Republic of Sudan
Ministry of Higher Education and Scientific Research
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Determination of Coagulation Profile among Patients under Antipsychotic Drugs

A thesis Submitted in Partial Fulfillment of the Requirement of the MSc degree in Medical laboratory science (Hematology)

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August 2018

الآيـــــــــة

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

قَالَ تَعَالَىٰ:

﴿لَهُۥ مَا فِي ٱلسَّمَٰوَٰتِ وَمَا فِي ٱلْأَرْضِ وَمَا بَيْنَهُمَا وَمَا تَحْتَ ٱلثَّرَىٰ ۝٦﴾

صدق الله العظيم

سورة طه - الآية (6)

Dedication

I would like to dedicate this research to …

My lovely parent…

My Greatest Supervisor…

My brother and my sister…

All My Friends…

All Who help me

Acknowledgement

I thank great full to Allahforgive me ability and strongly to complete this research

Firstly full thank to my supervisor Dr.OmKalthom who gave me a lot of her time and efforts without any complaints and to psychologist. Nagwa Omer Elamin who help me too.

Secondary our thanks to the medical staff of Elmak Nemir Hospital andTumor Therapy and Cancer Research Center for their vital assistant and help.

Finally, my thank to my family and my friends for their help me

List of Abbreviation

APTT	Activated partial thromboplastin time
ADP	adenosine diphosphate
ATP	Adenosine triphosphate
APDs	Antipsychotic drugs
Ca	Calcium
FDPs	fibrin degradation products
GP‑Ib	glycoprotein complex I
KCCT	kaolin cephalin clotting time
LAC	lupus anticoagulant
MPV	Main platelet volume
PT	Prothrombin Time
PTTK	partial thromboplastin time with kaolin
PDW	Platelet distribution width
PPP	Platelet-Poor Plasma
PG	Prostaglandin
ROTEM	rotational thromboelastometry
TxA2	thromboxane A2
tPA	tissue plasminogen activator
TGF‑α	tumor growth factor‑α
uPA	Urokinase
vWF	von Willebrand factor
WHO	World Health Organization

Abstract

Introduction: This is analytical descriptive case controlstudy carried out in refer clinic of Elmak Nemir Hospital.

The main objective of the study was to measure coagulation activity in psychiatric patients who were on antipsychotic drugs. The study was conducted from June to august 2018.

Materials and methods: Fifty sample were collected fromPsychiatric patients taken antipsychotic drugs in addition to thirty samples from individual don't take antipsychotic drugs were used as control group.

Results: The statistical results were observed significant decrease in platelets countsin patients take antipsychotic drugs when compare with control group. The mean of platelet counts in patients take antipsychotic drugs was ($185x10^9$/L) and control ($291x10^9$/L) and the p.value=0.00. Whileobserved significantincreasein Prothrombin time (PT) andActivated Partial Thromboplastin time (APTT) in patient take antipsychotic drugs when compared with the control group.PT in psychiatric patients take antipsychotic drugs was (18.7sec) and control (13.1sec) and the p.value=0.00. APTT in psychiatric patients take antipsychotic drugs was (35.6sec) and control (28.7sec) and the p.value=0.00.

ConclusionandRecommendation: The finding of this study supports the clinical observation that antipsychotic drugs cause increase risk of thrombosis or hemorrhage.

This study recommended forfurther investigation to investigate the mechanism involves the haemostatic changes which occur in psychiatric patient take antipsychotic drugs; such as platelets functions test &D-dimer.

خلاصة البحث

المقدمة:هدفت الدراسة الي قياس عدد الصفائح الدموية و نشاط عوامل التجلط في المرضى النفسيين الذين يتعاطون العقاقير المضادة للذهان . بمستشفي المك نمر الجامعي العيادة المحولة للصحة النفسية في الفترة ما بين يونيو الي اغسطس 2018م

كانت الدراسة تجريبية حيث قسمت عينة الدراسة الى مجموعة ضابطة (لم يتعاطوا اي ادوية نفسية) وتجريبية (يتعاطون عقاقير مضادة للذهان).

المواد والطريقة :تم اخذ 50 عينة من المرضى النفسيين الذين كانوا على العقاقير المضادة للذهان بالاضافة الي عدد30 عينة من اشخاص اصحاء (لم يتعاطوا العقاقير المضادة للذهان) ، وهولاء استخدموا للمقارنة (مجموعة ضابطة).

النتيجة :تمت المعالجة الاحصائية عن طريق الحزمة الاحصائية للعلوم الاجتماعية **(SPSS)** والتي اظهرت نتيجة الدراسة :ان متوسط عدد الصفائح الدموية في المرضى الذين يتعاطون مضادات الذهان ($185*10^9$/ليتر) وفي المجموعة الضابطة ($291*10^9$/ليتر) والقيمة المعنوية اقل من (0.05) مما يعني وجود علاقة ارتباط.وان معدل زمن البروثرومبين في المرضى الذين يتعاطون مضادات الذهان (18.7ثانية) وفي المجموعة الضابطة (13.1ثانية) والقيمة المعنوية اقل من (0.05) مما يعني وجود علاقة ارتباط .وان متوسط معدل زمن الثرومبوبلاستين في المرضى الذين يتعاطون مضادات الذهان (35.6ثانية) وفي المجموعة الضابطة (28.7ثانية) والقيمة المعنوية اقل من (0.05) مما يعني وجود علاقة ارتباط.

الاستنتاج والتوصيات :وقد خلصت الدراسة الي انخفاض في عدد الصفائح الدموية ومؤشراتها علي مضادات الذهان بينما لوحظت زيادة في البروثرومبين والثرومبوبلاستين النشط جزئيا على مضادات الذهان مقارنة بالمجموعة الضابطة.وهذا يعني أن الادويه المضادة للذهان تؤثر على نشاط عوامل تجلط الدم والتي قد تزيد من مخاطر الجلطة او النزف.

Table of Contents

List of Tables

List of Figures

Chapter One

Introduction

Objectives

Rationale

1-1 Introduction:

Blood coagulation is a complex process by which blood forms clots. It is an important part of haemostasis, where in a damaged blood vessel wall is covered by a platelet and fibrin containing clot to stop bleeding and begin repair of the damage vessel [Ochei,J and kolhatkar A,. (2008)].

Also Blood coagulation involves a biological amplification system in which relatively few initiation substance sequentially activate the proteolysis of thrombin, thus in turn, converts soluble plasma fibrinogen into fibrin [Hoffbrand, et al.(2004)]

Coagulation begins almost instantly after an injury to the blood vessel has damages the endothelium. Exposure of the blood to protein such has tissue factors initiate changes to blood platelet and the plasma protein fibrinogen a clotting factor. Platelets immediately form a plug at the side of injury; this is called primary haemostasis. Secondary haemostasis occurs simultaneously; protein in the blood plasma called coagulation factors or clotting factors, respond in a complex cascade to form fibrin strands, which strengthen plug [Furie, B.C. (2005)]

Disorder of coagulation can lead to an increase in risk of bleeding hemorrhage or thrombosis. Coagulation disorders are common intensive care patient and may range from isolated thrombocytopenia or prolonged global clotting test to complex defects, such as disseminated intravascular coagulation.

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 [Zornbery, G.L and Jick,H. (2000)].

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
[Perkins, D. O. (2002)]

Numbers of harmful and other side effects have been observed, including lower life expectancy, weight gain, enlarged breast, hyperprolactinaemia, Agranulocytosis, Diabetes and inability to sit stil
[Dilsaver, S.C. and Alessi, N.T (2000)]

1-2 Objectives

General Objective:

Coagulationprofileamong patients under antipsychotic drugs

Specific objective:

1-To measure platelets counts & platelets indices in psychiatric patients.
2-To measure prothrombin time in psychiatric patients.
3-To measure activated partial thromboplastin time in psychiatric patients.

1-3 Rationale

According to the report issued by the World Health Organization (WHO) for the Eastern Mediterranean in the first of September(2014), Sudan is ranked first among Arab countries in Africa and the suicide rate for each 100 thousand of the population at a rate of 22%, and thus increase in the abuse of antipsychotic drugs.

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

So this study was conducted to assess coagulation activities in patients on antipsychotic drugs using platelets indices, PT & APTT with a view to determine susceptability to hemorrhage or thrombosis

Chapter Two

Literature Review

2- Literature Review:

2-1Platelets:

Platelets are the smallest of blood cells, being only fragments of megakaryocyte cytoplasm, yet they have a critical role in normal haemostasis and are important contributors to thrombotic disorders. Understandings of the role of platelets in haemostasis and definition of disorders caused by abnormal platelet function have lead to important new therapies for thrombotic disease.

Platelet production

The development of megakaryocytes and production of platelets are unique processes. Megakaryocyte maturation involves nuclear duplication without cell division, resulting in giant cells. Cytoplasmic organelles are organised into domains representing nascent platelets, demarcated by a network of invaginated plasma membranes. Within the marrow, megakaryocytes are localised next to the sinusoidal walls, which

Facilitates the exit of large segments of cytoplasm into the circulation. The fragmentation of megakaryocyte cytoplasm into individual platelets then results from the shear forces of circulating blood, perhaps largely in the pulmonary circulation. [Behnke O, Forer A 1998]

Thrombopoietin is the dominant hormone controlling megakaryocyte development, but many cytokines and hormones take part, including interleukins 3, 6, and 11.[Kaushansky K. 1995]

Platelet structure and function

On activation, platelets change from the normal disc shape to a compact sphere with long dendritic extensions facilitating adhesion the cytoplasm is rich in actin and myosin which bring about the change in shape and retraction of the clot. There are two classes of secretary granules. The first type is dense granules that secrete ADP and calcium, which reinforce platelet aggregation and platelet-surface coagulation reactions.

The second type are granules, which secrete a vast array of proteins, such as von Willebrand factor and platelet factor 4, are synthesized by megakaryocytes; others, such as fibrinogen, are acquired from the plasma by receptor-mediated endocytosis; still others, such as the abundant plasma proteins, albumin and IgG, are acquired by fluid-phase pinocytosis.[George JN. 1990]

Platelet-membrane glycoprotein receptors mediate adhesion to subendothelial tissue and subsequentaggregation to form the initial haemostatic plug [Shattil SJ, et al. 1998].The largest glycoprotein is designated I, the smallest IX.

Glycoprotein Ib-V-IX is a constitutively active receptor for von Willebrand factor, causing immediate platelet attachment to exposed perivascular vonWillebrand factor. Glycoprotein Ia-IIa, a constitutively active receptor for collagen, is also involved in initial platelet adhesion to the subendothelial matrix. [Santoro SA, Zutter MM. 1995] – [Santoso S, et al.1999]

The most abundant surface protein, glycoprotein IIb-IIIa, requires conformational change during platelet activation to express receptor function, mainly for fibrinogen.[Shattil SJ, et al .1998]

Fibrinogen binding to glycoprotein IIb-IIIa mediates platelet aggregation.

Platelet circulation

Platelets survive for about 10 days on average; younger platelets have greater functional ability. The spleen continually but transiently sequesters about a third of circulating platelets. Splenomegaly, particularly when caused by passive congestion due to increased portal venous pressure, greatly increases the fraction of platelets retained in splenic sinusoids, without decreasing overall platelet survival time. This retention causes the mild thrombocytopenia associated with liver cirrhosis and portal hypertension.[Aster RH. 1966]

Most platelets are removed from the circulation after senescence, but a constant small fraction is continually removed by involvement in the maintenance of vascular integrity.

2-2Haemostasis

Haemostasis is the body's normal physiological response for the prevention and stopping of bleeding/hemorrhage. It results in the blocking of any vascular breach. Generally speaking, it helps ensure blood fluidity and blood vessel integrity. Abnormalities in Haemostasis can result in bleeding (hemorrhage) or blood clots (thrombosis).

Haemostasis consists of:

- Primary Haemostasis:

1) Local vasoconstriction (to reduce blood flow to the injury site), 2) platelet plug formation.

- Secondary Haemostasis or clotting of the plasma, involving interaction between numerous factors and inhibitors.
- Fibrinolysis: a process which dissolves the clot once blood vessel integrity has been restored.

When there is a breach in a blood vessel, the first priority (primary Haemostasis) is to "plug" this breach. The main players in the blood are the platelets and fibrinogen: these react together and block the breach by the formation of a platelet plug.

Primary haemostasis

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 heparinlike 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 plateletderived thromboxane A2 (TxA2).[Cines DB,et al 1998] [Triplett DA. 2000]

Platelets are disc shaped, anucleate cellular fragments derived from megakaryocytes. They have a pivotal role in haemostasis by forming the initial haemostatic plug that provides a surface for the assembly of activated coagulation factors leading to the formation of fibrin stabilized platelet aggregates and subsequent clot retraction.

Platelets have two types of granules:

• 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)

• δ granules or Dense granulescontain adenosine triphosphate (ATP), adenosine diphosphate (ADP), calcium (Ca), serotonin, histamine and epinephrine.[Heemskerk JW,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.[Andrews RK, Berndt MC 2001] .The formation of the platelet plug involves a series of steps

Platelet adhesion

After vascular injury vWf acts as a bridge between endothelial collagen and platelet surface receptors GpIb and promotes platelet adhesion. [Heemskerk JW, et al 2002] .The platelet glycoprotein complex I (GP‑Ib) is the principal receptor for vWf

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.

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 theconversion of this fibrinogen to fibrin which adds to the stability of the platelet plug and is now known as secondary haemostasis.[Heemskerk JW, et al 2002] Prostacyclin inhibits platelet aggregation (platelet anti aggregating effect) and the balance between TxA2 and prostacyclin leads to localized platelet aggregation thus preventing extension of the clot thereby maintaining the vessel lumen patency.

[Cines DB, , et al 1998][Ashby B, 1990.]

Secondary haemostasis (coagulation)

Coagulation, in physiology, the process by which a blood clot is formed. The formation of a clot is often referred to as secondary hemostasis, because it forms the second stage in the process of arresting the loss of blood from a ruptured vessel. The first stage, primary hemostasis, is characterized by blood vessel constriction (vasoconstriction) and platelet aggregation at the site of vessel injury. Under abnormal circumstances, clots can also form in a vessel that has not been breached; such clots can result in the occlusion (blockage) of the vessel (thrombosis).

Clotting is a sequential process that involves the interaction of numerous blood components called coagulation factors. There are 13 principal coagulation factors in all, and each of these has been assigned a Romannumeral, I to XIII.

The blood coagulation cascade is initiated through either the extrinsic or intrinsic pathway. Both pathways result in the production of factor X, an enzyme that marks the beginning of the common pathway of coagulation, which culminates in the stabilization of a fibrin clot.

The extrinsic pathway is generally the first pathway activated in the coagulation process and is stimulated in response to a protein called tissue factor, which is expressed by cells that are normally found external to blood vessels. However, when a blood vessel breaks and these cells come into contact with blood, tissue factor activates factor VII, forming factor VIIa, which triggers a cascade of reactions that result in the rapid production of factor X. In contrast, the intrinsic pathway is activated by injury that occurs within a blood vessel. This pathway begins with the activation of factor XII (Hageman factor), which occurs when blood circulates over injured internal surfaces of vessels. Components of the intrinsic pathway also may be activated by the extrinsic pathway; for example, in addition to activating factor X, factor VIIa activates factor IX, a necessary component of the intrinsic pathway. Such cross-activation serves to amplify the coagulation process.

[https://www.britannica.com/science/coagulation-of-blood]

2-3Fibrinolysis

Platelets are activated upon contact with subendothelial matrix proteins, including collagen, von Willebrand factor, and fibronectin, in response to vascular injury [Broos K, , et al 2011]. Platelet activation leads to exposure of cell surface anionic phospholipids, which serve as a nidus for the assembly of procoagulant proteins. In the ensuing activation of the coagulation cascade, a sequential series of serine protease-mediated cleavage events, thrombin is activated from its zymogen prothrombin [de Witt SM,et al 2014]. Active thrombin can then catalyze the polymerization of fibrin by cleaving small peptides from two of its three subunits. Polymerization converts soluble fibrinogen into insoluble fibrin, which stems the flow of blood, thus achieving "hemostasis," the prevention of major blood loss [Furie B. 2009].

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 Z,et al 2012]. Upon healing of the injured blood vessel, the effete thrombus is lysed through the action of plasmin. Plasmin is generated from the zymogen plasminogen on the surface of the fibrin clot, or on cell surfaces, by either tissue plasminogen activator (tPA) or urokinase (uPA) [Hajjar, KA. 2014.]. Proteolysis of fibrin gives rise to soluble fibrin degradation products (FDPs), some of which have immunomodulatory and chemotactic functions. The coagulation and fibrinolytic systems are highly regulated and inter-related through mechanisms that insure balanced hemostasis

2-4 Psychotropic Drugs

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

psychotropicmedication is used to treat certain "target" symptoms.[https://www.goodtherapy.org/drugs/psychotropic-medication.html]

Type of antipsychotics

1. Typical“conventional”antipsychotics

- Examples

- Chlorpromazine.
- Fluphenazine (Prolixin®)
- Haloperidol (Haldol®)
- Molindone.
- Thiothixene.
- Trifluoperazine.

2. Atypical antipsychotics

• More commonly used than typical agents

- Examples

- Risperidone.
- Olanzapine.
- Quetiapine.
- Ziprasidone.
- Aripiprazole.
- Paliperidone.
- Lurasidone
- Clozapine.

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 severedepression and severe anxiety.[https://www.nimh.nih.gov/health/topics/mental-health-medications/index.shtm]

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.[https://en.wikipedia.org/wiki/Atypical_antipsychoti]

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.

[https://www.vocabulary.com/dictionary/atypical]

Although the exact biological mechanism to explain the possible association between antipsychotic drugs and VTE is unknown,

[Liperoti R, Gambassi G.2010][Tripp AC. 2011]

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 R, Gambassi G. 2010]

Usually, antipsychotics start working within a few days. However, it sometimes can take up to 4-6 weeks for an acute psychotic or manic episode to resolve, even with optimal treatment

[https://en.wikipedia.org/wiki/Atypical_antipsychotic]

The side effects of antipsychotic medicines:

- Drowsiness.
- Dizziness.
- Restlessness.
- Weight gain (the risk is higher with some atypical antipsychotic medicines)
- Dry mouth.
- Constipation.
- Nausea.
- Vomiting.

[https://www.dfps.state.tx.us/Training/Psychotropic_Medication/page36.asp]

2-5 Platelet 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, et al., (2010**]** Platelet aggregation is regulated by the production of thromboxane and prostaglandin (PG) that originates from platelets, blood vessels, and other tissues [R. Vezza,et al, 2002] [S. Hammarstrom and P, 1977.]. The action and physiological roles of thromboxane A2 (TXA2) and prostacyclins are well-established

[A. Beitz, et al ,1990][M. L. Ehrman and E. A. Jaffe 1980.]. Many different physiological agonists such ascoagulation factors (thrombin), hormones (epinephrine),low-molecular-weight substances (serotonin and adenosinediphosphate [ADP]), lipid derivatives (platelet aggregatingfactor), TXA2, and collagen activate platelets. The most established platelet stimulus is ADP, which induces multiple platelet responses and potentiates platelet aggregation [C. Gachet, 2001].[S. P. Kunapuli, et al. 2003]. ADP acts on two G protein-coupled receptors, P2Y1 and P2Y12. The P2Y1 receptor is widely expressed throughout the body and couples to Gq, which leads to the activation of phospholipase Cβ, increases cytosolic calcium levels, and activates protein kinase C. The P2Y12 receptor couples with Gi to inhibit adenyl cyclase and activate PI3-kinase [Z.Li,M. et al. 2010] [A. Lecchi, et al 2015].

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 [R. Liperoti, et al 2005.]. Associated cardiovascular diseases may becaused by an interruption of blood platelet activity.

Despite the fact that APDs affect platelet aggregation in vitro[A. Dietrich-Muszalska, et al 2010], the precise mechanism of APD's effect on the aggregative ability of the whole blood still remains unclear inside-out signaling from the P2Y1 and P2Y12 receptors are necessary for phospholipase

A2 activation, arachidonic acid release, and thromboxane A2 generation in platelets [M. Cattaneo, et al 2002].

2-6 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 [Pruthi, RK .2001] In patients with anxiety and depressive disorders, factor VII and plasminogen activator inhibitor levels normalize after psychotherapy, indicating that improvement of psychiatric symptoms somehow reverses the procoagulant effect of these psychological states. [Geiser F, et al 2012]. 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 S, et al 2014].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-Evenzal Y, 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 F,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 J, et al 2013.]

Antipsychotics, especially clozapine and olanzapine, may promote weight accrual and increase the levels of insulin and triglycerides. [Wu RR, ,

et al 2006].Fat tissue stroma synthesizes PAI-1, and both insulin and triglycerides provide stimulus for PAI-1 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 J, et al 2005.]. Considering that hyperhomocysteinemia is an independent risk factor for both cardiovascular disease and thromboembolism, it remains to be defined if vitamin supplementation reduces morbidity and mortality in this group of patients.

2-7 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 [Chris Parker, 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 restraint 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 T, 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 J, et al 2013]

2-8Previous study

1. Chris Omisakin, et al 2014, Nigeria
   Coagulation Activities of Patients on Psychotropic Drugs
   The study is being aimed to assess Prothrombin Time and Activated Partial Thromboplastin Time activity in patients on psychotropic drugs. Fifty (50) samples were used, Forty (40) are from the patients on psychotropic drugs while ten (10) are apparently healthy individual that serves as control. The results obtained showed thatPT 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. While the result obtained from APTT test subject showed a mean value of 36.70 ± 17.00 compared with the control subject that have a mean value of 36.7.0 ± 3.81. When these results were compared statistically significant difference were observed P<0.01 which indicate a state of prolongation in PT and APTT.

[https://www.researchgate.net/publication/261636938]

2. Conoso et al 1977, American, coagulation disorder has been proved to arise from the consumption of psychotropic drugs. This can be association with the thrombocytopenia, platelet dysfunction and hepatomegaly.[Conoso et al 1977]
3. Mohammed et al2005 New York, 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 al2005]
4. Chang-ChiehWu et al 2016

52Antipsychotic drugs (APDs) used to treat clinical psychotic syndromes cause a variety of blood dyscrasias. APDs suppress the aggregation of platelets; however, the underlying mechanism remains unknown. We first analyzed platelet aggregation and clot formation in platelets treated with APDs, risperidone, clozapine, or haloperidol, using an aggregometer and rotational thromboelastometry (ROTEM). Our data indicated that platelet aggregation was inhibited, that clot formation time was increased, and that clot firmness was decreased in platelets pretreated with APDs. We also examined the role two major adenosine diphosphate (ADP) receptors, $P2Y_1$ and $P2Y_{12}$, play in ADP-mediated platelet activation and APD-mediated suppression of platelet aggregation. Our results show that $P2Y_1$ receptor stimulation with ADP-induced calcium influx was inhibited by APDs in human and rats' platelets, respectively. In contrast, APDs, risperidone and clozapine, alleviated $P2Y_{12}$-mediated cAMP suppression, and the release of thromboxane A2 and arachidonic acid by activated platelets decreased after APD treatment in human and rats' platelets.

Our data demonstrate that each APD tested significantly suppressed platelet aggregation via different mechanisms.
[https://www:ncbi.nim.nih.gov/pmc/articles/pmc4812202]

5. Ali Almuqdadi et al 2016 Amman, The effect of atypical antipsychotics on platelet aggregation .There is a high prevalence of arterial thrombosis in schizophrenia. Several studies investigated the cause of this high risk among schizophrenic patients and variable finding reported. The aim of this study was to investigate whether second generation antipsychotics exert antiplatelet action in the presence of different platelet agonists.We performed an in vitro study of different antipsychotics (risperidone, olanzapine and ziprasidone) effect on platelet aggregation induced by different platelet agonists (ADP, collagen, serotonin and epinephrine) when added to blood of healthy volunteers using Multiplate® analyzer.Risperidone and ziprasidone but not olanzapine showed clinically significant inhibition of platelet aggregation induced by by serotonin, while only ziprasidone showed statistically significant inhibition on serotonin aggregation. All tested antipsychotics showed clinically (but not statistically) significant inhibition on platelet aggregation induced by epinephrine treating schizophrenic patients with APDs.[Ali Almuqdadi et al 2016]
6. M. Semiz,et al 2013 . The aim of this study was to investigate what influenced MPV levels in patients with schizophrenia.We evaluated hospital records of 60 hospitalized schizophrenia patients. Thirty age- and sex-matched healthy control subjects were also included as a control group.MPV levels were significantly higher in patients who were on atypical antipsychotic drugs than in patients who were not using any drug (9.2 ± 0.8 vs. 8.6 ± 0.8 fL,) and also higher than control group (9.2 ± 0.8 vs. 8.1 ± 0.9 fL,). Furthermore, patients who were not using antipsychotics had higher MPV than control group (8.6 ± 0.8 vs. 8.1 ± 0.9 fL,). Atypical antipsychotic use [Odds ratio (OR) =6.152, 95% confidence interval (CI,)] and platelet distribution width (OR = 0.989, 95% CI,) were associated with high MPV levels in univariate analysis. In multivariate logistic regression model, only atypical antipsychotics use (OR = 6.152, 95% CI,) was found to be independent predictor of high MPV levels after adjustment of other potential confounders (age,

gender, presence of hypertension, diabetes mellitus, hyperlipidemia, and smoking).We conclude MPV seems to be influenced not only by schizophrenia itself but also by atypical antipsychotic drugs. It might be concluded that schizophrenic patients are under increased risk for cardio metabolic diseases and risk factors and this risk is higher in patients on atypical antipsychotic treatment.[M. Semiz,et al 2013]

Chapter Three

Materials and Methods

3- Material and Methods

3-1 Study design:

Analytical descriptive case control study, conducted between June and August 2018 .The aimed to assessment of coagulation profile among patients under antipsychotic drugs.

3-2 Study area:

This study carried out in Shendi and in village around the Shendi for patient takes antipsychotic drugs.

3-3 Study population:

Psychiatric patients aged 28-70 years with use antipsychotic drugs and control group

3-4 Sample Size

Total number of eighty blood samples wascollected;fifty were from patients on psychotropic drugs while the remaining thirty were from subjects not on psychotropic drugs to serves as control

3-5 Selection criteria:-

Inclusion criteria:

Patients who take antipsychotic drugs have age between (28-70) years and do not stop the drugs more than one month.

Exclusion criteria:

Patients who take antipsychotic drugs have age less than 28years and stop the drugs more than one month

3-6 Sample technique

The collection of data carried out in refer clinic of Elmak Nemir hospital and patient stay at home for Psychiatric and neurological diseasesby using questioner and agreement of patient or co patient. The data analysis by SPSS

3-7 Sample collection

Collected 3.5 ml venous blood and put 1.8 ml at (TSC 3.2%) Trisodum citrate anticoagulant for PT and APTT and the remaining sample are put in EDTA anticoagulant for platelet count and indices

3-8 Equipment

-venous blood
-cotton
-Disposablesyringe
-Mindray BC-3000 plus
-Centrifuge
-water bath
-test tubes
-PT solution
-APTT solution
-Micro pipette
-EDTA container
- Tri sodium citrate (TSC 3.2%) container
-Platelet-Poor Plasma (PPP)

3-9 Methodology:

The platelet count and indices:

Are calculated by using Hematology analyzerinstrument (Mindray BC-3000 plus)

Normal Values:

Plateletcount: (150-450) $x10^{9}$ **/L**
MPV: 7.5-11.5 fl
PDW: 9-14 %

Preparation of Platelet-Poor Plasma:

Most routine coagulation investigations are performed on platelet-poor plasma (PPP), which is prepared by centrifugation

at 2000 g for 15 min at 4_C (approx. 4000 rev/min in a standard bench cooling centrifuge). The sample should be kept at room temperature if it is to be used for PT tests, lupus anticoagulant (LAC) or factor VII assays and it should be kept at 4_C for other assays; the testing should preferably be completed within 2 h of collection..[Dacie and Lewis 2011]

Prothrombin Time

Principle

The PT test measures the clotting time of recalcified plasma in the presence of an optimal concentration of tissue extract (thromboplastin) and indicates the overall efficiency of the extrinsic clotting system. Although originally thought to measure prothrombin, the test is now known to depend also on reactions with factors V, VII and X and on the fibrinogen concentration of the plasma.

Reagents

1-Patient and control plasma samples

Platelet-poor plasma (PPP) from the patient and controlis obtained. Note that plasmastored at 4_C may have a shortened PT as a result of factor VII activation in the cold. .[Dacie and Lewis ,2011]

2-Thromboplastin

Thromboplastins were originally tissue extracts obtained from different species and different organs containing tissue factor and phospholipid. Because of the potential hazard of viral and other infections from handling human brain, it should no longer be used as a source of thromboplastin. The majority of animal thromboplastins now in use are extracts of rabbit brain or lung

3-CaCl2

0.025 mol/l.

Method:

1. Deliver 0.1 ml of plasma into a glass tube placed in a waterbath
2. Add 0.1 ml of thromboplastin.
3. Wait1–3 min to allow the mixture to warm.
4. Then add 0.1 mlof warmed CaCl2 and start the stopwatch.
5. Mix the contents of the tube and record the endpoint

Normal Values

The normal range is(10–12 s). Each laboratory should establish its own normal range

Activated Partial ThromboplastinTime

Specific variations of the APTT test are known as the partial thromboplastin time with kaolin (PTTK) and the kaolin cephalin clotting time (KCCT), reflecting the methods used to perform the test.

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,and so indicates the overall efficiency of the intrinsic pathway. To standardize the activation of contact factors, the plasma is first preincubated for a set period with a contact activator such as kaolin, silica or ellagic acid. During this phase of the test, factor XIIa is produced, which cleaves factor XI to factor XIa, but coagulation does not proceed beyond this in the absence of calcium. After recalcification, factor XIa activates factor IX and coagulation follows. A standardized phospholipid is provided to allow the test to be performed on PPP. The test depends not only on the contact factors and on factors VIII and IX but also on the reactions with factors X, V, prothrombin and fibrinogen. It is also sensitive to the presence of circulating

Anticoagulants (inhibitors) and heparin. .[Dacie and Lewi 2011]

Reagents

1. PPP. From the patient and a control,
2. Kaolin. 5 g/l (laboratory grade) in buffered saline, pH 7.4. Add a few glass beads to aid resuspension. The suspension is stable at room temperature. Other insoluble surface active substances such as silica, celite or ellagic acid can also be used.
3. Phospholipid. Many reagents are available; these contain different phospholipids.
4. CaCl2. 0.025 mol/l.

Method

1. Mix equal volumes of the phospholipid reagent and the kaolin suspension and leave in a glass tube in the waterbath at 37_C.
2. Place 0.1 ml of plasma into a second glass tube.
3. Add 0.2 ml of the kaolin–phospholipid solution to the plasma, mix the contents and start the stopwatch simultaneously. Leave at 37_C for 10 min with occasional shaking.
4. At exactly 10 min, add 0.1 ml of prewarmed CaCl2 and start a second stopwatch.
5. Record the time taken for the mixture to clot.

Normal Range

The normal range is typically 26–40 s.

Each laboratory should calculate its own normal range

Chapter Four

Results

4: Result

Table (4-1): Frequency of study group according to sex:

Gender	Frequency	Percent
Male	30	60%
Female	20	40%

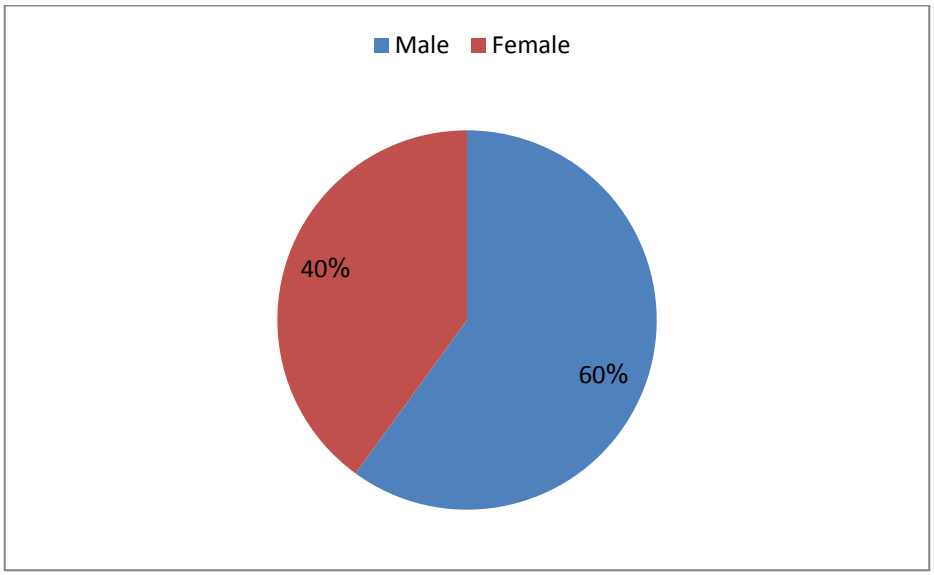


Figure (4-1) the frequency of Gender

Table (4-2): Mean of platelet according to sex:

Sex	Frequency	Mean(10^9/L)	p.value
male	30	172	0.00
Female	20	204	

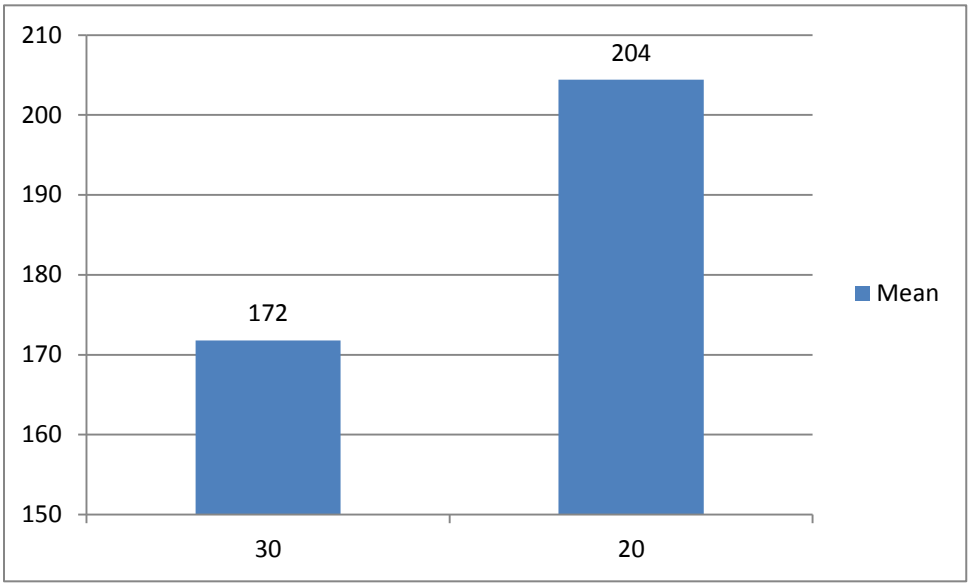
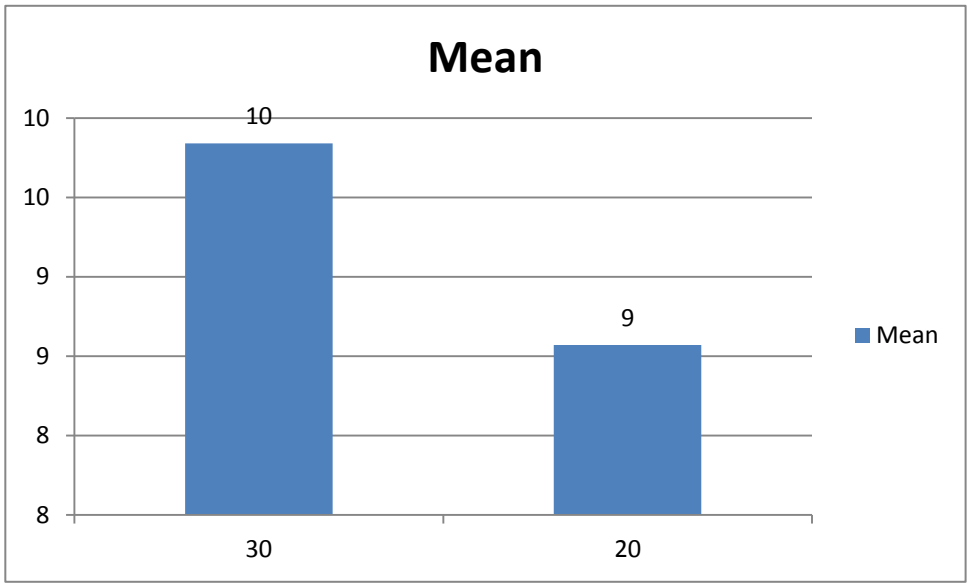


Figure (4-2) Mean of platelet according to sex

.

Table(4-3):Mean of MPV according to sex:

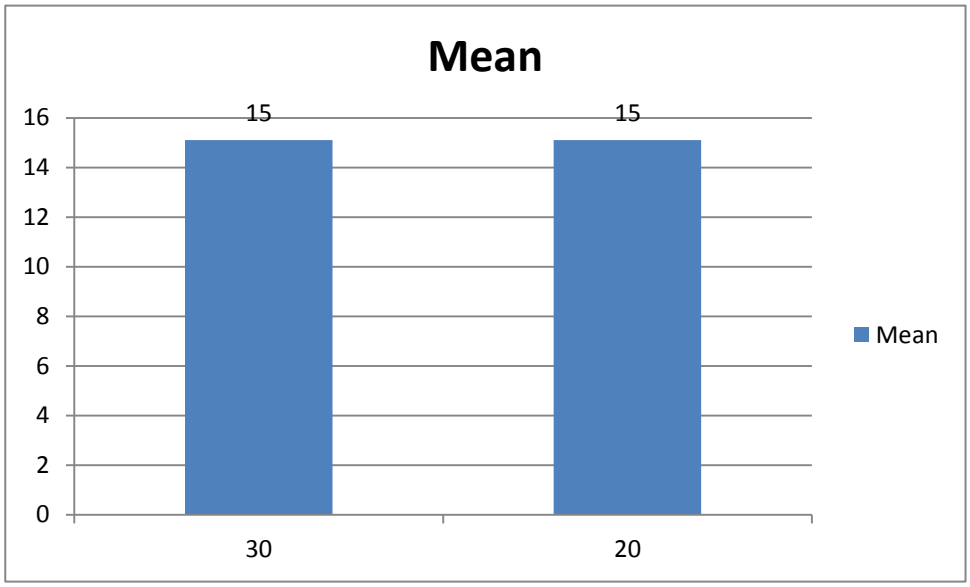
Sex	Frequency	Mean(fl)	p.value
Male	30	10	0.03
Female	20	9	



Figures (4-3): Mean of MPV according to sex:

Table(4-4):Mean of PDW according to sex:

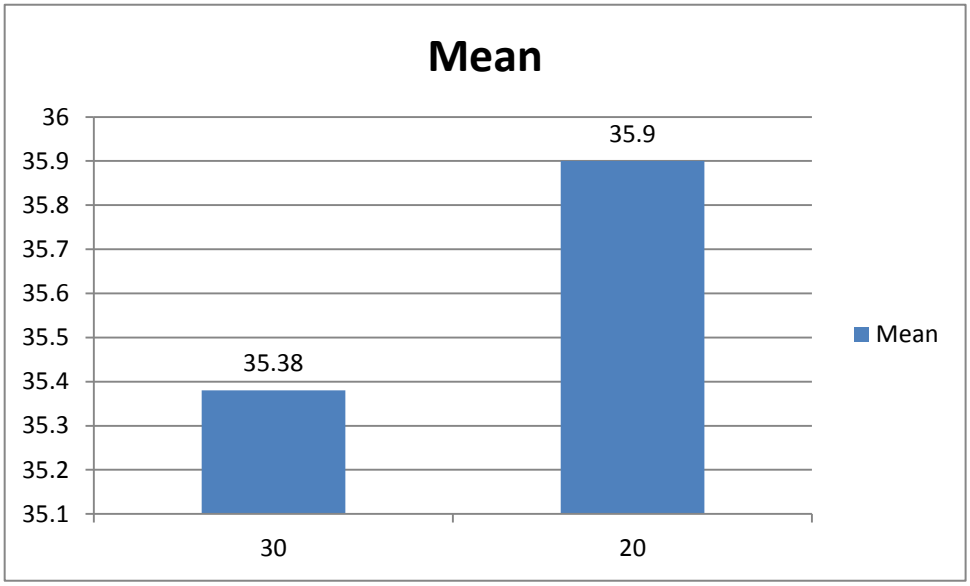
Sex	Frequency	Mean(%)	p.value
Male	30	15	0.80
Female	20	15	



Figures (4-4)Mean of PDW according to sex:

Table(4-5):Mean of APPT according to sex:

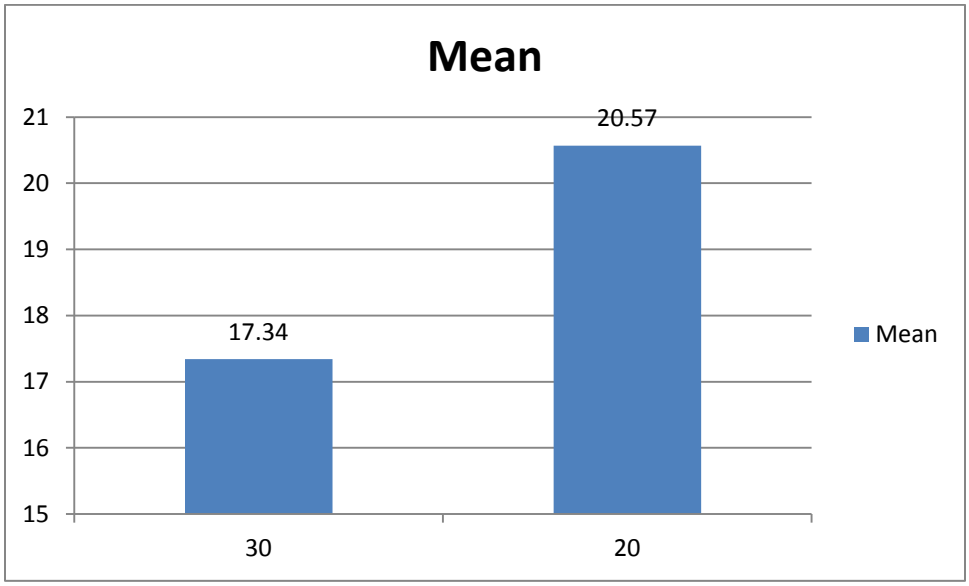
Sex	Frequency	Mean(sec)	p.value
Male	30	35.4	0.04
Female	20	35.9	



Figures (4-5): Mean of APPT according to sex

Table (4-6): Mean of PT according to sex:

Sex	Frequency	Mean(sec)	p.value
Male	30	17.3	0.03
Female	20	20.6	



Figures (4-6): Mean of PT according to sex:

Table (4-7): Mean of Platelet count in test and control

Sex	Frequency	Mean(10^9/L)	p.value	The correlation
Test	50	185	0.00	Significant
control	30	291		

Table (4-8): Mean of MPV in test and control

Sex	Frequency	Mean(fl)	p.value	The correlation
Test	50	9	0.03	Significant
Control	30	8		

Table (4-9): Mean of PDW in test and control

Sex	Frequency	Mean (%)	p.value	The correlation
Test	50	15	0.03	Significant
Control	30	16		

Table (4-10):Mean of PT in test and control

Sex	Frequency	Mean(sec)	p.value	The correlation
Test	50	18.7	0.00	Significant
Control	30	13.1		

Table (4-11):Mean of APPT in test and control

Sex	Frequency	Mean(sec)	p.value	The correlation
Test	50	35.6	0.00	Significant
Control	30	28.7		

Table(4-12): Mean of coagulation profile between patient whose stop and continues in anti-psychotic drugs

NO	Variables	Test	Mean	p.value	The correlation
1	Platelet	Stop	216	0.59	Not Significant
		continues	197		
2	MPV	stop	8	0.05	Not Significant
		continues	10		
3	PDW	stop	15	0.80	Not Significant
		continues	15		
4	PT	stop	17.3	0.38	Not Significant
		continues	17.8		
5	APPT	stop	35.7	0.05	Not Significant
		Continues	34.3		

Chapter Five

Discussion

Conclusion

Recommendations

5-1 Discussion

The study include 50 patient distributed as 30 male (60%) and 20 female (40%) and as shown in table and figure (4-1).The mean of platelet count according to six distributed as 30 male ($172x10^9$/L) and 20 female ($204x10^9$/L)and the p.value=0.00 its less than 0.05 then there is significant correlation between male and female and as shown in table and figure (4-2). The mean MPV according to six distributed as 30 male (10 fl) and 20 female(9 fl) and the p.value=0.03 its less than 0.05 then there is significant correlation between male and femaleand as shown in table and figure (4-3).The mean of PDW according to six distributed as 30 male (15%) and 20 female(15%) and the p.value=0.80 its more than 0.05 then there is not significant between male and femaleand as shown in table and figure (4-4). The mean of APTT according to six distributed as 30 male (35.4sec) and 20 female (35.9sec) and the p.value=0.04 its less than 0.05 then there is significant correlation between male and femaleand as shown in table and figure (4-5).The mean of PT according to six distributed as 30 male (17.3sec) and 20 female(20.6sec)and the p.value=0.03 its less than 0.05 then there is significant correlation between male and female and as shown in table and figure (4-6)

The mean of platelet count in test and control distributed as 50 psychotic patient (186x10 9 /L) and 30 control (291x10 9 /L) and the p.value=0.00 its less than 0.05 then there is significant correlation between psychotic patient and control and as shown in table (4-7). This result was in agree with previous work done by Chang-Chieh Wu et al [Chang-Chieh Wu et al 2016] and Ali Almuqdadi et al[Ali Almuqdadi et al 2016] .

The mean of MPV in test and control distributed as 50 psychotic patient (9 fl) and 30 control(8 fl) and the p.value=0.03 its less than 0.05 then there is

significant correlation between psychotic patient and control and as shown in table (4-8).This result was in agree with previous work done by Semiz et al [Semiz et al 2013].

The mean of PDW in psychotic patient and control distributed as 50 psychotic patient (15.1%) and 30 control (15.5%) and the p.value=0.03 it's less than 0.05 then there is significant correlation between psychotic patient and control and as shown in table (4-9).

The mean of PT in psychotic patient and control distributed as 50 psychotic patient (18.7sec) and 30 control (13.1sec) and the p.value=0.00 its less than 0.05 then there is significant correlation and as shown in table (4-10). This result was in agree with previous work done by Conoso et al[Conoso et al 1977], Mohammed et al [Mohammed et al 2005] and Chris Omisakin, et al[Chris Omisakin, et al 2014].

The mean of APTT in psychotic patient and control distributed as 50 psychotic patient (35.6sec) and 30 control (28.7sec) and the p.value=0.00 its less than 0.05 then there is significant correlation and as shown in table (4-11). This result was in agree with previous work done by Conoso et al [Conoso et al 1977], Mohammed et al [Mohammed et al 2005] and Chris Omisakin, et al [Chris Omisakin, et al 2014].

From Table (4-12) we found that the p.value its great than (0.05) then there is not significant correlation between psychotic patient whose stop anti-psychotic drugs less than one month and patient continue anti-psychotic drugs. That is means the effect of anti-psychotic drugs is still in the body.

5-2 Conclusion

1. Prothrombin time in psychiatric patients take antipsychotic drugs was (18.7sec) and control (13.1sec) and the p.value=0.00 its less than 0.05 then there is significant correlation.
2. Activated Partial Thromboplastin time (APTT) in psychiatric patients take antipsychotic drugs was (35.6sec) and control (28.7sec) and the p.value=0.00 it's less than 0.05 then there is significant correlation
3. Antipsychotic drugs induce thrombocytopenia.
4. The finding of this study supports the clinical observation that antipsychotic drugs causes increase risk of thrombosis or hemorrhage.

5.3 Recommendation

This study Recommended:

1. Further investigation should be done to investigate the mechanism involve the haemostatic changes which occur in psychiatric patient take antipsychotic drugs; such as platelets functions test &D-dimer.
2. Clinical and medical strategists should be adopted to control haemostatic changes in psychiatric patient take antipsychotic drugs.
3. It is pertinent for psychiatrist to put into the consideration the effect of psychotropic drugs on hemostasis especially coagulation before and during administration of antipsychotic drugs.

Chapter Six

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Appendix

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Assessment of Coagulation Profile For Patients Under Antipsychotic Drugs

Questionnaire

Sex:……

Male ( ) Female ( )

Age:……

Education:

Life Style:

High ( ) middle ( ) low ( )

Duration of Disease:

Type of Antipsychotic Drugs:

Signs and Symptoms:

Other Drugs:

Other Disease:

Type of Investigation:

Platelet count:

MPV:

PDW:

PT:

APTT: