Chapter One

Introduction and Literature Review

1.1 Introduction

Open heart surgery is any type of surgery where the chest is cut open and surgery is performed on the muscles, valves, or arteries of the heart, It is performed by cardiac surgeon frequently it is done to treat complications of heart disease, corrects congenital heart disease or treat valvlar heart disease caused by various thinges including endocarditic .

The heart beat is stopped during the procedure, and the person is placed on a heart lung machine to deliver blood to the body the heart lung machine temporarily serves in place of the heart and lungs by mixing oxygen with the blood and removing carbon dioxide from the blood, and pumping the blood throughout the body although every effort is made to perform minimally invasive procedures (Dearani, 2010).

Coronary heart disease is the most common outcome of the standard risk factors ,equaling in incidence all the other atherosclerotic CVD outcomes combined because it is the most common and most lethal of the atherosclerotic sequelae of the standard risk factors .

Coronary artery disease is the leading cause of death in males and females the presentation, evaluation and treatment of the disease however may differ between women and men (Douglas and Ginsburg, 1996).

The risk of developing coronary disease for any particular risk factor can be seen to vary widely depending on the burden of other associated risk factor ,changes in cardiovascular function during general anesthesia is due to many factors, including direct effects of the anesthetic agent on the heart and indirect effects mediated primarily by the nervous system, in addition depending on the anesthetic's effects on respiration, there may cause changes in oxygen and carbon dioxide contents which exert in direct effects on myocardial contractility and cardiac irritability. In

general, the dominant effects of all the anesthetic agents are to decrease cardiac contractility and lower blood pressure.

The first 48 hours after cardiovascular surgery involve electrolyte imbalance s and fluid shifts (Douglas and Ginsburg, 1996).

Homeostasis is one of number of protective processes that evolved in order to maintain a stable physiology, it has many features in common with other defense mechanisms, such as the immune system and in the inflammatory response (Zack P *et al*, 1994).

Considerable evidence indicates that haemostatic system plays an important role in the pathogenesis of atherosclerotic vascular disease, Yet few of prospective epidemiological studies have examined weather plasma level of haemostatic factors among initially healthy individuals can predict the subsequent incidence of chronic heart disease, an increased plasma fibrinogen concentration and white blood cells (Davies *and* Thomas, 2007).

Haemeostasis refers to the normal response of the vessel to injury by forming a clot that serves to limit hemorrhage; thrombosis is pathological clot formation that results when haemeostasis is excessively activated in the absence of bleeding (Rasche, 2001).

1.2 Literature Review

1.2.1 Physiology of heart

The heart is a muscle that pumps blood through your body, the blood moves through four chambers in the normal heart, the atria that collect blood and the ventricles that pump blood (Walker and Akins, 2007).

The heart functions as pump for the blood throughout both the pulmonary and systemic circulation it weight approximately 250g to350g and is the size of a human fit, it is located in the mediastinum between the lungs and is enclosed in a double walled pericardial sac with a serous membrane between the walls to provide lubricating fluid that facilitate heart movements (Michaell *et al* ., 2000).

The heart functionally separated into left and right halves: the atrium and ventricle on the left side of the heart constitute the left heart: the atrium and ventricle on the right side constitute the right heart, the atria and ventricles on either side of the heart are separated by a well called sptum that prevents blood in the left heart from mixing with blood in the right heart (Bylebyl *et al*, 2000) .

The human heart has four chambers, the upper two chambers the right and left atria are receiving chambers for blood ,the atria are sometimes known as auricles they collect blood that pours in from veins, blood vessels that return blood to the heart, The heart's lower two chambers the ventricles propel blood into arteries, blood vessels that carry blood away from the heart, Four valves within the heart help to prevent blood from flowing backward in the heart, The valves open easily in the direction of blood flow, put when blood pushes against the valves in the opposite direction, the valve close, Two of the valves are located between the atria and ventricles, the other two valves are located between the ventricles and arteries they are called semi lunar valves because each consists of three half moon shaped flaps of tissue (Bylebyl *et al*, 2000).

1.2.2 Heart valves:

Men force by one way flow of blood through the heart, from the atria to the ventricles and into the great arteries that leave the superior part of the heart, heart valves open (to allow blood flow) and close (to prevent the back flow of blood) in response to differences in blood pressure on each side of the valves (Elaine *et al*, 2007).

1.2. 3 Heart diseases

Heart diseases are a common and debilitating condition that affects millions of patients each year, yet obtaining an accurate and timely diagnosis remains difficult, the patient's medical history and results of radiologic and laboratory tests many times do not provide enough information to assure best medical care for each patient (Michaell, 2000).

1.2.4 Types of heart surgery

1-coronary artery bypasses grafting

Coronary artery bypass grafting (CABG) is the most common type of heart surgery, CABG improves blood flow to the heart. (Dearani, 2010).

2-transmyocardial laser revascularization

Tran myocardial laser revascularization (TLR) is a surgery used to treat angina when no other treatments work.

3-valve repair or replacement

This type of surgery repairs defective heart valves if can't repair the valve, it will be replaced with a donor either a biological or mechanical valve, and the valve is opened by cutting the points where the leaflets of the valve meet (Dearani, 2010).

4-ventricular assist devices

Ventricular Assist Devices (VADs) are mechanical pumps that support the heart or take over the heart's pumping action VSDs are used when the heart cant's pump enough blood to support the body.

5-heart transplant

The heart transplant is a surgical transplant procedure performed on patient with end, stage heart failure or severe coronary artery disease the most common procedure is to take a working heart from a recently deceased organ donor and implant it into the patient's own heart may either be removed or less commonly left in to support the donor heart, post operation survival periods average 15 years (Iowe and Baclogeorgy, 2005).

1.2.5 Post operating bleeding after heart surgery

Operative bloodshed into the chest is drained through chest tubes and collected in drainage canisters, and then it stops ,for others it can be more than a liter in these early hours after surgery great efforts are taken to support the patient until coagulation is restored and bleeding subsides, Some patients bleed more because the operation is urgent and the patient is in shock, while others bleed a quite unexpectedly when coagulation problems ensure without apparent cause, occasionally, patients bleed because of a surgical source that needs re-suturing for reinforcement ,whatever the cause, worse out comes and costs are directly tied to the volume of bleeding, and even what are seemingly small volumes can cause problems (Loor *et al* ,2013).

1.2.6 Potential complications during and after heart surgery

Some of the more common complications of heart surgery are routinely dealt with during the hours and days of recovery in the hospital, The patient is closely monitored for these complications by staff and through lab tests it includes:-

-Bleeding may occur at the incision site or from the area of the heart surgery

-ischemic heart damage

Damage to heart tissue caused by a lack of blood flow to the heart

-Death: the risk of death is increased in surgeries where the heart is stopped for the procedure.

-Blood clots: clots may form in and around the heart or travel through the blood stream

-Stroke: often caused by clots that form in the blood after surgery

-Blood loss: in some cases a transfusion may be necessary (Loor et *al.*, 2013).

The use of cardiopulmonary bypass distinguishes cardiac surgery from other types of surgery, it also introduces a unique set of potential postoperative complications, These include vasospasm, altered platelet – endothelial cell interactions and a generalized inflammatory response due to blood contacting the synthetic surfaces of the bypass equipment the result is low flow in the microcirculation of the heart, brain, and other organs which may lead to organ dysfunction(Loor et *al.*, 2013).

1.2.7. Components of normal haemeostasis:-

1.2.7.1 The blood vessel

The blood vessel wall has three layers: intima, media and adventitia the intina consists of endothelium and sub endothelial connective tissue and is separated from the media by the elastic lamina interna, the luminal surface of the endothelial cell is covered by the glycocalyx aproteoglycan coat (Lewis *et al, 2001*).

it contains heparin sulphate and other glycosaminoglycans which are capable of activating antithrombin an important inhibitor of coagulation enzymes, Tissue factor pathway inhibitor (TFPI) is present on endothelial cell surfaces bound to these heparins (Lewis *et al*, 2001).

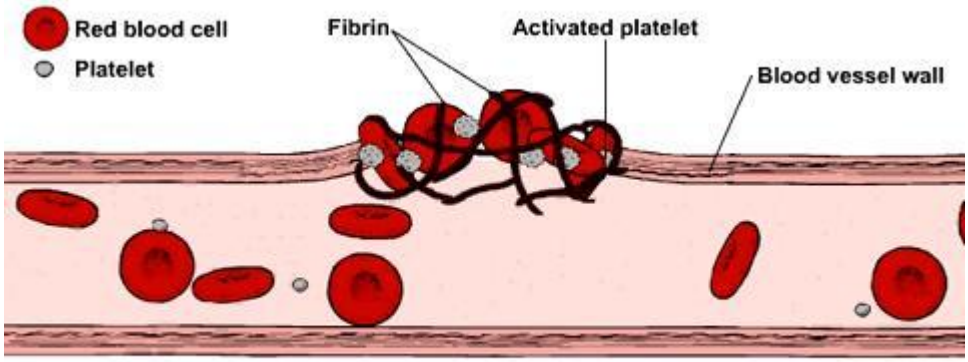

Figure 1.1Blood Clots: Plugging the Breaks

1.2.7.2 Endothelial cell

The luminal surface of the endothelial cell is covered by a glycocalyx, a protoeoglycan coat, it contains heparin sulphate and other glycosaminoglycans, which are capable of activating anti thrombin, endothelial cells express a number of coagulation active proteins that play an important regulatory role such as thrombomodulin and endothelial protein C (Lewis *et al*, 2001).

1.2.7.3 Vasoconstriction

Vessels with muscular coats contract following injury, thus helping to arrest blood loss. Although not all coagulation reactions are enhanced by reduced flow, this probably assists in the formation of a stable fibrin plug by allowing activated factors to accumulate to critical concentrations (Lewis *et al, 2001*).

1.2.7.4 Inhibitors of coagulation

A number of mechanisms exist to ensure that the production of the fibrin clot is limited to the site of injury and is not allowed to propagate indefinitely, there are a number of proteins that bind to and in active the enzymes of the coagulation cascade, probably the first of these to become active is TFPI, which rapidly quenches the factor V11a, TF complex that initiates coagulation (Rasche, 2001).

1.2.7.5. Fibrinolytic system

The deposition of fibrin regulated by the fibrinolytic system ,although this is a complex multi component system with many activators and inhibitors it centers around the fibrinogen and fibrin cleaving enzyme plasmin , plasmin circulates in it's in active precursor from plasminogen which is activated by proteolytic cleavage ,change fibrinogen into fibrin (Rasche, 2001).

1.2.7.6 Platelet

Platelets are small fragments of cytoplasm derived from megakaryocytic they do not contain a nucleus and are bounded by atypical lipid bilayer , the platelet membrane is the site of interaction with the plasma environment and with the damaged vessel wall, it consists of phospholipids,cholesterol,glycolipids and at least nine glycoprotein's ,named GP1 to GP1X the membrane phospholipids are asymmetrically distributed ,with sphingomyelin and phosphatidylcholine predominating in the outer leaflet and phosphatidyle ethanolamine-inositol and serine in the inner leaflet, After platelet activation the membrane also expresses binding sites for several coagulation proteins, including factor X1 and factorV111 (Lewis *et al* ,2001).

1.2.8 Functions of haemeostasis

The haemostatic mechanisms have several important functions:-

-To maintain blood in a fluid state while it remains circulating within the vascular system

-To arrest bleeding at the site of injury or blood loss by formation of a haemostatic plug

-To limit this process to the vicinity of the damage

-To ensure the eventual removal of the plug when healing is complete

Normal physiology thus constitutes a delicate balance between these conflicting tendencies and a deficiency or exaggeration of any one may

lead to either thrombosis or hemorrhage, There are at least five different components involved blood vessels, platelets, plasma coagulation factors and their inhibitors and the fibrinolytic System (Lewis *et al, 2001*).

1.2.9 Classification of haemeostasis

1.2.9.1-primary haemeostasis

Is characterized by vascular contraction ,platelet adhesion and formation of a soft aggregate plug ,it begins immediately aftr endothelial disruption ,injury cause temporary local contraction of vascular smooth muscle ,vasoconstriction slows blood flow ,enhancing platelet adhesion and activation (Germmann and Stanfield, 2005).

1.2.9.1.1 Platelet morphology

Normal platelets are 1-3micrometer in diameter ,they is irregular in outline with fine red granule that may be scattered or centralized, small number of larger platelets, up to 5 micrometer in diameter, may be seen in normal films, larger platelets are seen in the blood when platelet production is increased, and in hyposplenism very high platelet counts as a feature of myloproliferative neoplasm may be associated with extreme platelet anisocytosis, with some granular or hypo granular platelets, The platelet count frequently increases with acute inflammatory stress or bleeding; there is a slight diurnal variation in the platelet count this occurs during the course of a day as well from day to day (Ban and Seed, 1986).

Within the wide normal reference range, there are some ethnic differences and in healthy west Indians and Africans platelet counts may on average be 10-20% lower than these in Europeans living in the same environment, There may be a sex difference thus in women, the platelet count has been reported to be about 20% higher than in men .

A decrease in the platelet count may occur in women at about the time of menstruation, there are no obvious age difference ranges (Ban and Seed, 1986).

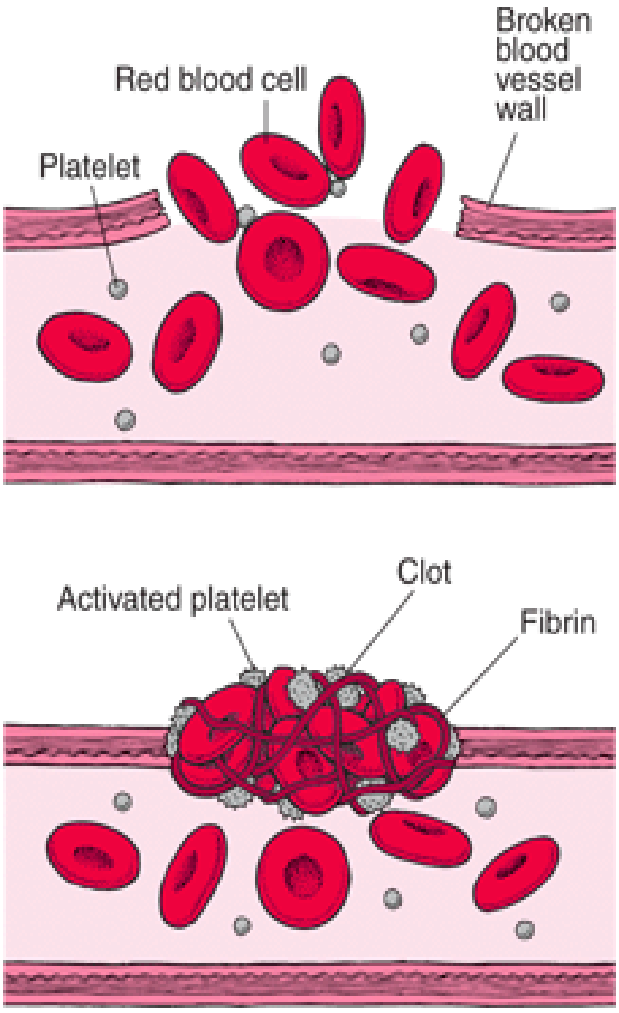

Figure 1.2Mechanism of clot formation

1.2.9.1.2 Platelet function in the haemostatic process

The main steps platelet functions are adhesion, activation with shape change and aggregation, When the vessel wall is damaged, the sub endothelial structures including basement membrane, collagen and micro fibrils are exposed ,vWF binds to collagen and micro fibrils and then captures platelets via initial binding to platelet GP1b resulting in an initial monolayer of adhering platelets binding via GP1b initiates activation of the platelet via a glycoprotein mechanism, once activated platelets immediately change shape from disc to a tiny sphere with numerous projecting pseudo pods, after adhesion platelet sticks to one another to

form aggregates, the aggregating platelet joing together and release reaction of the platelet granule (Lewis *et al*, 2001).

1- Platelet adhesion

Platelets are prevented from adhering to intact endothelial cells probably as a consequence of the high local concentration of platelet glycoprotein which bind to specific (but poorly characterized receptor on the platelet membrane and in a G protein dependent step, stimulate adenyluanylcyclase activity) causing a rise of intra platelet these inhibit phosphatidyl inositol turnover and promote calcium up take by the dense tubular system (Hoff brand *et al*, 2001).

2- Platelet activation

The inner wall of blood vessels is lined with a thin layer of endothelial cells that in normal homeostasis, acts to inhibit platelet activation by producing nitric oxide ,endothelial-ADPase ,and PGI2 ,endothelial ADPase clears away the platelet activator ,endothelial cells produce a protein called von Will brand factor (vWF), a cell adhesion ligand ,which helps endothelial cells adhere to collagen in the basement membrane ,under physiological conditions , collagen is not exposed to the blood stream ,vWF is secreted constitutively into the plasma by the endothelial cells and is stored in granules within the endothelial cell and platelets, When the endothelial layer is injured collagen vWf and tissue factor from the sub endothelium is exposed to the blood stream, When platelets contact collagen or vWF, they are activated (William, 2002).

3- Platelet aggregation

Platelet aggregation may occur by at least two independent but closely linked pathways, the first pathway involves arachidonic acid metabolism, activation of phospholipids enzymes (PLAs) release free arachidonic acid from membrane phospholipids , about 50% of free arachidonic acid is converted by a lipo oxyganase enzyme to a series of products including

leucotrienes, which are important chemo attractants of white cells, The remaining 50% of arachidonic acid is converted by the enzyme cyclooxygenase into labile cyclic endo peroxides, most of which are in turn converted by thromboxane synthetase into TXA2.

The second pathway of activation and aggregation can proceed completely independently from the first one various platelet agonists, including thrombin, TXA2 and collagen bind to receptors and via a glycol protein mechanism, activate phospholipase C (Lewis *et al* 2001).

4- Platelet release reaction

Platelets commence a specific release reaction ,which is sustained for several minutes and the intensity of which varies with the stimulus weak inducers such as low doses of ADP or adrenaline involve mainly the a-granule contents, A proportion of which may even leak out from unstimulated platelets in citrated blood .higher concentrations of ADP or adrenaline and low dose of collagen, result in secretion from both a-granules and dense bodies ,with the release of lysosomal enzymes, the extent to which these events are mirrored in vivo is unknown, although their physiological importance is substantiated by the fact that a deficiency, particularly the dense bodies or their contents (Hoff brand *et al*, 2001).

1.2.9.1.3 Platelet bleeding disorder

The most common cause of abnormal bleeding is platelet disorder caused by either reduced number of platelets or defective platelet function it is characterized by spontaneous skin purpura, mucosal hemorrhage and prolonged bleeding after trauma

1.2.9.1.4Thrombocytopenia

Failure to produce platelets is the most common cause of thrombocytopenia, drug toxicity or viral infections may result in selective megakaryocytic depression.

Neonatal thrombocytopenia occurs in new born infants as a result of intra uterine rubella or other infections, platelet antibodies, DIC, hereditary thrombocytopenia, giant hemangioma or congenital absence of megakaryocytic (Hoff brand and Pettit, 2000).

1.2.9.1.5 Evaluation of primary haemeostasis

1- Bleeding time test

The bleeding time is useful test for abnormal platelet function including the diagnosis of vWF deficiency, it has largely been replaced by the platelet function analysis it will be prolonged in thrombocytopenia but normal in vascular causes of abnormal bleeding, the test involve the application of precursor to the upper arm with a blood pressure enff, after which small incisions are made in the flexor surface forearm skin, bleeding stop normally 3-8 minutes (Hoff brand and Pettit, 2000).

2-Platelet aggregation test

Measure ability of platelets to aggregate in vitro when subjected to various stimulators (agonists) predominantly assses function of platelet glycoprotein 11b/111a receptor (Marlis, 2006).

3- Platelet count

The platelet count is performed to detect thrombocytopenia, which is defined as a platelet count of less than 150,000/µL. The test is usually performed as part of an automated blood cell profile and can be considered as reliable down to a platelet count of 30,000/µL. The finding of an unexpected thrombocytopenia should be confirmed by a review of the peripheral blood smear (Munker *et al*, 2007).

1.2.9.1.6. Causes of primary haemeostasis deficiencies

Causes of primary haemeostasis deficiencies may include : thrombocytopenia ,inherited disorders of platelet (Bernard soulier syndrome ,Glanzmann,s thrombasthenia and storage pool deficiency) von willbrand,s disease ,also medications ,asprin ticlopiding and defects

in the blood vessel wall which include hereditary hemorrhagic telangiectasia ,vacuities ,amyloidosis and senile purpura (Keren , 2002).

1.2.9.2 Secondary Haemeostasis

Secondary haemeostasis starts when the cascade system of coagulation is activated by substance released at the time of blood vessel injury.

Blood coagulation is a complex process by which blood clot is formed, it is an important part of haemeostasis where the blood clot occludes the blood vessel injury and hence stopping the bleeding and there after repair of the damaged vessel begins, Disorders of coagulation can lead to hemorrhage or thrombosis, Coagulation begins almost instantly after an injury to the blood vessel endothelial lining (Mayer, 2011).

The coagulation mechanism is one of the components of the haemeostatic mechanism, it comprises three separate, through related systems: the coagulation system, the coagulation inhibitory system and fibrinolytic system.

Coagulation cascade in secondary haemeostasis has two pathways which convert fibrinogen, a soluble protein, to insoluble strands of fibrin, which together with platelets, form a stable thrombus (Saxena and Manoranjan, 2013).

1.2.9.2.1 The coagulation pathway

The components of the blood coagulation cascade are pro enzyme pro cofactor and regulatory factor following the initiation of the blood coagulatory, the final steps involve the conversion of soluble plasma fibrinogen into fibrin by thrombin (Hoff brand and Pettit, 2009).

1.2.9.2.1.1 Extrinsic pathway

Normally no coagulation takes place in the blood stream , owing to the properties of the endothelium ,and the inactive form of the proteins which are either zymogens or pro cofactors .initiation of this cascade depends on exposure of the blood components that are not present physiologically in

the blood stream ,these activators of coagulation are revealed as result of mechanical injury ,endothelium damage or biochemical alteration such as the release of cytokines , which in turn induce biosynthesis of activators each of these events is capable of initiating coagulation via exposure of blood to a single critical component .Tissue Factor (TF) is a single chain membrane receptor for coagulation factor V11.

FactorV11 is one group of VK dependent proteins it bind constitutive and induced TF on fibroblast and monocytes ,respectively in all normal people trace level of active V11 are present in circulation (Keren, 2002).

1.2.9.2.1.2 Intrinsic pathway

The contact activation system comprises factor X11 (Hageman factor), high molecular weight kininogen (HMWK), prekalikrein and kallikrein, as mentioned earlier, these factors are not essential for homeostasis in vivo, Important activities are to activate the fibrinolytic system to activate the complement system and to generate vasoactive peptides (Lewis, 2001).

The contact activation system also has some inhibitory effect on thrombin activation of platelets and prevents cell binding to endothelium.

This pathway results in the activation of factor 1X by a novel dimeric serine protease ,factor X1a ,providing a pathway that is independent of factor V11 for blood coagulation .however an important difference exists between these two pathways in the clotting cascade .where as the activation of factor 1X by V11a requires both calcium and the protein co factor ,tissue factor ,the activation of factor 1X by X1a requires only the presence of ionized calcium ,initiation of the intrinsic system invitro is mediated by a group of proteins factor X11,HMWK and prekalikrein this group of protein called the contact system since activation occurs via binding to negatively charged surface such as kaolin dextran sulphate and sulfa tides (Lewis, 2001)

Factor X11a activates X1 to X1a, X1a activates 1X to1X to 1Xa, 1Xa activate X to Xa and so on deficiencies in any factors involved in the intrinsic pathway result in prolongation of the aptt factor (William, 2002).

1.2.9.2.1.3 Common pathway

Once factor Xa is formed either the extrinsic or intrinsic pathway it catalyzes the conversion of prothrombin to thrombin bu**t** the reaction is slow efficient activation of prothrombin requires few components factor Xa ,factor Va phospholipids 'and calcium ,factor V that participates in this prothrombinase complex is probably supplied by either fusion of plasma derived factor V with the platelet plasma membrane or via secretion from platelet a granules, The procofactor ,factor V is activated to factor Va by either factor Xa or thrombin ,factor Va then functions as cofactor in the prothrombinase complex has a markedly increased rate of prothrombine activation(William, 2002).

1.2.9.2.1.4 Causes of secondary haemeostasis disorders

Causes include hemophilia which inherited decrease in clotting factor levels or production of abnormal clotting factors, type of hemophilia include: hemophilia A is a recessive x linked genetic disorder involving a lack of functional clotting factor V111 and represents 80% of hemophilia cases, Hemophilia B is a recessive x linked genetic disorder involving a lack of functional clotting factor 1X it is comprises approximately 20% of hemophilia cases, Hemophilia c is an autosomal genetic disorder involving a lack of functional clotting factor X1 hemophilia c is not completely recessive as heterozygous individuals also show increased bleeding (Kern, 2002).

1.2.9.2.1.5 Evaluation of secondary haemeostasis

1- Prothrombin time

The prothrombin provides measure of the extrinsic and common pathways compared with PTT is more sensitive to deficiencies of the

vitamin k dependent liver factors (11 ,V11 ,1X and X) the assay is performed by adding back to circulate plasma both calcium ion and either a purified or recombinant thromboplastin tissue factor V11 and common pathway.

The prothrombin can vary significantly depending on the type of thromboplastin used; purified thromboplastins generally give normal values of 10-14 seconds, which is somewhat shorter than results for the recombinant tissue factor, When the prothrombin is used to monitor a patient receiving an oral warfarin, the sensitivity of the thromboplastin must be taken into account in interpreting the prolongation of the PT, this situation has led to development of standardized method of expressing the prolongation as an international normalized ratio as a screening for any single factor deficiency, the PT is most sensitive to a reduced level of factor V11 in patients with liver diseases the levels of vitamin k dependent factors must be reduced by more than 50-60% to prolong the PT as a general rule .

The PT also can be prolonged by large amounts of heparin in circulation, more rarely by a circulating inhibitor and either a reduced level of fibrinogen or the presence of abnormal fibrinogen molecules or fragments in circulation finally the PT may be prolonged if whole blood specimen is stored too long prior to assay owing to degradation of coagulation protein (Hillman *et al*, 2005).

The prothrombin test is used for assessment in pre operative detection of bleeding tendencies in risk groups, the monitoring of anticoagulant therapy, used for prevention and treatment of venous thromboembolism, prosthetic heart valves, arterial fibrillation and other indications (Hillman *et al*, 2005).

2- Activated Partial Thromboplastin

The activated partial thromboplastin time is the clotting time in second when citrated plasma is added to a contact activator , phospholipids and calcium ions, The aptt test for deficient activity of procoagulants in the intrinsic and common pathways including high molecular weigh kininogen ,prekallikren factors (FX11,FX1,F1X,FV111,FX,FV) prothrombin and fibrinogen. Deficiency or inhibition of any of these factors prolongs the APTT result (Fritsma, 1995).

The APTT measures both the intrinsic and common coagulation pathways, for this assay, citrated plasma is activated with a contact surface material such as kaolin, together with calcium ion and phospholipids'. Depending on the reagents .The normal APTT generally ranges from 25 -38 seconds ,the APTT can be prolonged by a deficiency of any of the factors in the intrinsic or common pathway by the presence of circulatory inhibitor ,or because of a fibrinogen abnormality , factor deficiency must be relatively sever ,that the levels below 30 -40% of normal multiple deficiencies or both to significantly prolong the APTT ,the APTT is more sensitive to the presence of circulatory anticoagulant ,to identify a circulatory anticoagulants the laboratory can perform a repeated APTT with 1:1 mix of patient and normal plasma , although the admixture of normal plasma will nearly completely correct a prolonged APTT secondary to a factor deficiency , it will have little or no impact on the APTT that is prolonged because of a high titer circulating anticoagulant, a prolonged APTT resulting from heparin in the sample either because of therapeutic anticoagulant or inadvertent contamination by drawing the sample through a line can be determined by mixing the patient plasma with polybrene this will neutralize the heparin and correct the APTT (Hillman *et al* ,2005).

Table 1.1 Coagulation factor nomenclature with preferred names and synonyms (Stiene *et al*, 2005).

Numeral	Preferred name	Synonyms
1	Fibrinogen	
11	Prothrombin	Prethrombin
111	Tissue factor	Tissue thromboplastin
1V	Calcium	Ca 2
V	Proaccelerin	Labile factor
V11	Proconvertin	Stable factor
V111	Antihemphilic factor	Antihemophilic globulin (AHG)
1X	Plasma thromboplastin component (PTC)	Christmas factor ,Antihemophilic factorB
X	Stuart prower factor	Stuart factor
X1	Plasma thromboplastin antecedent (PTA)	Antihemophilic factorC
X11	Hageman factor	Glass factor Contact factor
X111	Fibrin stabilizing factor	Laki-Lorand factor (LLF)
-	Prekallikrein	Fletcher factor
	High molecular weight kininogen	Fitzgerald factor Contact activation factor Willams factor

3- Thrombin Time

The Thrombin Time (TT) measures the last step in the common pathway that is conversion of fibrinogen to fibrin, it is performed by adding a dilute solution of bovine thrombin to circulated plasma, the normal control can be adjusted to give a TTof anywhere from 9 -35 seconds depending on the thrombin dilution, the TT is prolonged in patients with a decreased or abnormal fibrinogen or high levels of inhibitory fibrin degradation procedure (Hillman *et al*, 2005).

1.2.9.2.6 Fibrin Formation and Finbrinolysis

The formation of fibrin strands represents the second phase in homeostasis, the precursor of fibrin is fibrinogen, a large glycoprotein that is present in high concentration in plasma and in platelet granules, and fibrinogen interacts with other proteins including factor X111, fibrinonectin, a2 plasmin inhibitor, plasminogen and plasminogen activator (Kitchen *et al*, 2002).

The location and surface concentration of these modifying proteins influence the orderly process of fibrin formation, cross linking and lysis ,thrombin binds to the fibrinogen central domain and liberates fibrin peptides A and B, resulting in fibrin monomer and polymer formation, fibrinolysis Involves multiple enzymatic and regulatory proteins and reaction ,plasminogen is the circulation zymogene of plasmin , a serine protease that has high specificity for fibrin ,it is activated in vivo by plasminogen activator that are released from tissue stores by ischemia ,the activators generate plasmin ,the active fibrinolytic enzyme form the zymogene plasminogen ,plaminogen activation inhibitors these inhibitors appear to be the major components of the fibrinolytic system that are associated with thrombotic ris (Kitchen *et al*, 2002).

Previous study

A study conducted in USA with prospective in character and referred to the monitoring of changes in coagulation tests after surgical revascularization of the heart , included 60 consecutive patients who were hospitalized at the clinic for cardiovascular disease and the mean age was 59 ±7.3 years. The mean value of platelet before surgery was 254 ± 55 and after surgery was 152 ± 63 ,PT before surgery was 12.8 ± 4.1 and after surgery was 13.2 ±7.2 , APTT before surgery was 32 ± 5.2 and after surgery was 37 ± 6.5 (Bosn J, 2014).

1.2.10 Rationale:

Heart disease and heart surgery are a major public health concern that has great impact on both individuals and society, heart surgery is associated with significant mortality.

Recent research indicate that patients who had heart surgery may have to stimulate haemostatic disorders (coagulation deficiency) platelets dysfunction and thrombocytopenia , Patients show variable abnormalities in PT, APTT, PLTS Count following open heart surgery.

1.2.11 Objectives:

1.2.11.1 General objectives:

Measurements of prothrombin time ,activated partial thromboplastin time and platelets count among open heart surgery patients (before and after surgery),cross sectional study.

1.2.11.2 Specific objectives:

To measurements of PT, APTT, in open heart surgery patients.

To measurements platelet counts in open heart surgery patients.

To compare between PT, APTT and platelets count before and after open heart surgery.

Chapter Two

2. Material and Method:

2.1 Study design:

This is a hospital based cross sectional analytical study was conducted from February 2016 to May 2016 for determination of haemostatic mechanism in patients with open heart surgery.

2.2 Study area:

The study was conducted in Sudan Cardiac Center

2.3 Study population:

Patients with open heart surgery were investigated for PT, APTT, and PLTS count.

2.4 Inclusion criteria:

All patients who had a confirmed diagnosis as open heart surgery.

2.5 Exclusion criteria:

All patients who were not diagnoses as open heart surgery.

2.6Sample size:

According to design of study, the sample (patients) was selected by a simple random sampling method (probability sampling). Seventy samples of patients' before operation compared with seventy blood sample after operation.

2.7 Tool of data collection:

The data was collected by using of laboratory investigation to obtain PT, APTT, platelet count .Also the interviews were used to obtain age, sex and using of questionnaire as instrument.

2.8 Data analysis:

The data after collection was analyzed to obtain the mean standard deviation and the probability *(p. value).* By using SPSS computer program.

2.9 Ethical consideration:

All information that were obtained from patients was kept as highly confidential and specimens or result was not permitted.

The participants were provided with information about the study and any risk that may arise especially when collection technique was applied.

2.10 Sample collection:

Five ml of blood was take from patient, 2.5 ml was collected in Tri-Sodium citrate anticoagulant container to obtain plasma of patient to PT and APTT testing other 2.5 ml was collected in EDTA of platelets count.

2.11 Methodology:

2.11.1 Requirements

EDTA container.

Tri-sodium citrate container.

Cotton.

Alcohol (70%).

Syringes.

Tourniquet.

2.11.2 Procedure:

-Patients were comfortable sitting, tourniquet applied above elbow and superficial antecubtal for arm vein must be identified.

-The skin must be sterile with 70% ethanol and allowed to dry.

-Syringe needle should inserted correctly into the vein ,and 5ml of blood sample should take ,tourniquet will released ,needle remove ,and 2.5ml into EDTA and other 2.5 ml into 3.2 % tri sodium citrate ,to separate to plasma.

2.11.3Prothrombin Time:

Principle:

The prothrombin time measures the clotting time of re calcified plasma in the presence of an optimal concentration of tissue extract (thrombo plastin).and indicate the overall efficiency of the extrinsic clotting system

Reagent:

1. Patient and control platelets poor plasma (ppp).
2. Thromboplastin.
3. Calcium chloride (cacl2); 0.025mol/l.

Method:

Placed 0.1ml of plasma from patient into glass tube labeled as test in water path ,0.1ml from control into tube labeled as control and added 0.2 ml of thromboplastin reagent with calcium chloride in both tube and started stop watch, and time of clotted record, Must be duplicated.

Normal value:

10- 14 second.

2.11.4Activated Partial Thromboplastin Time:

Principle:

The test measures the clotting time of plasma after the activation of contact factors and the addition of phospholipid and calcium chloride ,so indicate the overall efficiency of the intrinsic path way .

Reagents:

1. Plasma for patient and control.
2. Kaolin; 5 g/l.
3. Phospholipid; 0.35-0.4 iu/ml.
4. Cacl2 (0.025 mol/l.)

Method:

Mixed equal volume of kaolin and phospholipids' and leave in glass tube in water path at 37c, Add to plasma then add 0.1ml from cacl2, mix content and start the stop watch and the time of clot record as APTT time.

Normal Range:

26 – 40 second.

2.13.5 Platelets count:

By sysmex 21.

Reagent and material:

-Cell pack.

-Stromatolyser.

-Detergent.

-Cell cleaner.

Principle of Sysmex 21 Hematological Analyzer:

Measurement of blood cells (red blood cells ,white blood cells, and platelets) and hemoglobin concentration obtained by aspiration of small volume of EDTA blood by sample probe and mixed isotonic diluents in nublazer diluted mixture aspiration delivered to RBCs aperture bath for providing information about RBCs and platelets based on cell size particles of 2 to 20 femtoliter counted as platelets ,above 36 femtoliter counted as Red blood cells .some portion of aspirated mixture induced into white blood cells bath in hemolytic reagent (Stromatolyser) was added automatically to measure hemoglobin concentration in build colorimeter ,based on cynomethemglobin method .

Blood cells counted and size information generated in triplicate pulses according to electronic conductivity, and translated into digital number using in build calculator programmed and designed for RBCs, WBCs, other value of red cell indices, platelets count, leukocyte differential and absolute count calculated from given information and automated

constructed histogram, the result printed out according to the setting mode.

Statistical analysis

Statistical analysis was performed by using SPSS computer program version 11.5 ,the value were expressed as mean ± Std.Devision by using paired sample T test for comparison before and after surgery ,also using independent T test and frequency to get mean ages and distribution between gender.

Chapter Three

3. Results

This study was carried out in Sudan Cardiac Center during the period from February to May to measurements of prothrombin time, activated partial thromboplastin time and platelet count in open heart surgery patients.

Demographic Data

The study included 50 patients adult (71%) and 20patients children (29%) as showed in table(3.1) , differentiated according to ages, adult male 25 with mean ages 64 years, adult female with mean ages56 years and children male 10with mean ages 5years and female 10 with mean ages 6 years as showed in figure(3.1)

Table 3.1 Distributions of Population

Population	Frequency	Percent
Adult	50	71
Children	20	29
Total	70	100

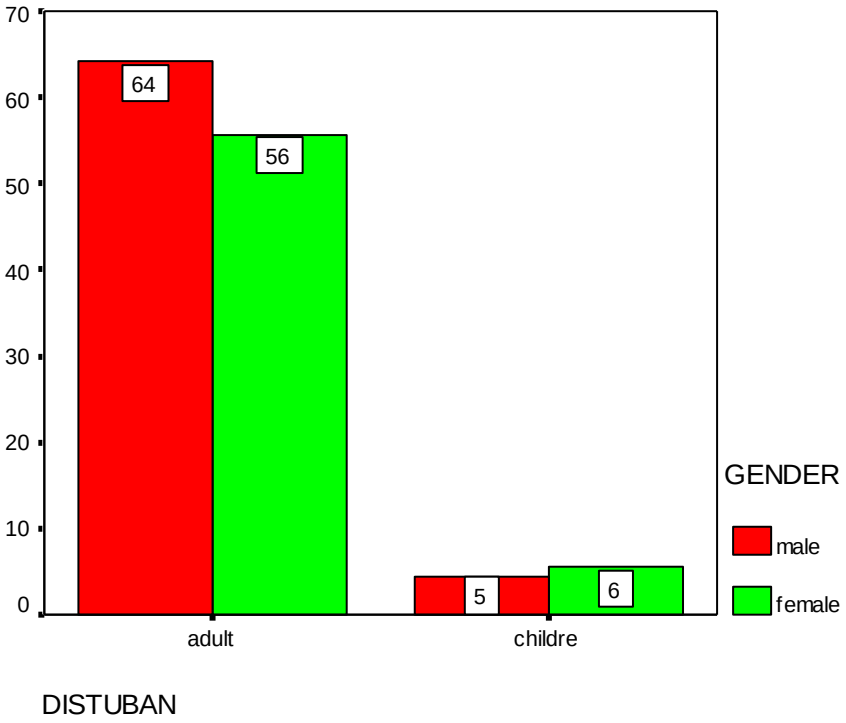

Figure 3.1 Distributions of patients according to ages

3.2 PT between Gender

Table 3.2 showed PT insignificantly equal between gender with *p.value (0.1)*

Table 3.2 PT between Gender

Parameter	Gender	Number	Mean	P.value
PT	male	35	22.8 ±7.2	0.1
	female	35	25.7 ±9.7	

3.3 APTT between Gender

Table 3.3 showed APTT insignificantly equal between gender *p.value (0.6)* .

Table 3.3 APTT between Gender

Parameter	Gender	Number	Mean	P.value
APTT	male	35	41.8 ±7.1	0.6
	female	35	41.1 ±7.1	

3.4 Platelet Count between Gender

Table 3.4 showed that Platelet count significant low in female in compared with male *p.value (0.05)*

Table 3.4 Platelet count between Gender

Parameter	Gender	Number	Mean	P.value
platelet	male	35	268 ±102	0.05
	female	35	226 ±71.4	

3.5 Comparisons of PT before surgery and after Surgery

Table 3.5 showed significant low PT before surgery in compared to PTafter surgery *p.value (0.00).*

Table 3.5 PT before surgery compared wih PTafter surgery

Parameter	Number	Mean	*P.value*
PTbefore surgery	70	24.32 ±8.6	0.00
PT after-surgery	70	27.46 ±9	

3.6 Comparisons of APTT before surgery and after Surgery

Table 3.6 showed significant low APTT before surgery in compared to APTTafter surgery *p.value (0.00).*

Table 3.6 APTT before surgery compared with APTTafter surgery

Parameter	Number	Mean	*P.value*
APTT before surgery	70	41.49 ±7	0.00
APTT after surgery	70	43.94 ±7.8	

3.7 Comparisons of Platelet before surgery and after Surgery

Table 3.7 showed significant low platelet after surgery in compared to platelet before surgery *p.value (0.00).*

Table 3.7 platelet before surgery compared with platelet after surgery

Parameter	Number	Mean	*P.value*
Platelet before surgery	70	247 ±89.9	0.00
Platelet after surgery	70	243 ±88.6	

Chapter Four

Discussion, Conclusion and Recommendations

4.1. Discussion

APTT and PT are used as routine test to check patients coagulation system, various studies has measured APTT following cardiac surgery and have found it to be commonly elevated, there were no significant differences between male and female in occurrences of disease but it most commonly affected older more than 50 years, our study showed prolonged APTT after surgery despite neutralization of heparin with protamine, also due to homodilution and reduction of coagulation factor the APTT show prolongation after surgery, with mean 41.49 ±7 seconds before surgery and 43.94 ±7.8 seconds after surgery with significant difference *(p.value=0.00).*

The prothrombin show prolongation after surgery with mean24.32 ± 8.6seconds before surgery and 27.46±9 seconds after surgery with significant difference *(p.value=0.00).*

Our finding are in accordance with other studies that have shown massive activation of homeostasis during and early after cardiac surgery, Agreed with study done by (Pouplard *et al,* 2005).

The platelet count showed decreased after surgery ,with mean 247 ±89.9 c\cumm before surgery and 243 ±88.6c\cumm after surgery with significant difference *(p.value=0.00)* , This decrease on platelet values might be due to homodilution contact activation of the homeostatic system or to the systemic inflammatory response, agreed with study done by (William and Matthaijr, 2005) is that surgery is most common cause for secondary thrombocytosis in contrast to most other operative procedures it result in initial fall in the platelet count in addition to drug – induced thrombocytopenia, the mechanical destruction of platelets and homodilution in the bypass circuit play important roles in the occurrence

of postoperative thrombocytopenia sepsis intraaortic ballon pumping and post transfusion purpura must be considered in selected cases.

After open heart surgery patients may receive a host of medications such as antibiotic which are known to cause thrombocytopenia, the drug most likely to cause thrombocytopenia is heparin, the exposure of the patient's blood to the cardiopulmonary bypass circuitry diminishes the hypercoagulable state and proceeds into an imbalanced hypocoagulable phase also it lead to activation of platelets and the intrinsic pathway.

In the other hand (Pouplard *et al*, 2005) shown that cardiac surgery is a clinical situation that induces strong platelet activation with release into the plasma of large amount of platelet factor 4 in addition patients are exposed to high doses of unfractionated heparin, That result in thrombocytopenia.

4.2. Conclusion

The study showed that heart surgery leads to prolonged coagulation test above the reference value ,this indicate hypercoagulability is more pronounced in these patients ,hypercoagulability and increases the risk for massive post operative bleeding it also affect platelet count we found that cardiac surgery seems to cause a marked decrease in platelet count .

The mean of PT before surgery was 24.32 ± 8.6seconds and 27.46±9 second after surgery.

The mean APTT before surgery was 41.49 ±7 seconds and 43.94 ±7.8 seconds after surgery.

The mean platelet count before surgery was 247 ±89.9 c\cumm and 243 ±88.6c\cumm after surgery .

4.3. Recommendation

-Coagulation screening should be done as routine test for all patients with heart disease and any surgery and must be check monthly to patients to prevent heart attack that leads to sudden death.

-Bypass machine should be adjusted through research to no normalize haemostasis.

Chapter Five

References

Ban B and Seed M, (1986) Platelet count and platelet size in healthy Africans and West Indians, clin lab haematology.8:43 -48.

Bosn J, (2014) Changes in APTT and INR on surgical revascularization of heart USA 14(2) 70-74.

Bylebyl B , Jerome j, William H, (2002) The professional and social content of the discover of the circulation, johns Hopkins university press ,A, classic biography 453 -506.

Davies M and Thomas A, (2007) Thrombosis and acute coronary artery lesions in sudden cardiac ischemic death, N England journal med line 310:1137 -1140.

Dearani J, (2010) cardiothoracic surgery, California 32:724 -729.

Doulgas P and Ginsburg G,(1996) The evaluation of chest pain in women ,N.Engl journal med 334.

Elanine N, Marieb Rand Mallatt J, (2007) Human anatomy fifth edition.page117.

Fritsma G, (1995) Laboratory evaluation of hemorrhage and thrombosis in Rodak PF Diagnostic hematology Philadelphia PA Saunders 719 -753.

Germann W and Stanfield C, (2005) Principle of human physiology second edition USA, 415- 419.

Hillman R, Ault K and Rinder H, (2005) Hematology in clinical practice fourth edition united state of America.328 -329.

Hoffbrand A and Pettit J, (2009) Clinical hematology fifth edition USA.

Hoffbrand A and Pettit J,(2000) Clinical hematology Third edition Harcourt publisher Barcelona spain page 267 -279.

Hoffbrand A, Lewis S and D E, (2001) Post Graduate hematology fourth edition USA page: 560 -563.

KernW, (2002) PDQ Hematology first edition USA 384 -398.

Kitchen C, Alving B and Kessler C, (2002) Consultative haemeostasis and thrombosis USA Page17.

Lewis S, Bain B and Bates, (2001) Dacie and Lewis practical hematology seventh edition, London 3:394- 413.

Loor G, Vivacqua A, Sabick and Jk, (2013) improvement in cardiac surgery and implementation of areoperation for bleeding check list journal pub med 146(5)1028 -1032.

Lowe Mand Baclogeorgy, (2005) Anesthesia and analgesia journal pubmed 56:234 -453.

Marlies I, (2006) Homeostasis principle 11edition 5:8- 14.

Mayer G, (2011) Immunology chapter one innate immunity university of South Carolina.

Michael L ,Janet B ,Duben L ,Edward E andFody P, (2000) Clinical chemistry principle procedure fourth edition USA page:423 -429.

Munker R,Hiller E,Glass Jand Paquett R,(2007) Modern hematology ,biology and clinical management second edition,humana press ,Totowa ,Newjersey 327-347.

Populard C, May M, Regina S ,Marchand M ,Fusciardi J and Gruel Y ,(2002) Change in platelet count after surgery, Black well publishing British Journal of hematology 837-841.

Rasche H, (2001) Haemeostasis and thrombosis department of hematology. Germeny, European heart journal supplement 3.

Saxena R and Manoranjan H, (2013) Degruchy,s clinical hematology in medical practice 6th edition.India page:378.

Stiene E, Lotspeich C and Koepke J, (2005) Clinical hematology USA .599.

Walker D and Akins C, (2007) The general hospital corporation, courtesy of Jennifer cs Anderson page 2.

William F, (2002) PDQ hematology Hamilton Ontario Canada 20:381-429.

William H andMathaijr, (2005) Thrombocytopenia in cardiovascular patient Journal publication chest 127:465-525.

Zack P, Aker V and Dincer B, (1994) The occurrence of angiographically detected intra coronary thrombus in patients with UN stable angina pectoris Am heart journal 108:1408 -1412.

Appendix 1:

Sudan University of Sciences and Technology

Collage of Medical Laboratory sciences

Hematology Department

Questionnaire

Name:…… No:

Gender:Male; ( ) Female; ( )

Age:

……

……

Investigation:

PTpre……sec

PTafter……sec

APTTpre……sec

APTTafter……..sec

Platelet pre :……c\cumm

Plateletafter……c\cumm

Date: Sig

Appendix 2:

Hematological Analyzer Sysmex