Sudan University of Science and Technology

College of Graduate Studies

Measurement of Prothrombin Time, Activated Partial Thromboplastin Time and Platelets Count among Heart disease Patients in Sudan Cardiac Center Khartoum State

قياس زمن البروثرومبين وزمن الثرومبوبلاستين الجزئي المنشط وعدد الصفائح الدمويه لدي المـصا بـيـن بامراض القلب في مركز السودان للقلب ولايه الخرطوم

A dissertation Submitted In partial Fulfillment of the Requirement for Master Degree (M.SC) in Haematology and Immunohaematology

By

Hala Alzobir Ali Mohammed

BSC in medical laboratoryscience (SUST2011)

Supervisor

Professor.Babker Ahmed Mohammed

2016 -2017

الايه

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

﴿٢٨٤﴾ ءَامَنَ ٱلرَّسُولُ بِمَآ أُنزِلَ إِلَيْهِ
مِن رَّبِّهِۦ وَٱلْمُؤْمِنُونَ ۚ كُلٌّ ءَامَنَ بِٱللَّهِ وَمَلَٰٓئِكَتِهِۦ
وَكُتُبِهِۦ وَرُسُلِهِۦ لَا نُفَرِّقُ بَيْنَ أَحَدٍ مِّن رُّسُلِهِۦ ۚ وَقَالُوا۟
سَمِعْنَا وَأَطَعْنَا ۖ غُفْرَانَكَ رَبَّنَا وَإِلَيْكَ ٱلْمَصِيرُ ﴿٢٨٥﴾ لَا يُكَلِّفُ
ٱللَّهُ نَفْسًا إِلَّا وُسْعَهَا ۚ لَهَا مَا كَسَبَتْ وَعَلَيْهَا مَا ٱكْتَسَبَتْ ۗ
رَبَّنَا لَا تُؤَاخِذْنَآ إِن نَّسِينَآ أَوْ أَخْطَأْنَا ۚ رَبَّنَا وَلَا تَحْمِلْ
عَلَيْنَآ إِصْرًا كَمَا حَمَلْتَهُۥ عَلَى ٱلَّذِينَ مِن قَبْلِنَا ۚ رَبَّنَا
وَلَا تُحَمِّلْنَا مَا لَا طَاقَةَ لَنَا بِهِۦ ۖ وَٱعْفُ عَنَّا وَٱغْفِرْ لَنَا
وَٱرْحَمْنَآ ۚ أَنتَ مَوْلَىٰنَا فَٱنصُرْنَا عَلَى ٱلْقَوْمِ ٱلْكَٰفِرِينَ ﴿٢٨٦﴾

صدق الله العظيم

سورة البقرة

Dedication

To my father and mother

For giving me the hope for life, for love and those give me power supply to all my life.

To my brother and husband

For giving me the chance for choice my live and support me by anything to my study, job, give me hope to tomorrow and future.

To my teachers

For showing me the excitement and joy of hematology.

To my dear friend Huda

To help me and support me in my research.

Acknowledgement

Thank to my supervisor proffessor.Babker Ahmed Mohammed for encouragement, advice, and interest this research.

I would like to acknowledge and thank the staff of the hematology department.

Also I would like to thank the staff of Sudan Cardiac Center, especially staff of hematology lab for their helpful and discussion.

Abstract

Heart diseases are major health problem and greatly affecting the economic and social status of such patients. The objective of this study to measure of prothrombin time, activated partial thromboplastin time and platelets count in heart disease patients compared to control, and compared between heart disease patients them self according to age and gender to observe change which can occur. The study was carried out at the Sudan Cardiac Center, at Khartoum state, Sudan. One hundred blood samples were collected, from 70 heart disease patients and matched by 30 health persons as control. The samples were tested forprothrombin time, activated partial thromboplastin time by manual method and platelets count by sysmex21 Automated Hematology Analyzer. SPSS (version14) was used for statistical analysis. The results showed prolongationin prothrombin time and activated partial thromboplastintime in patients compared with control.The mean of PT in the patientswas 30.4±9.7 second and that of control was 13.2±1.9 second. The mean of APTT in the patients was 43.6±8 second and that of control was 32±6.5 second (P value <0.05). Alsono significance change occur in the mean of platelets count in heart disease patients compared to control(P value >0.05). Also no significance change occur in prothrombin time , activated partial thromboplastin time and platelets count between heart disease patients them self according to gender group and different age group (P value >0.05). Therefore its recommended that the patients must be screened always to avoid the complications of thrombosis that cause heart attack and sudden death.

الخلاصه

امراض القلب مشكله صحيه رئسيه ولها تاثير كبير في الحاله الاقتصاديه والاجتماعيه عند المرضي .الهدف من هذه الدراسه لقياس زمن البروثرومبن وزمن الثرومبوبلاستين الجزئى المنشط وحساب الصفائح الدمويه عندمرضي القلب ومقارنتهامع الضبط وللمقارنه بين مرضي القلب انفسهم بدلالله النوع و الفئه العمريه لملاحظه التغير الذي يمكن ان يحدث اجريت هذه الدراسه في مركز السودان للقلب , ولايه الخرطوم السودان . مائه من عينات الدم جمعت من سبعون مريضا بمختلف امراض القلب مقابلين بثلاثين من الاصحاء كضبط . العينات اختبرت لزمن البروثرومبن وزمن الثرومبوبلاستين الجزئى المنشط بالطريقه اليدويه ،وعد الصفائح الدمويه بالسسمكس٢١محلل الدم الاوتوماتيكي ،وحللت العينات بستخدام الحزمه الاحصائيه للعلوم الاجتماعيه(١٤) برنامج احصائي تحليلي.
نتيجه هذه الدراسه ان هناك اطاله في زمن البروثرومبن وزمن الثرومبوبلاستين الجزئى المنشط عند المرضي حيث وجدت اكثر من المجموعه المقارن بها كاضبط حيث وجد متوسط زمن البروثرومبين عند المرضي(٤,٣٠±٩,٧ثانيه) وعند الضبط(١٣,٢±١,٩ثانيه) بينمامتوسط زمن الثرومبوبلاستين الجزئى المنشط (٨,٦±٤٣ ثانيه) وعند الضبط(٣٢±٦,٥ ثانيه) (بدرجه معنويه اقل من ٠,٠٥) .وايضاعدم وجود تغير ملحوظ في متوسط عدد الصفائح الدمويه عند المرضي مقارنه بالاصحاء(بدرجه معنويه اكبر من٠,٠٥)وكذلك لايوجد تغير ملحوظ في متوسط زمن البروثرومبن ,زمن الثرومبوبلاستين الجزئي المنشط وعدد الصفائح الدمويه بين المرضي بدلاله النوع والفئات العمريه المختلفه(بدرجه معنويه اكبر من٠,٠٥).نوصي بان يتم اختبار المرضي دائما وذلك لتجنب مضاعفات النوبه القلبيه والموت المفاجي .

Contents

List of table

List of figures

Abbreviations

APC : Activated Protein C

APTT : Activated Partial Thromboplastin Time

AT : AntiThormbin

BT : Bleeding time

CCDH: cyanotic congenital heart disease

DIC : Disseminated intravascular coagulation

EDTA : Ethylene di adenine tetra acetic acid

EPCR : Endothelial protein C receptor

FDP : Fibrin degradation product

HB : Hemoglobin

HCII : Heparin cofactor II

HiCN :Cynomethemoglobin

HMWH : High molecular weight heparin

IE : Infective endocarditis

LCD : Liquid crystal display

LMWH : Low molecular weight heparin

MI : myocardial infraction

PAI : Plasminogen activator inhibitor

PC : Protein C

PCI : Protein C inhibitor

PLG : Plasminogen

PLTS : Platelets

PT :Prothrombin time

PS : Protein S

PZ : Protein Z

RHD : Rheumatic Heart Disease

RBCS : Red blood cells

SK : Streptokinase

TAFI : Thrombin activatable Fibrinolysis inhibitor

TF : Tissue Factor

TM :ThromboModulin

TPA : Tissue plasiminogen activator

TT : Thrombin time

TXA2 : Thromboxane A2

UFH : Un fractionated heparin

UPA : Urinary plasiminogen activator

VCAM : Vascular cell adhesion molecule

VWF : Von will brand factor

WBCs : White blood cells

ZPI : Z- dependent protease inhibitor

Chapter one

Introduction and Literature Review

Chapter one

Introduction and Literature Review

1-1.Introduction and background:-

Heamostasis is one of a number of protective processes that have involved in order maintaining a stable physiology. Itinteracts with other body defence .Such as inflammatory system and immune system. For example of these disseminated intra vascular coagulation (DIC) can be initiated by Gram –negativesepticemia.[Hoff brand *et al*, 2016].

The heart is blood pump and net of vessels so the study is important.Several biomedical finding have established the effect of cardiovascular disease as arterial hypertension in the coagulation process. [Adaeze *etal* 2014].

Cardiovascular disease account for about one third of premature deaths in men and one quarter in women and arterial hyper tension is one of the most significant risk factors for cardiovascular disease .[Bernatova.I 2014]

Heart disease is major health problem and greatly affecting the economic and social status of such patients. Globally cardiovascular disease accounts for approximately 17 million deaths a year, nearly one-third of the total.[Chobanian.A.V *et al* 2003].

Cardiovascular disease develops 7to10 years later in women than in menand is still the main cause of the death in women. [Maas and Appelman,2010].

Coronary artery disease is most common disease, is cause of death in male and female evaluation and treatment of the disease howevercan differ between male and female [Douglas and Ginsburg, 1996].

Through the world many studies were done in this topic due to the important of the heart in the body.

In study it has been recognized that patients with cyanotic congenital heart disease (CCDH). Show significant bleeding tendency which can be secondary to coagluopathies in these patients. Some coagulation abnormalities, are thrombocytopenia and factor deficiency, fibrinolysis, anddisseminated intravascular coagulation (DIC). [Ghasemi *etal*, 2014]

In other study ,Although significant minority of patients with cyanotic congenital heart disease (CCHD) are thrombocytopenic .The pathogenesis and prevalence have been established .This study was designed to address these tow issue .The conclusion platelets count in CCHD appear to represent acontinuum beginning with low platelet counts and ending with thrombocytopenia .[Michael *etal*,2006] .

Other study platelets have been implicated in the pathogenesis of coronary artery disease ,and number of studies have examined platelets function and coagulation parameters in such patients .But these study designed to examined platelets coagulants activities ,volumes ,and aggregate ratios in patients with chest pain these were find platelets coagulation activities increased activated partial prothrombin time(APTT) in coronary artery disease .There are contribution in factor(seven ,eight ,fibrinogen)and deficiency in antithormbin three.[Kontiro *etal*,1984].

In other study aim to link between coagulation system and the development of chronic heart failure. Physical stress cause increase in concentration of hormones it is proved that it causes the disorder of the coagulation system an increase of the following factors of plasma (fibrinogen, seven, eight, fibrinopeptidA) thrombin – antithormbin complex, fibrinolysis (D-dimer), endothelium and decrease in E-selectin.[Mongirdine *et al*, 2010].

Other studies were done in children with congenital heart disease .were find increased of bleeding time indicating to amicrovascular abnormality or qualitative platelets defect .[Kontras *et al*, 2014].

Other study they suggest that the association between congestive heart failure and disseminated intra vascular coagulation (DIC) is an under recognized on .Thus the precise role of coagulation factors in congestive heart failure is unknown. [Sarcon *et al*,2015].

In other side were study done to clotting characteristic of pulmonary and systemic blood were studied in patients with chronic rheumatic mitral valve disease complicated by arterial fibrillation and other patients with aortic valve disease.

Both group of patients showed difference in patients platelets function between pulmonary and systemic blood patients with mitral valve disease aggregation of platelets was significantly greater in systemic than in pulmonary arterial blood at all time ;the converse was true during exercise .In aortic valve disease platelet aggregation was greater in systemic than pulmonary at all time. Only the patients with mitral valve disease patients showed change in blood coagulation during passage through lungs and left heart ;statistically significant shortening partial thromboplastin time in systemic compared with pulmonary arterial blood both at rest and during exercise . Similarly the effect of exercise on the various haemostatic factors measured were largely confined to the patients with mitral valve disease in these patients exercise stimulated in increase in factor VIII in pulmonary arterial blood .[Toy *etal*1980].

1-2.Literatuereviwe

1-2-1.Normal haemostasis:-

Heamostasis is one of number of protective process that has involved in order maintaining a stable physiology. It interact with other body defense mechanisms ,such as immune system and the inflammatory response .The high blood pressure generated on the arterial side almost instaneous , but strictly localized procoagulant response in order to compromising blood flow generally . Systemic anticoagulant and clot dissolving component have also evolved to prevent extension of the procoagulant response beyond viciation vascular injury resulting in unwanted thrombus formation .The result haemostatic mechanism is thus a complex mosaic of activating or inhibitory pathways that integrates its five major components(blood vessels, platelets, coagulation(factor and inhibitor), and fibrinolytic element). [Hoff brand A *et al*, 2016].

Blood coagulation occurs when the enzyme thrombin is generate and proteolysis soluble plasma fibrinogen forming the insoluble fibrin polymer, or clot. [Hoffbrand and Higgs,2016].

Heamostasis is processwhereby blood coagulation is initiated in tightly regulated fashion, together with the removal (or Fibrinolysis) of the clots parts of vascular remodeling .This process are maintained are the whole organism for its life time. [Hoffbrand *etal*, 2016].

The whole haemostatic mechanism is integrated in vivo so that thrombin generation is localized, limited and followed by Fibrinolysis.

1-2-2.Blood coagulation process:-

Blood coagulation initiated when exposure of blood to cells expressing tissue factor (TF) on their surface is both necessary and sufficient to initiated blood coagulation in vivo ,both in normal heamostasis and pathological situation .Present version of earlien cascade concept for intrinsic and extrinsic pathways of generation of thrombin .[Hoffbrand ,*etal* 2016].

Blood coagulation in vivo involves a biological amplification system in which relatively few initiation substances sequentially activated by proteolysis a cascade of circulating precursor protein (the coagulation factor enzyme).which culminates in the generation of thrombin .[Hoffbrand *et al*, 2016].

Although the contact system does not appear to have in physiological role in heamostasis it remains available role for understanding a common coagulation tests. Tissue factor (TF) is constitively expressed at biological boundaries such as skin, organ surfaces, vascular adventitia and epithelial, where function as a haemostatic envelop following disruption of vascular integrity, blood is immediately exposed to cells expressing TF, leading to the initiation of blood coagulation. [Hoffbrand *et al*, 2016].

1-2-3 .Blood vessels:-

1-2-3-1.The endothelium:-

Its functions including intracellular transport and maintenance of blood follow .Endothelial cells possess surface receptor for avarity of physiological substances for example thrombin and angiotensin II ,once activated ,endothelial cells express avarity of intracellular adhesion molecules ,some of which are released into the plasma these include .Vascular Cell Adhesion Molecules (VCAM),E-selectin ,

P-slectin and Von Will Brand Factor (VWF).Which modulate platelet adhesion and vascular permeability . Endothelial cell also have anticoagulant function and fibrinolytic factor. [Hoffbrand *et al* 2016].

1-2-3-2.The platelet-vessel interaction:-

Platelets (thrombocytes) are cellular fragments of megakrocyte; the function of the platelet in primary hemostasis is the formation of platelets plug.

Following break in the endothelial lining, there is initial adherence of platelets to exposed connective tissue mediated by VWF. Collagen exposure and thrombin generated through activation of tissue factor produced at site of injury cause adherent platelets to release the granule content and also activate platelet prostaglandin synthesis leading to formation of thromboxaneA2 (TXA2).Released ADP causes platelet to swelling and aggregate platelet rolling in direction of blood flow over exposed VWF with activation of GPII\IIIa receptors results in firmer binding .Additional platelets form the circulating blood are drawn to the area of injury . Continuingaggregation promotes the growth of haemostatic plug. The primary haemostatic plug produced by platelets in the first minute or so following injury is usually to provide temporary control of bleeding. [Hoffbrand and Moss,2016].

1-2-3-3. Von Will Brand Factor (VWF):-

VWF is multimeric glycoprotein that plays an important role in primary heamostasis by promoting platelet adhesion to the subendothelium at sites of vascular injury under high shearrate condition .It also acarrier of factor eight (FVIII) and this association protect FVIII from rapid protolysis .VWF synthesized by endothelial cells,megakaryocytic and platelets .[Hoffbrand *et al*, 2016].

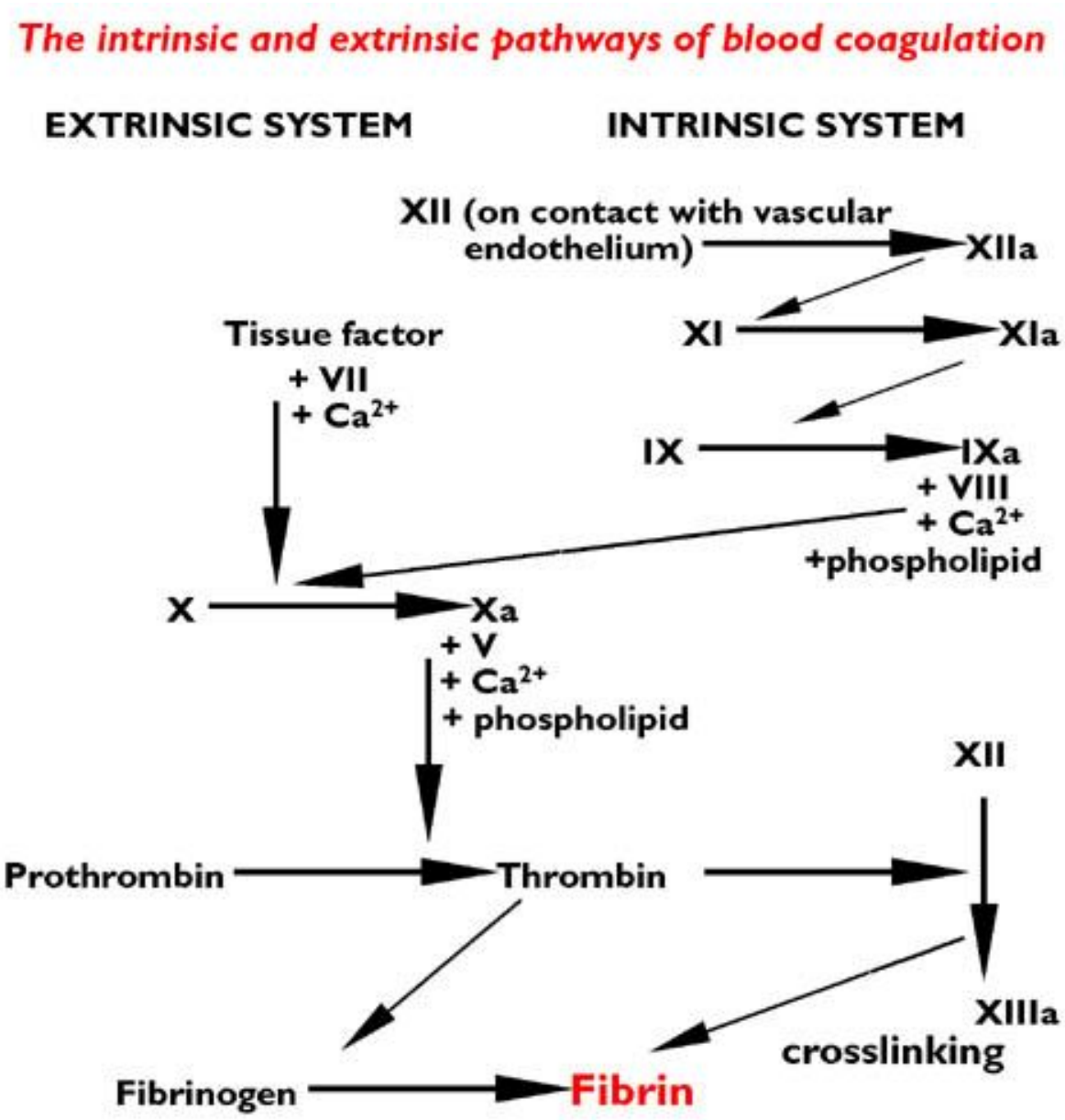
Table 1-1: The coagulation factor nomenclature with preferred names and synonyms (Hoffbrand and Moss, 2016) **:-**

Factor number	Descriptive name	Active forms
I	Fibrinogen	Fibrin subunit
II	Prothrombin	Serine protease
III	Tissue factor	Receptor \cofactor
V	Labile factor	Cofactor
VII	Proconvertin	Serine protease
VIII	Antihaemophic factor	Cofactor
IX	Christmas factor	Serine protease
X	Stuart –power factor	Serine protease
XI	Plasma thromboplastin - anticedent	Serine protease
XII	Hageman (contact) factor	Serine protease
XIII	Fibrin –stiblizing factor	Transglutaminase
	Prekalikrein (Fletcher factor)	Serine protease
	HMWK(fitzgerald factor)	Cofactor

1-2-4 .Amplification (intrinsic and extrinsic pathway) :-

An updated concept of TF-initiated thrombin generation, including the important feedback reactions of thrombin. Physiological initiator of blood coagulation is exposure of the circulating zymogen FVII to membrane bound TF activation of FVII to the protease FVIIa result in activation of FIX and FX by the TF-FVIIa complex .In the absence of its cofactor FVa,FXa generate only trace amount of thrombin from prothrombin (this extrinsic pathway).This amount insufficient to initiate significant fibrin polymerization but able to back activate FV,FVIII and FXI by limited protolysis in the amplification phase of coagulation ,FXIa activate FIXa, which form complex with FVIIIa. This is intrinsic tenase complex (FVIIIa-FXa) that activate sufficient FXa (intrinsic pathway) to form complex with FVa, producing the prothrombinase complex (FVa-FXa) .Result in the explosive generation of fibrin clot (common pathway).[Hoffbrand *et al*, 2016].

Figure 1-1: The intrinsicandextrinsicpathways).[Hoffbrand *et al*, 2016].



1-2-5. Coagulation factors:-

1-2-5-1 .Tissue factor (TF):-

The formation of FVIIa –TF complex as initiator of coagulation in both normal and pathological to coagulation TFis protein contain group of amino acid extra and transmembrane .Vascular adventitial cells ,neuralgia, vascular smooth muscle and epidermal cells express TF is initiate clot if leakage out of vessels . Intravascular exposure of TF by any route can result in pathological thrombosis. [Hoffbrand,*etal* 2016].

1-2-5-2. Factor VII:-

PlasmaFVII bind to TF after vessels trauma or rupture ,to form complete initiate coagulation by directly activation of FX .The FVIIgene lies adjacent to the FX gene .Is one vitamin k- dependent carboxylase (F X,IX,VII, Prothrombin ,PC) the life span ofFVII is 3 hours as zymogen ,and 2.5 hours asFVIIa . [Hoffbrand *et al,* 2016].

1-2-5-3. Factor X:-

Its gene and serine protease as FVII .the halve life is 36 hours .FX is activated by either FIX a-FVIIIa or TF-FVIIa on phospholipids surface in the presence of calcium ion .FXa forms aphospholipids –bound complex with FVa which efficiently activates prothrombin (prothrombinase complex).[Hoffbrand*et al,* 2016].

1-2-5-4. Factor IX:-

Is X-linked gene .Deficiency of FIX result in clinical heamophilia B,the main function of FIX is to participate in the tenase complex (IXa-FVIIIa) is liver specific transcription factor the plasma half life 8 hours.[Hoffbrand*et al*, 2016].

1-2-5-5.Factor XI:-

Is a zymogen of serine protease that have 4 apple (PAN 1-4)domain and aserine protease domain in each monomer . Activation of FXI is by single cleavage proformed bythrombin. FXa then activate FIX directly in free solution .FXIa activation by the contact protein FXIIa was originally thought to be arelevant step in intrinsic or contact activatedcoagulation, but it is now considered that the feedback activation of FXI by trace thrombin provides a physiologically relevant route for generation of increased amount of FIXa to assemble tenase during the amplification of the initial TF stimulus.[Hoffbrand *et al,*2016].

1-2-5-6. Factor XIII:-

Circulate asateteramer of 2A-chains and 2B-chains. The B-chain function as acarrier for the A-chains which after activation by thrombin ,function as transglutaminase to cross linked fibrin and other proteins in the clot result in a stable structure .[Hoffbrand *et al,* 2016].

1-2-5-7. Factor VIII:-

Its X chromosome linked gene. Released as 2- chain molecule. Because of internalhomology, the FVIIIdomain structure can be represented asA1, A2, C1, C2. TheB domain is not necessary for procoagulant function so deleted in full activity .FVIII is the essential cofactor activation of FXa by FIXa in the tenase complex. It has no function until protolysed to FVIIIa by thrombin or FXa .[Hoffbrand *et al,*2016].

1-2-5-8. Factor V:-

The structure of factor V, like that of FVIII, can be represented as A1-A2-B-A3-C1-C2. In contrast with FVIIIthe B-domain is required in full procoagulant function.FValso differ from FVIIIin that it lack 3 short acidic inter domain peptides implicated in FVIII function.

FV is the cofactor for the activation of prothrombin by FXa .it no functioning until protolysed by thrombin or FXa into Va .[Hoffbrand*et al*, 2016].

1-2-5-9. Fibrinogen:-

Its gene cluster is located in chromosome in order Beta, Alfa, Gama, linked by disulfide bond cross-linked.

Polymerization of fibrinogen occurs when thrombin cleaves 2 short negatively charged fibrin peptide A and B from the N-terminal sequences of the alfa and beta chain respectively .This release sequences in fragment E-region (called knob)that fit in holes in the fragment D-regions . Polymerization then occur spontaneously in staggered half –over lap array .Electron microscopy study still are important in resolve the molecular of fibrillar fibrin formation . [Hoffbrand *et al*, 2016].

1-2-5-10. Prothrombin:-

Its sequences similar to that found in other vitamin k dependant protein. FXa complexed with FVa activated prothrombin zymogen to thrombin on a phospholipids surface (prothrombinase) .On cleavage of 2 peptide bonds .Fully cleaved thrombin is termed is rapidly released from its site of participate in numerous haemostatic function free in solution ; acting as aprocoagulant against many substances including fibrinogen , FV,FVIII,FXI.[Hoffbrand *et al*, 2016].

1-2-6.Inhibitor of blood coagulation:-

The thrombin plug must be in the site of injury and must not release to other part of body;

1-2-6-1.Tissue factor path way inhibitor:-

Is a kunitz type inhibitor; the various serpin found in blood probably play on physiological role in the inhibition of FVIIa in the TF-FVIIa complex. Instead the action of this serine protease cofactor complex is modulated by tissue factor pathway inhibitor (TFPI), which located on the endothelial cell surface, with in platelets, inplasma and monocyte . [Hoffbrand *et al*,2016].

1-2-6-2. Serine protease inhibitor:-

Human plasma contain at least 7 type of serine protease inhibitor .Only antithormbin and heparin cofactor II(HCII)assume haemostatic significance. [Hoffbrand *et al*, 2016].

1-2-6-2-1.Antithrombin;-

AT is synthesized in liver, with a high plasma concentration. Antithormbin (AT) form astable with several serine protease coagulation factors, predominantly thrombin and FXa, but also some extent F (Xa, XIa, XIIIa, Kalikrein). [Hoffbrand *et al*, 2016].

1-2-6-2-2. Heparin cofactor II:-

It appear to be specific inhibitor of thrombin and have a little or no anti FXa activity the rate of thrombin neutralization by HCIIis increased approximately 1000-fold by heparin ,although because of it lower affinity it require 5-10 times more heparin than AT .[Hoffbrand*et al*, 2016].

1-2-6-3.Heparin and heparin like substance:-

Heparin implies asingle compound; it in factor refers to heterogeneous mixture of sulfated polysaccharides.

Unfractionated heparin (UFH) is an extremely hetrogenous polymer being composed of between 10-100 saccharide units .Yielding anumber of low molecular –weight heparin (LMWH) preparation 1-2 units that may inhibit the specific serine protease thrombin .[Hoffbrand *et al* 2016].

1-2-6-4.Protein Z :-

PZ vitamin k-dependent plasma protein that serves as cofactor for the inhibition of FXa by Z-dependent protease inhibitor (ZPI) a member of the serine super family.

PZ structure similar to those coagulation factors FVII,FIX,FX,and PC .Inhibition of FXa . [Hoffbrand *et al*, 2016].

1-2-6-5. Alfa 1 –antitrypsin:-

This is aserpin those primary target are pancreatic and leukocyteelasteases. In coagulation the major inhibitory activity is directed against FXIa,and FXa .[Hoffbrand *et al*, 2016].

1-2-6-6.protease nexin 2:-

This is akunitz type serine protease inhibitor that found in the alfa granules of platelets inhibitor of FXIa. [Hoffbrand*et al*, 2016].

1-2-6-7.Alfa 2-Antiplasmin:-

This is theprinciple inhibitor of the fibrinolytic enzyme plasmin.

1-2-6-8. Esterase inhibitor:-

Is aminor way to the neutralization of FXI a and plasmin.

1-2-6-9.Alfa2- microglobin:-

Is composed of four identical chain, it binds to coagulation factors at the site away from the active site and make inhibition.

1-2-6-10.Protein c and protein c path way:-

PCis vitamin k-dependent serine protease has an identical modular composition to the procoagulant factor FVII,FIX,and FX .In order to exert its anticoagulant effect ,PC must first be activated to APC .this by thrombin .

APC interact with protein S bound to the phospholipids surface of activated platelets, enhancing the anticoagulant activity of APC against FVa and FVIIIa.

Protein C pathway inhibits of cofactor FVa and FVIIIa, the activated form of FV, FVIII,enhance the activity of serine protease factors in the tenase and prothrombinase complex.

1-2-6-11.Thrombomodulin (TM):-

Is an integral transmembrane receptor found on endothelial cells in virtually all body tissues.TM forms acomplex with thrombin ,preventing binding of the protease to its various procoagulant substrates (Fibrinogen ,FV, FVIII, FXIII, and Protease –activated receptor involved in platelet aggregation) .

1-2-6-12. Endothelial protein C receptor:-

EPCR atransmembrane receptor on endothelial cells that binds PC and promotes its activation by the thrombin –TM complex.

1-2-6-13. protein Sand PC inhibitor:-

PS is asingle chain vitamin k-dependent glycoprotein chiefly synthesized in the liver by endothelial cells. Its bind to negatively charged phospholipids exposed on the surface of activated platelets.

APC is subject to inhibit by serpin, including APCinhibitor (PCI), PAI-1and alfa-1 antitrypsin, PCI slowly but progressively blocks the action of APC. [Hoffbrand*etal*, 2016].

1-2-7. Fibrinolysis:-

That the principle functions of the fibrinolytic system are to ensure that excess fibrin deposition is either prevented or rapid removed and following re-establishment of heamostasis ,the fibrin mesh is removed during wound healing .The system of pro fibrinolytic and antifibrinolytic factors that has evolved to meet the requirement to clot formation .[Hoffbrand et al, 2016].

1-2-7-1.compenent of the fibrinolyticsystem:-

These include plasiminogen (PLG) and plasmin; several endogenous tissue plasma derived or exchange PLG activators, and a number of inhibitor of plasma in or of the PLG activators. Both endogenous and exogenous fibrinolytic factors have been used clinically to treat thrombosis. [Hoffbrand et al, 2016].

1-2-7-2.Plasminogen and plasmin:-

PLG is asingle –chain glycoprotein zymogen of serine protease plasmin which carried out the enzymatic degradation of cross linked fibrin.

1-2-7-3.Actoin of plasmin in fibrin and fibrinogen:-

It can hydrolyses a variety of substrate as (FVand FVIII,but its major physiological target are fibrin and fibrinogen) and give hetrogenous mixture of small soluble peptides known collecting as fibrin degradation product (FDP).

Digestion of fibrin and fibrinogen give D-fragment, the residue known as Y attacked by plasmin to give fragment E.

Following the thrombin generation and consequent activation of FXIII, intracellular transmidation of the alfa and beta chain by FXIIIa occur and then the action of plasmin yield chacteristic D-dimer, D-dimer –E-fragment and oligomers of fragment Xand Y . However clinically, FDPassay are used to detectDIC, when mixed fibrin \fibrinogen degradationproduct appears in the circulation. [Hoffbrand et al, 2016].

1-2-7-4.Plasminogen activators:-

1-2-7-4-1.Tissue plasiminogenActivator (TPA):-

TPA is a serine protease secreted by endothelial cells .Itis not synthesized by the liver or kidney ,but is found in most extra vascular body fluids ,including saliva ,milk ,bile ,cerebrospinal fluid and urine .

1-2-7-4-2. Urinary plasiminogenActivator (UPA):-

First extracted from urine ,is synthesized by tubules and collecting ducts in the kidney and by fibroblast –like cells in the gastrointestinal tract .It secreted as an inactive zymogen that cleaved by activator in plasma (including kalikrien and plasmin).

1-2-7-4-3.Exogenous plasiminogenActivator:-

Derived from non human sources including animals and certain plants and microorganisms .known as streptokinase (SK).Is make non enzymatic polypeptide that forms a stable complex with plasiminogen .[Hoffbrand et al, 2016].

1-2-8. Inhibitor of Fibrinolysis:-

1-2-8-1.plasminogen activator inhibitor (PAI):-

1-2-8-1-1.Plasminogen activator inhibitor type one;-

PAI-1 is an important fast activity serpin inhibitor of tpA ,upA ,and to small extent ,plasmin,and secreted by endothelial cells .Also found in platelets alfa granules .It occur in 2 form active functionally complex with tpA .

1-2-8-1-2.Plasminogen activator inhibitor type 2:-

Produce by the placenta and thus contribute to the inhibition of Fibrinolysis that occur during pregnancy .Also synthesized in monocyte ,and epidermal cells but not usually found in no pregnant subject .Is more active in inhibition of upA and tpA . [Hoffbrand *et al,* 2016].

1-2-8-2.Inhibitor of plasmin:-

1-2-8-2-1.Alfa -2 Antiplasmin:-

Is active predominant plasmin inhibitor .Form a stable complex with plasmin**1-2-8-2-2.Lipoprotein A:-**

The protein portion of the lipoprotein Ais termed apo(a) .It is synthesized in the liver and circulate in plasma .It can compet with PLG for binding site on fibrinogen or tpA ,and may also increase PAI-1 expression .

1-2-8-2-3.Thrombin –activatable Fibrinolysis inhibitor:-

In the presence of Thrombomodulin activate carboxy peptidaseB,and TAFIa in turin inhibit Fibrinolysis. [Hoffbrand *et al,* 2016].

1-2-9.Tests of haemostatic functions:-

Defective of haemostatic with abnormal bleeding may results from a vasculardisorder, thrombocytopenia or platelets function disorder and may be defective in blood coagulation. [Hoffbrand and Moss, 2016].

1-2-9-1.Blood count and blood film examination:-

Thrombocytopenia, modern counters measure platelets volume .Also the absolute count of immature platelets correlate increased platelets production. Platelets count may be manually or electronic counting, platelets counting use full in clearing case of defect in haemostatic function due to quantities or qualitative platelets defect. [Hoffbrand and Moss , 2016].

1-2-9-2.screening tests of blood coagulation:-

It provides assessmentof the extrinsic and intrinsic system of blood coagulation and also the central conversion of fibrinogen and fibrin. [Hoffbrand and Moss ,2016].

Table 1-2 screening tests used in diagnosis of coagulation disorders [Hoffbrand and Moss ,2016].

Screening tests	Abnormalities indicated by prolongation	Most common cause of coagulation disorder
Thrombin time (TT)	Deficiency or abnormality of fibrinogen or inhibition of thrombin by heparin orFDPs.	DIC Heparin therapy.
Prothrombin time (PT)	Deficiency or inhibition of one or more of the following coagulation factors; VII, X, V, II, Fibrinogen.	Liver disease Warfarin therapy DIC
Activated partial thromboplastin time (APTT)	Deficiency or inhibition of one or more of the following factors XII, XI, VIII,X, V, II, Fibrinogen.	Heamophilia Christmas disease (+ condition above)
Fibrinogen quantitation	Fibrinogen deficiency	DIC and liver disease

1-2-9-2-1. Prothrombin time (PT):-

Measure factors VII, X, V, prothrombin and fibrinogen. Tissue thromboplastin (brain extract) or synthetic TFwith lipid and calcium is added to citrated plasma. [Hoffbrand andMoss, 2016].

1-2-9-2-2.Activated partial thromboplastin time (APTT):-

Measure factor VIII, IX, XI, and XII in addition to FX, V, Prothrombin and fibrinogen .Three substances –phospholipids, surface activator (kaolin) and calcium added to citrated plasma.

Prolonged PTandAPTT because of factor deficiency are corrected by the additionof normal plasma to the test plasma .To know deficiency from presence of inhibitor.[Hoffbrand and Moss, 2016].

1-2-9-2-3. Thrombin time (TT):-

Is sensitive to adeficiency of fibrinogen or inhibitor of thrombin .Diluted bovine thrombin is added to citrated plasma. [Hoffbrand and Moss,2016].

1-2-9-2-4. Specific assays of coagulation factors:-

Most based on a PTand APTTall factor except are to be measured are presented in substrate plasma. A number of chemical chromometricand immunological methods are available. [Hoffbrand and Moss, 2016].

1-2-9-2-5. Bleeding time (BT):-

Is not areliable assessment of platelet function as it in sensitive .It was used to identify abnormal platelet function ,including the diagnosis ofVWF deficiency it has been replaced by specific platelet aggregation tests ,platelet adhesion assay and platelet function analysis .[Hoffbrand and Moss, 2016].

1-2-9-2-6. Test of plateletsfunction:-

Platelets aggregaetory measured in full light absorbance in platelets –rich plasma platelets aggregate . [Hoffbrand andMoss,2016].

1-2-9-2-7. Test of Fibrinolysis:-

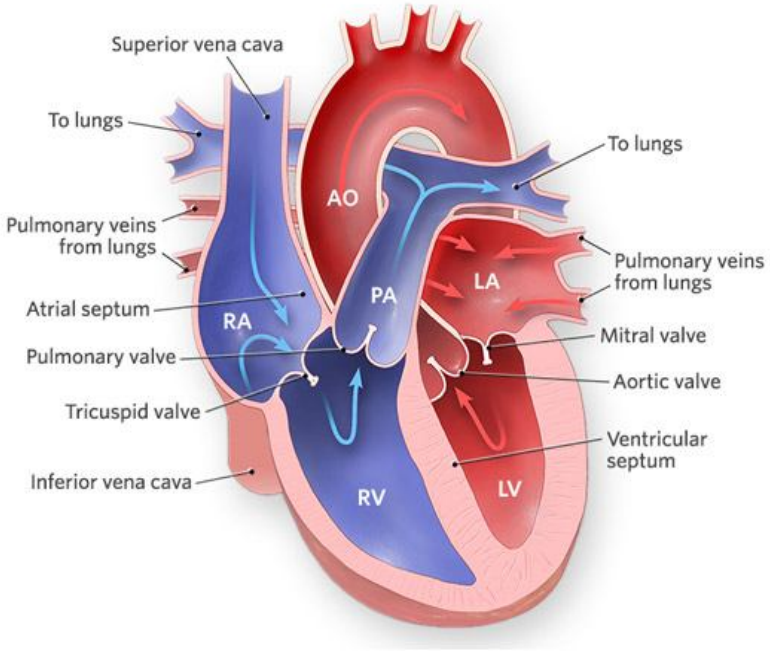
As thromboblastogrohy (TEG) or hromboelastmetery (ROTEM) D-dimer is measurement of FDP. [Hoffbrand and Moss, 2016].

1-3. Normal cardiovascular system:-

Cardiovascular system may be considered as being composed of a pump (heart) and plumbing (vessels) that take nutrient to tissue and remove metabolites from them .Metabolites travel by blood , lymphatic return tissue fluid to blood via the thoracic ducts.

The major diseases implicated in the cardiovascular system for this death areatherosclerosis, thrombosis, embolism and infraction. [vardaxis, 2000]

Figure 1-2; Normal heart anatomy [vardaxis , 2000]



1-3-1. Heart failure :-

It is clinical condition characterized by the in ability of heart pump blood with requirement of the metabolic tissues of the body or being able to do so at increased filling pressures .It may be divided in to systolic or diastolic failure depending on whether there is abnormality in the cardiac contractility.[Garg andGupta ,2013].

1-3-2 .Left ventricle failure:-

Mainly caused by ischemic heart disease,hypertension, aortic or mitral valvular disease and myocardial disease. Thefeature includes hyper atrophy and fibrosis in the myocardium .Arterial involvement result in the development of arterial fibrillation which is responsible for thrombus or embolic stroke. .[Garg andGupta ,2013].

1-3-3.Sudden cardiac death:-

It is defined as the death of an individual within 1 hour of onset of symptom commonly due to ventricular fibrillation.

In case of coronary vessel occlusion leading to ischemia, there is physiological compensatory vasodilatation resulting in augmentation of coronary blood follow .[Garg andGupta ,2013].

1-3-4.Stable angina:-

Occur when the myocardial oxygen demand is more than the supply .Is take place when the coronary artery occluded more than 75% .Characterized by the pain on exertion is relieved on taking rest or taking vasodilators.[Garg andGupta ,2013].

1-3-5.Prinzmetal or variant angina:-

It is an episodic angina due to coronary artery spasm resulting in pain at rest it is characterized by ST segment elevation on the ECG.[Garg andGupta ,2013].

1-3-6.Unstable orcrescendoangina:-

It is induced by a therosclerotic plaque disruption with superimposed partial thrombosis or vasospasm or both of them .The pain occur with increasing frequency and for a longer duration and characteristically precipited by progressively less exertion.[Garg andGupta ,2013].

1-3-7.Myocardial infractions (MI) :-

Table 1-3 type of myocardial infarctions..[Garg andGupta ,2013].

Subendocardial MI	Transmural MI
• Ischemic necrosis limited to 1/3rd of ventricular wall. • Caused by in complete coronary artery occlusion.	• Ischemic necrosis involves full thickness of ventricular wall. • Caused by sever coronary atherosclerosis with acute plaque rupture and occlusive thrombus.

1-3-8.Infective endocarditis (IE):-

It is colonization invasion of heart valve and mural endcardium by microbiologic agent leading to formation of bulky, friable vegetation composed of thrombotic debris and organism with destruction of under lying cardiac tissue..[Garg andGupta ,2013].

1-3-8-1. Morphology:-

The friable, bulky destructive vegetations containing fibrin. When the vegetation erode into myocardium, they can form an abscess, the systemic embolistion can result in septic interact.[Garg andGupta ,2013].

1-3-9.Rheumatic Heart Disease (RHD):-

Rheumatic fever is an acute immunologically mediated multisystem .inflammatory disease that occur few weeks after an attack of group A,B-hemolytic streptococcal pharyngitis not disease mainly in children between 5-15 years .Only 3% of patients with group A streptococcal pharyngitis develop acute rheumatic fever .[Garg andGupta ,2013].

1-3-10.Congenital heart disease:-

About 1 in 200 babies as born have a congenital heart defect .About 5 % of cardiac defects are attributed to the chromosomal abnormalities .Or may be to other disease .Defect are variables in severity ,ranging from the trivial and subclinical to the rapidly fatal .There are many types of congenital heart disease ,but only the most common are ;

1-3-10-1.Left to right shunt:-

Arterial septal defect is a connection between right and left arterial due to a hole in the interarterial septum. About 90% congenital heart disease most of this the

occurrence in adult .A complication associated with untreated cases of this disease is the occurrence of paradoxicalemboli.[Vardaxis,2000].

1-3-10-2.PlumonaryStenotic lesions:-

This involve narrowing of the pulmonary artery or the pulmonary valve which reduce the amount of blood .So the affected babies appear blue cyanotic this is probably due to emoblis of megakrocyte from the bone marrow. [Vardaxis ,2000].

1-3-10-3.Coarctation of the aorta:-

Is the condition in which there is narrowing or blockage of the aorta.Is about 5% of congenital heart disease .There are 2 type;

1-3-10-3-1.preductal type (infant):-

Sever narrowing of segment of the aorta, a patient duct allow blood to enter the systemic circulation from the pulmonary circulation

1-3-10-3-2. post ductal type (adult):-

More common and involves a shorter segment of the aorta frequently in ring fibrosis occurs in wall of aorta.[Vardaxis,2000].

1-5.Hypothesis:

Medical report ,laboratory investigations and medical record all wide the world clear that the heart disease lead to coagulation disorder and increase especially during major operation suggesting that the decrease of element ,crisis ,and frequent sever painful and hospital admission have association with coagulation disorders.

We will investigate whether this finding applies in patients with heart disease.

1-6.Rationale:

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

Recent researches indicate that patients who had heart disease may have ability to stimulate haemostatic disorders coagulation deficiency, platelets dysfunction and thrombocytopenia as results of heart disease. Patients show variable abnormalities in PT, APTT, PLTS Count and some experience no change from the base line value.

1-7. Objectives:-

1-7-1. General objectives:

To Measurement of Prothrombin Time, Activated Partial Thromboplastin Time and Platelets Count among Sudanese Heart disease Patients.

1-7-2.Specific objectives:

To Measure PT, APTT, in heart disease patients.compared to control.

To Measure platelet counts in heart disease patients compared to control .

To comparing of PT ,APTT and platelets counting in study group according to age group and gender .

Chapter tow

Material and methods

Chapter Two

Material and Method

2. Material and method:

2-1 .Study design:

A hospital base cross sectional analytical study was conducted forevaluation of haemostatic mechanism in patients with heart disease.

2-2 .Study area:

The study conducted in Khartoum state at Sudan cardiac center .

2-3-.Study population:

Patients with heart disease investigated for PT, APTT, and PLTS count.

2-4.Sampling:

The frame included all heart disease patients.

2-5.Inclusion criteria:

All patients who had a confirmed diagnosed as heart disease patients.

2-6.Exclusion criteria:

All patients who were not diagnosis as heart disease patients.

2-7. Sample size:

According to design of study, the sample (patients) selected by a simple random sampling method (probability sampling). Seventy samples of patients matched by thirtysamples as control.

2-8. Tool of data collection:

The data collected by using of laboratory investigation to obtain PT, APTT, PLTS count .Also the interviews used to obtain age ,sex ,family history ,clinical features and using of questionnaire as instrument .

2-9. Data analysis:

The data after collection analyzed to obtain the mean standard deviation and the probability (p_ value).between patients and control by using SPSS computer program.

2-10. Ethical consideration:

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

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

2-11. Time line:

The best of research about 3 month began in 1\4\ 2016.

2-12. Sampling:

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

2-13. Methodology:

2-13-1. Collection technique:

EDTA container.

Tri-sodium citrate container.

Cotton.

Alcohol (70%).

Syringes.

Tourniquet.

2-13-2. Procedure:

1. Patients' comfortable sitting, tourniquet applied above elbow and superficial antecubtal for arm vein identified.
2. The skinsterile with 70% ethanol and allowed to dry.
3. Syringe needle inserted correctly into the vein ,and 5ml of blood sample take ,tourniquet released ,needle remove ,and 2.5ml into EDTA and other 2.5 ml into 3.2 % tri sodium citrate .to separate to plasma. [Lewis*et al* 2012] .

2-13-3.Platelets count:

By sysmex 21Automated Hematology Analyzer.

2-13-3-1. Reagent and material:

1.Cell pack.

1. Stromatolyser.
2. Detergent.
3. Cell cleaner.

2-13-3-2 .Principle of sysmex 21Automated 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 nebulizer diluted mixture aspiration delivered to RBCs aperture bath for providing information about RBCs and platelets based on cell sizes, 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 (HiCN) .

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 forthat RBCs, WBCs counts . hence three values were directly measured (RBC,WBC,Hb) and displayed on (LCD).other values of red cell indices, platelets counts, leukocyte

differential and absolute count calculated from given information and automated constructed histogram, the result printed out according to the setting mode. [Bendette*et al* 1995].

2-13-4. PT and APTT estimation:

By manual method

2-13-4-1.Reagent and material:

1. Patient and control platelets poor plasma (ppp).
2. Thromboplastin.
2. Kaolin; 5 g/l.
3. Phospholipid; 0.35-0.4 iu/ml.
4. Cacl2 0.25 mol/l.

2-13-4-1-1.Preparation of plasma:

2.5 ml of citrated anti coagulated venous blood samples were collected (9 part blood to 1 part anti coagulant). Blood was thoroughly mixed with the anticoagulant. Samples were centrifuged at 3000 rpm for 15 minutes to obtain platelet –poor plasma (PPP).Plasma was separated from cells into eppendorf tube and tested.

2-13-4-2. Principle and method

Pro thrombin Time:

Principle:

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

Method:

Deliver 0.1mlof plasma into glass tube place in water path and add 0.1 ml of thromboplastin .wait 1-3 minute to allow the mixture to warm .then add 0.1ml of warmed cacl2 and start stop watch .and time of clotted record . Must be duplicated.

Normal value:

10- 12 second.

Activated partial thromboplastintime:

Principle:

The test measures the clotting time of plasma after the activation of contact factors and the addition of phospholipid and cacl2 ,but without added tissue thromboplastin.so indicate the overall efficiency of the intrinsic path way .

Method:

Mix equal volume of kaolin and phospholipid 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.

Statistical analysis

Statistical analysis was performed by using SPSS computer program version 14 , the value were expressed as mean ± Std .Devision by using Independent –T-test ,frequency and graph to get mean ages and distribution between gender.

Chapter three

Results

Chapter three

Results

3 . Results:

100 venous blood sample were collected , 70 sample collected from heart disease patients were recognized according to age 32 patients (45.7%) between 1-30 years ,23 patients (32.9%) between 31-60 years and15 patients (21.4%) more than +60 years . And 30 sample collected from healthy person matched as control and also recognized according to age 13 control (43 .3%) between 1 -30 years, 13control (43.3%) between 31-60 and 4 control (13.3%) more than 60 years. Also recognized according to number about 35 patients is male (50%), and 35 patient is female (50%), and the control 15male (50%), and 15 female (50%).

3-1.Comparison of PT, APTT level and PLTs count between study group and control group.

Parameters	**Mean ± STD**		**P.value**
	Study group	**control group**	
PT by second	30.4± 9.7	13.2±1.9	0.00
APTT by second	43.6± 8	32±6.5	0.00
PLTs count thousands per cumm	258±97.7	221.4±82	0.07

3-2.Age group in study group:-

Group	Range	Frequency
Group1	1-30 years	32
Group2	31-60 years	23
Group3	More than60 years	15

3-3.Comparison of PT,APTT level and PLTs count between(group1,group2 andgroup3) in study group

parameters	Mean±STD			p-value
	group1	group 2	group3	
PT by second	30.7± 10.4	31± 10.4	28.8± 7.2	0.7
APTT by second	43.7± 8.7	45±7.4	41± 7.2	0.3
PLTs count thousand per cumm	255±101	285±107	222±60.5	0.1

3-4.Comparison of PT,APTT level and PLTs count between male group and female group in study group .

Parameters	Mean ±STD		P-value
	Male	Female	
PT by second	29±9.4	36±3.5	0.25
APTT by second	44±7.2	43.2±8.8	0.73
PLTs countthaousand per cumm	312.3±184.4	221±61.6	0.07

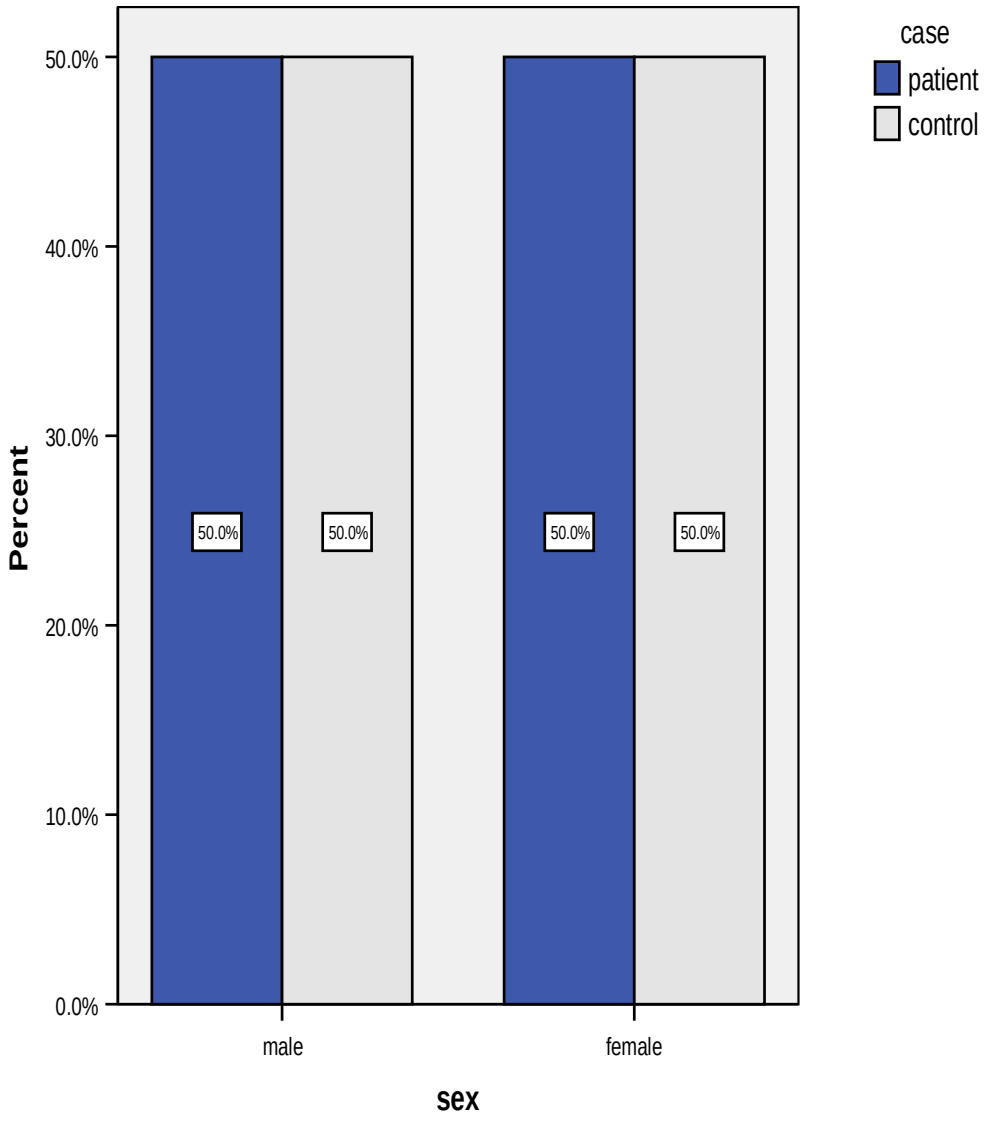


Figure3- 1;The percentage of male and female in study group compared tocontrol.

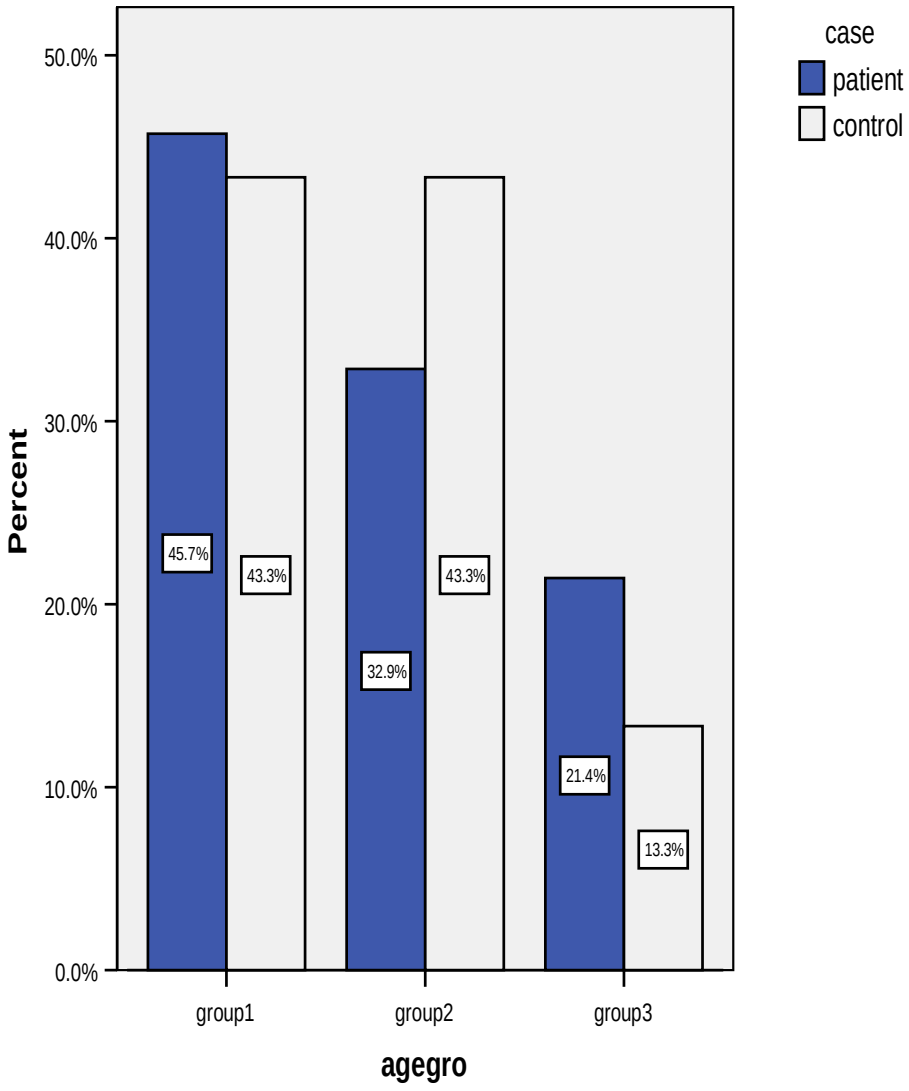


Figure3-2;The percentage of age group in study group compared tocontrol.

Chapter four

Discussion, conclusion and Recommendation

Chapter four

Discussion, Conclusion and Recommendation

4-1.Discussion

The result of this study show there was increased in prothrombin time (PT) were increased than control (p v< 0.05). The PT in our study which agree with that reported in [Adaeze*et al*2014] ,previous study .

Also our study show the significance increased in activated partial thromboplastin time (APTT) was increased than control (p v<0.05). The APTT in our study which agree with that reported in [Adaeze*et al* 2014] previous study .

This also agrees with study [Ghasemi*et al* 2014] in Iran.Were study done in cyanotic congenital heart disease (CCHD) were fund the patients have factor deficiency this cause increase of PTand APTT.

were find platelets coagulation activities increased activated partial prothrombin time(APTT) in coronary artery disease .There are contribution in factor(seven ,eight ,fibrinogen) and deficiency in antithormbin three.[Kontiro *et al*1984].
Also platelet count in our study no significance change between patients and control were no significance decrease or increase than control (p v >0.05).These may due to small sample size.
The PLTs count in our study agreeswith. Were this fund minority of heart disease patients with thrombocytopenia.The conclusion platelets count in CCHD appears to represent acontinuum beginning with low platelet counts and ending with thrombocytopenia. [Michael *et al*2006] .

When compared between patients according to the age group we found no significance change between them in PT, APTT(p v>0.05).Where there are no significance change in PLTs count in patients according to age group (p v >0.05).

Also we found no significance change in PT,APTT and PLTs count in study group associated to gender (male \ female) (p v >0.05).

We observed the equal percentage of male and female in study group.

Also observed the presence of different age group in study group.

4-2.Conclusion

The study showed that ;-

1-The mean of PT in the patients 30.4±9.7 second, were in control 13.2±1.9 second.

2-The mean of APTT in the patients 43.6±8 second, were in control 32±6.5 second.

3-The platelets count in patients 258±97.7 thousand cells per cumm, were in control 221±82 thousand cells per cumm. Were no significance decrease between patients and control plateletscount

4- Nosignificance changein PT ,APTT and platelets count in study group according to age group.

5- Nosignificance change PT,APTTand platelets count in male and female study group.

4-3.Recommendation

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

-CBC also must be done monthly to avoid complication of thrombocytopenia.

Chapter five

References

Chapter five

References

AdaezeN,EmeribeA,NasirI,Babayo A and Emmanuel K(2014): Evaluation of prothrombin time and activated partial thromboplastin time in hypertensive patients Attending at ertiary Hospital in calabar ,Nigeria.

Benadette et al (1995).

Bernatova I(2014),Endothelial dysfunction in experimental models of arterial ,hypertension cause or consequence .Biomed research international .1(2)14.

ChobanianA.V,BakrisG.L,BlackH.R,et al(2003); Seventh report of the joint national committee .on prevention ,detection ,evaluation and treatment of high blood pressure – Hypertension ,42(6).

Doulgus P and Ginsburg G(1996);the evaluation of chest pain in women. N EngJornal med 334.

Lewis S .M ,Bain B , Bates I and LaffanM .A (2012) ; DACIE and LEWIS Practical hematology .Eleven ed.

Garg G ,Gupta S(2013),Review of pathology and genetic ,fifth ed.

GhasemiA,HorriM,Salah Y(2014); Coagulation Abnormalities in Pediatirc Patients with Congenital Heart disease :International Journal of pediatric 2(2.2);14.

Hoffbrand A ,Higgs D,MehtaD(2016);Post Graduate Hematology seventh edition ;676- 698.

HoffbrandA ,Moss P (2016);Essential Hematology .seventh edition ;265- 277.

KonetiraoA,Paul D, MintzD, Steveen J , Alfreda B, Nuchalt M , Jamesf S,Andpetern W (1984). Coagulation activities of platelets in coronary artery disease .circulation Journal (69); 15-21.

KontrasS,SirkH,and Newton W(2014): Hematologic abnormalities in children with congenital heart disease .JAMA 195(8);611-615.

Mass A and Appelman A (2010): Gender differences in coronary heart disease ;Netherlands Heart Journal , 18(12);598.

Michael C, Perloff J and Child J(2006) : pathogenesis of thrombocytopenia in cyanotic congenital heart disease ;AMJ Cardial 2006 ;98:[254-258].

MongirdineA, KursvietieneL,KasaukasA(2010). The coagulation system changes in patients with chronic heart failure medicine (Kaunas).2010;46(9):642-647.

Sarcon A ,Liu X D ,Ton D, Wood J and Hitch cook T (2015). Journal of Investigative medicine HIGH IMPACT CASE REPORTS .2015;3(4).

Stella B,HowardD andWilliamA:Hematologic Abnormalities in children with congenital heart disease .JAMA.thejornal of the American medical association 195 (8) ;611-615.

Toy J, Ederer D, Tulpuie A, Tandon A (1980). Coagulation Studies in rheumatic heart disease .Br Heart Journal ;(43):301-305.

Vardaxis N (2000), Atext of pathology second ed;304- 317.

Appendix 1

Sudan University of Sciences and Technology

Collage of Medical Laboratory sciences

Hematology Department

Data sheet

Name:…… No: ( )

Gender:Male; ( ) Female; ( )

Age: ……

Investigation:

PT:……second.

APTT:……..second.

PLTS Count:……..c\cmm

Date: Sig:

Appendix 2

sysmex 21Automated Hematology Analyzer