated. ACT 80-140.

## 2.15 Procedure

Clinical trials were undertaken after An-Najah National University Institutional Review Board (IRB) gave its approval for conduct of this research and signing of consent form by the patients. After arriving in the operating room and the setup of routine monitoring procedures, 99 patients were randomly divided into three groups (33 patients per group) for this study. For anticoagulation, 350 units\kg of Heparin Sulphate

intravenously were provided until the Active Clotting Time (ACT) was more than 480 seconds.

**Tranexamic Acid Infusion Protocol**

After randomizing the participants, the infusions for the research were prepared the morning before surgery and labeled either as:

Infusion 1

Infusion 2

Infusion 3

Infusion 4

**TXA pre-CPB 2Group : TXA before initiation of and during CPB**

**Infusion 1:** The patient received TXA (15 mg /kg) in 50 ml of normal saline or a placebo (50 ml of normal saline) 20 minutes after anesthesia induction was administered, and before sternotomy was performed.

**Infusion 2: This** comprised of 500 mg of TXA combined with 250 ml of normal saline or a placebo (250 ml normal saline). After the conclusion of infusion 1, the second infusion was administered at a regular rate of 0.5ml/kg /h (1mg/kg/h).

**TXA post – CPB Group: TXA after Termination of CPB**

Infusion 3 was started following the cessation of CPB and the reversal of heparin.

**Infusion 3:** This included TXA (15 mg/kg) and 50 ml of normal saline or placebo (50 ml normal saline); they were administered over a period of 20 minutes.

After completion of the third infusion, the fourth infusion started.

**Infusion 4:** This comprised of 500 mg of TXA combined with 250 ml of normal saline or a placebo (250 ml normal saline)0.5ml\kg\h (1mg\kg\h) for 5 hours, same to infusion 2, is given (Table 1).

Table 1 shows the four infusions used to provide placebo, post-CPB TXA, or pre-CPB TXA to the patient groups during the trial.

**Table 2.1**

*TXA Infusion Matrix*

| Group | Infusion 1 | Infusion 2 | Infusion 3 | Infusion 4 |
|---|---|---|---|---|
| Control | Carrier | Carrier | Carrier | Carrier |
| Post-CPB TXA | Carrier | Carrier | TXA 15Mg/KG | TXA 1mg*kg*h |
| Pre -CPB TXA | TXA 15mg/kg | TXA 1mg*kg*h | Carrier | TXA 1mg*kg*h |

There was a total of 50ml in the first and third infusions and a total of 250ml in the second and fourth infusions. About 2 grams (23/25 milligrams per kilogram) of TXA were administered to the TXA groups. Saline is the infusion fluid used to carry out the procedure. Infusions are solely identified by their unique number. A typical infusion rate of 0.5 ml/kg/h was used for the 50 ml infusions and the 250ml infusion was provided over a period of 20 minutes.

### 2.16 CPB Management

An arterial filter, a membrane oxygenator, a cardiotomy reservoir and polyvinyl tubing were all part of the CPB circuit's non-occlusive roller pump. Plasmalytes (1000 cc), sodium bicarbonate (50 mEq), heparin (5000 units), and Potassium heparin were added to the oxygenator's pre-infusion mixture (40mEq), 0.5% Mannitol per kilogram of body weight. Heparin was infused into a central vein prior to aortic cannulation to produce systemic anticoagulation. A celite ACT of more than 480 s. was observed. A hypothermic CPB was done (32-35c). 2.5 - 3.0 l/min is the ideal flow rate. ACT, ABGs (arterial blood gases), and RBS were monitored every 20 minutes and supplemented the treatment with heparin (5000 units) when needed. Cold, high-potassium (20mEq) 4:1 blood to crystalloid cardioplegia was administered through the aortic root after aortic occlusion to protect the myocardium from damage. The patient was given retrograde and through the vein grafts every 20 minutes to administer 7.5ml of crystalloid cardioplegia (7.5ml/kg). An automated protamine titration was used to neutralize systemic heparinization following the termination of CPB.

It was necessary to administer an additional 50mg of protamine after the celite ACT had reached 140s for 10 minutes after the calculated dose of protamine had been administered.

Protamine sulphate ACT was used to neutralize the heparin at the end of surgery. Chest tube drainage was evaluated for 24 hours before allogeneic PRBCs were given to patients with hemoglobin levels ≤ 9 mg/dl. When the APtt and PT were prolonged (>1.5 times the control value), during active bleeding or when the ACT was above 140, FFP was administered. Platelet transfusion was indicated if the platelet count fell below 50, 000 per microliter or if bleeding persisted following FFP transfusion. If bleeding persisted at a rate of >500 ml/h, the first 1h, >400 ml/h after 2 h, or > 300cc after 3h post operation, surgical re-exploration may be an option. Chest tube, urine output, random blood sugar (RBS), blood transfusions, CBC (hemoglobin hematocrit and platelet count), potassium serum, preoperatively, and immediately, 6 and 24 hours after CCU admission, neurological deficits (drowsiness, agitation and focal neurological deficits), and renal failure at the time of surgery were among the major parameters evaluated in this study. Both before and after surgery, the patients' indicators of renal failure were examined.

**2.17 Transfusion Policies**

At Hemoglobin rate of 9g/dl or lower, infusions of RBCs are required during CPB. Hemoglobin 9 g/dl is an indication for allogeneic RBC transfusions. CPB is terminated, and washed cellular contents of the CPB circuit are administered. Components of blood were supplied in the operating room following a diagnosis of diffuse mammary vein bleeding (MVB). MVB was characterized as diffuse bleeding with little to no clot formation in the anastomoses and the internal mammary artery bed. Blood components were administered in the CCU for excessive mediastinal chest tube drainage (MCTD)and then tested in the lab. One hour of blood loss of more than 500ml is considered excessive, while two consecutive hours of blood loss greater than 400 ml/h constitutes an abnormal amount of blood loss. If a platelet count was less than 50,000 cells per microliter, six units of platelets were administered. Bleeding caused by increased prothrombin (>20s) or activated partial Prothrombin time (>60s) or ACT>140s requires two to four units of FFP. To treat excessive bleeding, ten-units of cryoprecipitate were given as an adjunct therapy. Surgical re-exploration was

performed if excessive bleeding was found to be occurring despite the presence of normal laboratory results.

### 2.18 Outcome Measures and Complications

For the first 24 hours, the mediastinal chest tubes blood loss was monitored in the CCU. Losses more than 1L were considered excessive in terms of 12-hour MCTD. To determine the hemoglobin concentration, a sample was taken from the MCTD after it had been in the reservoir for 24 hours and properly mixed. Time of allogeneic blood product administration was recorded. A second-day postoperative ECG with a fresh Q wave longer than 40 ms duration was considered to be evidence of a Q wave myocardial infarction.

At 48 hours, blood loss and product transfusions were the major outcomes. Blood transfusions, repeat surgeries, TXA-related adverse events and death were among the secondary outcomes of this study.

### 2.19 Ethical Consideration

The protocol for this prospective, experimental study was authorized by the IRB of An-Najah National University, The researcher received approval and facilitation of tasks from the Ministry of Health's Health Education and Scientific Research Unit and the Palestinian Medical Complex Research Committee. Before considering participation in the study, all patients were provided with verbal and written information regarding the goal and objectives of the investigation. The study adhered to the World Health Organization's Declaration of Helsinki on ethical criteria for human medical research (World Medical Association, 2013). Patients were advised that participation in the trial was voluntary, and that they may quit at any moment without penalty. No one, other than the researcher, had access to the data, which was kept confidential. Privacy, respect, integrity, anonymity, and integrity were all taken into account.

# Chapter Three

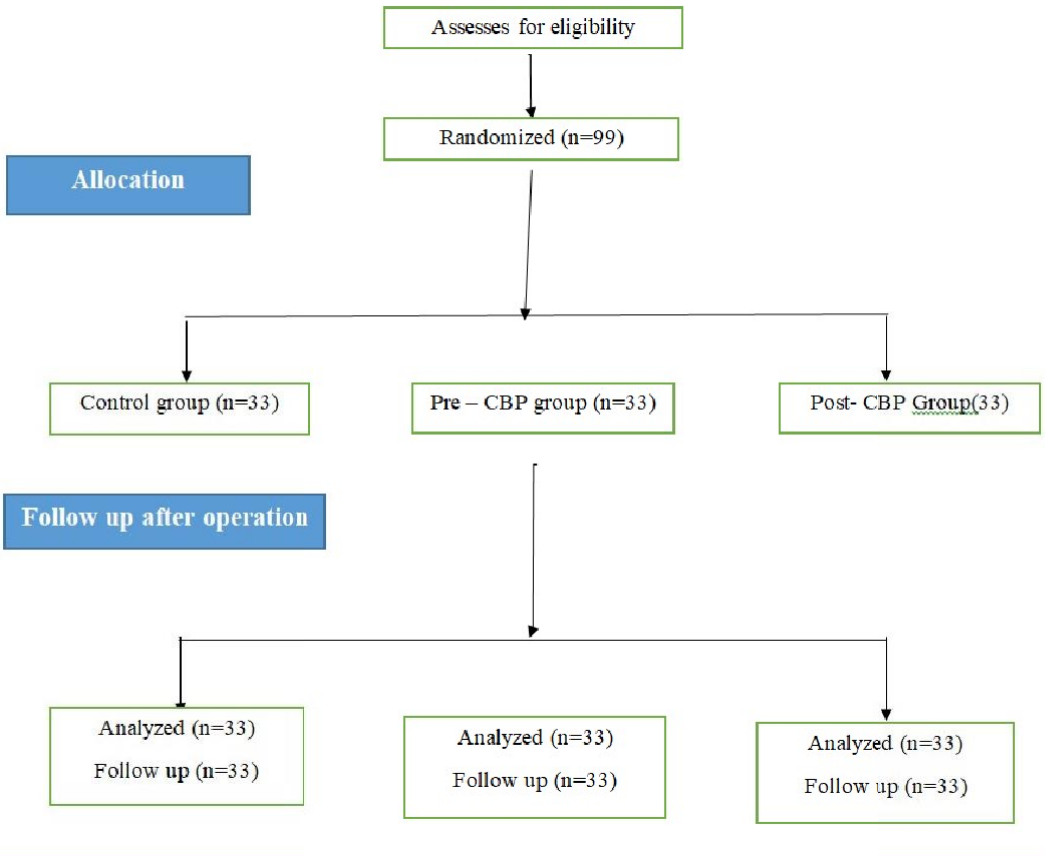
# Results

## 3.1 Patient Characteristics

Between November 2020 and January2022, 99 patients were scheduled to receive elective CPB in the medical center .Ninety patients (86 male a d 13 female) were included and randomized. Thirty-three patients in each group received their intervention, and no patients were lost to follow up. There were no statistical differences in pre-CBP, post-CBP, and control group variables among the groups.

**Figure 3.1**

*Analyzed data*



### 3.2 Statistical Methods

SPSS Version 20 is used for data analysis. Descriptive statistics (frequencies, percentages, means, standard deviations) were used. The following tests and methods were used to analyze the results assuming that the P-Value < 0.05 is considered significant:

1. Chi-Square test: This test tests the differences in percentages between the study groups of patients for qualitative variables such as operation, sex, hypertension, atrial fibrillation, previous heart surgery, coronary artery diseases, chronic obstructive pulmonary disease, ASA, aspirin, protamine to CCU time, side effect of Tranexamic Acid, and outcome measurements.

2. One Way Analysis of Variance (ANOVA) test with the Post-hoc multiple comparisons S-N-K tests: This tests the differences in means between the study groups for quantitative variables such as age, weight, height, body mass index, ejection fraction, Isoflurane, Heparin, NaCO3, Mannitol, Insulin, time on bypass in minute, CCT in minutes, time of operation in minutes, total heparin dose, total protamine dose, laboratory preoperative indicators, laboratory intra-operative indicators, laboratory postoperative indicators, intraoperative blood transfusion indicators, postoperative blood transfusion indicators, and the blood loss indicators.

## 3.3 Study Results

**Table 3.1**

*Comparisons between study groups regarding general information and demographic data (N=99)*

| General Information Demographic Data | and Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Operation: CABG1 | 0(0%) | 1(3%) | 2(6.1%) | 3(3%) | 0.357 |
| CABG2 | 3(9.1%) | 1(3%) | 7(21.2%) | 11(11.1%) | 0.057 |
| CABG3 | 18(54.5%) | 14(42.4%) | 15(45.5%) | 47(47.5%) | 0.591 |
| CABG4 | 5(15.2%) | 11(33.3%) | 5(15.2%) | 21(21.2%) | 0.114 |
| AVR | 2(6.1%) | 3(9.1%) | 2(6.1%) | 7(7.1%) | 0.858 |
| MVR | 5(15.2%) | 5(15.2%) | 2(6.1%) | 12(12.1%) | 0.426 |
| MVL_MASS | 0(0%) | 0(0%) | 1(3%) | 1(1%) | 0.364 |
| Age | 52.7 ± 12.8 | 54.15 ± 12.94 | 55.76 ± 12.05 | 54.2 ± 12.54 | 0.616 |
| Sex: Male | 28(84.8%) | 30(90.9%) | 28(84.8%) | 86(86.9%) | 0.702 |
| Female | 5(15.2%) | 3(9.1%) | 5(15.2%) | 13(13.1%) | |
| Weight (Kg) | 78.29 ± 14.46 | 77.98 ± 13.34 | 82.97 ± 13.57 | 79.75 ± 13.84 | 0.263 |
| Height (cm) | 169.5 ± 7.27 | 166.88 ± 7.3 | 170.68 ± 7.94 | 169.02 ± 7.6 | 0.115 |
| Body Mass Index | 27.15 ± 4.33 | 28.02 ± 4.62 | 28.5 ± 4.67 | 27.89 ± 4.53 | 0.476 |

* P-values are related to Two Independent Samples T-test test for quantitative variables and Chi-square test for qualitative variables. Numbers in the table represent Mean ± Standard Deviation or N. %.

The results in Table 3.1 show that there were no significant differences at 0.05 level between the three study groups in all general information and demographic data. All the P-values were higher than 0.05, and all the mean values or percentages between the three study groups were not significantly different.

**Table 3.2**

*Comparisons between study groups regarding diseases indicators (N=99)*

| Diseases Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Hypertension | 20(60.6%) | 17(51.5%) | 29(87.9%) | 66(66.7%) | 0.005 |
| Atrial Fibrillation | 1(3%) | 4(12.1%) | 1(3%) | 6(6.1%) | 0.203 |
| Diabetes | 15(45.5%) | 9(27.3%) | 18(54.5%) | 42(42.4%) | 0.074 |
| Coronary Artery Diseases | 21(63.6%) | 23(69.7%) | 22(66.7%) | 66(66.7%) | 0.873 |
| Chronic Obstructive Pulmonary Disease | 15(45.5%) | 13(39.4%) | 16(48.5%) | 44(44.4%) | 0.751 |
| ASA(I.II.III,VI,VI): 2 | 3(9.1%) | 5(15.2%) | 0(0%) | 8(8.1%) | 0.124 |
| 3 | 30(90.9%) | 26(78.8%) | 31(93.9%) | 87(87.9%) | |
| 4 | 0(0%) | 2(6.1%) | 2(6.1%) | 4(4%) | |
| Ejection Fraction | 53.09 ± 7.46 | 48.94 ± 8.43 | 50.12 ± 9.8 | 50.72 ± 8.71 | 0.136 |

* P-values are related to TwoIndependent Samples T-test test for quantitative variables and Chi-square test for qualitative variables.Numbers in the table represent Mean ± Standard Deviation or N.%.

Table 3.2 shows no significant differences at 0.05 level between the three study groups except for hypertension. The results of the Post-hoc Chi-square tests show that the percentage of the hypertension cases in Post-CPB TXA group(N=29, P=87.9%) was significantly higher than both the percentages of the hypertension cases in Pre –CPB TXA group(N=17, P=51.5%) and in the control group (N=20, P=60.6%).The P-value of the test was $0.005<0.05$.

However, Table 3.2shows no significant differences at 0.05 level between the three study groups in all the other diseases indicators since the P-values of the tests were higher than 0.05, and all the mean values or percentages between the three study groups were not significantly different.

**Table 3.3**

*Comparisons between study groups regarding medication measurements (N=99)*

| Medication Measurements | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Aspirin (100mg) | 0(0%) | 0(0%) | 0(0%) | 0(0%) | ----- |
| Heparin (unit) | 24818.18 ± 3778.68 | 26333.33 ± 4826.14 | 26212.12 ± 3935.08 | 25787.88 ± 4219.18 | 0.271 |
| NaCO3 (mEq) | 65.76 ± 22.92 | 65.15 ± 24.51 | 64.24 ± 22.5 | 65.05 ± 23.1 | 0.965 |
| Mannitol (cc*) | 236.67 ± 62.68 | 236.36 ± 51.95 | 242.42 ± 57.93 | 238.48 ± 57.17 | 0.891 |
| Insulin (unit) | 11.24 ± 10.77 | 7.36 ± 10.99 | 6.39 ± 8.26 | 8.33 ± 10.2 | 0.124 |

* P-values are related to Two Independent Samples T-test test for quantitative variables and Chi-square test for qualitative variables. Numbers in the table represent Mean ± Standard Deviation or N.%. * Mannitol 20%

Table 3.3 shows no significant differences at 0.05 level between the three study groups in all the medication measurements since the P-values of the tests were higher than 0.05, and all the mean values or percentages between the three study groups were not significantly different.

**Table 3.4**

*Comparisons between study groups regarding surgical measurements (N=99)*

| Surgical Measurements | Control N=33 | Pre –CPB N=33 | TXA | TXA | Post-CPB N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|---|---|
| Time on bypass in minutes | | 91.67 ± 18.78 | 100.88 ± 19.93 | | 87.33 ± 23.12 | 93.29 ± 21.25 | 0.029* |
| Cross clamp time(CCT)in minutes | | 57.91 ± 14.07 | 67.15 ± 17.33 | | 52.67 ± 18 | 59.24 ± 17.45 | 0.002* |
| Time operation in minutes | | 300.3 ± 62.02 | 301.21 ± 75.2 | | 279.09 ± 71.74 | 293.54 ± 69.92 | 0.351 |
| Total heparin dose (unit) | | 29848.48 ± 4206.55 | 31575.76 ± 4763.34 | | 32136.36 ± 4810.91 | 31186.87 ± 4658.54 | 0.115 |
| Total protamine sulfate dose (mg) | | 303.03 ± 46.67 | 322.73 ± 48.56 | | 318.18 ± 48.12 | 314.65 ± 48.05 | 0.220 |
| Protamine sulfate was given to CCU | (mg): 0 | 26(78.8%) | 32(97%) | | 31(93.9%) | 89(89.9%) | 0.030* |
| 50 | | 7(21.2%) | 1(3%) | | 1(3%) | 9(9.1%) | |
| 100 | | 0(0%) | 0(0%) | | 1(3%) | 1(1%) | |

* P-values are related to Two Independent Samples T-test test for quantitative variables and Chi-square test for qualitative variables. Numbers in the table represent Mean ± Standard Deviation or N. %.

As the table above shows, there were significant differences at 0.05 level between the three study groups but only in Time on Bypass in Minute, Cross Clamp Time CCT in Minute, and Protamine Sulfate given in CCU.

Regarding the Time on Bypass, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the Time on Bypass in Pre –CPB TXA group (Mean=100.88) group was significantly higher than the mean of the Time on Bypass in Post-CPB TXA group (Mean=87.33) mint. The P-value of the test was 0.029<0.05.

Regarding the CCT, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the CCT Pre –CPB TXA (Mean=67.15) mint group was significantly higher than the mean of the CCT in Post-CPB TXA group (Mean=52.67); the P-value of the test was 0.002<0.05.

Regarding Protamine Sulfate given in the CCU, the results of the Post-hoc Chi-square tests show that the percentage of cases, when the Protamine Sulfate was given in CCU =50 mg in the control group (N=7, P=21.2%), was significantly higher than both the percentages of cases when the Protamine sulfate was given to CCU =50mg in Pre – CPB TXA group (N=1, P=3%) and in post-CPB TXA group (N=1, P=3%); the P-value of the test was 0.030<0.05.

However, Table 3.4 shows that no significant differences at 0.05 level between the three study groups in all the other surgical measurements since the P-values of the tests were higher than 0.05, and all the mean values or percentages between the three study groups were not significantly different.

**Table 3.5**

*Comparisons between study groups regarding laboratory preoperative indicators (N=99)*

| Laboratory Preoperative Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Hematocrit (%) | 39.5 ± 4.29 | 41.64 ± 4.6 | 41.53 ± 5.38 | 40.89 ± 4.83 | 0.129 |
| Hemoglobin (g\dl) | 13.21 ± 1.3 | 14.22 ± 1.49 | 13.67 ± 1.86 | 13.7 ± 1.61 | 0.035* |
| Platelet count ($10^3$\μL) | 247.68 ± 95.62 | 241.47 ± 71.88 | 241.28 ± 94.22 | 243.48 ± 87.06 | 0.945 |
| Prothrombin time (s) | 13.92 ± 1.65 | 14.1 ± 3.77 | 12.66 ± 1.1 | 13.56 ± 2.52 | 0.039* |
| Partial Prothrombintime (s) | 37.75 ± 6.96 | 37.12 ± 5.29 | 35.68 ± 5.98 | 36.85 ± 6.11 | 0.375 |
| International normalized ratio | 1.01 ± 0.15 | 0.98 ± 0.11 | 0.93 ± 0.18 | 0.97 ± 0.15 | 0.061 |
| Creatinine (mg\dl) | 0.9 ± 0.16 | 0.92 ± 0.17 | 0.85 ± 0.17 | 0.89 ± 0.17 | 0.196 |
| Blood urea nitrogen (mg\dl) | 19.1 ± 6.89 | 16.07 ± 5.42 | 15.52 ± 3.92 | 16.9 ± 5.71 | 0.022* |
| Random Blood Sugar (mg\dl) | 134.34 ± 42.95 | 123.21 ± 36.8 | 135.76 ± 53.32 | 131.1 ± 44.77 | 0.464 |

* P-values are related to TwoIndependent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

Table 3.5 shows significant differences at 0.05 level between the three study groups but only in hemoglobin, prothrombin time, and blood urea nitrogen.

Regarding hemoglobin, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the hemoglobin indicator in Pre –CPB TXA group (Mean=14.22) g\dl was significantly higher than the mean of the hemoglobin indicator in the control group (Mean=13.21) g\dl; the P-value of the test was 0.035<0.05.

Pertaining to the Prothrombin time, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the Prothrombin time in Pre –CPB TXA group (Mean=14.1) s was significantly higher than the mean of the Prothrombin time in Post-CPBTXA group (Mean=12.66) s; the P-value of the test was 0.039<0.05.

Concerning the blood urea nitrogen, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the blood urea nitrogen in the control group (Mean=19.1) was significantly higher than the mean of the blood urea nitrogen in Post-CPB TXA group (Mean=15.52); the P-value of the test was 0.022<0.05.

However, Table 3.5 shows no significant differences at 0.05 level between the three study groups in all the other laboratory preoperative indicators because the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

**Table 3.6**

*Comparisons between study groups regarding laboratory intraoperative indicators (N=99)*

| Laboratory Intraoperative Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| ACT (s) | 511.76 ± 66.55 | 522.27 ± 73.22 | 496.21 ± 109.07 | 510.08 ± 84.84 | 0.459 |
| Hematocrit (%) | 30.04 ± 5.6 | 30.44 ± 5.24 | 30.27 ± 5.51 | 30.25 ± 5.4 | 0.958 |
| Hemoglobin (g\dl) | 10.25 ± 1.41 | 10.76 ± 2.05 | 10.45 ± 1.9 | 10.49 ± 1.8 | 0.514 |
| Platelet count ($10^3$\μL) | 225.67 ± 53.65 | 220.01 ± 83.62 | 234.1 ± 90.27 | 226.59 ± 76.93 | 0.759 |
| Random Blood Sugar (mg\dl) | 161.61 ± 49.83 | 160.18 ± 55.62 | 173.64 ± 59.83 | 165.14 ± 55.01 | 0.556 |

* P-values are related to TwoIndependent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

As Table 3.6shows, that there were no significant differences at 0.05 level between the three study groups in all laboratory intra-operative indicators because the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

**Table 3.7**

*Comparisons between study groups regarding laboratory postoperative indicators (N=99)*

| Laboratory Postoperative indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Hematocrit (%) | 35.15 ± 3.68 | 35.19 ± 3.57 | 35.53 ± 3.76 | 35.29 ± 3.64 | 0.901 |
| Hemoglobin (g\dl) | 11.6 ± 1.74 | 12.05 ± 1.29 | 11.64 ± 1.51 | 11.77 ± 1.52 | 0.415 |
| Platelet count ($10^3$\μL) | 231.24 ± 64.17 | 232.55 ± 60.21 | 225.88 ± 74.75 | 229.89 ± 66.04 | 0.912 |
| Prothrombin time (s) | 15.37 ± 2.03 | 16.32 ± 6.26 | 15.12 ± 3.59 | 15.61 ± 4.32 | 0.495 |
| Partial Prothrombin time (s) | 36.96 ± 5.44 | 35.91 ± 5.37 | 36.21 ± 7.44 | 36.36 ± 6.11 | 0.777 |
| International normalized ratio | 1.13 ± 0.14 | 1.07 ± 0.22 | 1.1 ± 0.12 | 1.1 ± 0.17 | 0.342 |
| Creatinine (mg\dl) | 0.94 ± 0.23 | 0.98 ± 0.2 | 0.9 ± 0.22 | 0.94 ± 0.22 | 0.283 |
| Blood urea nitrogen (mg\dl) | 18.98 ± 7.06 | 17.8 ± 4.99 | 16.82 ± 4.75 | 17.87 ± 5.71 | 0.309 |
| Random blood Sugar (mg\dl) | 141.27 ± 32.48 | 134.88 ± 32.4 | 143.91 ± 41.03 | 140.02 ± 35.38 | 0.571 |

* P-values are related to Two Independent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

Table 3.7 shows no significant differences at 0.05 level between the three study groups in all laboratory postoperative indicators since that the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

**Table 3.8**

*Comparisons between study groups regarding intraoperative blood transfusion indicators (N=99)*

| Intraoperative Blood Transfusion Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Units of RBCs | 1.79 ± 1.05 | 1.48 ± 0.97 | 1.21 ± 1.05 | 1.49 ± 1.04 | 0.080 |
| Units FFP | 1.97 ± 1.72 | 1.64 ± 1.41 | 1.76 ± 1.28 | 1.79 ± 1.47 | 0.653 |
| Units Platelets | 4.88 ± 2.39 | 4.55 ± 1.75 | 4.7 ± 1.91 | 4.71 ± 2.02 | 0.802 |
| Cryoprecipitate | 1.09 ± 1.72 | 1.42 ± 1.95 | 1.09 ± 1.81 | 1.2 ± 1.82 | 0.695 |

P-values are related to Two Independent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

Table 3.8 shows no significant differences at 0.05 level between the three study groups in all intra-operative blood transfusion indicators since the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

**Table 3.9**

*Comparisons between study groups regarding postoperative blood transfusion indicators (N=99)*

| Postoperative Blood Transfusion Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Units of RBCs | 1.42 ± 0.87 | 0.61 ±0.93 | 0.64 ± 0.65 | 0.89 ± 0.9 | <0.001* |
| Units FFP | 0.24 ± 0.75 | 0.06 ±0.35 | 0.15 ± 0.71 | 0.15 ± 0.63 | 0.506 |
| Units Platelets | 0.15 ± 0.51 | 0.39 ±1.27 | 0.06 ± 0.35 | 0.2 ± 0.82 | 0.235 |
| Cryoprecipitate | 0.24 ± 0.66 | 0.18 ±0.77 | 0.12 ± 0.7 | 0.18 ± 0.71 | 0.787 |

The P-values are related to Two Independent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

As Table 9shows, there were significant differences at 0.05 level between the three study groups but only in Units of RBCs .The results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the Units of RBCs in the control group (Mean=1.42) were significantly higher than both the means of the units of RBCs in

Pre–CPB TXA group (Mean=0.61) and in Post-CPB TXA group(Mean=0.64).The P- value of the test was <0.001.

However, Table 3.9 shows no significant differences at 0.05 level between the three study groups in all the other postoperative blood transfusion indicators because the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

Table C.1 shows significant differences at 0.05 level between the three study groups but only in RBC units. The results of the Post-hoc multiple comparisons S-N-K tests show that the percentage of patients who took RBCs units in control group (97%) was significantly higher than the percentages of patients who took Units of RBCs in Post – CPB group (69.7%); the P-value of the test was 0.007.

However, the results in the aforementioned table show that no significant differences at 0.05 levels between the three study groups in all the other intra-operative blood transfusion indicators because the P-values of the tests were higher than 0.05, and all the percentages between the three study groups were not significantly different.

Table C.2 show significant differences at 0.05 level between the three study groups but only in RBC units. The results of the Post-hoc multiple comparisons S-N-K tests show that the percentage of patients who took RBC units in the control group (87.9%) was significantly higher than both the percentages of patients who took RBC units in pre-CPB group (36.4%) and in post-CPB group (54.5%); the P-value of the test was <0.001.

However, the results in Table C.2 show no significant differences at 0.05 level between the three study groups in all the other postoperative blood transfusion indicators because the P-values of the tests were higher than 0.05, and all the percentages between the three study groups were not significantly different.

Table C.3 shows significant differences at 0.05 level between the three study groups but only in 48 h post mediastinal chest drainage and in 72 h post mediastinal chest drainage.

Regarding 48 h post-op mediastinal chest drainage, the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the 48 h post (mediastinal chest drainage) in the control group (Mean=209.45) was only significantly higher than the mean of the 48 h post (mediastinal chest drainage) in the Post-CPB TXA group (Mean=110.52); the P-value of the test was 0.005<0.05.

Regarding 72 h postop (mediastinal chest drainage), the results of the Post-hoc multiple comparisons S-N-K tests show that the mean of the 72 h post (mediastinal chest drainage)in the control group (Mean=41.67) was only significantly higher than the mean of the 72 h post (mediastinal chest drainage)in the Post-CPB TXA group (Mean=14.87); the P-value of the test was 0.006<0.05.Table C.2 however, shows no significant differences at 0.05 level between the three study groups in all the other blood loss indicators because the P-values of the tests were higher than 0.05, and all the mean values between the three study groups were not significantly different.

Table C.4, however, shows no significant differences at 0.05 level between the three study groups in all side effects of TXA measurements since the P-values of the tests were higher than 0.05, and all the percentages between the three study groups were not significantly different.

Table C.5 shows significant differences at 0.05 level between the three study groups only in the percentage of the dead people. The results of the Post-hoc multiple comparisons Chi-square tests show that the percentage of the deceased in the Post-CPB TXA group (N=4, P=12.1%) was only significantly higher than the percentage of those in the control group (N=0, P=0%); the P-value of the test was 0.044<0.05.

The total number of deaths was five, and the reasons for that were that one patient suffered from infection after the surgery, another patient had a stroke, a third patient had brain hemorrhage after 9 days, a fourth patient had cardiac tamponade, and the last one had a V-TAK global hypokinesia.

However, Table C.5 shows no significant differences at 0.05 level between the three study groups in all the other outcome measurements; the P-values of the tests were higher than 0.05, and all the percentages between the three study groups were not significantly different.

# Chapter Four

# Discussion and Conclusion

## 4.1 Introduction

In a prospective, randomized, placebo-controlled, double-blind trial of adult patients undergoing primary CABG surgery, the researcher assessed the effects of TXA provided before and after CPB TXA 15 mg/ kg before CPB, followed by a TXA infusion of 1 mg / kg /h for 5 h (n = 33) or TXA 15 mg/ kg after CPB, followed by a TXA infusion of 1 mg / kg /h for 5 h (n = 33) were given to the patients. Data on the patient's demographics, health, and surgical history, lab results, Mediastinal Chest Tube Drainage (MCTD), hemoglobin loss and blood transfusion were gathered. Administration of blood products was closely monitored. All the three groups shared similar demographic, medical, and surgical traits.

The patients were operated on by a single team of doctors and followed up on attentively. There was a close eye on any indicators of a medical bleed. Packet cell transfusions were decided on the basis of hemoglobin.

In the developed countries, coronaries artery disease, one of the heart diseases, is the common cause of death. It is responsible for thousands of fatalities every year. Individuals and society alike bear a heavy financial burden because of the high cost of diagnosing, treating, and managing this disease and the disabilities it causes (Gaziano et al., 2006). One of the most important tasks of anesthesiologists and cardiac surgeons is to find an appropriate medication to reduce post-operative bleeding (CABG). In this study, the researcher evaluated the clinical efficacy and safety of TXA to reduce blood loss, the need for blood transfusions, which were candidates for primary CABG. In this investigation, post-operative bleeding, received packed cell differed significantly between the control and TXA groups. Particularly, it was found that the TXA group had less postoperative bleeding than the control group in CABG patients. This case demonstrates that TXA therapy was successful in minimizing post-CABG hemorrhage.

## 4.2 Demographic Data

Age, BMI, weight, ASA, the number of times patients had to return to the operating room, and the number of times they were released were not significantly different from one another in the current study. As a result, neither the demographic information nor the patients' prior medical histories had any bearing on the study's findings, which were also unaffected by gender or age. The current study's findings are in line with those of Rostami et al., who found no significant differences in the patient's age, sex, or return to the operating room. (Rostami and others, 2020).

### Blood Loss

It has long been known that coagulopathies can develop during cardiac surgery. In the CPB, during open cardiac surgery, when blood comes into touch with extracorporeal or non-endothelial surfaces, numerous cellular and humoral pathways, including the coagulation, complement, and fibrinolytic ones, are triggered. These interactions lead to hyper fibrinolysis, or excessive bleeding following surgery. Because of the hemostatic dysfunction, generated by extracorporeal circulation, this fibrinolysis, following CBP, is obvious in the increased production of plasmin and fibrinogen degradation, both of which restrict platelet function and lead to bleeding. In addition to the extracorporeal CPB circuit producing the non-surgical bleeding, hemocytopenia, clotting factor depletion, and liberal use of heparin all contribute to increased fibrinolysis (Yousuf, 2022).

A common side effect of on-pump cardiac surgery is the development of widespread microvascular bleeding, which is known as non-surgical bleeding. It is common practice in open heart surgery to use anti-fibrinolytic medicines applied topically as a means of reducing non-surgical blood loss and the resulting requirement for blood transfusions. The lysine analogues are as effective and safe as lysine itself. Antifibrinolytic TXA is a synthetic antifibrinolytic that prevents fibrinogen from being converted to fibrin depolysaccharide via plasmin. By blocking the lysine binding site of plasminogen and fibrinogen, TXA inhibits inflammation. TXA can reduce plasmin-mediated platelet dysfunction by decreasing plasmin production. It has a longer half-life than EACA, another antifibrinolytic compound, although it performs similarly to TXA (Robert, et al 1997).

The findings of the current study demonstrate that the Post-CPB TXA group significantly differed from the control group only after 48 and 72 hours after surgery (MCTD), favoring the Post-CPB TXA group. The current study's findings are also in line with those of Rostami et al., who found significant differences between the two groups (TXA and control groups) when it came to post-surgical bleeding, duration of surgery, platelet transfusion, packed cell volume, and received FFP (all of which were lower in the TXA group) (Rostami, et al, 2020). The findings of the present study also concur with those of Zufferey et al., who found that low-dose TXA appeared to be a reasonable regimen for reducing bleeding outcomes during CPB surgery (Zufferey et al., 2021). Also, the current study is on line with an earlier non-blind, nonrandomized, retrospective evaluation study which found that post-CPB TXA had a marginal impact on MCTD. Ovrum et al. gave TXA as a single 40-mg/kg bolus without an infusion during their research. In the TXA group, the 18-hour bleeding was statistically less severe (1993).

Fawzy, et al. (2009) conducted a study to find out whether using TXA locally could reduce blood loss following CABG. In this randomized, double-blind, prospective trial, 38 patients scheduled for primary isolated CABG were enrolled. Nineteen individuals in the TXA group got 1 gram of TXA diluted in 100 ml of ordinary saline. Nineteen participants in the placebo group only received 100 cc of ordinary saline. The pericardial and mediastinal cavities were filled with the solution. The authors came to the conclusion that topical administration of TXA to patients having primary CABG significantly reduced postoperative blood loss without putting the patient at increased risk).

Robert (1997)’s study finding that TXA administration before CPB was effective in reducing MCTD and mediastinal hemoglobin loss is not in line with the current study. In addition to reducing MCTD, the pre-CPB TXA group showed hemoglobin loss at a rate that was 25% lower than that of the other groups. In conclusion the results of the current study are not in line with the conclusions of other studies. In their studies, Rousou et al. (1995) Speekenbrink et al., (1995) showed a 30%–70% reduction in MCTD when TXA was administered prior to CPB.

The current findings differ from those of the other randomized, blind studies that contrasted the delivery of TXA pre- and post-CPB. In a small cohort of 17 patients, Soslau et al. (1991) discovered a greater than 50% reduction in MCTD when TXA was administered before CPB as opposed to after CPB administration (Soslau et al., 1991).

### 4.3 Blood Transfusion

Although antifibrinolytic drugs have been compared in numerous studies for cardiac surgery, no firm recommendation has yet been established. Since 2006, most centers have implemented more cautious transfusion procedures to reduce the amount of blood transfused as a result of the realization that allogeneic blood may affect results in some patients (Koch et al., 2006). Therefore, previous research done with more lax transfusion policies may not be applicable to current clinical care.

The current study results show significant differences between the three study groups but only in RBC units. The mean of the RBC units in the control group (Mean=1.42) was significantly higher than both the means of the RBC units in Pre –CPB TXA group (Mean=0.61) and in the post-CPB TXA group (Mean=0.64), P= 0.001.

In the current study, the percentage of patients who took RBC units in the control group (87.9%) was significantly higher than both the percentages of patients who took RBC units in the Pre –CPB TXA group (36.4%) and in the post-CPB TXA group (54.5%). The current study's findings concurred with those of Robert et al (2020). Pre-CPB TXA was shown to reduce MCTD and hemoglobin loss in this trial. There were also noticeable decreases in the proportion of patients getting allogenic blood products (27% vs. 66%). The number of units to which the patients were exposed to were statistically significant. These outcomes have been observed in one TXA trial before. When preventive TXA was compared to retrospective controls by Rousou et al. (1995), it was found that TXA-treated patients required considerably less allogenic and MCTD transfusions. Despite including transfusion procedures and exposing patients at risk for postoperative bleeding, the trial was neither blinded nor nonrandomized or retrospectively controlled. The findings of Robert's study, which showed that post-CPB TXA did reduce the percentage of patients receiving allogenic

blood products, had no impact on the total amount of transfusions. The current study concurs with Blaine, et al. (2016)'s that compared the efficacy of TXA and εACA in a retrospective cohort analysis. All sequential cardiac surgery patients (n = 128) who were hospitalized to the cardiac-surgical intensive care unit following surgery were included in the study. Although patients receiving εACA were more likely to need additional hemostatic medications, the substitution of TXA with εACA induced equal postoperative hemorrhage and red cell transfusions, proving that TXA is preferable to εACA(Blaine et al., 2016).

In a prospective, double-blind, randomized, placebo-controlled clinical trial involving 90 patients was conducted by Mansouria (2012). It was found that TXA was ineffective in reducing bleeding and lowering the components of blood product when compared with Aprotinin. The three groups were randomly assigned to receive aprotinin, TXA, or *a control*. There was evaluation of renal and neurological problems, transfusion needs, and chest tube drainage. According to the authors, low-dose aprotinin is considerably superior to TXA or a placebo in valvular heart surgery for reducing postoperative bleeding and allogenic transfusion, without worsening outcomes (Mansouri et al., 2012).

### 4.4 Dose of TXA

It is still unclear what dosage of TXA is ideal. In a multicenter, double-blinded, randomized research, Sigaut et al. (2004) examined two dosages of TXA used during heart surgery. Prior to being randomly assigned to one of two TXA doses—10 mg/kg bolus followed by 1 mg/kg/h infusion (low dose) until the conclusion of surgery or 30 mg/kg bolus followed by 16 mg/kg/h infusion (high dose)—patients were stratified based on their transfusion risk. The frequency of blood product transfusions up to day 7 was the main goal. Secondary outcomes were death, blood loss, repeat surgery, TXA-related adverse events, and transfusion occurrences for each kind of blood product and amounts transfused. The authors came to the conclusion that while a high dose of TXA is more efficient than a low dose at reducing transfusion demands, blood loss, and repeat surgery, it does not reduce the incidence of blood product transfusion up to day 7.

### 4.5 Tranexamic Acid's Side Effects

The findings of the current study indicate no significant changes in any of the TXA side effect assessments, including agitation, focal neurological impairment, convulsion, and coma, between the three study groups. Four patients passed away in the post-CPB TXA group as opposed to one in the Pre-CPB TXA group and none in the control group (p=.0.044). On the other hand, in patients having coronary artery surgery, TXA was associated with a decreased incidence of bleeding than placebo without an increased risk of mortality or thrombotic complications within 30 days following surgery (Myles et al., 2017). Hypersensitivity responses, cerebrovascular infarction, myocardial infarction, and pulmonary embolism appeared to have more frequent adverse reactions to TXA, according to a systemic review research by Calapai et al (2015). After nine days following surgery, two patients in the Post group suffered strokes passed away, while one patient in the Pre—CPB TXA group suffered brain hemorrhage (Calapai et al (2015). The current investigation showsit is not the case.

### 4.6 Conclusion

In patients undergoing cardiac surgery, at risk for postoperative bleeding, this study has decisively demonstrated that post-CPB TXA has profoundly favorable hemostatic and blood conservation benefits. Giving TXA post -CPB has the best hemostatic effects. When compared to placebo, it reduces blood loss over the course of 48 and 72 hours and the need for blood product administration. Pre-CPB TXA's positive impact is less obvious.

### 4.7 Recommendations

Based on the results of this study and previous studies, TXA is effective in reducing post-operative bleeding and decrease amount of blood transfusion, so it’s recommended to be in the protocol of cardiac surgery For future research, the researcher recommends studying dose outcome and examining topical use of TXA and including larger sample.

### 4.8 Limitations

The study has a number of limitations. First and foremost, the research was conducted at a single facility with a small number of participants and a brief time of follow-up. Secondly, this study did not assess the effect of the dose outcomes on patients in this study.

# List of Abbreviations

| Abbreviation | Meaning |
|---|---|
| CBP | Cardiopulmonary Bypass |
| CABG | Coronary Artery Bypass Tranexamic |
| Acid | Grafting TXA |
| MVB | Microvascular Bleeding |
| CS | Cardiac Surgery |
| MCTD | Mediastinal Chest Tube |
| Drainage SVR | Systemic Vascular Resistance |
| PVC | Polyvinyl Chloride |
| TOE | Transesophageal Echocardiograph |
| ACT | Activated Coagulation Time |
| PRBCs | Packed Red blood Cells |
| RBCs | Red Blood Cells |
| PT | Prothrombin Time |
| aPTT | Activated Partial Thromboplastin ClottingTime |
| INR | The International Normalized Ratio |
| FEcho | Echocardiogram |
| CBC | Complete Blood Account |
| CCU | Critical Care Unit |
| SD | Stander Division |
| IRB | Institutional Review Board |
| FFP | Fresh Frozen Plasma |
| EACA | Eaminoacaproic Acid |
| mg | Milligram |
| mcg | Microgram |
| L | Litter |
| kg | Kilogram |
| CCT | Cross Clamp Time |

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# Appendices

## Appendix A
## Consent Form

موافقة الاشتراك في البحث العلمي

اسم الباحث : مريم إسماعيل شراكة – طالبة ماجستير تمريض تخدير –جامعة النجاح الوطنية

د. عبد الحليم أبو حلتم – اخصائي طب تخدير في مجمع فلسطين الطبي

د. عايدة القيسي – عميد كلية التمريض والقبالة – منسق برنامج ماجستير تمريض تخدير – جامعة النجاح الوطنية

انا الموقع ادناه .....

اقر انه تم شرح طلب المشاركة في مشروع البحث العلمي (فعالية اعطاء حمض الترانيكساميك قبل وبعد المجازة القلبية الرئوية مقابل الدواء الوهمي في الحد من فقدان الدم ونقل الدم في جراحة القلب : تجربة مستقبلية ،عشوائية ، خاضعة للتحكم الوهمي ،مزدوجة التعمية)

توقيع المشترك: .....

التاريخ:.....

## Appendix B

## Study Data Sheet

**Age in years: Sex:**

**Weight in Kg: Height CM:**

**Body Mass Index:**

| | Placebo group | TXA (Pre CPB) | TXA(After CPB) |
|---|---|---|---|
| Hypertension | | | |
| Atrial Fibrillation | | | |
| Previous Heart Surgery | | | |
| Diabetes | | | |
| Coronary Artery Diseases | | | |
| Chronic Obstructive Pulmonary Disease | | | |
| ASA(I.II.III,VI,VI) | | | |
| Body Mass Index | | | |
| Ejection Fraction | | | |
| Medical | | | |
| Isoflurane | | | |
| Aspirin | | | |
| Heparin | | | |
| NaCO3 | | | |
| Mannitol | | | |
| Insulin | | | |
| Surgical | | | |
| Time on Bypass | | | |
| Time Operation | | | |
| Total Heparin Dose | | | |
| Total Protamine Dose | | | |
| Protamine to CCU Time | | | |

## Laboratory

| | Placebo | TXA-Pre | TXA-post |
|---|---|---|---|
| **Preoperative** | | | |
| Hematocrit (%) | | | |
| Hemoglobin (g\dl) | | | |
| Platelet count ($10^3$\$mm^{3)}$) | | | |
| Prothrombin time (s) | | | |
| Partial Prothrombin time (s) | | | |
| International normalized ratio | | | |
| Creatinine | | | |
| Blood urea nitrogen | | | |

| **Intraoperative** | | | |
|---|---|---|---|
| ACT | | | |
| Hematocrit (%) | | | |
| Hemoglobin (g\dl) | | | |
| Platelet count ($10^3$\$\mu L^{)}$) | | | |

| **Postoperative** | | | |
|---|---|---|---|
| Hematocrit (%) | | | |
| Hemoglobin (g\dl) | | | |
| Platelet count ($10^3$\$\mu L^{)}$) | | | |
| Prothrombin time (s) | | | |
| Partial Prothrombintime (s) | | | |
| International normalized ratio | | | |
| Creatinine | | | |
| Blood urea nitrogen | | | |

**Blood Transfusion (unit)**

| Group | Placebo | TXA-pre | TXA-post |
|---|---|---|---|
| Preoperative | | | |
| Units of RBCs | | | |
| Units FFP | | | |
| Units Platelets | | | |
| Cryoprecipitate | | | |

| Intraoperative | | | |
|---|---|---|---|
| Units of RBCs | | | |
| Units FFP | | | |
| Units Platelets | | | |
| Cryoprecipitate | | | |

| | | | |
|---|---|---|---|
| Postoperative | | | |
| Units of RBCs | | | |
| Units FFP | | | |
| Units Platelets | | | |
| Cryoprecipitate | | | |

**Total Blood Loss (ML)**

| Group | Placebo | TXA-pre | TXA-post |
|---|---|---|---|
| Intra-operative | | | |
| First 24 h post-op(Mediastinal chest tube drainage) | | | |
| 48 h post –op(Mediastinal chest tube drainage) | | | |

**Side Effect of Tranexamic Acid**

| Group | Placebo | TXA-pre | TXA-post |
|---|---|---|---|
| Drowsiness | | | |
| Agitation | | | |
| Focal Neurological Deficit | | | |
| Convulsion | | | |
| Coma | | | |

## Appendix C

## Tables of Study

**Table C.1**

*Comparisons between study groups regarding intraoperative blood transfusion indicators (Number of patients who took units ≥1) (N=99)*

| Intraoperative Blood Transfusion Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Units of RBCs | 32(97%) | 29(87.9%) | 23(69.7%) | 84(84.8%) | 0.007 |
| Units FFP | 25(75.8%) | 26(78.8%) | 26(78.8%) | 77(77.8%) | 0.943 |
| Units Platelets | 30(90.9%) | 31(93.9%) | 30(90.9%) | 91(91.9%) | 0.873 |
| Cryoprecipitate | 11(33.3%) | 13(39.4%) | 10(30.3%) | 34(34.3%) | 0.731 |

The P-values are related to Chi-square test for qualitative variables. Numbers in the table represent %.

**Table C.2**

*Comparisons between study groups regarding Postoperative Blood Transfusion Indicators (Number of patients who took units ≥1) (N=99)*

| Postoperative Bloo d Transfusion Indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Units of RBCs | 29(87.9%) | 12(36.4%) | 18(54.5%) | 59(59.6%) | <0.001 |
| Units FFP | 4(12.1%) | 1(3%) | 2(6.1%) | 7(7.1%) | 0.341 |
| Units Platelets | 3(9.1%) | 3(9.1%) | 1(3%) | 7(7.1%) | 0.541 |
| Cryoprecipitate | 4(12.1%) | 2(6.1%) | 1(3%) | 7(7.1%) | 0.341 |

* P-values are related to Chi-square test for qualitative variables. Numbers in the table represent n%.

**Table C.3**

*Comparisons between Study groups regarding the Blood Loss Indicators (N=99)*

| Blood loss indicators | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| INTRAOPERATIVE | 348.33 ± 287.61 | 327.88 ± 182.75 | 303.64 ± 145.23 | 326.62 ± 212.46 | 0.698 |
| First 24 h post-op(Mediastinal chest drainage) | 651.36 ± 374.58 | 567.27 ± 260.58 | 500.33 ± 217.65 | 572.99 ± 295.49 | 0.114 |
| 48 h post –op(Mediastinal chest drainage) | 209.45 ± 148.93 | 166.27 ± 126.33 | 110.52 ± 60.08 | 163.14 ± 124.4 | 0.005 |
| 72 h post –op(Mediastinal chest drainage) | 41.67 ± 37.87 | 27.12 ± 34.19 | 14.87 ± 22.72 | 28.15 ± 33.9 | 0.006 |

***** P-values are related to the Two Independent Samples T-test and numbers in the table represent Mean ± Standard Deviation.

**Table C.4**

*Comparisons between study groups regarding side effect of Tranexamic Acid (N=98)*

| Tranexamic Acid | N=33 | TXA N=33 | TXA N=32 | N=98 | |
|---|---|---|---|---|---|
| Drowsiness | 2(6.1%) | 6(18.2%) | 1(3.1%) | 9(9.2%) | 0.082 |
| Agitation | 0(0%) | 1(3%) | 0(0%) | 1(1%) | 0.370 |
| Focal Neurological Deficit Seizure | 0(0%) | 0(0%) | 0(0%) | 0(0%) | ----- |
| | 0(0%) | 0(0%) | 0(0%) | 0(0%) | ----- |
| Coma | 0(0%) | 1(3%) | 1(3.1%) | 2(2%) | 0.595 |

* P-values are related to the Chi-square test and numbers in the table represent n %.

**Table C.5**

*Comparisons between study groups regarding the Outcome Measurements (N=99)*

| Outcome Measurements | Control N=33 | Pre –CPB TXA N=33 | Post-CPB TXA N=33 | Total N=99 | P-value* |
|---|---|---|---|---|---|
| Re-opening | 2(6.1%) | 1(3%) | 3(9.1%) | 6(6.1%) | 0.587 |
| Died | 0(0%) | 1(3%) | 4(12.1%) | 5(5.1%) | 0.044* |
| V-TAK GLOBAL HYPOKINESIA | 0(0%) | 0(0%) | 1(3%) | 1(1%) | 0.364 |
| STROKE | 0(0%) | 0(0%) | 2(6.1%) | 2(2%) | 0.130 |
| Cardiac tamponade | 0(0%) | 1(3%) | 0(0%) | 1(1%) | 0.364 |
| V.FIB | 0(0%) | 0(0%) | 1(3%) | 1(1%) | 0.364 |
| Infection | 0(0%) | 0(0%) | 1(0%) | 1(1%) | 0.364 |
| BRAIN HEMRRAHGE AFTER 9 DAYS | 0(0%) | 1(3%) | 0(0%) | 1(1%) | 0.364 |

* P-values are related to the Chi-square test and numbers in the table represent n%.

جـامعـــة النجاح الوطنية
كليـــة الدراســـات العليـــا

# فعالية إعطاء حمض الترانيكساميك قبل وبعد المجازة القلبية الرئوية مقابل الدواء الوهمي في الحد من فقدان الدم ونقل الدم في جراحة القلب: تجربة مستقبلية، عشوائية، خاضعة للتحكم الوهمي، مزدوجة التعمية

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قدمت هذه الرسالة استكمالا لمتطلبات الحصول على درجة الماجستير في تمريض التخدير، من كلية الدراسات العليا، في جامعة النجاح الوطنية، نابلس– فلسطين.

2022

# فعالية إعطاء حمض الترانيكساميك قبل وبعد المجازة القلبية الرئوية مقابل الدواء الوهمي في الحد من فقدان الدم ونقل الدم في جراحة القلب: تجربة مستقبلية، عشوائية، خاضعة للتحكم الوهمي، مزدوجة التعمية

**إعداد**

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## الملخص

المجازة القلبية الرئوية هي تقنية مستخدمة للسيطرة على كل من القلب والرئتين اثناء اجراء العملية الجراحية، ولها فوائد كثيره ولكن لها ايضا نصيبها من المضاعفات واهمها فقدان الدم والنزيف، يمكن استخدام مضادات الفبرين مثل حمض الترانيكساميك للحد من فقدان الدم.

تهدف هذه الدراسة لتقييم الفعالية والأمان السريريين لدواء حمض الترانيكساميك في تقليل النزيف وفقد الدم، والحاجة إلى عمليات نقل الدم باستخدام المجازة القلبية الرئوية.

دراسة مستقبلية، عشوائية، خاضعة للتحكم الوهمي، مزدوجة التعمية. تتكون عينة الدراسة من 99 مريضاً ينقسمون الي 3 مجموعات. مجموعة قبل المجازة الرئوية حيث يعطى المريض 3 جرع من حمض الترانكسميك اولها قبل بداية المجازة والمجموعة الثانية بعد المجازة الرئوية حيث يعطى حمض الترانكسميك بجرعتين اولهما بعد المجازة الرئوية والمجموعة الاخيرة هي مجموعة الدواء الوهمي حيث لا تعطى اي جرعة من حمض الترانكسميك.

أظهرت النتائج فروق ذات دلالة إحصائية بين مجموعات الدراسة الثلاث في اعطاء وحدات كرات الدم الحمراء، حيث أظهرت النتائج أن متوسط وحدات كرات الدم الحمراء في مجموعة العلاج الوهمي

(المتوسط=1.42) وحدة أعلى من مجموعة قبل المجازة القلبية الرئوية (المتوسط = 0.61) ومن المجموعة ما بعد المجازة القلبية الرئوية (المتوسط =0.64). وفيما يتعلق بكمية الدم النازف من خلال انبوب تصريف الصدر بعد 48 ساعة من العملية، تُظهر نتائج متوسط (انبوب تصريف الصدر) في المجموعة العلاج الوهمي (المتوسط = 209.45 سم ) بشكل ملحوظ فقط. وهو أعلى من متوسط مجموعة ما بعد المجازة القلبية الرئوية (المتوسط = 110.52 سم) P = 0.005.

وفيما يتعلق بالدم النازف بعد 72 ساعة من العملية، تُظهر النتائج متوسط مجموعة العلاج الوهمي (المتوسط = سم41.67) وهو أعلى من متوسط ما بعد المجازة القلبية الرئوية حيث =14.87، P = 0.006.

أثبتت الدراسة بشكل حاسم أن اعطاء حمض الترانيكساميك بعد الانتهاء من المجازة القلبية الرئوية لها فوائد جيدة للغاية بالتقليل من فقدان الدم الناتج بعد العمليات القلبية المستخدم فيها المجازة القلبية الرئوية. فإن إعطاء حمض الترانيكساميك في مجموعة بعد المجازة القلبية الرئوية له أفضل التأثيرات عند مقارنته بمجموعة العلاج الوهمي، فإنه يقلل من فقدان الدم على مدار 48 و72 ساعة والحاجة إلى نقل وحدات دم اقل. اما بالنسبة للتأثير الإيجابي لمجموعة قبل المجازة القلبية الرئوية كان اقل وضوحًا.

**الكلمات المفتاحية:** المجازة القلبية الرئوية، تطعيم مجازة الشريان التاجي، حمض الترانيكساميك، النزيف، نقل الدم.