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Evaluation of Prothrombin Time and Partial Thromboplastin Time among Sudanese Hypertensive Patients in Shendi Town

A thesis submitted for partial fulfillment of the degree of M.Sc. in medical laboratory sciences (Haematology)

By

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الآيـــــة

﴿وَقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ

وَرَسُولُهُ وَالْمُؤْمِنُونَ﴾

صدق الله العظيم

(١٠٥)سورة التوبة

Dedication

To my spirit father…

-To my mother....

-To my teachers…

-To my colleagues…

-To everyone who helped me to complete this research.

Acknowledgements

First of all thanks for Allah, giving me the power and willingness to complete this research.

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Abstract

Background: Hypertension is a common condition in which the long term force of the blood against your artery walls is high enough that it may eventually cause health problem.

Aim: The main aim of the study is to evaluate prothrombin time, activated partial thromboplastin time in hypertensive patients.

Methods: This is a cross-sectional descriptive study conducted at El-Mek Nimer University Hospital in Shendi Town in the period between (March 2018- August 2018).30 blood samples were collected of hypertenive patients and 20 blood samples from normal individual as control. PT and PTT were measure .Data was collected and analyzed by SPSS using independent T test.

Results: The results showed that mean of prothrombin time and partial thromboplatin time were 16.5sec and 33.7 sec respectively when compare with the mean of control group 13.9 sec and 32.5sec respectively .

Conclusion: The coagulation parameters in hypertensive patients were significent increase in prothrombin time and insignificant increase in partial thromboplastin time .The age and duration of disease have no effect in prothrombin and partial thromboplastin time.

ملخص البحث

مدخل: مرض الضغط الدموي هو اضطراب شائع يحدث نتيجة قوة دفع الدم في الأوردة ويودي إلي مشاكل صحية.

الهدف هدفت هذه الدراسة لتقييم زمن البروثرمبين والثرومبلاستين الجزئي في مرضي ضغط الدم.

الطريقة: أجريت هذه الدراسة المقطعية الوصفية في مستشفي الملك نمر الجامعي بمدينة شندي في الفترة ما بين مارس٢٠١٨-اغسطس٢٠١٨. وكانت عينة الدراسة عبارة عن ٣٠ مريض تم اختيارهم بصورة عشوائية ٢٠عينه دمويه من العينه الضابطه وتم تحليلها معمليا وثم تحليل النتائج بواسطة برنامج الحزم الإحصائية للعلوم الاجتماعية الذي يعرف ببرنامج (SPSS) لتحليل بيانات الدراسة.

النتائج:أظهرت النتائج ان متوسط الزمن البروثرومبين والثرومبلاستين الجزئي كان ١٦,٥ثانيه و٣٣,٧ ثانيه تتابعيا ومتوسط العينه الضابطه ١٣,٩ ثانيه ٣٢,٥ ثانيه تتابعيا.

الخلاصة: خلصت الدراسة أن هنالك فرق ذو دلالة إحصائية في زمن البروثـــرومبين وفـــرق ليس ذو دلاله احصائيه في زمن الثرومبلاستين الجزئي وخلصت الدراسه ايضا الي ان العمـــر ومده الاصابه بالمرض لاتؤثر في زمن البروثرومبين والثرومبلاستين الجزئي.

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List of Abbreviations

Abbreviation	Term
ADP	Adinin Diposphat
APC	Activating protein c
APTT	Activated Partial Thromboplastin Time
CO	Cardiac out put
COX	Cyclo oxgenase
DM	Diabetes Mellitus
GP	Glycoproteins
HMWK	High Molecular-Weight Kininogen
HTN	Hypertension
PF3	Platelet phospholipid
PARS	Protease activated receptor
PT	Prothrombin Time
PVR	Peripheral vascular resistance
TF	Tissue factor
SPSS	Statistical Package for Social Sciences
VWF	Von Willebnllld Factol'

Chapter One

Introduction
Rationale
Objectives

1.1 Introduction

Blood pressure is the product of cardiac output multiplied by peripheral resistance. Cardiac output is the product of the heart rate multiplied by the stroke volume. In normal circulation, pressure is exerted by the flow of blood through the heart and blood vessels. High blood pressure, known as hypertension, can result from a hange in cardiac output, a change in peripheral resistance, or both. The medications used for treating hypertension decrease peripheral resistance, blood volume, or the strength and rate of myocardial contraction.

Hypertension is a systolic blood pressure greater than 140 mm Hg and a diastolic pressure greater than 90 mm Hg over a sustained period, based on the average of two or more blood pressure measurements taken in two or more contacts with the health care provider after an initial screening .(Brunner and Suddarths, 2010)

Hypertension is seen more commonly among people with a family history of hypertension. Indeed, people with a family history have almost twice the risk of developing hypertension as those with no family history. People with a family history of hypertension should be encouraged to have their blood pressure checked regularly. ncontrolled hypertension is caused by non-adherence to the antihypertensive drugs.

patients understanding their drug regimens help to improve their adherence, hus will help prevent the complications of hypertension which are debilitating and if not Prevented can increase the burden of a disease that is already on the increase. (Kumar & Halesh, 2010)

Thrombosis often appears to complicate the course of patients with hypertension; thrombosis in some patient with hypertension could be organ damage which makes a dramatic difference to clinical outcome in hypertension.

Hypertension causes target organ damage by the direct physical effect of increased blood pressure, as well as the active promotion of atherosclerosis and

thrmobogenesis. More importantly related and many of basic concepts of thrombogenesis can be applied to atherosclerosis.

The APTT is a screening test of the intrinsic clotting system. It will detect the inhibition or deficiency of one or more of the following factors: prothrombin, V, VIII (antihaemophilic factor), IX, X, XI, XII and fibrinogen.

The PT is a screening test for the extrinsic clotting system, i.e. factor VII. It will also detect deficiencies of factors, prothrombin, V, X, and fibrinogen. (Monica Cheesbrough.2000)

1.2 Rationale

Hypertension is most common disease in Sudan. Hypertension is risk factor for arterial disease. It is the major underlying factor leading to the most clinically relevant cardiovascular events and these events are usually due to formation of thrombus at the site of an atherosclerotic plaque, so in this research we want to study coagulation pathway to detect the possibility of thrombosis in hypertensive patients and may help to establish secondary preventive medication in individual patients.

1.3 Objectives

1.3.1 General objective

-To evaluate the prothrombin time and partial thromboplastin time among Shendi hypertensive patients.

1.3.2 Specific objectives

-To measure PT in hypertensive patients.

-To measure APTT in hypertensive patients.

-To detect the relation between PT, APTT and age and sex of patients and duration of hypertension.

Chapter Two

Literature Review

2. Literature Review

2.1.Hypertension (HTN)

is a condition in which the blood pressure, on at least two or more readings on different dates after an initial screening, is found to be higher than normal. If the systolic blood pressure is above 140 mm Hg or the diastolic blood pressure is above 90 mm Hg. (Lina. S and Pauta .D , 2003)

2.2. Pathophysiology of Hhypertension

Normally the heart pumps blood through the body to meet the cells' needs for oxygen and nutrients. As it pumps, it forces blood through the blood vessels to the vital organs and tissues. The pressure exerted by blood on the walls of the blood vessels' is measured as blood pressure. Blood pressure is determined by cardiac output (CO). Peripheral vascular resistance (PVR; the ability of the vessels to stretch), the viscosity (thickness) of the blood, and the amount of circulating blood volume. Decreased stretching ability and increased viscosity and fluid volume increase blood pressure. Several processes influence blood pressure by controlling CO and PVR.

These processes include nervous system regulation, arterial bar receptors and chemoreceptors, the renin-angiotensin-Aldosterone mechanism, and balancing of body fluids. One way blood pressure is influenced is through adjustment of the CO, which is the amount of blood that the heart pumps out each minute. The heart rate rises to increase CO in response to either physical or emotional activities that require more oxygen for the organs and tissue.

PVR also influences blood pressure; it is the opposition that blood encounters as it flows through vessels. Anything causing blood vessels to become narrower increases PVR. Any time PVR is increased, more pressure is needed to push the blood through the vessel, so blood pressure is increased as a result. If PVR is

decreased, less pressure is needed. Increased arteriolar PVR is the main mechanism that elevates blood pressure in hypertension, (Lina. S and Pauta .D, 2003)

2.3. Classification of hypertension

2.3.1Primary Hypertension

Primary or essential hypertension is the chronic elevation of blood pressure from an unknown cause. These unknown causes influence the factors that control blood pressure, resulting in a hypertensive state.

2.3.2.Secondary Hypertension

Secondary hypertension has a known cause. In other Words, it is a sign of another problem, such as a kidney abnormality, a tumor of the adrenal gland, or a congenital defect of the aorta. When the cause of secondary hypertension is treated before permanent structural changes occur, blood pressure usually returns to normal. Treatment may include surgery or medication. (Lina. S and Pauta .D, 2003).

2.4. Risk Factors for Hypertension

2.4.1. Family History of Hypertension

Hypertension is seen more commonly among people with a family history of hypertension. Indeed, people with a family history have almost twice the risk of developing hypertension as those with no family history. People with a family history of hypertension should be encouraged to have their blood pressure checked regularly.

2.4.2. Age

People age differently because of their genetic and environmental risk factors and lifestyle habits. Thus the results of the aging process may be reflected in wide variations of blood pressure among elderly people. As a person ages, plaque builds up in the arteries and the blood vessels become stiffer and less elastic, causing the heart to work harder to force blood through the vessels. These vessel changes

increase cardiac output to maintain blood flow into the circulation and subsequently raise blood pressure in the elderly.

2.4.3.Race and Ethnicity

Cultural Consideration discusses hypertension among various ethnic groups.

2.4.4.Diabetes Mellitus

Two-thirds of adults who have diabetes mellitus also have hypertension. The risk of developing hypertension with a family history of diabetes and obesity is two to six times greater than when there is no family history. Approximately 80 percent of people with type 2 diabetes mellitus (non– insulin dependent) are overweight.

2.5.Modifying Risk Factors

These modifications include weight reduction, stress management, moderation of dietary sodium and alcohol intake, increased physical activity, and smoking cessation .Lifestyle modifications are most often used with antihypertensive drugs to control hypertension and enhance the drug effects.

2.5.1. Weight Reduction

There is a strong relationship between excess body weight and increased blood pressure. Weight reduction is one of the most important, if not the most important, lifestyle modification to lower blood pressure. The health care provider and dietitian should be consulted to help the patient develop a weight-reduction diet and other methods of weight loss. (Lina. S and Pauta .D, 2003)

2.5.2.Stress Management

Reducing stress can play a major role in the treatment of patients with hypertension. Stress stimulates the sympathetic nervous system (fight-or-flight response). This stimulation causes the vessels to constrict and activates the rennin angiotensin mechanism.

2.5.3.Meal Planning

2.5.3.1. Salt intake

Research has shown that some people may develop high blood pressure by eating a diet high in salt. Patients whose blood pressure can be lowered by restricting dietary sodium are called salt sensitive. This sensitivity is particularly common among African-Americans, elderly persons, and patients with diabetes and obesity. Patients with hypertension should be instructed not to add salt while cooking and not to add table salt to their food. Processed foods or foods in which salt can be easily tasted (e.g., canned soups, ham, bacon, salted nuts) should also be avoided.

2.5.3.2. Intake of Potassium, Calcium, and Magnesium

Recent studies are inconclusive as to the role that low dietary potassium, calcium, and magnesium intake play in the development of high blood pressure. A balanced diet that ensures adequate intake of these nutrients is important in maintaining general health. Foods rich in potassium include oranges, bananas, and broccoli. Milk, yogurt, and spinach are rich in calcium. Vegetables such as spinach, garbanzo beans, and lima beans are good sources of magnesium. Whenever possible, fresh or frozen foods should be selected rather than canned foods to increase intake of these nutrients. (Lina. S and Pauta .D, 2003)

2.5.4.Alcohol Consumption

The regular consumption of three or more drinks per day can increase the risk of hypertension and cause resistance to antihypertensive therapy. The nurse should counsel hypertensive patients who drink alcohol to avoid it or at least limit their daily intake. Blood pressure may decrease or return to normal when alcohol consumption is limited or eliminated.

2.5.5. Exercise

People with sedentary lifestyles have an increased risk of hypertension compared with people who exercise regularly. Exercise helps prevent and control

hypertension by reducing weight, decreasing peripheral resistance, and decreasing body fat. Moderate activity, Patients with hypertension should be evaluated by a health care provider before starting any exercise program.

2.5.6. Smoking

Smoking is a major risk factor for cardiovascular disease and is associated with a high incidence of stage 3 hypertension. Patients who smoke may show an increase in blood pressure because nicotine constricts the blood vessels. The nurse should instruct patients with hypertension to quit or decrease smoking to reduce the risk of myocardial infarction and stroke. A referral by the nurse to a smoking cessation program can be helpful (Lina. S and Pauta .D , 2003)

2.6. Signs and symptoms of hypertension

Often hypertension causes no signs or symptoms other than elevated blood pressure readings. As a result, hypertension is referred to as the "silent killer." Patients with hypertension are often first diagnosed when seeking health care for reasons unrelated to hypertension. In a small number of cases, a patient with hypertension may complain of a headache, bloody nose, or blurred vision, although it is usually impossible for a patient to correlate the absence or presence of symptoms with the degree of blood pressure elevation. Most signs and symptoms of hypertension stem from long-term effects on the large and small blood vessels of the heart, kidneys, brain, and eyes. These effects are known as target organ disease. (Brunner and Suddarths , 2010).

2.7. Diagnosis of hypertension

Diagnosis is based on a health history to assess a patient's risk factors for hypertension, any previous diagnosis of hypertension, presence of any signs and symptoms, history of kidney or heart disease, and current use of medications. Although there are no diagnostic studies specifically for hypertension, there are diagnostic tests that can be helpful in identifying related information, such as

damage to organs or blood vessels. The types of diagnostic tests performed depend on the stage of the hypertension or other medical conditions that may be present at the time of evaluation .(Brunner and Suddarths , 2010).

2.8. Hemostasis

Hemostasis is the physiological process that stops bleeding at the site of an injury while maintaining normal blood flow elsewhere in the circulation. Blood loss is stopped by formation of a hemostatic plug. The endothelium in blood vessels maintains an anticoagulant surface that serves to maintain blood in its fluid state, but if the blood vessel is damaged components of the subendothelial matrix are exposed to the blood. Several of these components activate the two main processes of hemostasis to initiate formation of a blood clot, composed primarily of platelets and fibrin. This process is tightly regulated such that it is activated within seconds of an injury but must remain localized to the site of injury.

There are two main components of hemostasis. Primary hemostasis refers to platelet aggregation and platelet plug formation. Platelets are activated in a multifaceted process and as a result they adhere to the site of injury and to each other, plugging the injury. Secondary hemostasis refers to the deposition of insoluble fibrin, which is generated by the proteolytic coagulation cascade. This insoluble fibrin forms a mesh that is incorporated into and around the platelet plug. This mesh serves to strengthen and stabilize the blood clot. These two processes happen simultaneously and are mechanistically intertwined. The fibrinolysis pathway also plays a significant role in hemostasis. Pathological thrombus formation, called thrombosis, or pathological bleeding can occur whenever this process is dis-regulated. The complexity of these systems has been increasingly appreciated in the last few decades.

Multiple anticoagulant mechanisms regulate and control these systems to maintain blood fluidity in the absence of injury and generate a clot that is proportional to the

injury. The proper balance between procoagulant systems and anticoagulant systems is critical for proper hemostasis and the avoidance of pathological bleeding or thrombosis.

2.8.1.Primary Hemostasis

Platelets are small anuclear cell fragments that bud off from megakaryocytes, specialized large polyploid blood cells that originate in the bone marrow (Schulze et al., 2005). Platelets are present at 150 to 400 million per milliliter of blood and circulate for about ten days (Zucker-Franklin, 2000). In a healthy blood vessel, and under normal blood flow, platelets do not adhere to surfaces or aggregate with each other. However, in the event of injury platelets are exposed to subendothelial matrix, and adhesion and activation of platelets begins.

Primary hemostasis; the platelet response. Platelet aggregation at the site of injury is mediated by platelet receptors, platelet-derived agonists, platelet-derived adhesive proteins and plasma-derived adhesive proteins. Fibrin deposition around the resulting...

Multiple receptors on the surface of platelets are involved in these adhesive interactions, and these receptors are targeted by multiple adhesive proteins. Detailed descriptions are available in these recent reviews (Jackson, 2007). The key for all of these receptors is that the adhesive interaction only takes place in the event of an injury to the blood vessel. This restriction is maintained in several different ways.

Receptor GPIb-IX-V binds to immobilized von Willebrand factor (VWF) specifically through an interaction between GPIbα and the A1 domain of VWF. VWF is a large multimeric protein secreted from endothelial cells and megakaryocytes that is always present in the soluble state in the plasma as well as in the immobilized state in subendothelial matrix (Ruggeri, 2007). However, soluble VWF in the circulation does not bind with high affinity to GPIbα (Yago et

al., 2008). The high affinity interaction may be dependent upon high sheer stress exerted by flowing blood on immobilized VWF, whether that VWF is immobilized on subendothelial matrix or other activated platelets (Siedlecki et al., 1996).

Receptor GPVI is constitutively active but its ligand is collagen, which is present in the subendothelial matrix and thus is only exposed to the blood in the event of injury. GPVI and GPIb-IX-V are critical for adhesion of platelets to subendothelial matrix at the site of injury and for their subsequent activation (Kehrel et al., 1998).

Activation of platelets is critical for aggregation. In particular the integrins, αIIbβ3, α2β1 and αvβ3 are normally present on the platelet surface in an inactive form, but platelet activation induces a conformational transition in these receptors that exposes ligand binding sites (Luo et al., 2006). αIIbβ3 is arguably the most important of these receptors as it is present at the highest density on the platelet surface. In addition, αIIbβ3 binds to multiple ligands that promote platelet-platelet aggregation. These include fibrinogen, VWF, collagen, fibronectin and vitronectin (Varga-Szabo et al., 2008).

Feedback activation of nearby platelets surrounding a new site of injury is critical for further aggregation and propagation of the platelet plug. This activation is mainly mediated by agonists released by activated platelets themselves acting on G protein-coupled receptors. ADP is released from platelet dense granules .Serotonin is also secreted from dense granules and contributes to platelet activation.

Another critical mechanism of platelet activation that links secondary hemostasis to platelet function is activation by thrombin. Thrombin is the terminal serine protease of the coagulation cascade .Thrombin cleaves 2 protease activated receptors (PARs) on human platelets, PAR1 and PAR4. These are also G protein-coupled receptors, and cleavage by thrombin exposes a new N-terminus that serves as a tethered ligand to activate the receptor (Kahn et al., 1998; Vu et al., 1991). All of these receptors initiate cell-signaling pathways when they are ligated, which result

in platelet granule secretion, integrin activation and platelet cytoskeleton remodeling (Brass, 2000).

2.8.2. Secondary Hemostasis

Secondary hemostasis consists of the cascade of coagulation serine proteases that culminates in cleavage of soluble fibrinogen by thrombin Thrombin cleavage generates insoluble fibrin that forms a crosslinked fibrin mesh at the site of an injury. Fibrin generation occurs simultaneously to platelet aggregation (Falati et al., 2002). In intact and healthy blood vessels this cascade is not activated and several anticoagulant mechanisms prevent its activation. These include the presence of thrombomodulin and heparan sulfate proteoglycans on vascular endothelium. Thrombomodulin is a cofactor for thrombin that converts it from a procoagulant to an anticoagulant by stimulating activation of the anticoagulant serine protease protein C (Esmon et al., 1981). Heparan sulfate proteoglycans stimulate the activation of the serine protease inhibitor (or serpin) antithrombin, which inactivates thrombin and factor Xa (Shimada et al., 1991).

Secondary hemostasis; the coagulation cascade. At the site of injury, tissue factor (TF) initiates the coagulation cascade that results in the formation of the serine protease thrombin. Thrombin performs multiple functions, including fibrin generation, ...

When the vascular system is injured, blood is exposed to extravascular tissues, which are rich in tissue factor (TF), a cofactor for the serine protease factor VIIa (Kirchhofer et al., 1996). The complex of TF and factor VIIa activates factor X and factor IX. This activation pathway is historically termed the extrinsic pathway of coagulation. Factor IXa also activates factor X, in the presence of its cofactor factor VIIIa. Factor Xa, also in the presence of its cofactor factor Va, then activates prothrombin to generate thrombin (Dahlback, 2000).

Thrombin is the central serine protease in the coagulation cascade, and it executes several critical reactions (Lane et al., 2005). Thrombin critically cleaves fibrinogen to generate insoluble fibrin. Thrombin activates platelets via cleavage of PAR1 and PAR4 (Kahn et al., 1998). Thrombin is also responsible for positive feedback activation of coagulation that is critical for clot propagation. Thrombin activates factor XI, which then activates factor IX and thrombin activates cofactors VIII and V (Lane et al., 2005). This has historically been called the intrinsic pathway of coagulation, but it is more appropriate to think of it as a positive feedback loop (Bouma et al., 1998).

The updated cell-based model of hemostasis focuses on the important fact that these reactions are controlled by their localization on different cellular surfaces. Coagulation is initiated by the cofactor TF (the extrinsic pathway), which is a transmembrane protein present on fibroblasts and other extravascular tissues. The factor Xa generated here forms prothrombinase complex on these surfaces sufficient to generate only a small amount of thrombin. Then amplification and propagation of coagulation via the positive feedback loop occurs on the surface of platelets, which are activated near the site of injury by that trace thrombin and by adherence to extracellular matrix. Thus, the active coagulation complexes of this positive feedback loop form on the surface of activated platelets (Hoffman et al., 2001).

Ultimately thrombin also plays an important role in down regulation of the coagulation cascade by binding to thrombomodulin on endothelial cells and then activating protein C (APC) (Esmon et al., 1981). The activated protein C anticoagulant system is important for the down regulation of the coagulation cascade. APC cleaves and inactivates the procoagulant cofactors VIIIa and Va (Fulcher et al., 1984;Guinto et al., 1984). This reaction also requires a cofactor, protein S; in addition, factor V provides anticoagulant function as a cofactor for

APC/protein S in the inactivation of factor VIIIa and factor Va (Cramer et al., 2010;Shen et al., 1994;Walker, 1980). These complexes between proteases and cofactors (procoagulant and anticoagulant) form on negatively charged membrane surfaces that are provided by activated platelets (Mann et al., 1990). This localization of the coagulation cascade reactions is critical to restrict coagulation to the site of injury.

The coagulation cascade is also down-regulated by inactivation of all the serine proteases by serine protease inhibitors. Most of these inhibitors are in the serpin family of inhibitors (Rau et al., 2007). Antithrombin is arguably the most important of these (Egeberg, 1965). Antithrombin inhibits thrombin and factor Xa, as well as factor IXa and factor XIa in the presence of heparin or heparan sulfate (Quinsey et al., 2004). Other serpins that play roles in coagulation include heparin cofactor II (thrombin inhibitor), protein Z-dependent protease inhibitor (factor Xa inhibitor), protein C inhibitor (APC inhibitor) and C1-inhibitor (factor XIa inhibitor) (Han et al., 2000). Two non-serpin inhibitors, tissue factor pathway inhibitor and alpha-2-macroglobulin, also play a significant role, inhibiting factor Xa and thrombin, respectively (Broze, Jr. et al., 1988).

2.8.2.1. Extrinsic Pathways:

The extrinsic pathway is initiated by the release of tissue thromboplastin that has been expressed after damage to a vessel. Factor VII forms a complex with tissue thromboplastin and calcium. This complex converts factors X and Xa, which in turn converts prothrombin to thrombin. Thrombin then converts fibrinogen to fibrin. This process takes between 10 and 15 seconds. (PT) measures the extrinsic pathways.

2.8.2.2 . Intrinsic pathways

Contact activation is initiated by changes induced by vascular trauma. Prekallikrein is required as a cofactor for the auto activation of factor XII by factor XIIa. XI is activated and requires a cofactor of HMWK. XIa activates IX to IXa, which in the presence of VIIIa converts X to Xa. Also present are platelet phospholipids PF3.

Calcium is required for the activation of X to proceed rapidly. The reaction then enters the common pathway where both systems involve factors I, II, V, and X. This results in a fibrin monomer polymerizing into a fibrin clot. Factor XIII, or fibrin stabilizing factor, follows activation by thrombin. This will convert initial weak hydrogen bonds, cross-linking fibrin polymers to a more stable covalent bond. (Barbara Caldwell) .(APTT)measures the intrinsic pathway.

2.8.2.3. Common Pathways

The common pathway is the point at which the intrinsic and extrinsic pathways come together and factors I, II, V, and X are measured. It is important to note that the PT and the APTT will not detect qualitative or quantitative platelet disorders, or a factor XIII deficiency. Factor XIII is fibrin stabilizing factor and is responsible for stabilizing a soluble fibrin monomer into an insoluble fibrin clot. If a patient is factor XIII deficient, the patient will form a clot but will not be able to stabilize the clot and bleeding will occur later. Factor XIII is measured by a 5 mol/L urea test that looks at not only the formation of the clot but also if the clot lazes after 24 hours. (Barbara Caldwell)

2.9.Thrombosis

Arterial thrombi are composed largely of aggregated platelets, whereas venous thrombi are composed more of fibrin with red blood cells enmeshed. The composition of these different thrombi is dictated by the different conditions in the arterial circulation and the venous circulation. One important aspect of this is blood flow, with higher flow rates and therefore higher sheer forces in the arterial

circulation (Tangelder et al., 1988). Classically, arterial thrombosis and venous thrombosis are thought to have different risk factors. However, recent studies have suggested that some of the classic risk factors for arterial thromboses, such as obesity and high cholesterol, are also risk factors for venous thrombosis (Franchini et al., 2008). The classic risk factors for venous thrombosis cause a hypercoagulable state and result in an increased tendency for activation of the coagulation cascade. These include acquired risk factors such as cancer, surgery, immobilization, fractures and pregnancy. Genetic risk factors include multiple variants in the coagulation cascade. The most common are factor VLeiden and prothrombin G20210A. Others are protein C or protein S heterozygosity and mutations in antithrombin (Bauer, 2000).

Arterial thrombosis is generally treated with drugs that inhibit platelet aggregation. Acetylsalicylic acid (aspirin) is a cyclo-oxygenase (COX) inhibitor and irreversibly inhibits COX-1 in the thromboxane A2 synthesis pathway Burch et al., 1978). Clopidogrel (trade name Plavix) blocks adenosine diphosphate (ADP) activation of platelets by inhibiting the ADP receptor P2Y12 (Mills et al., 1992). Dipyridamole (Persantine) is an oral drug that inhibits adenosine reuptake and thromboxane synthesis and is used for secondary prevention of stroke and transient ischaemic attack (Weber et al., 2009).

2.10. Previous Study

1- Evaluation of Prothrombin Time and Activated Partial Thromboplastin Time in Hypertensive Patients Attending a Tertiary Hospital in Calabar, Nigeria

Nnamani Nnenna Adaeze, Anthony Uchenna Emeribe, and Emmanuel K. Uko

Results : Systolic blood pressure (SBP) and diastolic blood pressure (DBP) correlated positively with APTT ($r = 0.3072$, $r = 0.4988$; $P < 0.05$) in hypertensive patients. DBP, SBP, PT, and APTT were significantly higher in hypertensive patients when compared to normotensive subjects ($P < 0.05$). DBP correlated

negatively with duration of illness ($r = -0.3097$; $P < 0.05$) in hypertensive patients and positively with age of normotensive subjects ($r = 0.3523$; $P < 0.05$).

2- Prothrombin time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR) as predictive factors of coagulopathy in newly diagnosed hypertensive patients.

Ali Jiskani S,1 Shafia Memon,2 Lubna Naseem1

Results: All coagulation parameters were higher in hypertensive group with mean PT of 15.07±1.92 seconds (p=0.02), APTT 37.14±4.06 seconds (p=0.001) and INR 1.04±0.18($p \leq 0.001$), in contrast to control group having mean PT 12.36±0.74 seconds, APTT 30.4±2.39seconds and INR 0.87±0.07.

Chapter Three

Material and Methods

3. Materials & Methods

3.1 Study Design

This is a cross sectional descriptive study, conducted in period from March to August 2018 to evaluate PT and PTT in hypertensive patients.

3.2 Study Area

The study was conducted at Almek Nimir hospital which located in Shendi town in Sudan.

3.3 Study Population

Thirty blood samples collected form hypertensive patients and 20 blood samples as normal control without hypertension.

3.4 Inclusion Criteria

Patients of both sexes with hypertension (who take drugs or not take).

3.5 Exclusion Criteria

Patients with other severe diseases such as liver diseases and haematological diseases.

3.6 Data collection tools

The primary data was collected by using questionnaire.

3.7 Sampling

Venous blood collected using sterile disposable plastic syringe after cleaning the venepuncture area with 70% ethanol, the blood was add to the anticoagulant at ratio of 4.5ml to .5ml of citrate (3.2% (0.109M) buffered sodium citrate and gently mixed.The sample was centrifuge at 1300 rpm for 15min to obtain platelet poor plasma (ppp). The ppp placed into plastic tubes, capped and frozen at -70°C used for PT, APTT.

Methods

3.8.1 Prothrombin time (PT)

3.8.1.1 Principle of PT

The PT was performed by automated testing measure the clotting time of plasma in the presence of an optimal concentration of tissue extract (thromboplastin) with calcium chloride ($CaCl_2$) which indicates over all the efficiency of the extrinsic clotting system.

3.8.1.2 Reagents and materials

Phospholipid + ca^{2+} + tissue factor.

Cotton, automatic piped, water path, alcohol, stop watch.

3.8.1.3 Assay procedure

Pipit 0.1ml plasma in to clean test tube and pre warm within 2-3 min at $37C^{o}$ add 0.2ml of thrompoblastin (pre warm 2-3 min in $37c^{o}$) and start the time observe clot formation and stop watch at the appearance of the first fibrin web get the main of the dabble reading.

3.8.1.4 Normal value

11 – 17 seconds (depend on PT reagent).

3.8.2 Activated partial thromboplastin APTT)

3.8.2.1 Principle of APTT

The APTT was performed by automated testing in the batch or state mode. in the APTT an aliquot of undiluted, platelet poor plasma was incubated at 37c with a particulate factor XII activator(i.e. ,silica, celite, kaolin ,ellagicacid ,etc. A reagent containing phospholipid (partial thromboplastin) was added, followed by $CaCl_2$ .the time required for clot formation after the addition of $CaCl_2$ .it measure over all activity of in intrinsic pathway.

3.8.2.2 Reagents and materials

Kaolin 5g/d, barbitone puffer slain, cevalin, ca^{2+}.

Cotton, automatic piped, water path, alcohol, stop watch.

3.8.2.3 Assay procedure

Pipit o.1ml of p.t plasma in test tube and add o.1 ml of the thromboplastin mix and incubate in $37c^{o}$ in 5 min. after that add o,1 ml of the pre warm $cacl_2$ and start the stop watch allow tube to remain in water path with gentle mix .after 20sec title the tube back and forth entail clot form at which point the time is stop.

3.8.2.4 Normal value

27 – 42 seconds (depend on APTT reagent).

3.9 Ethical consideration

The consent of the selected individuals to the study was taken after being informed with all detailed objectives of the study and it is health emphasis in the future.

3.10 Data analysis

The collected data code in master sheet and proceed for analysis using SPSS version 11.5) . mean, standard deviation, standard error mean, P.value by using independent T. test.

Chapter Four

Results

4. Results

4.1 Demographic Data of participant

Total of 30 blood sample collected from hypertensive patient and 20 samples collected as control include frequency of sex was 25 female and 5 male, frequency of age group 31-40 years were 7 and group 41-50 years were 23 frequency of duration group1-4 years were13 group 5-8years were 9 group 9-12 years were 6

Table (4.1) Demographic data of study group

		Frequency	Percentage
groups	Case	30	60%
	Control	20	40%
Sex	Male	5	17%
	Female	25	83%
Age	31 – 40	7	23%
	41 – 50	23	77%
Duration of disease	1 – 4	13	43%
	5 – 8	9	30%
	9 – 12	6	27%
DM	Yes	14	47%
	No	16	53%

Table (4.2) Comparison of PT & PTT among participant

	Age	N	Mean	Std. Deviation	P .value
PT	Case	30	16.5	4.2	0.010
	Control	20	13.9	1.2	
PTT	Case	30	33.7	7.0	0.478
	Control	20	32.5	4.7	

Table (4.3) Mean of PT & PTT according to sex

Sex		N	Mean	Std. Deviation	P .value
PT	male	5	17.0	2.3	0.764
	female	25	16.3	4.6	
PTT	male	5	37.6	34.3	0.181
	female	25	33.6	10.5	

Table(4.4) Mean of study group according to Age

Age		N	Mean	Std. Deviation	P .value
PT	31 – 40 years	7	15.9	3.9	0.672
	41 – 50 years	23	16.7	4.4	
PTT	31 – 40	7	31.4	11.4	0.329
	41 – 50	23	34.4	5.2	

Table(4.5) Mean of study group according to Duration of disease

Duration		N	Mean	Std. Deviation	P .value
PT	1 – 4 yrs	13	17.2	5.7	0.753
	5 – 8 yrs	9	16	1.7	
	9 – 12 yrs	8	15.9	3.7	
PTT	1 – 4 yrs	13	34.1	5.6	0.854
	5 – 8 yrs	9	34.2	4.9	
	9 – 12 yrs	8	32.5	1.1	

Chapter Five

Discussion
Conclusion
Recommendations

5.1 Discussion

Hypertension is one of the most common diseases effecting human through the world, because of associated morbidity and mortality and the cost of society.

The result of this study denoted that, the more affected by hypertension more frequent in females than males.

our result demonstrated that there was a significant increase in mean of PT in cases more than control (P.value 0.010) and insignificant increase in PTT (0.478) compare to control.

This finding was similar in PT and different in PTT when compared to study done by Ali Jiskani S,1 Shafia Memon,2 Lubna Naseem1, which state that: All coagulation parameters were higher in hypertensive group with mean PT of 15.07±1.92 seconds (p=0.02), APTT 37.14±4.06 seconds (p=0.001) in contrast to control group having mean PT 12.36±0.74 seconds, APTT 30.4±2.39seconds .

The study finding showed that insignificant an increase the mean of PT and PTT in male than female of study group.

Finding of the parameters examined, reflected insignificant in mean of PT and PTT in age between (41 – 50 years) compare to age (31 – 40 years), this study agree with study done by Nnamani Nnenna Adaeze. Anthony Uchenna in Calabar. Nigeria which correlated negatively with duration of illness in hypertensive patients and positively with age.

The result of this research confirmed insignificant in the mean of PT and PTT in duration between (1 – 4 years) this result was agree with study done by Nnamani Nnenna Adaeze. Anthony Uchenna in Calabar. Nigeria which correlated negatively with duration of illness in hypertensive patients.

5.2 Conclusion

- Significant increase in prothrombin time in hypertensive patients when compare with control group.
- Insignificant increase in partial thromboplastin time in hypertensive patients when compare with control group.
- The age and duration not effect in prothrombin and partial thromboplastin time.
- The evaluation of coagulation parameters in newly diagnosed hypertensive. patients showed significant rise which indicated their susceptibility towards coagulopathy and hemostatic abnormalities.

5.3 Recommendations

- Coagulations studies should be included in the investigation work-up of hypertensive patients.
- More investigation should be done for hypertensive patients, to determine which risk factors and thrombotic markers are important predictors of bleeding and thrombotic risk among hypertensive patients.
- Increase sample size, and further studies are needed to elucidate the pathological basis of this observation.

Chapter Six

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Appendix

6.2 Appendix I

Shendi University

Faculty of Graduate Studies and Scientific Research

Evaluation of some Coagulation Test among Sudanese Hypertensive Patients in Shendi town

Questionnaire

Sex : male ( ) b- female ( )

Age : 20 – 30 ( ) b- 31 – 40 ( ) c- 41 – 50 ( )

Resident :_____

Education : Yes ( ) No ( )

Life style : mild ( ) modrate ( ) high ( )

Duration of hypertension : 1 – 4 ( ) 5 – 8 ( ) 9 – 12 ( )

Risk factor :

Smoke ( ) b- hyperlipidemia ( ) c- alchoholic ( )

d- family history ( ) e- diabetes mellitus ( )

Result : PT = sec

PTT = sec

6.2.Appendix II

إقـرار بالمــوافقة

الاسم.....

العمر..... العنوان.....

أوافق بمحض إرادتي بالمشاركة في البحث العلمي المتعلق بدراسة تقييم زمن البروثــرمبين والثرمبوبلاستين في مرضى الضغط بمدينة شندي.

أسماء بابكر حسن بابكر

بعد أن شرحت له بأنه لا يترتب عليه أي أذى جسدي أو نفسي واعلم أن المشاركة في هــذا البحث لن تؤثر بأي حال من الأحوال في الرعاية الطبية التي أتلقاها كما انه يحق لي بــدون إبداء أسباب الانسحاب من هذا البحث في أي مرحلة من مراحله.

البحث بإشراف:

د. حمزة أحمد حسن

التوقيع..... التاريخ.....