Chapter one

Introduction

1.1 Introduction:

Coagulation is the process by which blood changes from a liquid to a gel, forming a blood clot, It potentially result in hemostasis, the cessation of blood loss from a damaged vessel ,followed by repair, The mechanism of coagulation involve activation, adhesion, and aggregation of platelets along with deposition and maturation of fibrin (Lillicrap *et al*.,2009).

Several important functions of hemostasis including : maintain blood in a fluid state while it remains circulating within the vascular system, also arrest bleeding at the site of injury or blood loss by formation of a haemostatic plug, also limit process to the vicinity of the damage ,and to ensure the eventual removal of the plug whilst healing is completed, Normal physiology thus constitutes a delicate balance between these conflicting tendencies, and a deficiency or exaggeration of any one may lead to either thrombosis or hemorrhage (Bain *et al*.,2017).

There are different stages and phases in hemostasis process, which have involved different cell lines and different proteins (soluble in idle status) of blood. The final result is the formation of a red/fibrin mesh (insoluble protein in the blood) inside it encompassed blood cells (platelets, erythrocytes). This grid/mesh acts as a barrier and prevents the loss of blood vessel injury by until The vascular tree is repaired (Guzzetta and Miller, 2011).

A psychotropic drug is a chemical substance that crosses the blood brain barrier and such acts primarily upon the central nervous system, where it affects brain function, resulting in change in perception, mood, consciousness, cognition and behavior (Wong *et al*.,2004).

The using of multi antipsychotics can induce Neuroleptic Malignant Syndrome (NMS) which is uncommon but fatal idiosyncratic reaction to neuroleptics , some risk factor have been reported for (NMS) such as increase and rapidly titrated antipsychotic doses, agitation, dehydration and iron deficiency (Yilmaz *et al*.,2017).

These substances may be used recreationally to alters one’s consciousness as entheogens and Shamanic purpose of these as a tool for studying the therapeutically as medication, Because psychoactive substance bring about subjective change in consciousness and mood that the user may find advantage Therefore, the use of psychotropic drugs can extremely help reducing psychotic symptoms and agitation in a patient with several mental illnesses, These drugs may

produce serious side effect that can range from mild to severe, also they can added as a significant burden, reducing patient quality of life (Godwin *et al* ,2008).

1.2 Rationale:

An increasing of reports suggest a link between hematological abnormalities and use of antipsychotics, using of typical antipsychotic drugs have an increase risk of serious ventricular arrhythmias and sudden cardiac death however is less known regarding the cardiac safety of the typical antipsychotic drugs which replaced the older agent in clinical practice (Wanyne, 2009).

Many studies conducted in Sudan about this study and its association with venous thromboembolism but there was no sufficient information's so this study was conducted to assess coagulation activities in patients on antipsychotic drugs using PT & APTT with a view to determine susceptibility to hemorrhage or thrombosis.

1.3 Objectives:

1.3.1 General Objective:

Estimation of PT and APTT among sudanese patients taking antipsychotic drugs.

1.3.2 Specific objective:

-To measure (PT/INR) in psychiatric patients and controls.

-To measure (APTT) in psychiatric patients and controls.

-To compare (PT, APTT and INR) among study volunteers.

- To compare between these profiles with other risk factors (age, gender, duration, type of drugs and educational level).

Chapter two

2.1 Literature review:

2.1.1 Hemostasis

Is the process by which bleeding is stopped after an injury by the formation of a clot, and at the same time, maintaining blood in a fluid state elsewhere. It has three major steps: 1) vasoconstriction, 2)temporary blockage of a break by a platelets , and 3) blood coagulation , or formation of fibrin clot These processes seal the hole until tissue are repaired (Bhaskar *et al*.,2016).

It is divided into two principal phases, The first, defined as primary hemostasis, involves the platelet-vessel interplay, whilst the second, defined as secondary hemostasis, mainly involves coagulation factors, damaged cells and platelet surfaces, coagulation cascade rapidly develops (Gale ,2011).

The activation and amplification of the coagulation cascade is finely modulated by the activity of several physiological inhibitors, Once bleeding has been efficiently stopped by blood clot formation, dissolution of the thrombus is essential to restore vessel permeability, This process, known as fibrinolysis, also develops through coordinate action of a vast array of proteins and enzymes (Lippi and –Favaloro, 2018).

2.1.1.2 Primary hemostasis

Primary haemostasis results from complex interactions between platelets, vessel wall and adhesive proteins leading to the formation of initial ‘platelet plug’, The endothelial cells lining the vascular wall exhibit the antithrombotic properties due to multiple factors viz: negatively charged heparin like glycosaaminoglycans, neutral phospholipids, synthesis and secretion of platelet inhibitors, coagulation inhibitors and fibrinolysis activators, In contrast, subendothelial layer is highly thrombogenic and contains collagen, Von Willebrand factor (vWF) and other proteins like laminin, thrombospondin and vitronectin that are involved in platelet adhesion, Any vascular insult results in arteriolar vasospasm, mediated by reflex neurogenic mechanisms and release of local mediators like endothelin and platelet derived thromboxane A2 (TxA2) (Beck ,2009).

Platelets are small anuclear cell fragments that bud off from megakaryocytes, specialized large blood cells that originate in the bone marrow they are present at 150 to 400 million per milliliter of blood and circulate for about ten days (Hoffbrand *et al*.,2006).

Platelets have two types of granules: 1) α granules-contain P-selectin, fibrinogen, fibronectin, factor V, factor VIII, platelet factor IV, platelet-derived growth factor and tumor growth factor-α (TGF-α); 2) δ granules or Dense granules contain adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium (Ca), serotonin, histamine and epinephrine (Heemskerk *et al*.,2002).

Normally platelets do not adhere to intact vascular endothelium, Subsequent to the vascular injury, platelets adhere to collagen and vWF in the subendothelial tissue and undergo a morphological change by assuming irregular surface, forming numerous pseudo pods thus drastically increasing their surface area (Deloughery, 2015).

In a heal thy 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, Multiple receptors on the surface of platelets are involved in these adhesive interactions, and these receptors are targeted by multiple adhesive proteins (Gale , 2011).

2.1.2Platelets functions:-

The main steps in platelet functions are adhesion, activation with shape change and aggregation, When the vessel wall is damaged, the subendothelial structures, including basement membrane, collagen and microfibrils, are exposed (Bain *et al*.,2017).

vWF binds to collagen and microfibrils and then captures platelets via initial binding to platelet GPIb, resulting in an initial monolayer of adherent platelets, Binding via GPIb initiates activation of the platelet via a G-protein mechanism Once activated, platelets immediately change shape from a disc to a sphere with numerous projecting pseudopods, After adhesion of a single layer of platelets to the exposed subendothelium, and stick to one another to form aggregates. Fibrinogen, fibronectin, further vWF released from platelets and the glycoprotein IbIX and IIbIIIa complexes are essential at this stage to increase the cell-to-cell contact and facilitate aggregation (Ciesla, 2007).

2.1.2.1 Role of platelets in haemostasis:

2.1.2.2 Platelet production

Platelets are produced in the bone marrow by fragmentation of the cytoplasm of megakaryocytes, one of the largest cells in the body, The precursor of the megakaryocyte-the megakaryoblast-arises by a process of differentiation from the haemopoietic stem cell the megakaryocyte matures

active, by end mitotic synchronous replication enlarging the cytoplasmic volume as the number of nuclear lobes increase in multiples of two, Platelets form by fragmentation of megakaryocyte cytoplasm, approximately each megakaryocyte giving rise to 1000-5000 platelets, The time interval from differentiation of the human stem cell to the production of platelets averages approximately 10 days (Hoffbrand *et al*., 2006).

Adhesion and aggregation forming the primary haemostatic plug, clot retraction, release of platelet activating and procoagulant molecules, provision of a procoagulant surface for the reactions of the coagulation system (Munker *et al*.,2007).

The initiation of clotting begins with the activation of two enzymatic pathways that will ultimately lead to fibrin formation: the intrinsic and extrinsic pathways, Both pathways are necessary for fibrin formation, but their activating factors are different. Intrinsic activation occurs by trauma within the vascular system, such as exposed endothelium, This system is slower and yet more important versus the extrinsic pathway, which is initiated by an external trauma, such as a clot and occurs quick (Barbara, 2007).

2.1.2.3 Platelet adhesion:

After vascular injury VWF acts as a bridge between endothelial collagen and platelet surface receptors GpIb and promotes platelet adhesion, The platelet glycoprotein complex I (GP‑Ib) is the principal receptor for VWF (Turgeon,2005).

2.1.2.4 Platelet secretion:

After adhesion, degranulation from both types of granules takes place with the release of various factors, Release of calcium occurs here, Calcium binds to the phospholipids that appear secondary to the platelet activation and provides a surface for assembly of various coagulation factors (Lazarus and Schamaier, 2018).

2.1.2.5 Platelet aggregation:

Thromboxane A2 produced by activated platelets provide stimulus for further platelet aggregation, TxA2 along with ADP enlarge this platelet aggregate leading to the formation of the platelet plug, which seals off vascular injury temporarily, ADP binding also causes a conformational change in GpIIb/IIIa receptors presents on the platelet surface causing deposition of fibrinogen. Thrombin generation also catalyses the conversion of this fibrinogen to fibrin which adds to the stability of the platelet plug and is now known as secondary hemostasis (Heemskerk *et al* .,2002).

2.1.3 Secondary hemostasis:

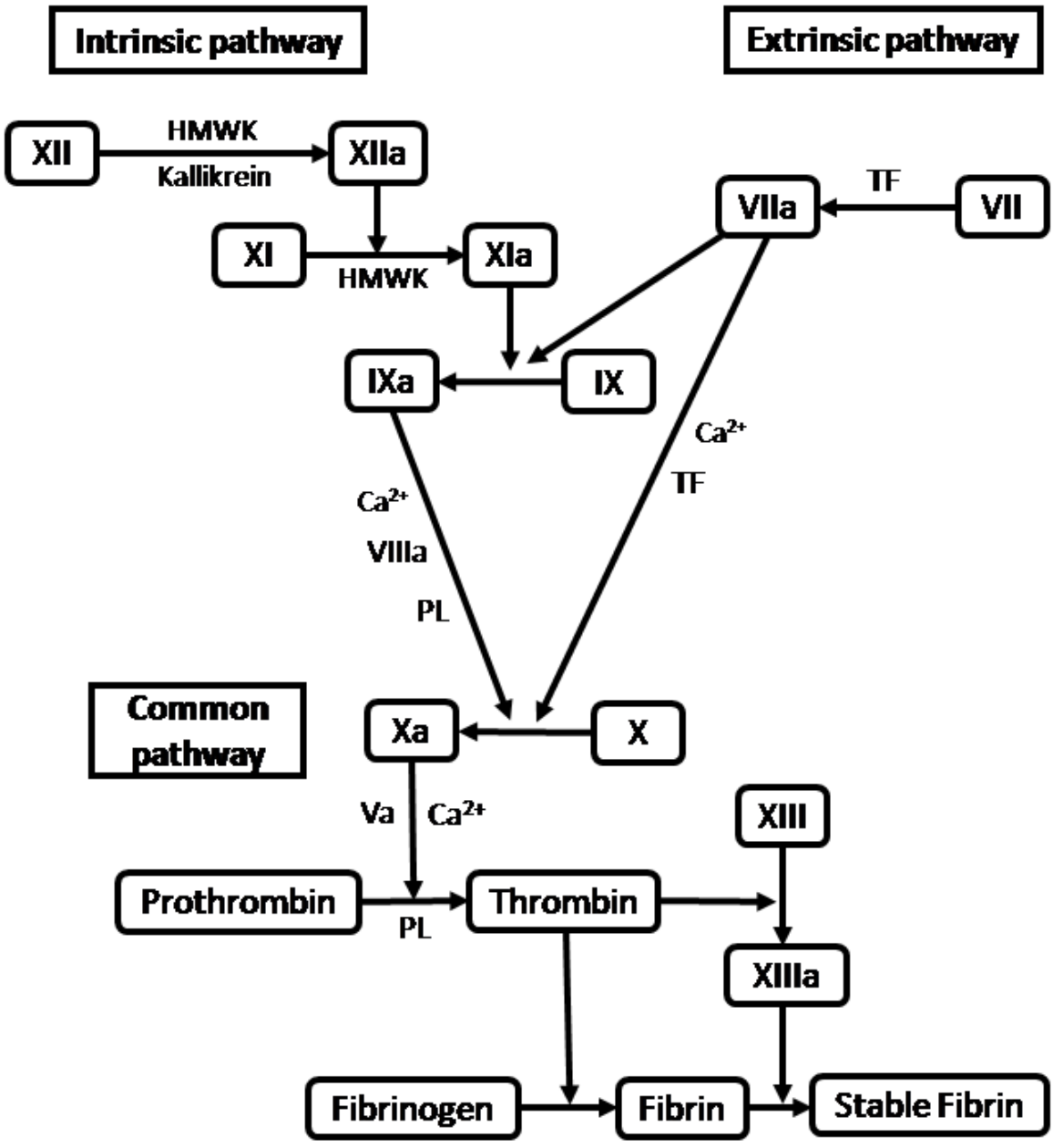
Secondary hemostasis involves a series of blood protein reactions through a cascade-like process that concludes with the formation of an insoluble fibrin clot, This system involves multiple enzymes and several cofactors as well as inhibitors to keep the system in balance, Coagulation factors are produced in the liver, except for factor VIII, which is believed to be produced in the endothelial Cells, When the factors are in a precursor form, the enzyme or zymogen is converted to an active enzyme or a protease (Beutler *et al*.,2010).

The initiation of clotting begins with the activation of two enzymatic pathways that will ultimately lead to fibrin formation: the intrinsic and extrinsic pathways. Both pathways are necessary for fibrin formation, but their activating factors are different. Intrinsic activation occurs by trauma within the vascular system, such as exposed endothelium. This system is slower and yet more important versus the extrinsic pathway, which is initiated by an external trauma, such as a clot and occurs quickly (Lippi and Favaloro., 2018).

2.1.3.1 Phases of Coagulation:

Coagulation can be divided into three separate phases: *1*) an initiation phase, in which low amounts of active coagulant factors are generated; *2*) an amplification phase, in which the level ofactive coagulation factors is boosted; and *3*) a propagation phase, in which coagulation factors bind to highly procoagulant membranes of activated platelets and fibrin clots are formed and extrinsic pathway is still widely used (Versteeg *et al*., 2013).

extrinsic pathway" occurs when plasma factor VIIa forms a complex with the integral membrane protein tissue factor, Tissue factor is not normally found at high concentrations in blood, but is present on cell membranes in subendothelial layers of blood vessels and is exposed to factor VIIa when the endothelium is injured. Alternatively, coagulation may be initiated through the "intrinsic pathway" when factor XII is activated on a charged surface by a process called contact activation, Activation of factor XII is followed sequentially by activation of factor XI and factor IX, The intrinsic and extrinsic pathways converge at the level of factor X activation, Factor Xa activates prothrombin to thrombin in the presence of the cofactor factor Va, and thrombin subsequently converts fibrinogen to fibrin (Turgeon, 2005).



2.1.3.1The cascade model of haemostasis:-

Ca2+- Calcium ion, HMWK – High molecular weight kininogen. TF – Tissue factor (Bhaskar *etal*.,2016).

2.1.4 Regulation of blood coagulation:

The regulation of blood coagulation to ensure the action of thrombin is limited to the site of injury and it regulate by : Antithrombin inactivates serine proteases, principally factor Xa and thrombin, Heparin activates antithrombin, α2 macroglobulins, α2 antiplasmin, α2 antitrypsin and heparin cofactor II also inhibit circulating serine proteases, Proteins C and S are vitamin K-dependent proteins made in the liver (Munker *et al*.,2007).

Protein C is activated via a thrombin–thrombomodulin complex and, like p rotein S, inhibits coagulation by inactivating factors Va and VIIIa; it also enhances fibrinolysis by inactivating the tissue plasmogen activator (TPA) inhibitor, Tissue factor pathway inhibitor (TFPI) inhibits the coagulation pathway by inhibiting factors VIIa and Xa (Mehta and Hoffbrand.,2005).

Antithrombin is the most important of these inhibitors, the second most (clinically) important natural anticoagulant system is that of PS-PC (Lippi and Favaloro, 2018).

2.1.5 Fibrinolysis

Fibrinolysis is the process in which plasmin degraded the fibrin. Following injury, TPAand urokinase-like plasminogen activator (UPA) released from damaged or activated cells, or exogenous agents, e.g. streptokinase, or therapeutic TPA or UPA ,it activate plasminogen and convert it to plasmin, It digests fibrin (or fibrinogen) into fibrin degradation products (FDPs) and also degrades factors V and VII, Free plasmin is inactivated by plasma α2 antiplasmin and α2 macroglobulin (Mehta and Hoffbrand, 2005).

As the clot or "thrombus" forms, circulating red blood cells, white blood cells, and platelets become incorporated into its structure. In addition, fibrin becomes cross-linked through the action of factor XIIIa, which is also activated by thrombin, and provides further structural stability (Bagoly *et al*., 2012).

2.1.6 Psychiatric disease

Psychiatric disorder is a mental illness diagnosed by a mental health professional that greatly disorders your thinking, moods, and behavior and seriously increase your risk of disability, pain, death or loss of freedom. In addition, your symptoms must be more severe than expected response to an upsetting events, such as normal grief after the loss of a loved one (Gross and Huber, 2010).

2.1.7 Psychotropic Drugs:

2.1.7.1 Definition

Psychotropic drug: Any drug capable of affecting the mind, emotions, and behavior. Some legal drugs, such as lithium for bipolar disorder, are psychotropic, Many illicit drugs, such as cocaine, are also psychotropic, Also known as psychodynamic drug Psychotropic medications act on the brain and central nervous system, They change the way chemicals in the brain called "neurotransmitters" send messages between brain cells through a synapse or crossing, Each psychotropic medication is used to treat certain "target" symptoms (Allison and Casey 2001).

2.1.7.2 Type of antipsychotics: 1) Typical“conventional”antipsychotics

- Examples: Chlorpromazine, Fluphenazine (Prolixin®), Haloperidol (Haldol®), Molindone, Thiothixene, Trifluoperazine ; and 2) Atypical antipsychotics More commonly used than typical agents, Examples: Risperidone, Olanzapine, Quetiapine, Ziprasidone, Aripiprazole, Paliperidone, Lurasidone , Clozapine (Meltzer, 2013).

2.1.7.3 Uses:

Antipsychotics are a group of medicines that are mainly used to treat mental health illnesses such as schizophrenia, or mania caused by bipolar disorder, They can also be used to treat severe depression and severe anxiety (Miyamoto *et al*,.2008).

2.1.7.4 Mechanism of action:

The exact mechanism of atypical antipsychotics is unknown. They are thought to block certain chemical receptors in the brain and hence relieve the symptoms of psychotic disorders. Risperdal Oral (risperidone) works by blocking the receptors of chemical messengers called dopamine and serotonin, Although the principal brain target that all antipsychotic drugs attach to is the dopamine D2 receptor, traditional or typical antipsychotics, by attaching to it, induce extrapyramidal signs and symptoms (EPS), They also, by binding to the D2 receptor, elevate serum prolactin (Horacek *et al*,.2006).

Although the exact biological mechanism to explain the possible association between antipsychotic drugs and VTE (Venous Thromboembolism) is unknown (Tripp , 2011). Once antipsychotics are injected, changes in platelet function, plasma coagulation, or fibrinolysis seem more likely to be responsible for the increase in thrombotic events, Metabolic changes due to

antipsychotics would take long periods of time to have an effect (Liperoti and Gambassi ., 2010).

2.1.7.5 Side effect of antipsychotics:

Common side effects of antipsychotics include: Drowsiness, Dizziness, Restlessness, Weight gain (the risk is higher with some atypical antipsychotic medicines), Dry mouth, Constipation, Nausea, Vomiting (DiBonaventura *et al*., 2012).

2.1.8Platelet Dysfunction in antipsychotic drugs:

Blood platelets play an important role in haemostasis and their hyperaggregability may lead to thrombosis and cardiovascular diseases. Increased incidence of mortality, caused by cardiovascular disease, and the increased risk of thrombotic complication in schizophrenic patients treated with antipsychotics has been reported. The obtained results indicate that antipsychotic drugs, especially clozapine and olanzapine, contrary to haloperidol, reduced response of blood platelets to ADP measured as platelet aggregation. This suggests that therapy with such antipsychotics, particularly with second-generation antipsychotics (Anna, 2010).

Many different physiological agonists such as coagulation factors (thrombin), hormones (epinephrine), low-molecular-weight substances (serotonin and adenosine diphosphate (ADP), lipid derivatives (platelet aggregating factor), TXA2, and collagen activate platelets. The most established platelet stimulus is ADP, which induces multiple platelet responses and potentiates platelet aggregation, Both outside-in signaling from the fibrinogen receptor and APDs cause a variety of blood dyscrasias, Numerous reports discuss the risks of adverse hematological effects, such as neutropenia or thrombocytopenia, associated with psychotropic drug usage. For example, schizophrenic patients treated with APDs are more likely to develop cardiovascular diseases (Liperoti and Gambassi ,2010).

2.1.9 Coagulation System Dysfunction in antipsychotic drugs:

The risk for venous thromboembolism seems to be highest during the initial months of treatment with antipsychotics. The biological mechanisms responsible for this possible adverse drug reaction are unknown, but a number of hypotheses have been suggested. The increased risk may be the result of drug-induced sedation, obesity, hyperleptinaemia, antiphospholipid antibodies and increased activity in the coagulation system. The association could also be related to underlying risk factors present in patients with psychosis such as smoking (Hoirisch, *et al*.,2014).

The same may occur with pharmacological treatment. Of note, compared to nonserotoninergic antidepressants, serotoninergic antidepressants may decrease the risk of arterial occlusive events, such as myocardial infarction, but may also increase the risk for abnormal bleeding, which includes preoperative, gastrointestinal, and brain hemorrhage(Hoirisch-Clapauch *et al* .,2016). The increased bleeding risk observed in some patients on serotoninergic anti-depressants has been related to platelet and fibrinolytic abnormalities. Platelets of serotoninergic antidepressant-medicated patients display a lower serotonin content and lower ADP, collagen, or epinephrine-induced aggregation. .(Bismuth *et al* .,2012).

Furthermore, patients on serotonergic antidepressants appear to have fibrinogen and PAI-1 plasma levels that are similar to those of healthy controls, but lower than in depressed patients receiving non-serotonergic antidepressants. (Geiser *et al* .,2011).

In a group of psychotic patients, plasma levels of soluble P-selectin varied significantly in the course of 1-year antipsychotic treatment, mainly between 3 and 6 months after therapy was started, but plasma levels of D-dimer and factor VIII remained elevated (Masopust *et al* .,2013). Fat tissue stroma synthesizes PAI-1, and both insulin and triglycerides provide stimulus for PAI1 synthesis, which may increase cardiovascular risk. Schizophrenia patients with hyperhomocysteinemia might benefit from B-vitamin supplementation: when these patients were treated with folic acid, B_{12}, and pyridoxine, clinical symptoms as measured by the Positive and Negative Syndrome Scale declined significantly (Levine *et al* .,2005).

2.1.10 Antipsychotic drugs and risk of venous thromboembolism:

There is an association between use of antipsychotic drugs and risk of venous thromboembolism in a large primary care population. The increased risk was more marked among new users and those prescribed atypical antipsychotic drugs (Parker *et al*., 2010).

Schizophrenia patients may also be at increased risk of thromboembolic events. Thrombotic tendency has been usually associated with psychotropic medication and with immobility, as in restrai nt or catatonia. In a study conducted in restrained psychotic patients, the incidence of deep vein thrombosis was 12% inspite of prophylaxis with graduated compression stockings and subcutaneous injection of unfractionated heparin (Ishida *et al* .,2014).

The finding of high levels of thrombogenesis markers and platelet activation in first-episode psychosis patients suggests that mechanisms involved in the pathogenesis of psychosis might also contribute to the thrombotic tendency. (Masopust *et al* .,2013).

2.1.11Previous study:

In Nigeria 2014 Omisakin and his colleges concluded that prolongation in PT and APTT among patients using antipsychotics. The results obtained showed that PT and APTT of the test subject have a mean value of 26.01 ± 11.04 in compared with the control subject showed a mean value 11.80 ± 1.3. (Omisakin *et al*., 2014).

Mohammed and his colleges study coagulation disorder in Chloromazine treated patient, showed in their work prolong result was observed in APTT in patient on long time usage of psychotropic drug (Mohammed *et al* .,2005).

In Nigeria 2014 Afolabi and his colleges study coagulation disorder has been arise from the consumption of psychotropic drugs. This can be association with the thrombocytopenia, platelet dysfunction and hepatomegally (Afolabi**,** et *al*.,2014).

In 2016 Hoirisch-Clapauch and his colleges tested 52 Antipsychotic drugs (APDs) used to treat clinical psychotic syndromes cause a variety of blood dyscrasias, APDs suppress the aggregation of platelets via unknown mechanism. (Hoirisch-Clapauch *et al*., 2016).

In 2013, Semiz and his colleges investigate MPV (mean platelet volume) level in patients with schizophrenia, they conclude that higher MPV in patient who were on atypical antipsychotic drugs. (Semiz *et al* ., 2013).

Edgardo Carrizo and his colleges in 2008 conclude that coagulation and inflammation markers during atypical or typical antipsychotic treatment in schizophrenia patients and drug-free first-degree relatives.(Edgardo *et al* .,2008).

In 2010, Liperoti and his college conclude that venous vhromboembolism among elderly Patients treated with atypical and conventional antipsychotic agents. (Liperoti and Gambassi .,2010).

In 2014, Hoirisch and his college conclude that dysfunction in the coagulation system and schizophrenia, they screened 70 drug-treated schizophrenia patients and 98 controls.(Hoirisch *et al*.,2014).

Chapter Three

Material and Methods

3.1 Study design:

This was prospective case control and hospital based study.

3.2 Study Area and Duration:

This study was conducted in Al-Tigany Al-Mahy Mental Health Hospital during the period from March to November 2019.

3.3 Study population:

Psychiatric patients using antipsychotic drugs and control group.

3.4 Inclusion Criteria:

Cases included Patients who take antipsychotic drugs and do not stop the drugs more than one month.

Control included only apparently healthy individual.

3.5 Exclusion Criteria:

Patients who take antipsychotic drugs and stop the drugs more than one month.

3.6Ethical Considerations: Participants were informed verbally in their simple language about the research, its benefits and method of sample collection, then their approval taken.

3.7 Sample Size:

This study included 100 cases and 100 control individuals.

3.8 Sample collection and preparation:

One point eight ml of venous blood to 0.2 ml of 3.2% tri sodium citrate was collected from each patient/control using disposable sterile syringe after disinfecting collection site with 70% alcohol, platelet poor plasma was obtained by centrifugation at 4000 rpm for 15 minute then PT and PTT test done within two hours of collection.

3.9 Data Collection:

Data were collected using questionnaires. These questionnaires was specifically designed to collect information about age, sex, type of antipsychotics drugs and duration of these drugs.

3.10Principle and Procedures:

3.10.1Principle of Coagulometer:

Light of specified wave length passes throw plasma, and it is intensity (OD) is recorded by photo Photo-optical (turbidometric) coagulometer detect a change in plasma optical density during clotting. detector. The OD depends on the color and clarity of sample and is established as the baseline. Formation of the fibrin strand causes light to scatter, allowing less to fall on the photo detector and thus generation an increase in OD. When the OD rise to predetermined variance from base line, the timer stops, indicating clot formation (Yao-chong *et al*.,2008)

3.10.2Principle of Prothrombin Time:

The PT test measures the clotting time of re calcified plasma in the presence of an optimal concentration of tissue extract (thromboplastin) and indicates the overall efficiency of the extrinsic clotting system (Bain *et al*.,2017).

3.10.3 Test Prosedurer:

Cuvettes were placed in incubation area for pre warming at 37C for 3 minute at least.

100 ml op pre warmed (37C) control or patient PPP was dispensed in cuvette in incubation area.

Then cuvettes transferred to test area and 200ul of well mixed calcified thromboplasin reagent were added to cuvette, the analyzer timer started automatically when reagent was added.

When clot formed timer was stopped automatically as result of OD changes, the analyzer is bi channel, get the mean of the two tested cuvettes and express it as

PT on instrument display screen per seconds.

Normal Values:

10-15 seconds (according to manufacture).

3.10.5 Principle of Activated partial Thromboplastin Time:

The test measure the clotting time of plasma after the activation of contact factors and the addition of phospholipid and CaCl2 but without added tissue thromboplastin, and so indicates the overall efficiency of the intrinsic pathway. To standardize the activation of contact factors, the

plasma is first pre incubated for a set period with a contact activator such as kaolin, silica or ellagic acid (Bain *et al*.,2017).

3.10.6 Test Procedure:

Curettes were placed in incubation area for pre warming at 37c for 3 minute at least.

100 ml op pre warmed (37c) control or patient PPP was dispensed in cuvette in incubation area.

After 3 minute incubation 100ul of calcium chloride were added to each cuvette after they transferred to test area.

When clot formed timer was stopped automatically as result of OD changes, the analyzer is bi channel, get the mean of the two tested cuvettes and express it as APTT on instrument display screen per seconds.

Normal Values:

28-40 seconds (according to manufacture).

3.11 Statistical analysis :

The statistical analysis of the results was performed by using the Statistical Package for Social Sciences (SPSS) version 20 for windows version 7 using T-test for testing difference significance and Pearson correlation test .*P* value 0.05 was considered statistically significant.

Mean ±SD and frequencies measured.

CHAPTER FOUR

Results

Two hundred volunteers were enrolled in this study classified to 100 psychiatric patients as case while 100 were apparently healthy as control.

Percent of gender in cases and controls was 46% (46/100) were male and 54% (54/100) for female compared to control group 43% (43/100) for male and 57% (57/100)for female. Figure (4.1)

According to study volunteers age was classified into three groups (<18), (18-39), (>39). The highest frequent one was 18-39 years (81.5%), followed by >39 years (24%), while the least one was <18 years (13%), in case as controls. Figure (4.2).

The mean±SD of PT in male and female of the case group was 17.7 ± .5 and 19.3 ± .4 respectively and in control group was 13.7 ± 1.2 in male and 13.4 ± 1.4 in female with statistical correlation *p*.value 0.00. Table(4.1).

The mean±SD of PTT in male and female of case group was 35.6 ±1.4 and 37.2 ± 1.1 respectively and in control group was 31.6±2.4 in male and 31.4±2.6 in female with statistical correlation *p.value* 0.00.Table (4.1).

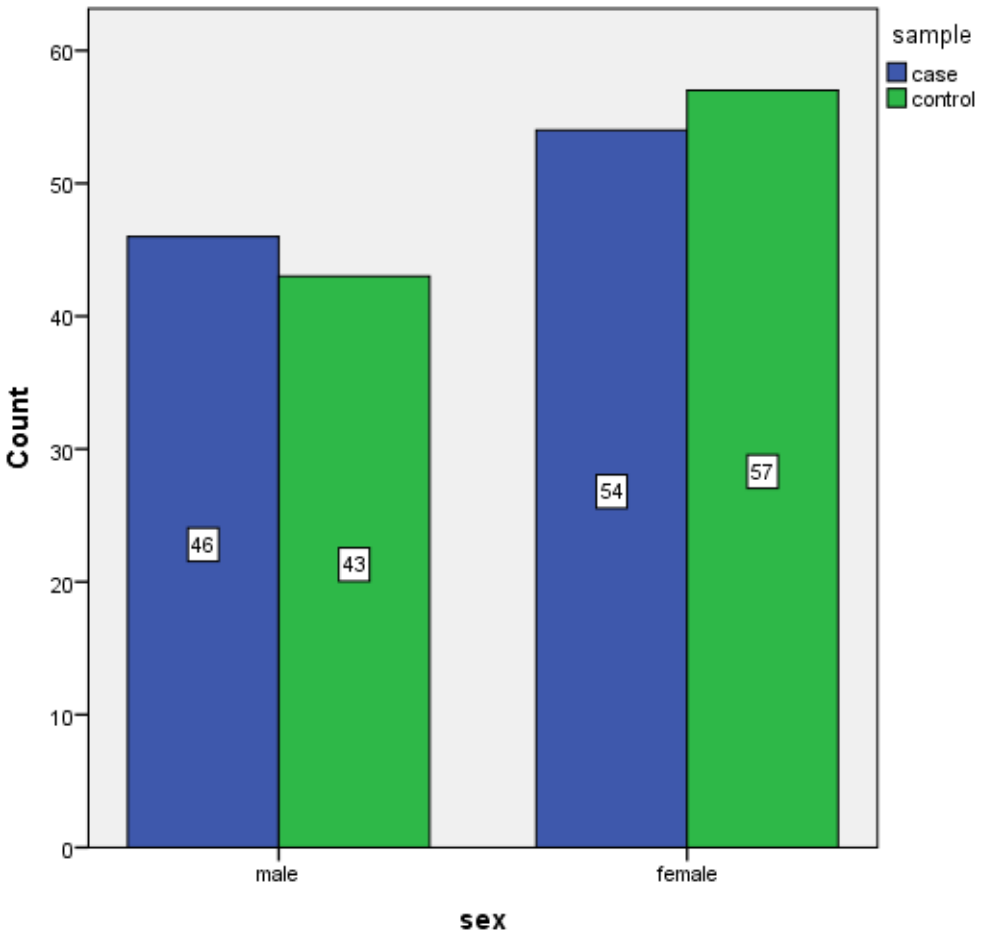
The mean±SD of INR in male and female of case group was 1.4± 0.04 and1.5±0.04 respectively and in control group was 1.2 ± 1.3 in male and 1.3 ± 1.4 in female with statistical correlation *p*.value 0.13. Table(4.1).

mean±SD of PT, APTT, INR in age was 16.1±2.8, 34.0±3.2 and 1.4±0.93 respectively with no statistical correlation *P.value* 0.29, 0.80 and 0.43 respectively. While mean±SD of PT, APTT, INR in was 15.8±2.21, 33.7±2.9 and 1.3±0.84 for male and for female was 16.3±3.15, 34.3±3.5 and 1.4±1respectively with no statistical correlation *P.value* 0.43, 0.25 and 0.16 respectivelly. In educational, the illiterate was 16.6±2.8, 34.8±2.9 and 1.3±0.23, in primary was 15.1±2.6, 32.4±3.9 and 1.15±0.20, in secondary was 15.7±2.9, 33.7±3.3 and 1.6±1.6, in graduate was 16.8±2.5, 34.9±2.7 and 1.3±0.3 with significant correlation *P.value* in PT and APTT but not with INR. In education, the illiterate was 18.8±0.8, 36.5±1.4 and 1.5±0.01, in primary 18.2±1.2, 36.8±1.5 and 1.4±0.03, in secondary 18.5±0.9, 36.5±1.3 and 1.4±0.01 and in graduate was

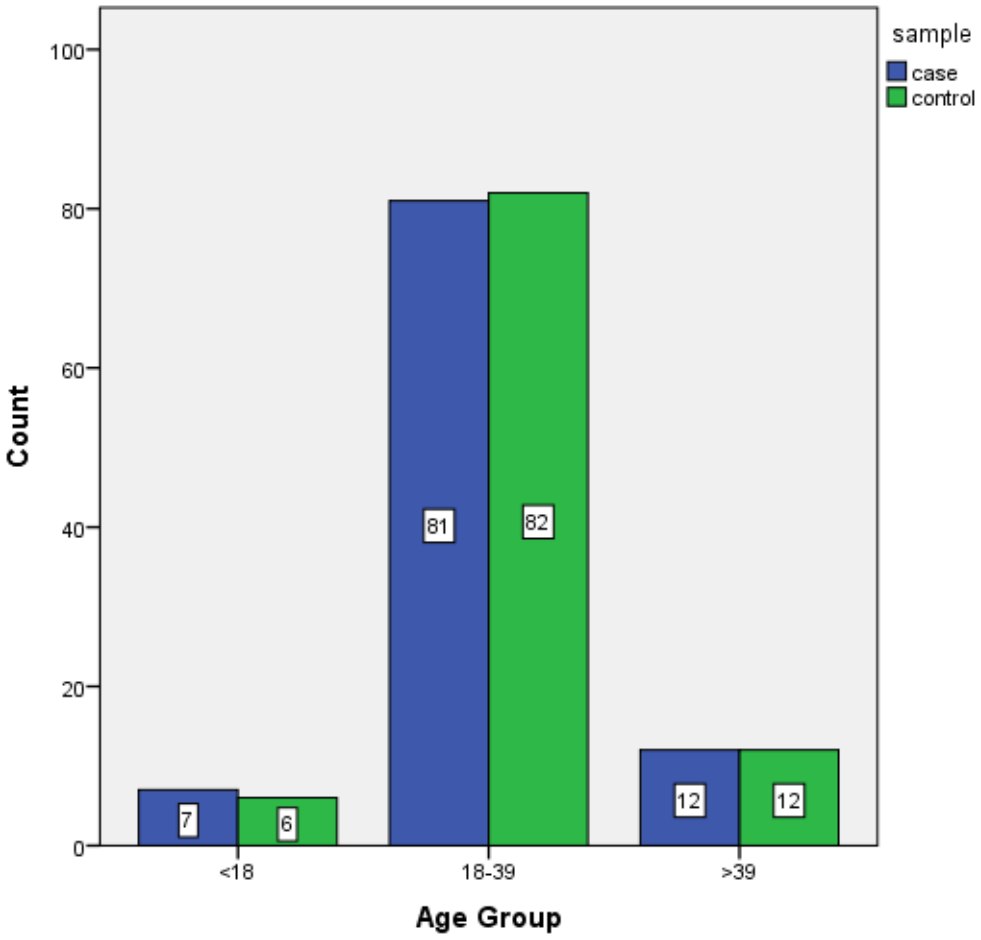
18.5±0.09, 36.4±1.7 and 1.4±0.01 with no statistical difference *P*.value 0.33, 0.84 and 0.51 respectively. Table(4.2).

Regarding to drugs in cases, quetiapine was 18.5±0.9, 36.5±1.5 and 1.4±0.07, Olanzapine was 18.4±0.9, 36.5±1.4 and 1.4±0.08, in Sepram was 18.7±0.9, 36.4±1.7 and 1.5±0.08 and Sodiumvalporate was 18.7±0.09, 36.5±1.5 and 1.4±0.09 with no statistical correlation *P.value0*.77, 0.94 and 0.75. Duration was18.6±0.9, 36.5±1.2 and 1.4±0.08 with no statistical correlation *P.value* 0.22, 0.41 and 0.16 respectively. Table(4.3).

Mean±SD of age in cases and controls was 30.1±7.7 and 30.0±7.3 respectively, Mean±SD of gender in cases and controls was 1.5±0.5 and 1.5±0.4 respectively, Mean±SD of educational level in cases and controls was1.7±1.1 and 1.6±1 respectively. Table (4.4).



Figure(4.1) percent of gender among cases and controls:-



Figure(4.2) percent of age group among cases and controls:-

Table (4-1): Means of coagulation profile among study volunteers:

Groups / variables		Case study	Control	*p.value*
PT	Male	17.7 ± .5	13.7±1.2	
	Female	19.3 ± .4	13.4±1.4	0.00
APTT	Male	35.6±1.4	31±2.4	
	Female	37.2±1.1	31±2.6	0.00
INR	Male	1.4 ± .04	1.2±0.02	
	Female	1.5 ± .04	1.3±0.04	0.13

Table (4-2): Comparison between Parameters and Study Variables:-

Variables		PT	PTT	INR	*P.value*
Age		16.1±2.8	34.0±3.2	1.4±0.93	0.43 0.80 0.29
Sex	Male	15.8±2.21	33.7±2.9	1.3±0.84	0.16 0.25
	Female	16.3±3.15	34.3±3.5	1.4±1	0.43
Educational level	Illiterate	16.6±2.8	34.8±2.9	1.3±0.23	0.01
	Primary	15.1±2.6	32.4±3.9	1.15±0.20	
	Secondary	15.7±2.9	33.7±3.3	1.6±1.6	0.01
	Graduate	16.8±2.5	34.9±2.7	1.3±0.3	0.21

Table (4-3) Comparison between Parameters and case study volunteers:-

Variables		PT	PTT	INR	P.value
Drugs	Quetiapine	18.5±0.9	36.5±1.5	1.4±0.07	0.77
	Olanzapine	18.4±0.9	36.5±1.4	1.4±0.08	0.94
	Sepram	18.7±0.9	36.4±1.7	1.5±0.08	0.75
	Sodiumvalporate	18.7±0.09	36.5±1.5	1.4±0.09	
Duration		18.6±0.9	36.5±1.2	1.4±0.08	0.22 0.41 0.16

Table (4.4) Demographic data between study volunteers:-

Variables	Case	Control
Age	30.1±7.7	30.0±7.3
Gender	1.5±0.5	1.5±0.4
Educational level	1.7±1.1	1.6±1

Chapter Five

Discussion, Conclusions and Recommendations

5.1 Discussion

This is case control study conducted in Al-Tigany Al-Mahy Mental Health Hospital during the period from March to November 2019.The study performed to determine coagulation profile among patients under antipsychotic drugs, it include 100 psychiatric patients and 100 age and sex matched group of apparently healthy control, mean of age in case group and control group 30.1±7.7, 30±7.3 respectively.

The present study reflect significant prolongation in PT/INR and APTT in cases when compared with control group (*P.value* ≤0.05) this result full agreement with study of Omisakin and his colleges in Nigeria which concluded that prolongation in PT and APTT among patients using antipsychotics. The results obtained showed that PT and APTT of the test subject have a mean value of 26.01 ± 11.04 in compared with the control subject showed a mean value 11.80 ± 1.3(Omisakin *et al*., 2014). Partial agreement present study with Mohammed and his colleges study coagulation disorder in Chloromazine treated patient, showed in their work prolong result was observed in APTT in patient on long time usage of psychotropic drug (Mohammed *et al* .,2005).

The present study reflect that most of cases members are female (54%) rather than male (46%) this disagree with study of Mohammed which report that(60%) male and(40%) female in their study determination of coagulation profile among psychiatric patients(Mohammed, 2018).

This was first study search in effect of educational level on coagulation profile in psychiatric patients which give significant correlation (*P.value* 0.01). In my opinion antipsychotic drugs under study (Quetiapine, Olanzapine, Sepeam and Sodiumvalporate) cause prolongation in PT&APTT through decreasing of some coagulation factors.

5.2 Conclusions:-

1. Prolongation in PT in patients using antipsychotic drugs.
2. Prolongation in APTT in patients using antipsychotic drugs.
3. There was significant statistical correlation between gender, PT and APTT.
4. There was significant statistical correlation between educational level, PT and APTT.

5.3 Recommendations:-

1. Further studies should be done to determine the cause of prolongation in PT and APTT (factor assay).
2. Investigate the mechanism involve the haemostatic changes which occur in psychiatric patient take antipsychotic drugs; such as D-dimer test.
3. Studding individual effect of drugs on (PT and APTT).
4. Follow-up of coagulation profile as routine test.

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Appendix I

Questionnaire

Sudan University of Science & Technology

College of Graduate Studies

Determination of Coagulation Profile among Patients under Antipsychotic Drugs

تحديد صورة التخثر بين المرضى تحت تاثير الادويه المضاده للذهان

Sex:……

Male ( ) Female ( )

Age:……

Education:

Illiterate( ) primary( ) Secondary( ) Graduate( )

Type of Antipsychotic Drugs:

Quetiapine ( ) Olanzapine ( ) Sepram ( ) Sodiumvalporate ( )

Duration of Drugs:

Type of Investigation:

PT:

INR:

APTT

Appendix II

A. Reagents:-

-PT solution.

-APTT solution.

-Calcium Chloride(0.25M).

B. Equipments:

- Sterile disposable syringe.

-Gloves.

-Centrifuge.

-Test tubes.

-Micro pipette.

-White tips.

-Yellow tips.

- Tri sodium citrate (TSC 3.2%) container.

- Coagulometer.

- Racks.

-Small cuvettes.

Appendix III

Coagulometer