Chapter One

1. Introduction and Literature Review

1.1 Introduction

The haemostatic mechanism have several important function. first maintain blood in fluid state .second to arrest bleeding at the side of injury or blood loss by formation of hemostatic plug . Third they must insure the eventual removal of the balance between these conflicting tendencies and deficiency of any one may lead to either thrombosis or hemorrhage(john *et al*., 1995).

Cardiac surgery activates the coagulation system with an initial hyper coagulable state and platelet activation, followed by factor and platelet consumption. Hypothermia, acidosis, Hypocalcaemia and the dilutional effects of circuit priming all increase the risk of bleeding.(Prisco *et al*., 2003).

Platelet transfusion in the per operative period has been associated with an increased risk of serious adverse events (Spiess *et al*., 2004).

Indeed both red cell and platelet transfusion have been shown to have a negative risk-adjusted effect on health-related quality of life after cardiac surgery. The haemostatic status of a patient undergoing cardiopulmonary bypass can change very quickly because of hemorrhage or the use of high dose heparin or protamine and as such blood component administration in cardiac surgery can often be empiric. This is compounded by the limited utility of the standard coagulation tests, which have a slow turnaround time in a setting where there can be rapid changes in coagulation status. All patients presenting for cardiac surgery will be anticoagulated in the preoperative period, either for cardiac or non-cardiac reasons, and an

appropriate balance needs to be struck between minimizing preoperative blood loss and use of homologous blood products, and avoiding pathological thrombosis. Coagulation status can be measured by means of laboratory tests or near-patient tests (also referred to as point-of-care tests). Effective use and interpretation of these tests can guide physicians and surgeons alike in the use of medications and homologous blood products and timely intervention of surgery to optimize patient outcomes (Koch *et al*., 2006).

1.2. Literature Review

1.2.1 Haemostasis:

1.2.1.1 Normal haemostasis:

Is a consequence of tightly regulated processes that maintain blood in a fluid state in normal vessels, yet also permit the rapid formation of a haemostatic clot at the site of a vascular injury (Hoffbrand and Moss, 2010).

1.2.1.2Primary hemostasis:

Primary hemostasis involves platelets and vwf and results in the formation of platelet plug. If the endothelial injury is small, this may be adequate to stop bleeding however, if the injury is greater, participation by the coagulation csscad is required. Platelets and blood vessels play key role in primary hemostasis (Hoffbrand, 2002).

1.2.1.3 Blood vessels:

Blood vessels Contain three layers:inteima, media,adventia.It is materials that make up that make up these layers and the size of these layers themselves that differentiate arteries from vein .The endothelium function in multitude of physiological processes including the control off cellular trafficking, the regulation of vasomotor and maintenance of blood fluidity .ECs possess surface receptors for avariety of physiological substance example thrombin and angiotensin II,which may influence vascular tone directly or directly .Once activated ,ECs express at their surface,and in some cases release into the plasma, avariety of intracellular adhesion molecules which modulate platelet adhesion and vascular permeability (Hoffbrand, 2005).

The normal haemostatic response to vascular damage depend on closely linked interaction between the blood vessels wall, circulating platelet and

blood coagulation factors. An efficient and rapid mechanism for stopping bleeding from sites of blood vessel injury is clearly essential for survival .nevertheless, such a response needs to the tightly controlled to prevent extensive colt developing and to break down such clot once damage is repaired.|(Hoffbrand, 2005)The haemostatic system thus represent delicate balance between anticoagulant and procoagulant mechanisms allied to the process for fibrinolysis (Hoff brand and Moss, 2010).

There are five major component involve in homeostasis include: blood vessels, platelets, coaculation factors ,natural inhibitors of the coagulation cascade ,and fibrinolysis (Hoff brand and Moss, 2010).

1.2.1.4 Platelets:

Platelets are disc-shaped, anucleate cell fragments that are shed from megakaryocytic in the bone marrow into the bloodstream (Hoff brand, 2002)**.**

They play a critical role in normal haemostasis by forming the haemostatic plug that initially seals vascular defects, and by providing a surface that recruits and concentrates activated coagulation factors. Their function depends on several glycoprotein receptors, acontractile cytoskeleton, and two types of cytoplasm granules. α-Granules have the adhesion molecule P-selectin on their membranes and contain fibrinogen, fibronectin, factors V and VIII, platelet factor 4 (a heparin-binding chemokine), platelet derived growth factor (PDGF), and transforming growth factor-β (TGF-β). Dense (or δ) granules contain ADP and ATP, ionized calcium, histamine, serotonin, and epinephrine (Hoff brand, 2002)**.**

1.2.1.4.1 Platelet function in haemostasis

Platelets respond to vascular wall damage by adhesion, aggregation, release of granule content and morphological changes. Von Willebrand

Factor is a plasma protein that acts as abridge between platelets and the exposed collagen of damaged tissue. The platelet binding site is the membrane glycoprotein GPIb-VIX. Von Will brand Factor also acts as a carrier protein for, and stabilizer of FVIII, preventing premature photolytic degradation by Protein C (Hoff brand, 2005)**.**

1.2.1.5Coagulation pathways

Coagulation requires complex interactions of cellular and molecular components, mainly involving platelets, plasma and red blood cells. The process was classically described as a cascade of 'Intrinsic', 'Extrinsic', and 'Common' pathway. These pathways The Intrinsic Pathway is activated when FXII binds to exposed collagen of damaged endothelium. The cascade of activations occur as shown, and amplification also occurs (for example FXIIa converts prekallikrien to kallikrien and auto-activates more FXII). The resulting "Tenase" complex (aare useful in terms of interpreting some of the coagulation tests, but in vitro coagulation is less linear and occurs by a combination of these pathways. Current understanding of thecoagulation process is best described by the cell-based model. (Hoffbrand, 2002)**.**

The coagulation factors were discovered in the 1940s and 1950s. They are proenzymes found in plasma, which are converted to active enzymes during the coagulation process. The factors were assigned roman numerals in the order they were discovered; each factor also has one or more names (Monroe *et al*., 2007).

The numerals are prefixed by "F" is used to indicate the activated form of the factor activates FX. The Extrinsic Pathway is initiated by Tissue Factor, and results in a TF/FVIIa complex (in a dashed yellow line) that activates FX (Hoffbrand and Moss, 2010).

Table (1.1) The coagulation factors (Hoff brand and Moss, 2010)**.**

Factor number	**Descriptive name**	**Active form**
I	Fibrinogen	Fibrin submit
II	Prothrombin	Serine protease
III	Tissue factor	Receptor/cofactor*
V	Labile factor	Cofactor
VII	Proconvertin	Serine protease
VIII	Ant haemophilic factor	Cofactor
IX	Christmas factor	Serine protease
X	Stuart-power factor	Serine protease
XI	Plasma thromboplastin antecedent	Serine protease
XII	Hageman (contact) factor	Serine protease
XIII	Fibrin-stabilizing factor Prekallikrein (Fletcher factor) HMWK (FitzGerald factor)	Transglutaminas Serine protease Cofactor*

1.2.1.5.1 The coagulation cascade:

The coagulation cascade of secondary haemostasis has two pathways which lead to fibrin formation. These are the contact activation pathway (formerly known as the intrinsic pathway), and the tissue factor pathway (formerly known as the extrinsic pathway). It was previously thought that the coagulation cascade consisted of two pathways of equal importance joined to a common pathway. It is now known that the primary pathway for the initiation of blood coagulation is the tissue factor pathway. The pathways are a series of reactions, in which a

zymogene (inactive enzyme precursor) of a serine protease and its glycoprotein co-factor are activated to become active components that then catalyze the next reaction in the cascade, ultimately resulting in cross-linked fibrin.(paltt, 2008)

The coagulation factors are generally serine protease (enzymes). There are some exceptions. For example, FVIII and FV are glycoproteins, and Factor XIII is a transglutaminase. Serine proteases act by cleaving other proteins at specific sites. The coagulation factors circulate as inactive zymogen. The coagulation cascade is classically divided into three pathways. The tissue factor and contact activation pathways both activate the "final common pathway" of factor X, thrombin and fibrin (pallister and Watson, 2010).

1.2.1.5.2 Contact activation pathway (intrinsic)

The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), prekallikrein, and FXII (Hageman factor). Prekallikrein is converted to kallikrein and FXII becomes FXIIa. FXIIa converts FXI into FXIa. Factor XIa activates FIX, which with its co-factor FVIIIa form the tenase complex, which activates FX to FXa. The minor role that the contact activation pathway has in initiating clot formation can be illustrated by the fact that patients with severe deficiencies of FXII, HMWK, and prekallikrein do not have a bleeding disorder. Instead, contact activation system seems to be more involved in inflammation. Patients without FXII (Hageman factor) suffer from constant infections (Platt, 2008).

1.2.1.5.3 Final common pathway

Thrombin has a large array of functions. Its primary role is the conversion of fibrinogen to fibrin, the building block of a haemostatic

plug. In addition, it activates Factors VIII and V and their inhibitor protein C (in the presence of thrombomodulin), and it activates Factor XIII, which forms covalent bonds that crosslink the fibrin polymers that form from activated monomers (pallister and Watson, 2010).

Following activation by the contact factor or tissue factor pathways, the coagulation cascade is maintained in a prothrombotic state by the continued activation of FVIII and FIX to form the tenase complex, until it is down-regulated by the anticoagulant pathways (pallister and Watson, 2010).

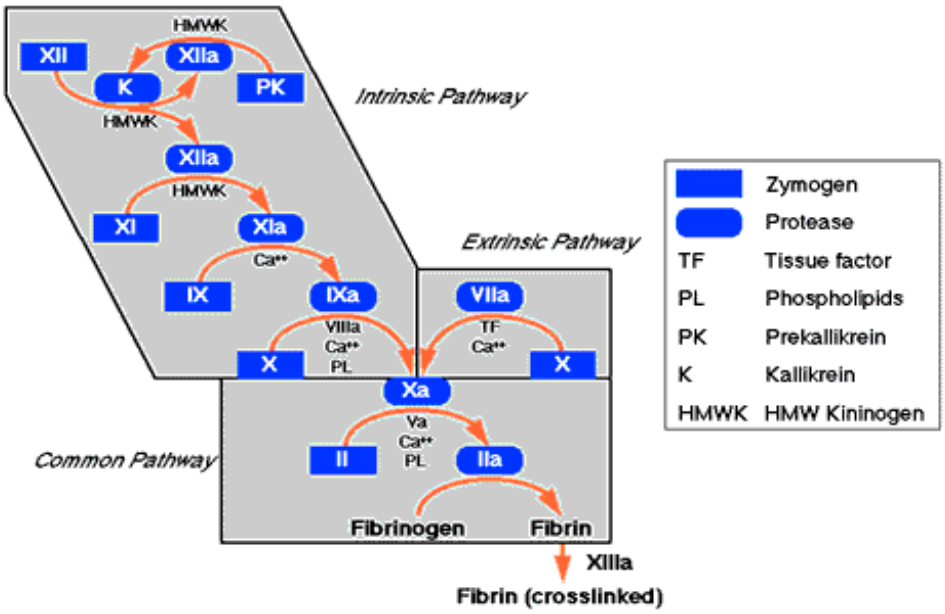

Figure (1) The classical blood coagulation pathway.(john *et al.*, *1995*)

1.2.1.5.4 Cofactors:

Various substances are required for the proper functioning of the coagulation cascade.(Hoff brand, 2002).

Firstly: Calcium and phospholipid, (a platelet membrane constituent) are required for the tenase and prothrombinase complexes to function. Calcium mediates the binding of the complexes via the terminal gamma-carboxyl residues on FXa and FIXa to the phospholipid surfaces expressed by platelets, as well as procoagulant micro particles or micro

vesicles shed from them. Calcium is also required at other points in the coagulation cascade. (Hoff brand 2002) .

Secondly: Vitamin K, is an essential factor to a hepatic (t-PA), which is synthesized and secreted by endothelium. Plasmin proteolytically cleaves fibrin into fibrin degradation products that inhibit excessive fibrin formation. . Fourthly, Prostacyclin (PGI2) is released by endothelium and activates platelet Gs protein-linked receptors. This, in turn, activates, which synthesizes cAMP. cAMP inhibits platelet activation by decreasing cytosolic levels of calcium and, by doing so, inhibits the release of granules that would lead to activation of additional platelets and the coagulation cascade (pallister and Watson, 2010).

1.2.2 Fibrinolysis:

Eventually, blood clots are reorganized and desorbed by a process termed fibrinolysis. The main enzyme responsible for this process (plasmin) is regulated by various activators and inhibitors.(David *et al.,* 2009).

1.2.2.1 Inhibitors of plasminogen activater

Just as there are inhibitor to plasmin ,there are also inhibitor-1 (PAI-I). a second inhibitor of plasminogen activation is called plasminogen activator inhibitor-2 (PAI-2).the concentration of PAI-2 is high during pregnancy and is present in high concentration in placental circulation . Otherwise, it plays a relatively minor role (David *et al*., 2009).

1.2.3The Heart

The heart is a muscular organ about the size of a closed fist that functions as the body’s circulatory pump. It takes in deoxygenated blood through the veins and delivers it to the lungs for oxygenation before pumping it into the various arteries (which provide oxygen and nutrients to body tissues by transporting the blood throughout the body). The heart is

located in the thoracic cavity medial to the lungs and posterior to the sternum (Tanya Lewis, 2015).

1.2.3.1 Pre –cardiac surgery

Preoperative investigations in cardiac surgery can be divided into diagnostic studies and assessment of fitness for surgery. Diagnostic investigations are used to detect and evaluate coronary, valvular, myocardial and thoracic aortic disease. Knowledge of an individual patient's co-morbidities helps to determine the risk of postoperative morbidity and mortality, and allows for more accurate informed consent. Furthermore, the results of preoperative investigations may predict the likely postoperative support required in order to maximize the chances of uneventful recovery. New innovations such as transcatheter aortic valve implantation (TAVI) procedure are increasingly being used as alternatives to open heart surgery for very high-risk patients with severe aortic stenosis. This contribution highlights the tests for preoperative diagnosis and assessment of fitness for surgery in adult cardiac patients. In combination they guide clinicians in making appropriate management decisions, particularly with regard to elderly, frail or complex cardiac cases discussed in the setting of joint cardiology and cardiothoracic meetings (Pat Melanson , 2001).

1.2.3.2 Post- cardiac surgery

The resident should be present in the ICU when the patient arrives from the operating room to receive a sign-over from the anesthesiologist and the cardiac surgical team. During this period, the ICU nurses will be transferring the patient to the ICU monitors and checking all lines and infusions. The nurse will then do the initial set of hemodynamic readings. The Respiratory Technician will place the patient on a ventilator. Unless

the patient is unstable it is best to stay out of the way of the nurses during this period, and wait until they are finished with their assessment before examining the patient (Kunal *et al* .,2001).

1.2.4 Risks of heart surgery

The development of cardiac surgery and cardiopulmonary bypass techniques has reduced the mortality rates of these surgeries to relatively low ranks. For instance, repairs of congenital heart defects are currently estimated to have 4–6% mortality rates (Stark *et al*., 2000) . A major concern with cardiac surgery is the incidence of neurological damage. Stroke occurs in 2–3% of all people undergoing cardiac surgery, and is higher in patients at risk for stroke (klitzner *et al.*, 2006).

cardiopulmonary bypass is known as post perfusion syndrome, sometimes called "pumphead". The symptoms of post perfusion syndrome were initially felt to be permanent (Newman *et al*., 2001). But were shown to be transient with no permanent neurological impairment. Neuropsychological and psychopathologic changes following open heart surgery have been recognized from the very beginning of modern heart surgery (Vandijk *et a l.*, 2002). Variables correlated with nonpsychotic mental disorder after cardiac surgery must be divided into pre-, intra- and postoperative. The incidence, phenomenology, and duration of symptoms diverge from patient to patient, and are difficult to define (Bendet *et al*., 1980).

1.2.4.1Bleeding

Bleeding can be divided into:

- Medical" bleeding secondary to defects in the coagulation cascade, platelets, or fibrinogen.

- Surgical" bleeding secondary to operative trauma including leaks at sites of vascular anastomosis or cannulation sites or bleeding from small mediastinal arteries or veins. Surgical bleeding requires a return to the or for re-exploration and hemostasis.
- Surgical bleeding: Consider a "surgical" source of bleeding in the following situations: Persistent bleeding in the absence of a specific haemostatic defect normal coagulation parameters. (Pat Melanson, 2001)

Sudden onset of fresh, rapid bleeding; especially if associated with a preceding sudden increase in BP. Note that repositioning the patient (turning on their side) may also cause the drainage of a pre-existing collection of "old" darker blood that had pooled in the thorax . Greater than 500 cc of bleeding in the first post-op hour ,> 400 cc/hr x 2 hours, > 300 cc/hr x 3 hours,> 200 cc/hr x 4 hours ,if any of the above criteria are noted you must notify the ICU should be notified about any significant bleeding whether it is believed to be "medical" or "surgical. Etiology of "medical" bleeding: Residual heparin effect; patients are anticoagulated before going on CPB with a large dose of heparin to maintain their ACT >400. The heparin is 'reversed' at the end of the case with protamine. Occasionally, the calculated dose of protamine given is not sufficient to completely reverse the heparin effect. Patients may also receive additional heparin if they are given back blood that remained in the bypass circuit when the patient was disconnected from CPB ("pump blood").

A "heparin rebound phenomenon" can also occur several hours post-op. An ACT will be done as soon as the patient arrives in the ICU. Normal values are between 100 and 120 seconds. Qualitative platelet defects. Platelet function may be impaired for several reasons. Many patients are

on anti-platelet agents pre-operatively. CPB also leads to impaired platelet function, and the longer the duration of CPB, the greater the impairment. Quantitative platelet defects. Platelet numbers can be decreased following CPB due to hemodilution, destruction, and aggregation. Clotting factor deficits. Hemodilution on CPB or consumption.Pre-operative defects secondary to hepatic disease. Fibrinogenolysis; plasminogen activation during CPB. Clinical DIC is rare (PatMelanson, 2001).

1.2.5Causes of Heart Disease

Coronary heart disease (CHD) begins with damage to the lining and inner layers of the coronary heart) arteries. Several factors contribute to this damage.

They include:

- Smoking, including secondhand smoke.
- High amounts of certain fats and cholesterol in the blood.
- High blood pressure.
- High amounts of sugar in the blood due to insulin resistance or diabetes.
- Blood vessel inflammation

1.2.6Types of heart surgery

- Coronary artery bybas grafting CABG
- Open heart surgery
- Heart valve repair or replacement
- Mitral valve repair MVR
- Cardiac catheterization (national institute of health, 2010)

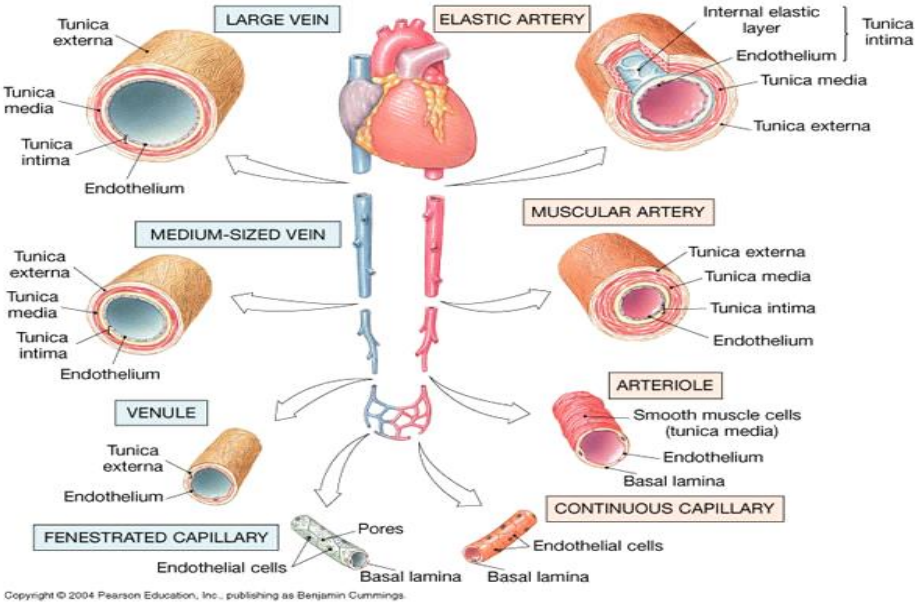

Figure :(2) Heart Structure(Tanya Lewies, 2015).

1.2.4 Laboratory coagulation tests:

1.2.4.1 Evaluation of primary hemostsis:

1.2.4.2 Bleeding time test:

The bleeding time is a useful test for abnormal platelet function including the diagnosis of VWF deficiency. It has largely been replaced by the platelet function analysis (PFA-test). It will be prolonged in thrombocytopenia but is normal in vascular causes of abnormal bleeding. The test involves the application of pressure to the upper arm with blood pressure cuff ,after which small incision are made in the flexor surface forearm skin .bleeding stops normally in 3-8 min (Hoff brand and Moss, 2010).

1.2.4.3 Platelet count:

Was count plt by automated hematology cell counter (sysmex Kx21N) this counter are based on the coulter principle (electrical resistance principle) which depend on the fact that the blood cells are non

conductive to electricity, so when they pass through an electrical field they will increase the electrical impedance (resistance).

1.2.4.4 APTT Activated Partial Thromboplastin Time:

The APTT uses phospholipid usually derived from an extract of rabbit or bovine brain tissue (the partial thromboplastin reagent) and an activator of the contact activation system such as silica particles. The anticoagulated test plasma is added to the partial thromboplastin/activator mix and incubated briet1. CaCI2 is added to initiate clotting and clot formation (Lewis *et al. ,2006*).

The APTT is prolonged with deficiencies of the contact activation pathway (factors XII, XI. IX. VlII also HMWK and PKK) and the common pathway (X. V. prothromhin. And fibrinogen). The PTT will be normal with pure factor VII deficiency. It is prolonged in liver disease, vitamin K deficiency therapeutic warfarin and heparin anticoagulation, DIC, and with high levels of Fl, Ps (Lewis *et al. ,2006*).

1.2.4.5 Prothrombin time

The prothrombin time (PT)-along with its derived measures of prothrombin ratio (PR) and international normalized ratio (INR) — are assays evaluating the extrinsic pathway of coagulation. This test is also called "ProTime INR" and "PT/INR". They are used to determine the clotting tendency of blood, in the measure of warfarin dosage, liver damage, and vitamin K status. PT measures factors I (fibrinogen), II (prothrombin), V, VII, and X. It is used in conjunction with the activated partial thromboplastin time (APTT) which measures the intrinsic pathway and common pathway. The reference range for prothrombin time depends on the analytical method used, but is usually around 12–13 seconds (results should always be interpreted using the reference range from the laboratory that performed the test), and the INR in absence of

anticoagulation therapy is 0.8-1.2. The target range for INR in anticoagulant use (e.g. warfarin) is 2 to 3. In some cases, if more intense anticoagulation is thought to be required, the target range may be as high as 2.5-3.5 depending on the indication for anticoagulation. In The Netherlands, the target INR for 'low intensity' is between 2.5 and 3.5 and for 'high intensity' between 3.0 and 4.0 (Fritsma,2002; print *et al.*, 1999).

1.2.4.6 Historical background

The prothrombin time was developed by Dr Armand Quick and colleagues in 1935, and a second method was published by Dr Paul Owren, also called the "p and p" or "prothrombin and proconvertin" method. It aided in the identification of the anticoagulants dicumarol and warfarin(Jak Anesl, 2005). and was used subsequently as a measure of activity for warfarin when used therapeutically.

The INR was invented in the early 1980s by Tom Kirkwood working at the UK National Institute for Biological Standards and Control (and subsequently at the UK National Institute for Medical Research) to provide a consistent way of expressing the prothrombin time ratio, which had previously suffered from a large degree of variation between centres using different reagents. The INR was coupled to Dr Kirkwood's simultaneous invention of the International Sensitivity Index (ISI), which provided the means to calibrate different batches of thromboplastins to an international standard.(Kirkwood, 1983). `

The INR became widely accepted worldwide, especially after endorsement by the World Health Organization (Anonymous, 1983).

1.2.4.7PT and INR

Are used to monitor the effectiveness of the anticoagulant warfarin. This drug affects the function of the coagulation cascade and helps inhibit the

formation of blood clots. It is prescribed on a long-term basis to people who have experienced recurrent inappropriate blood clotting. The goal of warfarin therapy is to maintain a balance between preventing clots and causing excessive bleeding. This balance requires careful monitoring. The INR can be used to adjust a person's drug dosage to get the PT into the desired range that is right for the person and his or her condition. (Lewis *et al. ,2006*).

Warfarin may be prescribed for conditions such as:

- Irregular heartbeat (atrial fibrillation)
- The presence of artificial heart valves
- Deep vein thrombosis (DVT), pulmonary embolism (PE)
- Antiphospholipid syndrome
- Occasionally, in heart attacks with certain risk factors (American Association, 2001).

1.3 Rational:

Cardiac surgery has been prevalence Rate in Sudan which with high morbidity and mortality patient.

Patient under cardiac surgery affected by bleeding and thrombotic tendency which is fatal.

There are some changes realize in coagulation parameters were an increase in PT, INR, APTT, and decrease in Platelets count in postoperative cardiac surgery.

1.4. Objective:

1.4.1General Objective:

- Measurement of Hemostatic profile in Pre and Post cardiac surgery among patients in Khartoum state.

1.4.2 Specific Objectives:

- To measure PT, APTT, and Platelets count pre and post cardiac surgery.
- To measure Platelets count Pre and post cardiac surgery.
- To compare between PT, APTT, and Platelets count pre and post cardiac surgery .
- To correlate the finding of PT, APTT with age, with possible risk factors gender in cardiac pre and post and types of cardiac surgery.
- To correlate PT, APTT, and Platelets count with types of cardiac surgery .

Chapter Tow

2. Material and Methods

2.1 Study Design:

This is was an analytical cross sectional study subject in Khartoum state in heart hospital center in period from march to may 2015.

2.2: Study population:

The study covered one hundred individuals which include 50% pre cardiac surgery and 50% post cardiac.

2.3 Sample collection:

Five ml Venous blood was collected in tri-sodium citrate anticoagulant container, for test of PT,INR, APTT which was measure by coagulometer and for platelets count five ml in EDTA container.

2.4 Inclusion criteria:

All patients with cardiac diseases, not taken any anticoagulant therapy e.g (warfarin) and other drugs that affect the result in this study were included .

2.5 Exclusion criteria:

Pregnant ladies, neonates, HBV and HIV patients, other medical conditions were excluded from this study.

2.6 Data Collection:

Data was collected using self administrated pre-coded questionnaire which was specifically designed to obtain information including age, sex, duration of the disease and other information.

2.7 Ethical consideration:

Verbale why consent of were taken from all participant after being informed about all detailed objectives of the study and its health benefit future

2.8 Methods:

Coagulation profile PT, APTT were measure using Stago analyzer

2.8.1 Stago coagulometer:

The Stago Coagulation analyzer is an automated system used for in vitro testing of the coagulation system.

2.8.2 Principle:, The Stago analyzer measures the time of clot formation, using an electro-magnetic mechanical clot detection system.

The Prothrombin time (PT) is a basic coagulation screening test for the assessment of congenital and acquired deficiencies of the extrinsic pathway (factors II, V, VII, X). It is also used in monitoring warfarin therapy because of its sensitivity to variations in the concentration of vitamin-K dependent factors.

The activated partial thromboplastin time (APTT) is a basic screening test for the intrinsic coagulation pathway (factors XII, XI, IX, VIII, X, V, II, and I). It is used to detect congenital and acquired deficiencies of these factors and to monitor heparin therapy. (Stago, 1996)

2.8.3 Procedure:

Changing Sampling Modes

1. The Compact Stago can operate in two different patient loading modes, auto mode or manual mode. To change loading modes, select Loading from the main menu.
2. Select Samples. The mode will be displayed near the top of the screen. If you wish to change modes press ESC for options. Choose the desired mode.

Loading Patient Samples in Auto Mode.

1. Choose Loading from the main menu.
2. Select Samples (the sample drawer will open)
3. Ensure that the sample mode is set to auto.
4. Scan or type the accession and press enter on the keyboard
5. Load the tube into the sample drawer.
6. After loading the last sample, press ESC. The drawer will close and processing will begin.

The normal range:

PT: 11-16 sec

APTT: 30-40 sec (lewis *et al*., 2006)

2.9 International normalized ratio

The result (in seconds) for a prothrombin time performed on a normal individual will vary according to the type of analytical system employed. This is due to the variations between different batches of manufacturer's tissue factor used in the reagent to perform the test. The INR was devised to standardize the result. Each manufacturer assigns an ISI value (International Sensitivity Index) for any tissue factor they manufacture. The ISI value indicates how a particular batch of tissue factor compares to an international reference tissue factor. The ISI is usually between 1.0 and 2.0. The INR is the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system being used. (Lewies *et al.*, 2006).

$$INR = \left(\frac{P\ T\ test}{P\ T\ normal}\right)^{ISI}$$

2.10 Interpretation

The prothrombin time is the time it takes plasma to clot after addition of tissue factor (obtained from animals such as rabbits, or recombinant tissue factor, or from brains of autopsy patients). `This measures the quality of the extrinsic pathway (as well as the common pathway) of coagulation. The speed of the extrinsic pathway is greatly affected by levels of functional factor VII in the body. Factor VII has a short half-life and the carboxylation of its glutamate residues requires vitamin K. The prothrombin time can be prolonged as a result of deficiencies in vitamin K, warfarin therapy, malabsorption, or lack of intestinal colonization by bacteria (such as in newborns). In addition, poor factor VII synthesis (due to liver disease) or increased consumption (in disseminated intravascular coagulation) may prolong the PT.(Lewies *et al*., 2006).

The INR is typically used to monitor patients on warfarin or related oral anticoagulant therapy. The normal range for a healthy person not using warfarin is 0.8–1.2, and for people on warfarin therapy an INR of 2.0–3.0 is usually targeted, although the target INR may be higher in particular situations, such as for those with a mechanical heart valve. If the INR is outside the target range, a high INR indicates a higher risk of bleeding, while a low INR suggests a higher risk of developing a clot. (Lewies *et al*., 2006).

2.11 Platelets count:

Platelets count measure using cell counter (sysmex Kx21N)

2.11.1 Principle sysmex:

PLT was count by automated hematology cell counter (sysmex Kx21N) this counter are based on the coulter principle (electrical resistance principle) which depend on the fact that the blood cells are non conductive to electricity , so when they pass through an electrical field they will increase the electrical impedance (resistance). The counter has two chambers one for blood cell count and PL counting and sizing , while the other one is for WBC counting and sizing according to their size cells /particles they can be discriminated into cell type or population

2.11.2 procedure:

The sample was mix sufficiently and set it was the sample probe, the start switch was press , when the buzzer sounds two times and when the LCD screen displays analyzing remove the sample .at pressing the start switch the LCD screen displays aspirating ,then make analyzing .

2.11.3 Normal value:

The normal range of PLTcount is between 150-450x/ul (Lewies *et al*., 2006)

2.12 Data analysis:

The data was analyzed using the SPSS computer programmed version 11.5 , T test one way anova test and correlation lated data were presented in tables and figures.

Chapter Three

3. Results

In this study 100 samples (50 pre and 50 post surgical) were examined for comparison of PT, INR, APTT, PLT count in patients suffering from cardiac surgery.

3.1 Demographic data:

The distribution of the study sample by ages between (30 -75) years with mean and STD age and showed high frequency of surgery from (46 – 61) years in Table (3.1) mortality them distribution of study population according to gender showed (29/50%) male and (21/50%) female in figure (3.1).

According to types of cardic disease our data showed that coronary artery by pass was high prevalence(20/50/40/%) followed by cardiac catheter (15/50/30%) and open heart surgery (10/50/20 %) compared with mitral valve only (5/50/10%). in table (3.2).

3.2 Laboratory data:

According to pre cardiac surgery the mean± STD of PT/ sec, APTT/sec, INR the our data show (14.8 ± 1.9), (30.8 ± 3.5), (1.04 ± .148) ,(252 ± 346.5). Respectively show significant decreased P.value (<0.05)in Compare with post cardiac surgery(22.8 ± 5.3), (48.6 ± 21.5), (1.6± .468)

But the Mean ± STD of PLT c/ul in pre cardiac surgery (252 ±346.5) Show insignificant difference p. value (0.011) in compare with post cardiac surgery **(**205±546.3) in table(3. 3).

According to age group 30- 45 the mean ± STD of PT/sec, PTT/sec, INR in pre cardiac surgery our data (14.6±1.6), (30.1±3.4),(1.1±0.19) respectively Show significant decrease p. value (< 0.05) in Compare

with post cardiac surgery (21.4 ±2.8), (47.± 21.4) ,(1.4.±0.25), but the mean ± STD of PLT c/ul in pre cardiac surgery (260.± 149) show insignificant difference p. value (0.138) in compare with post cardiac surgery (255.±64). In table (3.3)

In age group 46- 60 the mean ± STD of PT/sec, PTT/sec, INR , in pre cardiac surgery the our data (14.6±1.6), (47.±21.4), (1.0±99) respectively, Show significant decrease P. value (<0.05) in compare with post cardiac surgery (21.1±2.8) , (30±3.4), (1.4±0.25) but the mean ± STD of PLT c/ul in pre cardiac surgery (225±64) has insignificant difference P. value (0.136) compare with post cardiac surgery (206±54). According to age group 61- 75 the mean ± STD of PT/sec, PTT/sec, INR in pre cardiac surgery the our data (14.6±1.6), (30.±3.9), (0.9±0.07), respectively Show significant decrease p. value (<0.05) in compare with cardiac (21.1±2.8),(52.6.±30.2), (1.3±.130) but the mean ± STD of PLT c/ul in pre cardiac Surgery (242±68) has insignificant difference value (0.119) compared with post cardiac Surgery (260±54). In table (3.4)

According to gender the mean ± STD of PT /sec , APTT/sec ,INR , in 29 male in pre cardiac surgery our data (15.5±2.2), (30±3.43), (1.08±0.16), respectively show significant decrease p- value (<0.05) in compare with post cardiac surgery (25.2±5.6),(44.3±8.27), (1.84±50). But the mean ± STD of PLT c/ul in pre cardiac surgery (258±117) show insignificant difference p-value (0.08) in compare with post cardiac surgery (208±99).

In (21) female the mean ± STD of PT/sec , APTT/sec , INR, in per cardiac surgery our data (13.9±1.1), (30.0±3.6), (0.97±0.08) respectively show significant decrease p- value (<0.05) in compare with post cardiac surgery (19.5±2.0),(54.6±31.3),(1.31±0.11).

But the mean ± STD of PLT c/ul in pre cardiac surgery (249.7±27.4) show significant increase p-value (0.02) in compare with post cardiac surgery (201±47) in table (3.5).

According to types of cardiac surgery the Mean ± STD of PT /sec, APTT/sec ,INR , and PLTS count in coronary artily by pass in pre cardiac surgery our data show (15.7±2.3) , (31.9±3.5), (1.12±0.17) ,respectively significant decrease with p. value (<0.05)in compare with post cardiac surgery (26.9±5.8),(45.5± 7.9), (1.9± 0.52)but the mean± STD of PLTc/ul in pre cardiac surgery (267± 134) with insignificant difference p.value (0.062) in compare with post cardiac surgery (201±69).

In cardiac catheterization the mean ± STD of PT/ sec APTT/sec ,INR ,and PLT c/ul in pre cardiac surgery our data show (14.6±1.6), (29.7±2.6) (1.01± 1.12), respectively with significant with p.value (<0.05) in compare with post cardiac surgery (20.6±2.6), (48.9 ±24), (1.45±0.22), but the mean±STD of PLTc/ul in pre cardiac surgery (240 ± 54) .with insignificant difference p.value (0.383)in compare with post cardiac surgery (211±115) .

in open heart surgery the mean ± STD of PT/sec , APTT/sec ,INR, in pre cardiac surgery our data show (13.8±0.97), (29.8±3.8), (0.96± 0.06) respectively with significant decrease with p. Value(<0.05)in compare with post cardiac surgery , (19.7± 1.7),(56.9 ±36) ,(1.3 ± 0.137) but the mean± STD of PLT c/ul in pre cardiac surgery(230.1± 50)with insignificant difference p. value(0.0117)in compare with post cardiac surgery (197 ± 37) .

According to mitral valve the mean ± STD of PT/sec , APTT/sec / INR , in pre cardiac surgery (14.1±1.2) , (31.3± 4.2), (0.96± 1.03), respectively

with significant with decrease p. value (<0.05) compare with post cardiac surgery (18.8 ± 3.1), (31.3 ± 4.2),(1.3±0.13) but the mean± STD of PLTc/ul in pre cardiac surgery(268 ± 98)with insignificant difference p.value (0.46) compare with post cardiac surgery(224 ± 82). In table (3.6)

Table (3.1): Distribution of study population according to age groups

Age group	Pre	Post	Present
(30-45)yrs	15	15	30%
(46-60) yrs	20	20	40%
(61-75) yrs	15	15	30%
Total	**50**	**50**	**100%**

Figure (3.1): Distribution of study population according to gender.

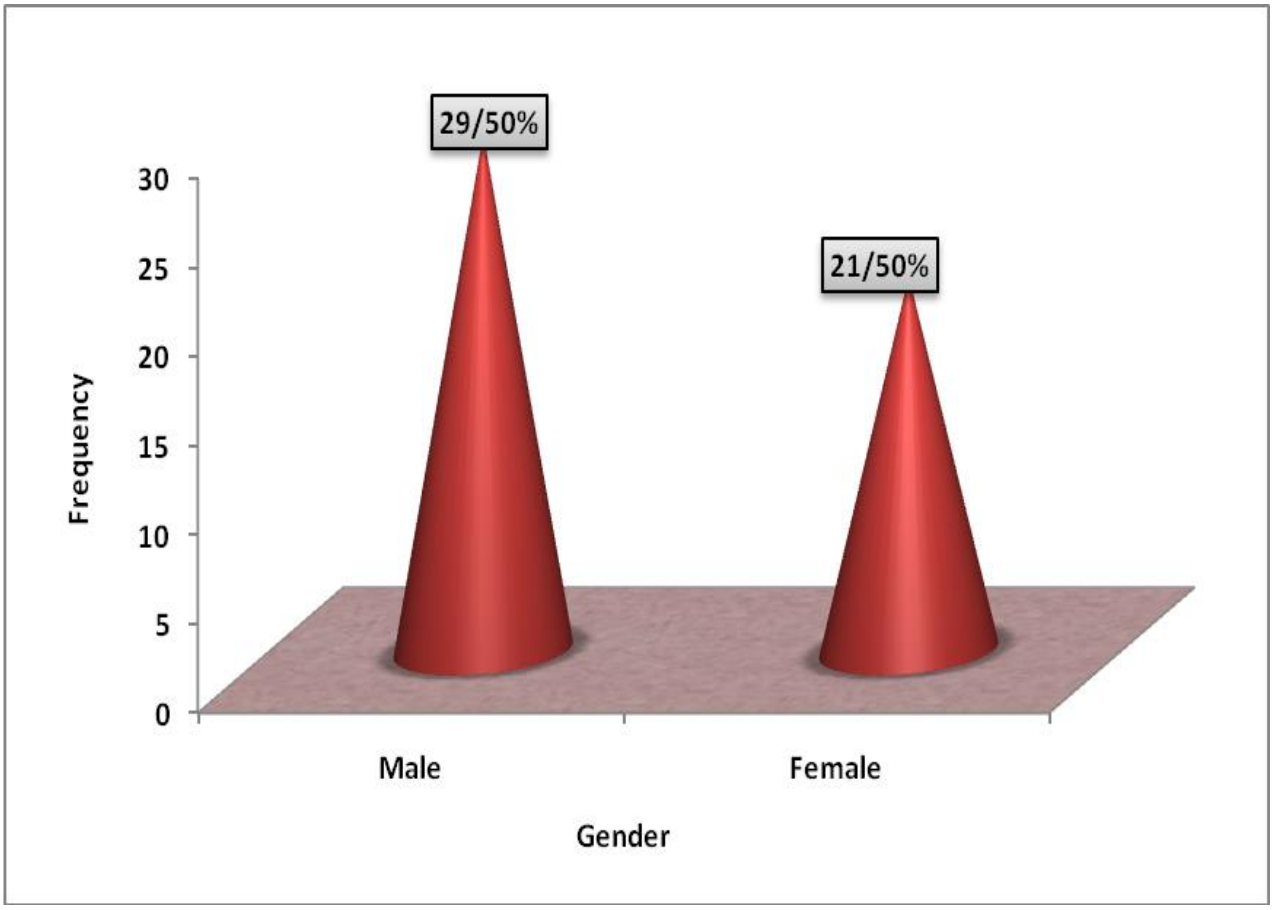

Table (3.2): The distribution of study population according to cardiac surgery

Type of surgery	**Number**	**Percentage**
Coronary artery bypass crafting	20/50	40%
Cardiac catheterization	15/50	30%
Open heart surgery	10/50	20%
Mitral valve repair surgery	5/50	10%
Heart valve repair of replacement	0/50	0%
Total	**50/50**	**100%**

Table (3.3): Comparison of Mean of parameter in pre and post cardiac Surgery

Prameters	**Mean ± STD pre**	**Mean ± STD post**	**P. value**
PT/sec	(14.8 ± 1.9)	(22.8 ± 5.3)	0.000
APTT/sec	(30.8 ± 3.5)	(48.6 ± 21.5)	0.000
INR/sec	(1.04 ± .148)	(1.6± .468)	0.000
PLT c/uL	(252 ± 346.5)	**(**205±546.3)	0.011

Table (3.4): Comparison of mean PT\sec, APTT/sec, INR, Platelets count In case group according to age group

parameters	**Age**	**Mean ± STD in pre**	**Mean ± STD in Post**	**P.value**
	30- 45			
PT/sec		(16.1±2.4)	(28.3±5.8)	0.000
PTT/sec		(30.1±3.0)	(47±21.4)	0.002
INR/sec		(1.1 ±0.19)	(2.1. ± 0.52)	0.000
PLT c/ul		(260 ± 149)	(255 ± 64)	0.138
	46- 60			
PT/sec		(14.6±1.6)	(21.1±2.8)	0.000
APTT/sec		(30±3.4)	(30±3.4)	0.002
INR/sec		(1.0±99)	(1.4±0.25)	0.000
PLT c/ul		(225±64)	(213±101)	0.136
	61- 75			
PT/sec		(14.6±1.6)	(21.1±2.8)	0.000
APTT/sec		(30.±3.9)	(52.6±30.2)	0.013
INR/sec		(.9±.07)	(1.3±.130)	.0.000
PLT c/ul		(242±68)	(206±54)	0.119

Table (3.5): Comparison of mean value PT\sec, PTT\sec, INR, Platelets count according to gender

Parameter	**Gender**	**No**	**Mean ± STD Pre**	**Mean ± STD Post**	**P. value**
PT/sec	Male	29	(15.5±2.2)	(25.2±5.6)	0.000
	Female	21	(13.9±1.1)	(19.5±2.0)	0.000
APTT/sec	Male	29	(30.1±3.43)	(44.3±8.27)	0.000
	Female	21	(30.0±3.6)	(54.6±31.3)	0.002
PLT c/uL	Male	29	(258±117)	(208±99)	0.08
	Female	21	(249.7± 60)	(201±47)	0.02
INR	Male	29	(1.08±0.16)	(1.84±.50)	0.000
	Female	21	(0.97±0.08)	(1.31±0.11)	0.000

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Table (3.6): Comparison of mean of PT\sec, APTT/sec, INR, Platelets count according to different type of surgery

Types of cardiac surgery	Parameters	Mean± SD in pre	Mean± SD in post	P. value
Coronary artery by pass	PT/sec	(15.7±2.3)	(26.9± 5.8)	0.000
	APTT/sec	(31.9±3.5)	(45.5± 7.9)	0.000
	Platelets	(267±134)	(201±69)	0.062
	INR	(1.12± 0.17)	(1.9± 0.52)	0.000
Cardiac catheter	PT/sec	(14.6±1.6)	(20.6± 2.6)	0.000
	APTT/ sec	(29.7±2.6)	(48.9 ± 24)	0.009
	Platelets	(240±54)	(211± 115)	0.383
	INR	(1.01± 0.12)	(1.45 ± 0.22)	0.000
Open heart sugary	PT /sec	(13.8±0.97)	(19.7 ± 1.7)	0.000
	APTT/sec	(29.8±3.8)	(56.9 ± 36)	0.044
	Platelets	(230.1± 50)	(197 ± 37)	0.117
	INR	(0.96± 0.06)	(1.3 ± 0.137)	0.000
Mitral replacement	PT/sec	(14.1±1.2)	(18.8 ±3.1)	0.015
	APTT/sec	(31.3± 4.2)	(44. ±8.2)	0.015
	Platelets	(268 ± 98)	(224 ± 82)	0.46
	INR	(0.96± 1.03)	(1.3 ± 0.13)	0.001

Chapter Four

3. Discussion, Conclusions and Recommendations

4.1 Discussion

Males among patients with heart disease in the current study predominated.

Previous studies showed different findings regarding distribution of heart disease according to gender; In Europe, about 55% of all female deaths are caused by cardiovascular disease (CVD), especially CHD and stroke, compared with 44% of all male deaths (*ECS, 2005*). Other studies by Ford ES and Capewell S also disagrees with our findings, reporting predomination of CVD in females; they justified that, female sex is associated with a longer life expectancy than male sex, women constitute a larger proportion of the elderly population in which the prevalence of CVD is greatest (*Ford ES and Capewell Sm 2007*).

Cases of coronary artery bypass grafting was reported as the most common type of cardiac surgery done among the current participants followed by cardiac catheterization which represented by nearly third of participants .

According to our trail of research there is no similar study record in literature review.

The mean of PT/sec, APTT /sec INR, Platelets count result of study showed an increase in PT/sec, APTT/sec, INR in post cardiac without statistically significant association; p value (<0.05), This agrees with a

study in USA which found a significant increased in PT/sec, APTT/sec, INR, in post operatively because after cardiac surgery occur bleeding as result coagulation factors consumption by (Timothy, 2002).

The mean of Platelets count decreased in post operatively This finding agreed with study in Pakistan by he found Platelets count slightly decreased after surgery dempission for hemostasis in cardiac surgery occur excessive bleeding after cardiac surgery because attraction in haemostatic system and thrombocytopenia. They found the Platelets count insignificant decreased in post operative surgery and also disagreed with study done by (Samuel, 2013).

Showed significant decreased in post cardiac surgery quantitative Platelet abnormality (Thrombocytopenia).

The mean of PT sec, APTTsec, INR in both male and female was significantly increased in post operative cardiac surgery compare with pre cardiac surgery with p.value (<0.05) but the Platelets count was significantly decreased in female post operative cardiac surgery compare with pre cardiac surgery p value (0.02) and decreased insignificantly in male p.value (0.08).

The mean of PT/sec, APTT/sec, INR, in all age groups between was significant increased p.value (<0.05) in post operative cardiac surgery compare with pre cardiac surgery but the Platelets count insignificantly decreased p. value (>0.05).

The mean of PT/sec, APTT/sec, INR was significant increased P. value (<0.05) in all types of cardiac surgery post operatively and PLT count is

decreased insignificantly P. value (>0.05). According to our trial of research, there was no similar study record in literature review.

4.2 Conclusions:

After completion of study the result concluded that:

- There was a significant increasing in PT\sec, APTT\sec INR, and insignificant decreased Platelets count result in patient with cardiac surgery compare with pre cardiac surgery.
- The study revealed that significant difference in PT\sec, APTT\sec, INR, PLT count result according to different types of cardiac surgery.
- There was insignificant increasing in PT/sec ,APTT/sec, INR,and insignificant decraese Platelets count in patient with cardiac surgery compare with pre cardiac surgery according to age group
- There was significant increasing PT/sec, APTTsec, INR , insignificant decreased Platelets count in patient with cardiac surgery compare with pre cardiac surgery according to gender .
- Male predominate more than female.
- No Assosiatin with type of cardiac surgery.
- Most common type of cardiac surgery is coronary artery by bass grafting.

4.3 Recommendations:

Our data recommended the following:-

- Another study should be done with large sample size.
- Coagulation test and CBC should be routine test and it could be done regulatory for patient with cardiac surgery.
- CBCShould be done routinely in all cardiac patient.
- Coagulation center should be established in cardiac centers.
- Farther studies using large sample size.

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Questionnaire 1

- Name:
- Age:
- Sex(male\female):
- What's the type of cardiac surgery?
- Do you exposed to any cardiac surgery/ (yes)-name type of surgery and date?
- Do you have any problem in bleeding or thrombotic tendency?
- What is the results of(PT, APTT,INR,Platelet) Pre and Post cardiac surgery :-
- PT(pre) PT(post)
- APTT (pre) APTT (post)
- INR (pre) INR(post)
- PLT (pre) PLT (post)

Appendix 2

Sysmex (Platelet count)

Stago coagulometer (PT/sec, APTT/sec, INR)