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Assessment of Plasma Urea and Creatinine levels among Sudanese Children using Antiepileptic Drugs in Khartoum state

تقييم مستويات اليوريا والكرياتينين في بلازما الدم لدي الأطفال الذين يستخدمون العقاقير المضادة للصرع في ولاية الخرطوم

A dissertation submitted in partial fulfillment for the requirements of
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الآيـــــه

قال تعالي:

فَتَبَسَّمَ ضَاحِكاً مِنْ قَوْلِهَا وَقَالَ رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحاً تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ

سورة النمل الآية (19)

صدق الله العظيم

DEDICATION

THIS THESIS IS DEDICATED TO:

My fabulous parents, who never stop giving of themselves in countless way,

The great martyrs of Sudanese revolution

My beloved brothers and sister

My friend who encourage and support me

All people in my life touch my heart

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I would firstly like to express my very profound gratitude to **God**, who gave me the well and strength to pursue, complete this research and also I do appreciate **my parent** attempts for providing me with unfailing support and continuous encouragement throughout my years of study and through the process of researching and writing this thesis. This accomplishment would not have been possible without them. Thank you.

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Abstract

Background and Aim of the study: antiepileptic drugs such as valproic acid (VPA) and carbamazepine (CBZ) may disrupt renal function. Plama Urea and creatinine may reflect renal dysfunction and may be useful in detecting renal injury. The aim of this study was to determine the levels of plasma urea and creatinine in Sudanese children used antiepileptic drugs (CBZ and VPA).

Materials and Methods: this was cross sectional comparative study, conducted from May to September 2019, at Soba Teaching Hospital (Sudan-Khartoum state). Sudanese children aged between 1 to 15 years with epilepsy on VPA (n=23), CBZ (n=17) and 40 apparently healthy Sudanese children as control group, both age and sex were matched . Plasma urea and creatinine levels were measured, by using spectrophotometer(Mindary PA 88 A), and commercial reagent kits from Bio system Company. The data obtained were analyzed by both Student's Independent T test and person correlation test using SPSS version 22 computer program.

Results: showed significant increase in means of plasma urea in case group (mean ± SD 27.4 ± 9.12 mg/dL) when compared to control group (mean ± SD 17.0 ± 4.04 mg/dL *p value* 0.00), also significant increases in mean of plasma creatinine level in case group (mean ±SD 0.54 ± 0.02 mg/dL) when compared to control group (mean ±SD 0.44±0.14 mg/dL).

There was significantly increased in mean of urea among children used valproate when compared to carbamazepine (Mean± SD 30.0±9.70 mg/dl vs 23.0±6.70) respectively, and significantly increase in mean of plasma creatinine in children used carbamazepine when compared to patient used valproate (Mean± SD 0.67±0.11 vs 0.43±0.09) respectively. There were no correlation between plasma urea level and duration of the antiepileptic drugs (VPA, CBZ), and significantly positive correlation between creatinine and duration of antiepileptic drugs (VPA, CBZ) (r= 0.64, *p- value* 0.05) and (r= 0.56, *p- value* 0.05) respectively.

Conclusion: Sudanese children with epilepsy used antiepileptic drugs (VPA, CBZ) treatment**,** had higher plasma urea and creatinine level, and creatinine level positively correlate with duration of treatment in this study.

المستخلص

الخلفية والهدف من الدراسة: العقاقير المضادة للصرع مثل حمض فالبرويك (VPA) وكاربامازيبين (CBZ) قد يعطل وظيفة الكلى.البلازما يورياوالكرياتينين قد تعكس اختلال وظيفي في الكلى وقد تكون مفيدة في الكشف عن الاصابة الكلوية.
كان الهدف من هذه الدراسة هو تحديد العلاقة بين استخدام علاج فالبرويك وكاربامازيبين والخلل الكلوي لدى الأطفال الذين يعانون من الصرع عن طريق قياس اليوريا البلازما والكرياتينين.
الطريقة التي أجريت بها دراسة الحالات والشواهد من مايو إلى سبتمبر 2019 في مستشفى سوبا التعليمي (السودان ، ولاية الخرطوم). 40 طفلاً سودانيًا تتراوح أعمارهم بين 1 إلى 15 عامًا مصابين بالصرع على VPA (عدد = 23) ، و CBZ (عدد = 17) و 40 طفلًا سودانيًا يتمتعون بصحة جيدة كمجموعة تحكم ، تمت مطابقة كل من العمر والجنس. في دراسة مجموعة اليوريا البلازما ومستوى الكرياتينين تم قياسها في حالة والسيطرة ، وذلك باستخدام الطيف الكاشف ومجموعات الكاشف التجاري من شركة نظام الحيوي. تم تحليل النتائج باستخدام الفرق بين المتوسطين غير المعتمدين في برنامج الحزم الاحصائية للعلوم الاجتماعية المحوسب الاصدار22 .
النتائج: أظهرت الدراسة زيادة معنوية في اليوريا في البلازما (ضمن المعدل الطبيعي) في مجموعة الحالات (9.12 ± 27.4 ملغم / ديسيلتر) عند مقارنتها بمجموعة التحكم (4.04 ± 17.0). والزيادات الكبيرة في كرياتينين البلازما (ضمن المعدل الطبيعي) في مجموعة الحالات (156. ± 0.536 ملغ / ديسيلتر) عند مقارنتها بمجموعة التحكم (يعني ± 140. SD 0.440 ملغ / دل). كان هناك ارتباط إيجابي ضعيف ضئيل بين مستوى اليوريا في البلازما ومدة العقاقير المضادة للصرع (VPA و CBZ) ، وهناك علاقة إيجابية ملحوظة بين الكرياتينين ومدة العقاقير المضادة للصرع (VPA و CBZ) (ص = + .642 ** ، قيمة 005. p) و (ص = +. 562 * ، قيمة 0.05 p) على التوالي.
الخلاصه البلازما يوريا والكرياتينين كان بها زيادة كبيرة في الأطفال السودانيين الذين يعانون من الصرع ويستخدمون الأدوية المضادة للصرع (VPA، CBZ) للعلاج ، وكان هناك ارتباط إيجابي كبير بين مدة العلاج ومستوى الكرياتينين.

Table of content

List of tables

List of figures

List of Abbreviation

Abbreviation	Full text
AEDs	**Anti-epileptic drugs**
AKI	**acute kidney injury**
ASDs	**Anti-seizure drugs**
CBZ	**Carbamazepine**
CT	**Computed tomography**
CNS	**Central nervous system**
EEG	**Electroencephalogram**
GABA	**Gama amino butyric acid**
GFR	**glomerular filtration rate**
GTCS	**Generalized tonic–clonic seizures**
IBE	**International Bureau for Epilepsy**
ILAE	**International League Against Epilepsy**
IV	**Intravenous**
JAE	**juvenile absence epilepsies**
LCM	**Lacosamide**
MRI	**Magnetic resonant imaging**
NMDA	**demonstrated that N-methyl-D-aspartate**
NPN	**Non protein nitrogenous**
PHT	**Phenytoin**
TCAs	**tricyclic antidepressants**
VPA	**Valproic acid**

1. Introduction, Rationale, and Objectives

1.1 Introduction

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. Epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al., 2005).

Antiepileptic drug (AEDs) therapy, the mainstay of treatment for most patients, has four goals: to eliminate seizures or reduce their frequency to the maximum degree possible, to evade the adverse effects associated with long-term treatment, and to aid patients in maintaining or restoring their usual psychosocial and vocational activities, and in maintaining a normal lifestyle (Goldenberg and Therapeutics., 2010)

The older and most commonly used medications in the treatment of childhood epilepsy are sodium valproate and carbamazepine. Phenytoin and phenobarbitone, previously drugs of first choice for most seizure types before the advent of carbamazepine and sodium valproate, are no longer considered to be first, second or third-line drugs because of their relatively unsatisfactory long-term safety profile (Greenwood *et al* ., 1999).

The use of common antiepileptic drugs can potentially result in some toxic reactions such as dermatitis, nephritis, hepatitis, as well as severe anemia. data from experimental, cross-sectional and prospective studies have evidence for deleterious effect of some AEDs on the kidney(Hamed. 2017). Valproic acid (VPA) is commonly used as an antiepileptic drug (AED) (Knorr et al., 2004). Carbamazepine is mostly used in partial seizures with complex symptoms (Juberta *et al*., 1994). In recent years, it has been reported that sodium valproate occasionally can cause renal tubular impairment (Hergüner et al., 2006). However, there is growing evidence that valproate can cause renal tubular injury in children, and there are increasing reports of valproate induced Fanconi's syndrome where the renal tubules lose their ability to reabsorb electrolytes, urea, glucose and protein (Knights and Finlay 2014). Experimental and in vitro studies have shown that VPA induces Oxidative stress, inflammation and fibrosis in renal tissue

in mice (Hamed et al. 2018).Over the last two decades, a number of studies have shown that VPA and CBZ are nephrotoxic (Trihono et al., 2018).

1.2 Rationale

The kidneys perform essential functions of excretion and hormone production. One of the excretory functions is to eliminate foreign chemicals (xenobiotics), such as drugs and their metabolites. A long-term use of some drugs could be harmful for the kidney. Nephrotoxic agents account for approximately 20% cases of acute kidney injury (AKI). The typical course of AKI involves multiple mechanisms including hemodynamic changes in the glomeruli, tubular cell toxicity, and interstitial nephritis.

Long term use of antiepileptic drugs associated with number of somatic condition, thus treatment with antiepileptic drugs such as valproic acid (VPA) and carbamazepine (CBZ) may disrupt renal tubular function. Several cross sectional as well as prospective studies reported signs of renal glomerular or/and tubular dysfunction in children with VPA and CBZ mono- or polytherapies (Hamed. 2017).

In Sudan there was no published data concerning the association between antiepileptic drugs (VPA, CBZ) and level of urea and creatinine among Sudanese epileptic children, That why we attempt to do this study.

1.3 Objectives

1.3.1 General objective:

To asses plasma urea and creatinine levels in Sudanese children receive antiepileptic drugs.

1.3.2 Specific objectives:

-To measure plasma urea and creatinine levels in study group.

- To compare between plasma urea and creatinine levels in Sudanese children according to types of drug used.

- To correlate between plasma urea and creatinine levels and duration of antiepileptic drugs (VPA, CBZ) using.

2. Literature review

2.1 Epilepsy

Epilepsy is one of the most common neurologic illnesses.characterized by recurrent seizure (Sarma et al ., 2016). Seizures are defined as a transient occurrence of signs and symptoms due to the abnormal, excessive, or synchronous neuronal activity in the brain characterized by abrupt and involuntary skeletal muscles activity(Minardi et al., 2019). The term epilepsy is derived from the Greek word epilambanein, meaning to attack or seize(Goldenberg and Therapeutics., 2010) . Epilepsy has numerous causes, each reflecting underlying brain dysfunction (Shorvon et al., 2011). In 2014 the International League Against Epilepsy (ILAE) Task Force proposed the operational (practical) clinical definition of epilepsy, intended as a disease of the brain defined by any of the following conditions:

At least two unprovoked (or reflex) seizures occurring > 24 h apart, One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years and Diagnosis of an epilepsy syndrome (Minardi et al., 2019).“Epilepsy syndrome” refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, EEG findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs) (Stafstrom and Carmant., 2015).

2.1.1 Classification of epilepsy

The diagnosis of epilepsy has become a multilevel process, which is designed to allow the classification of epilepsy in different clinical environments, meaning that different levels of classification will be possible depending on the available resources. Indeed, the classification includes three levels: seizure types, epilepsy type, epilepsy syndrome(Minardi et al., 2019).

2.1.1.1 Classification of epilepsy according to seizure type

The International League Against Epilepsy (ILAE) in 1981 proposed this classification based on clinical feature and electroencephalogram finding. Accordingly, seizure can be classified into 3 main groups, namely partial, generalized and unclassified (Gamage et al., 2012).

Partial (focal) seizure is caused by electrical discharge restricted to a limited part of the cortex of one cerebral hemisphere, Partial seizures are further sub-divided according to whether or not there is loss of awareness include Simple partial seizure (Consciousness is not impaired during episode), Simple partial seizures result when the ictal discharge occurs in a limited and often circumscribed area of cortex, the epileptogenic focus(Merritt et al., 2000). E. g: one limb jerking (a Jacksonian seizure) (Kumar and Clark ., 2008).

Complex partial seizure (Consciousness is not impaired during episode) Defined by impaired consciousness and imply bilateral spread of the seizure discharge, at least to basal forebrain and limbic areas (Merritt et al., 2000). E. g: a temporal lobe seizure.

Partial seizures with secondary generalization: Partial seizures with electrical activity confined to one part of the brain may spread after a few seconds, due to failure of inhibitory mechanisms, to involve the whole of both hemispheres causing a secondary generalized seizure (Kumar and Clark ., 2008).

Generalized seizure there is simultaneous involvement of both hemispheres, always associated with loss of consciousness or awareness.

Generalized seizure type include typical absence seizure (petit mal): the affected individual, usually a child or adolescent, loses awareness for a number of seconds resulting in a blank stare. This may be accompanied by more subtle signs, such as flickering of the eyelids and mouth movements (Brodie et al., 2018). Children with absence seizures may go on to develop generalized convulsive seizures (Kumar and Clark ., 2008). Generalized tonic–clonic seizures (GTCS, grand mal seizures) Seizures are characterized by abrupt loss of consciousness with bilateral tonic extension of the trunk and limbs (tonic phase), often accompanied by a loud vocalization as air is forcedly expelled across contracted vocal cords (epileptic cry), followed by synchronous muscle jerking (clonic phase). In some patients, a few clonic jerks precede the tonic-clonic sequence; in others, only a tonic or clonic phase is apparent. Postictally, patients are briefly unarousable and then lethargic and confused, often preferring to sleep. Many patients report inconsistent nonspecific premonitory symptoms (epileptic prodrome) for minutes to a few hours before a generalized tonic-clonic seizure. Common symptoms include ill-defined anxiety, irritability, decreased concentration, and headache or other

uncomfortable feelings(Merritt et al., 2000) . Myoclonic seizures Are characterized by rapid brief muscle jerks that can occur bilaterally, synchronously or asynchronously, or unilaterally. Myoclonic jerks range from isolated small movements of face, arm, or leg muscles to massive bilateral spasms simultaneously affecting the head, limbs, and trunk(Merritt et al., 2000). Atonic (astatic) seizures Also called drop attacks, are characterized by sudden loss of muscle tone, which may be fragmentary (e.g., head drop) or generalized, resulting in a fall. When atonic seizures are preceded by a brief myoclonic seizure or tonic spasm, an acceleratory force is added to the fall, thereby contributing to the high rate of self-injury with this type of seizure(Merritt et al., 2000).

Unclassifiable seizures do not fit a category above (Kumar and Clark ., 2008).

2.1.1.2 Classification of Epilepsy (Epileptic Syndromes)

Attempting to classify the kind of epilepsy a patient has is often more important than describing seizures, because the formulation includes other relevant clinical data of which the seizures are only a part. The other data include historical information (e.g., a personal history of brain injury or family history of first-degree relatives with seizures); findings on neurologic examination; and results of EEG, brain imaging, and biochemical studies. The ILAE classification separates major groups of epilepsy first on the basis of whether seizures are partial (localization-related epilepsies) or generalized (generalized epilepsies) and second by cause (idiopathic, symptomatic, or cryptogenic epilepsy)(Merritt et al., 2000). The 2017 ILAE Position Papers on Classification of Seizure Types and the Epilepsies presented a framework for classification including seizure types, epilepsy types, and syndromes. There is an emphasis on defining etiology at all levels of clinical classification in addition to consideration of comorbidities (Pressler et al., 2017).

2.1.2 Pathophysiology of epilepsy

The exact mechanism of seizure onset is unknown. There could be either a deficit of neuronal inhibition or an excess of excitatory stimuli. Most authors suggest that the onset of seizures depends on a deficit in the neuronal inhibition, in particular amino butyric acid (GABA) deficit, the most important neurotransmitter of CNS; alternatively it depends on the alteration of the GABA function which determines prolonged and high intensity stimulation(Minardi et al., 2019).

Other studies, in experimental animal models, demonstrated that N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, both glutamate receptors, the most important excitatory receptor of CNS, are involved in seizure physiopathology(Minardi et al., 2019).

2.1.3 Diagnosis of epilepsy

The diagnostic evaluation has three objectives: to determine if the patient has epilepsy; to classify the type of epilepsy and identify an epilepsy syndrome, if possible; and to define the specific underlying cause(Merritt et al., 2000).

The history and neurologic examination are the cornerstones of the diagnosis of seizures and epilepsy, whereas laboratory evaluations serve as adjunctive tests. Important historical features include the clinical context in which the seizure occurred, including premonitory signs, details of the seizure itself, such as phenomenology, responsiveness, focal features, and the postictal state. The neurological examination assesses focal signs that might implicate or localize cerebral pathology(Stafstrom and Carmant., 2015).

An EEG is a recording of the brain's electrical activity(Stafstrom and Carmant., 2015).The EEG is the most important laboratory test in evaluating patients with seizures. The EEG helps both to establish the diagnosis of epilepsy and to characterize specific epileptic syndromes. EEG findings may also help in management and in prognosis(Merritt et al., 2000).

Computed tomography (CT) and magnetic resonance imaging (MRI) scans are important adjuncts to the clinical examination and EEG in the evaluation of a person with seizures. Neuroimaging techniques are especially sensitive for central nervous system (CNS) structural lesions. MRI is more sensitive than CT. MRI abnormalities can be correlated directly with EEG activity(Stafstrom and Carmant., 2015).

Routine blood tests are rarely diagnostically useful in healthy children or adults. They are necessary in newborns and in older patients with acute or chronic systemic disease to detect abnormal electrolyte, glucose, calcium, or magnesium values or impaired liver or kidney function that may contribute to seizure occurrence. In most patients, serum electrolytes, liver function tests, and a complete blood count are useful mainly as baseline studies before initiating antiepileptic drug treatment(Merritt et al., 2000).

Neuropsychological assessment is required in individual with learning disabilities and cognitive dysfunction, particularly in regard language and memory (Gamage et al., 2012).

2.1.4 Management of epilepsy

The care of patients with epilepsy aims to eliminate or reduce seizures, minimize the adverse effects of treatment, improve medical and neuropsychiatric comorbidities. ASDs are the primary therapy for epilepsy and are symptomatic treatments that reduce seizure occurrence and severity but do not mitigate the course of the disorder (Devinsky et al., 2018).

2.1.5 Medical treatment of epilepsy

Therapy of epilepsy has three goals: to eliminate seizures or reduce their frequency to the maximum extent possible, to avoid the side effects associated with long-term treatment, and to assist the patient in maintaining or restoring normal psychosocial and vocational adjustment(Merritt et al., 2000) . Drugs used to treat epilepsy work by decreasing the electrical activity of the brain, either by preventing neuronal depolarization by blocking sodium channels or calcium channels, enhancing potassium channel function, inhibiting excitation mediated by the neurotransmitter glutamate, or promoting inhibition mediated by GABA (Stafstrom and Carmant., 2015). The decision to start AED therapy should be based on an informed analysis of the likelihood of seizure recurrence, the consequences of continuing seizures for patients, and the beneficial and adverse effects of the pharmacological agent chosen(Goldenberg and Therapeutics., 2010).

Historically, AEDs can be classified into three generations:

The first generatio includes potassium bromide, phenobarbital and a variety of drugs that were derived mainly by modification of the barbiturate structure, including phenytoin, primidone, trimethadione and ethosuximide, The second generation AEDs including carbamazepine, valproate and the benzodiazepines (Löscher and Schmidt., 2011) and The third-generation drug includes lacosamide (LCM) and eslicarbazepine acetate(Hanaya and Arita 2016). As a general principle, medication should be started at a low dose to avoid side effects (Stafstrom and Carmant., 2015). The ideal AED should suppress all seizures without causing any unwanted adverse effects(Goldenberg and Therapeutics., 2010). Starting antiepileptic drugs after a first seizure reduces the risk of a second seizure

compared with no treatment or delayed treatment (Schmidt ., 2014). Many different ASDs are available for the treatment of epilepsy. The initial ASD should be individualized on the basis of the epilepsy syndrome and seizure type, the adverse effects profile, the pharmacokinetic profile, potential interactions with other drugs or other medical conditions, the age of the patient, reproductive issues and cost .After starting ASDs, 80% of patients will have adverse effects, which minimized by starting these drugs at low doses and slowly increasing the dose (Devinsky et al., 2018), Particularly old generation [e.g. phenytoin or PHT, carbamazepine or CBZ, valproate or VPA, etc] is associated with adverse side effects which include: metabolic and endocrine, vascular, cognitive, behavioral, bone disease and nonalcoholic fatty liver. Kidney dysfunction or injury has been reported as an adverse effect of some AEDs(Hamed 2017). The high prevalence of epilepsy may result in the long-term use of antiepileptic drugs, such as valproic acid (VPA) and carbamazepine (CBZ). Over the last two decades, a number of studies have shown that VPA and CBZ are nephrotoxic(Trihono et al., 2018).

The Majority of antiepileptic drugs possess more than one mechanism of action. Which divided into three groups according to their action:

First group: Consists of antiepileptics (f.e.: carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproate) which blockade of voltage-dependent sodium or calcium channels. These drugs are effective against generalized tonic-clonic and partial seizures (Czapinski et al., 2005).

The second group: Includes drugs enhancing inhibitory events mediated by g – aminobutyric acid (GABA): benzodiazepines, gabapentin, phenobarbital, tiagabine, topiramate, vigabatrin, and valproate. These drugs may be used in all seizure types (absence, generalized tonic-clonic, and partial seizures) (Czapinski et al ., 2005).

The third group: Consists of one drug–ethosuximide which blocks T-type calcium channels and is active against absences siezure. Also zonisamide may be a T-type calcium channel inhibitor (Czapinski et al ., 2005).

2.1.5.1 Valporic acid and valporate

Valproic acid is a carboxylic acid. Its chemical name is di-Npropyl acetic acid. Valproate is available in many formulations including extended release, sprinkles, liquid, and

IV(Goldenberg and Therapeutics., 2010). Valproic acid is a commonly used anti-epileptic drug (AED) for prescription to control convulsion attacks (Tolou-Ghamari and palizaban ., 2015). Valproic acid has been effective in partial and generalized seizures and is indicated as monotherapy and adjunctive therapy for complex partial seizures, also indicated for patients with simple and complex absence seizures and as an adjunctive therapy with Lamotrigine, levetacetam or zonisamide for patients with multiple seizure types, including absence seizures. Valproate is the drug of main option for management in juvenile absence epilepsies (JAE) accompanied by generalized tonic-clonic seizures (Tolou-Ghamari and palizaban ., 2015). The mechanisms by which valproate exerts its antiepileptic effects have not been established(Goldenberg and Therapeutics., 2010).it effect by inhibiting gamma-aminobutyric acid (GABA) transaminase and then increases the amount of GABA within brain, also suppress both sodium and calcium channels (Tolou-Ghamari and palizaban., 2015). The initial dose is 10 to 15 mg/kg per day

2.1.5.2 Carbamazepine

Carbamazepine is related to the tricyclic antidepressants (TCAs) (Goldenberg and Therapeutics., 2010). Carbamazepine (CBZ) is one of the older antiepileptic drugs (AEDs) in worldwide, CBZ is the oldest in this class of dibenzazepine AEDs. Carbamazepine is indicated for use as an anticonvulsant drug. The mechanism of action is thought to be inhibition of the voltage-gated sodium channel (Gierbolini et al., 2016). It is available as an immediate release formulation, both oral suspension and tablet (Tegretol). Carbamazepine is indicated for use as an anticonvulsant drug. Evidence supporting its efficacy as an AED was derived from studies that Enrolled patients with partial seizures with complex symptomatology (psychomotor, temporal lobe); generalized tonic–clonic seizures (grand mal); and mixed seizure patterns, including the latter two types or other partial or generalized seizures. Absence (petit mal) seizures do not appear to be controlled by carbamazepine(Goldenberg and Therapeutics., 2010).

2.2 Kidney

The kidneys are complex organs that are vital in maintaining normal body functions (Wallace 1999), The kidneys perform a variety of important functions:

They regulate the osmotic pressure (osmolality) of the body fluids by excreting osmotically dilute or concentrated urine, regulation of the concentrations of numerous ions in blood plasma, including Na^{+}, K^{+}, Ca^{+2}, Mg^{+2}, Cl^{-}, bicarbonate (HCO_3^{-}), phosphate, and sulfate, also play an essential role in acid–base balance by excreting H+ when there is excess acid or HCO_3^{-} when there is excess base, regulate the volume of the ECF by controlling Na+ and water excretion and regulate arterial blood pressure by adjusting Na^{+} excretion and producing various substances (e.g., renin) that can affect blood pressure too, They eliminate the waste products of metabolism, including urea (the main nitrogen-containing end product of protein metabolism in humans), uric acid (an end product of purine metabolism), and creatinine (An end product of muscle metabolism), remove of many drugs (e.g., penicillin) and foreign or toxic compounds, it's the major sites of production of certain hormones, including erythropoietin and 1, 25-dihydroxy vitamin D3, degrade several polypeptide hormones, including insulin, glucagon, and parathyroid hormone, synthesize ammonia, which plays a role in acid–base balance also synthesize substances that affect renal blood flow and Na^{+} excretion, including arachidonic acid derivatives (prostaglandins, thromboxane A2) and kallikrein (a proteolytic enzyme that results in the Production of kinins) (Tanner ., 2003).

The two kidneys are located in the upper abdominal cavity on either side of the vertebral column, behind the peritoneum (retroperitoneal) (Scanlon, and Sanders., 2007).The functional unit of kidney is the nephron. Each kidney may contain up to one million nephrons. The nephron consists of a glomerulus, proximal tubule, loop of Henle, distal tubule and collecting duct. The collecting duct ultimately combines to develop into the renal calyces, where the urine collects before passing along the ureter and into the bladder (Burtis et al., 2008).

2.2.1 Renal blood supply

The kidneys are highly vascular organs perfused with approximately 1,200 mL of blood per minute. This equals 20% to 25% of the body's cardiac output. Approximately 80% of the renal plasma flows through the efferent arterioles to the peritubular capillaries. The other 20% is filtered at the glomerulus and passes into Bowman's capsule. The filtration of the plasma per unit of time is known as the glomerular filtration rate (GFR). The GFR is directly related to the perfusion pressure in the glomerular capillaries (Wallace 1999).

2.2.2 Renal physiology

There are three basic renal processes:

2.2.2.1Glomerular filtration

There are several factors facilitate filtration. One factor is unusually high pressure in the glomerulus capillaries which is result of their position between two arterioles. Another factor is semi permeable glomerulus basement membrane, which has a molecular size cut off value of approximately 66,000 Dalton, about the molecular size of albumin. In addition because the basement membrane is negatively charge, negatively charge molecules such as protein are repelled (Bishop *et al*,.2010) .

2.2.2.2Tubular Function

Function of the proximal tubule is to return the bulk of each valuable substance from the glomerular filtrate back to the circulation, such as water, sodium, chloride, glucose, amino acids, vitamins and proteins. With the exception of water and chloride ions, the process is active, that the tubular epithelial cells use energy to bind and transport the substances across the plasma membrane to the blood. The second function of the proximal tubules is to secrete tubular cell metabolic products such as hydrogen ions and drugs such as penicillin (Bishop *et al*,.2010) .

Loop of henle its functions to maintain hyper osmolality that develops in the medulla to facilitate thee reabsorption of water, sodium, and chloride the osmolality at the tips of the papillae can reach about 1200 moms/kg of water, approximately four times that of plasma. The descending limb of henle loop is permeable to water, due to the presence of aquaporin-1 in both the apical and basolateral membrane, but the ascending limb is impermeable to water, there for, the fluid in the descending limb of henle loop become hypertonic, as water moves out of the tubule to the hypertonic interstitium. Sodium, potassium, and chloride are transported out of the tubular cells, therefore fluid in the ascending limb become more dilute (Bishop *et al*,.2010) .

2.2.3 Non protein nitrogenous compounds

The determination of nonprotein nitrogenous substances in the blood has traditionally been used to monitor renal function. The NPN fraction comprises about 15 compounds of clinical interest; compounds arise from the catabolism of proteins and nucleic acids. Which include urea, creatinine, uric acid and ammonia.

2.2.3.1 Creatinine

Creatine is synthesized in kidney, liver and pancreas by two enzymatically mediated reactions. In the first, transamidation of arginine and glycine forms guanidinoacetic acid. In the second reaction, methylation of guanidinoacetic acid occurs with s-adenosylmethionine as methyl donor. Creatine is then transport in blood to other such as muscle and brain, where it's phosphorylated to phosphocreatine a high energy compound (Burtis *et al., 2008).*Small amounts of creatinine are secreted by the proximal tubule and reabsorbed by the renal tubules.

Measurement of creatinine concentration is used to determine sufficiency of kidney function and the severity of kidney damage and to monitor the progression of kidney disease, Plasma creatinine concentration is a function of relative muscle mass, the rate of creatine turnover, and renal function. The amount of creatinine in the bloodstream is reasonably stable, although the protein content of the diet does influence the plasma concentration (Bishop *et al,*.2010).

2.2.3.2 Urea

The NPN compound present in highest concentration in the blood is urea. Urea is the major excretory product of protein metabolism. It is formed in the liver from amino groups (-NH2) and free ammonia generated during protein catabolism. Protein metabolism produces amino acids that can be oxidized to produce energy or stored as fat and glycogen. These processes release nitrogen, which is converted to urea and excreted as a waste product. Following synthesis in the liver, urea is carried in the blood to the kidney, where it is readily filtered from the plasma by the glomerulus. The concentration of urea in the plasma is determined by renal function and perfusion, the protein content of the diet, and the rate of protein catabolism. Measurement of urea is used to evaluate renal function, to assess hydration status, to determine nitrogen balance, to aid in the diagnosis of renal disease, and to verify adequacy of dialysis (Bishop *et al,*.20)

Materials and methods

3.1 Materials:

3.1.1 Study design, area and period:

This was an analytical comparative cross sectional study was conducted in Khartoum state; at Soba Teaching Hospital in epileptic children were receive antiepileptic drugs. During the period from May to September 2019.

3.1.2 Target population and sample size:

Forty Sudanese children with epilepsy received antiepileptic drugs were enrolled in this study as a case group and forty apparently healthy children were include as a control group.

3.1.3 Inclusion and Exclusion criteria:

Epileptic children receive antiepileptic drugs (VPA, CBZ) were including as test group and healthy subject children as control group .Patient with diabetes, renal impairment, and hypertension had been excluded from this study.

3.1.4 Ethical consideration:

- Permission of this study was obtained from local authorities in the area of the study.
- The objectives of the study were explained to all parents participating in the study.
- Verbal an informed consent was obtained from each parent's participant in the study.

3.1.5 Data Collection:

Interview with parents of children were done to obtain the clinical data. questionnaire (see appendix I) was specially designed to obtain information which help in either including or excluding certain individual in or from the study.

3.1.6 Sampling

Three ml of venous blood sample was collected from each participant; the blood sample was drawn in heparin containers, and then centrifuged at 4000 rpm for three minutes to get plasma. The plasma prepared was collected into 1.5 ml eppendorf tubes and kept frozen at (-20ċ) until analysis.

3.2 Methodology:

3.2.1 Estimation of Plasma urea:

3.2.1.1 Principle of urea:

Urea in the sample originates by means of the coupled reactions below colored complex that can be measured by spectrophotometry (Burtis et al., 2008)

3.2.1.2 Reagent composition, storage and reagent preparation

(See appendix II)

3.2.1.3 Procedure and Calculation

(See appendix II)

3.2.2 Estimation of Plasma creatinine:

3.2.2.1 Principle of creatinine

Creatinine in the sample reacts with picrate in alkaline medium forming a colored complex (jaffe method). The complex formation rate is measured in a short period to avoid interferences. plasma samples contain proteins react in a non-specific way nevertheless; the result can be corrected subtracting a fixed value. The use of this correction is known as the jaffe method compensated (Buttis et al., 2008).

3.2.2.2 Reagent composition, storage and reagent preparation

(See appendix III)

3.2.2.3 Procedure and Calculation

(See appendix III)

3.3 Quality control:

The precision and accuracy of the method used in this study were checked each time a batch was analyzed by including commercially prepared control sera.

3.4 Statistical analysis:

The data collected in this study were analyzed using Statistical Package for the Social Science program (SPSS program) version 22. **0.5 %** was taken as cut off limit for **95 %** statistical significance. Frequency and percentage testes were used and then the data were presented in tables. Pearson correlation coefficient and linear regression were used for

quantitative variables, and chi-square test for qualitative variables; P value ≤ 0.05 was considered as the level of significance.

4. Results

A total of 40 (23 boys, 17 girls) Sudanese children patients with epilepsy their ,age between (1-15) years old, at Soba Teaching Hospital (Sudan, Khartoum state) taken as test group and 40 (21 boys, 19 girls) apparently healthy children as control group, age and sex were matched.

Table (4.1):

Shows significant increase in means of plasma urea and creatinine levels in case compared to control group.

Table (4.2):

Shows significant increase in plasma urea in epileptic children on valproate treatment when compared with carbamazepine. Significant increase in plasma creatinine levels on carbamazepine when compared with valproate.

Figure (4.1):

shows 57.5% were boys.

Figure (4.2):

A Scatter plot show no correlation between plasma urea level and the duration of sodium valproate treatment in case group. p- Value (.07).

Figure (4.3):

A scatter plot shows significant positive correlation between the creatinine and duration of sodium valporate treatment in case group. p- Value (.005)

Figure (4.4):

A Scatter plot show insignificant positive correlation between the plasma urea level and duration of carbamazepine treatment in case group. p- Value (.769).

Figure(4.5)

scatter plot shows significant positive correlation between the creatinine and duration of carbamazepine treatment in case group. p- Value (.046).

Figure (4.6):

A scatter plot show significant positive correlation between creatinine and body weight in cases group. p- Value (.04).

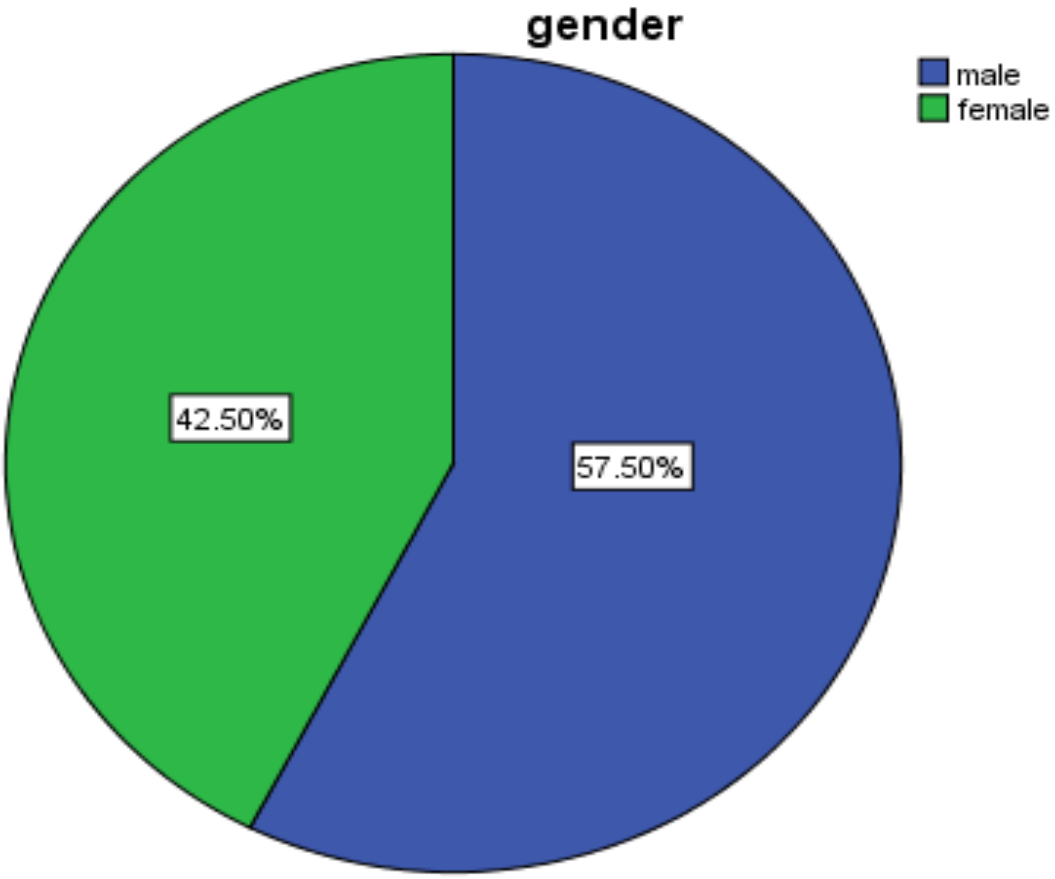

Figure (4.1): Distribution of case groups according to gender.

Table (4.1):comparison between Mean ± standard deviation and *P*-value of plasma urea and Creatinine levels in case and control groups.

Parameters	**Mean± SD of control**	**Mean± SD of cases**	**p. value**
Urea mg/dL	17.0 ± 4.04	27.4 ± 9.12	0.00*
Creatinine mg/dL	0.44 ± 0.14	0.54 ± 0.16	0.02*

The tables show the mean ± standard deviation and probability (p).

Independent t-test was used for comparison.

p- Value ≤ 0.05 considered significant.

Table (4.2): comparison between mean± standard deviation and p. value of plasma urea and creatinine in case group according to type of drugs.

Parameters	Drugs	Mean± SD	p. value
Urea mg/dl	**Valproate**	30.0 ± 9.70	0.02 **
	Carbamazepine	23.0 ± 6.70	
Creatinie mg/dl	**Valproate**	0.43 ± 0.09	0.00***
	Carbamazepine	0.67 ± 0.11	

The tables show the mean ± standard deviation and probability (p).

Independent t-test was used for comparison.

p- Value ≤ 0.05 considered significant.

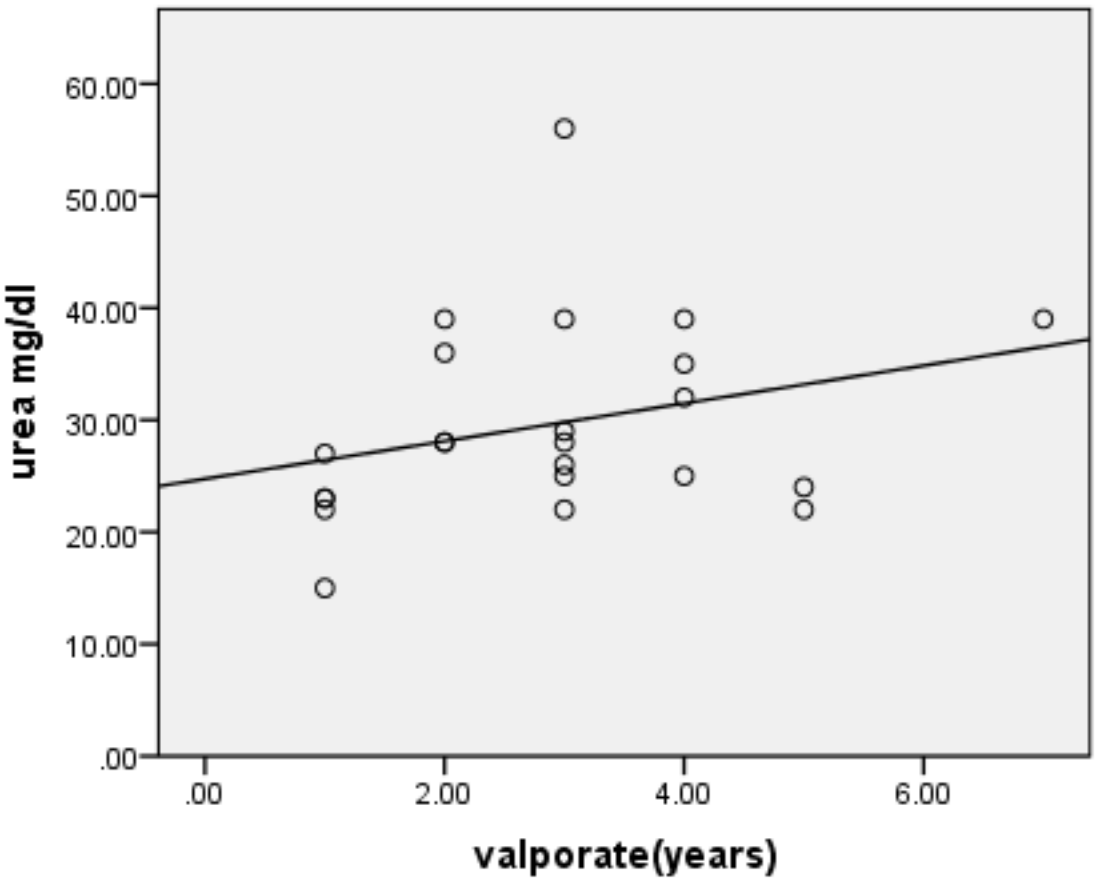

Figure (4.2): A Scatter plot show insignificant positive correlation between plasma urea level and the duration of sodium valproate treatment in case group. r= (0.45), p- value (0.07).

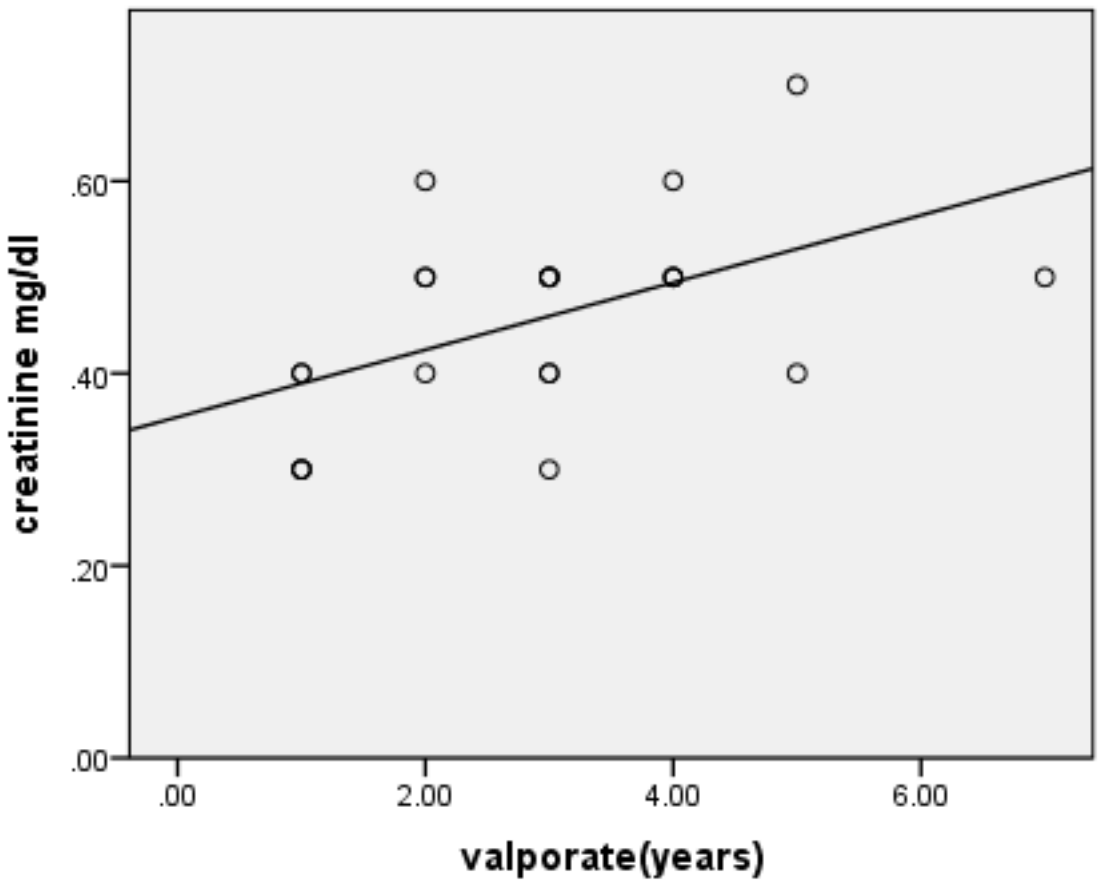

Figure (4.3): A scatter plot shows significant positive correlation between the creatinine and duration of sodium valporate treatment in case group. r= (0.64**), p- value (0.00).

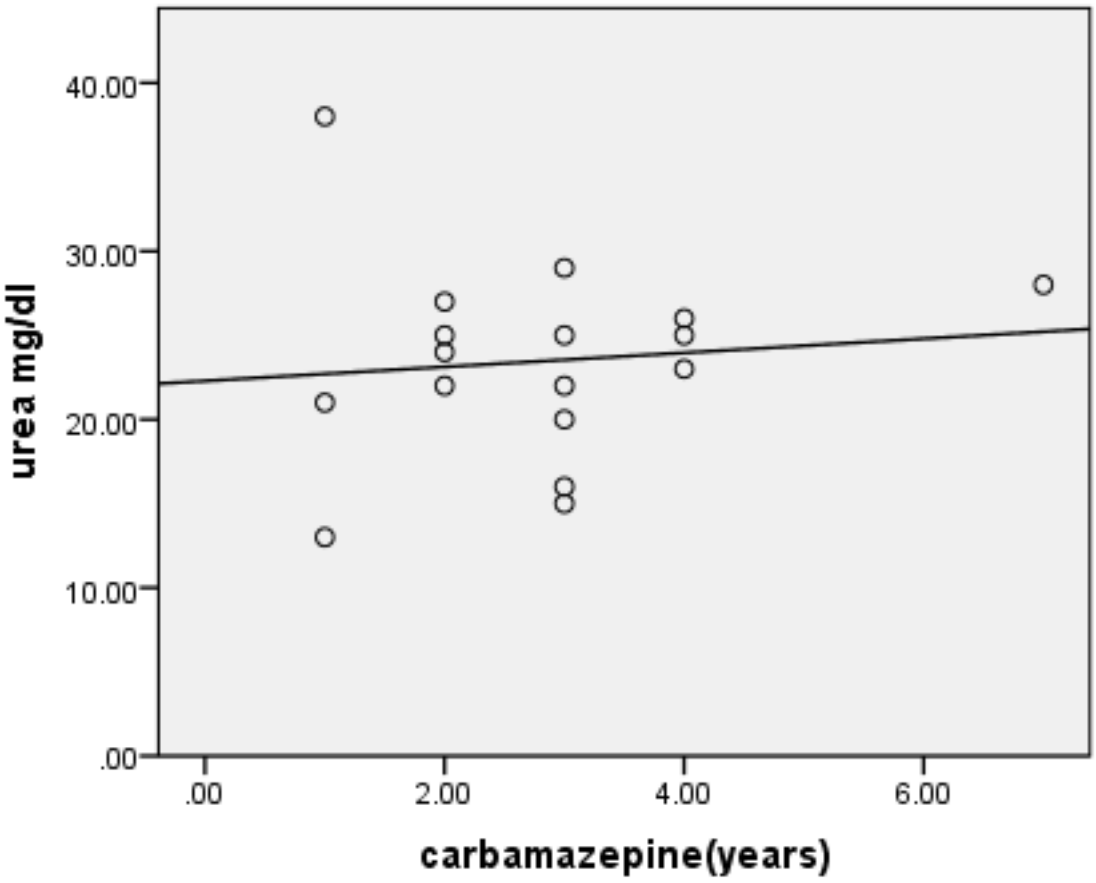

Figure (4.4): A Scatter plot show insignificant weak positive correlation between the plasma urea level and duration of carbamazepine treatment in case group. r= (0.09), p-value (0.77).

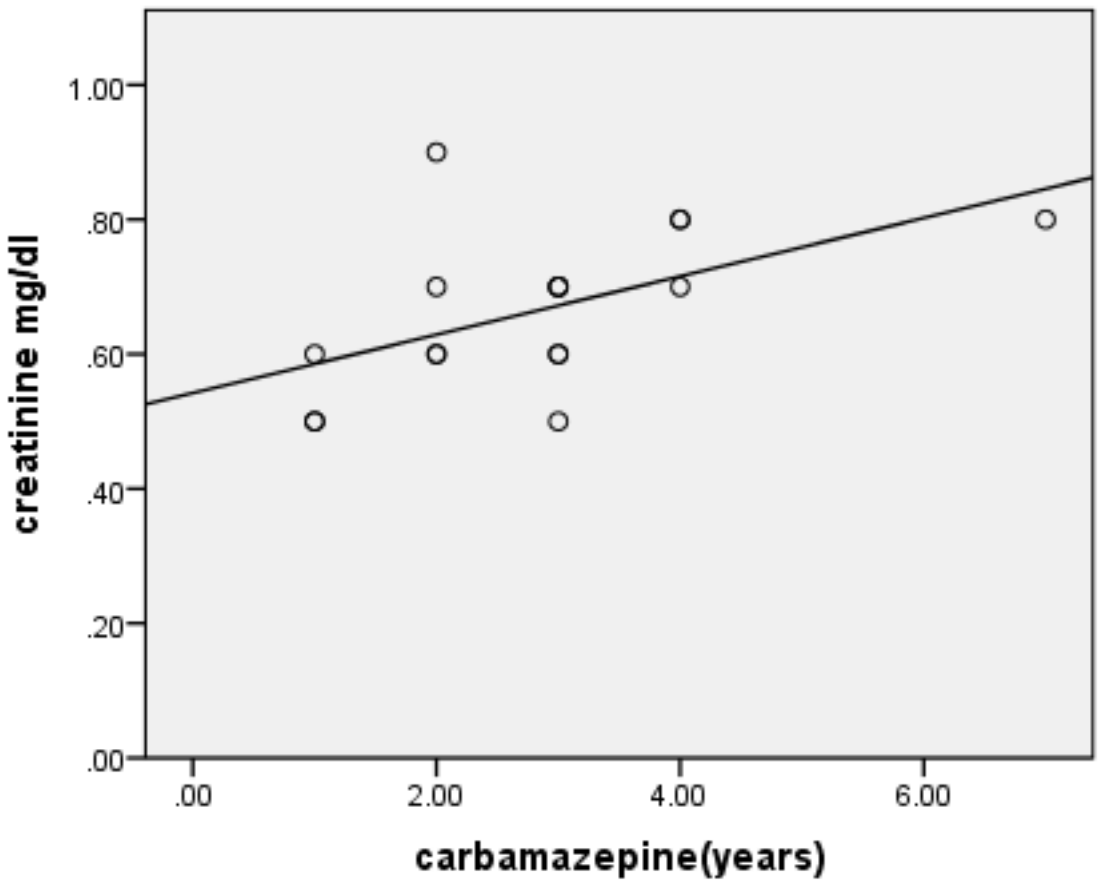

Figure (4.5): A scatter plot shows significant positive correlation between the creatinine and duration of carbamazepine treatment in case group. r= (0.56*), p- value (0.05).

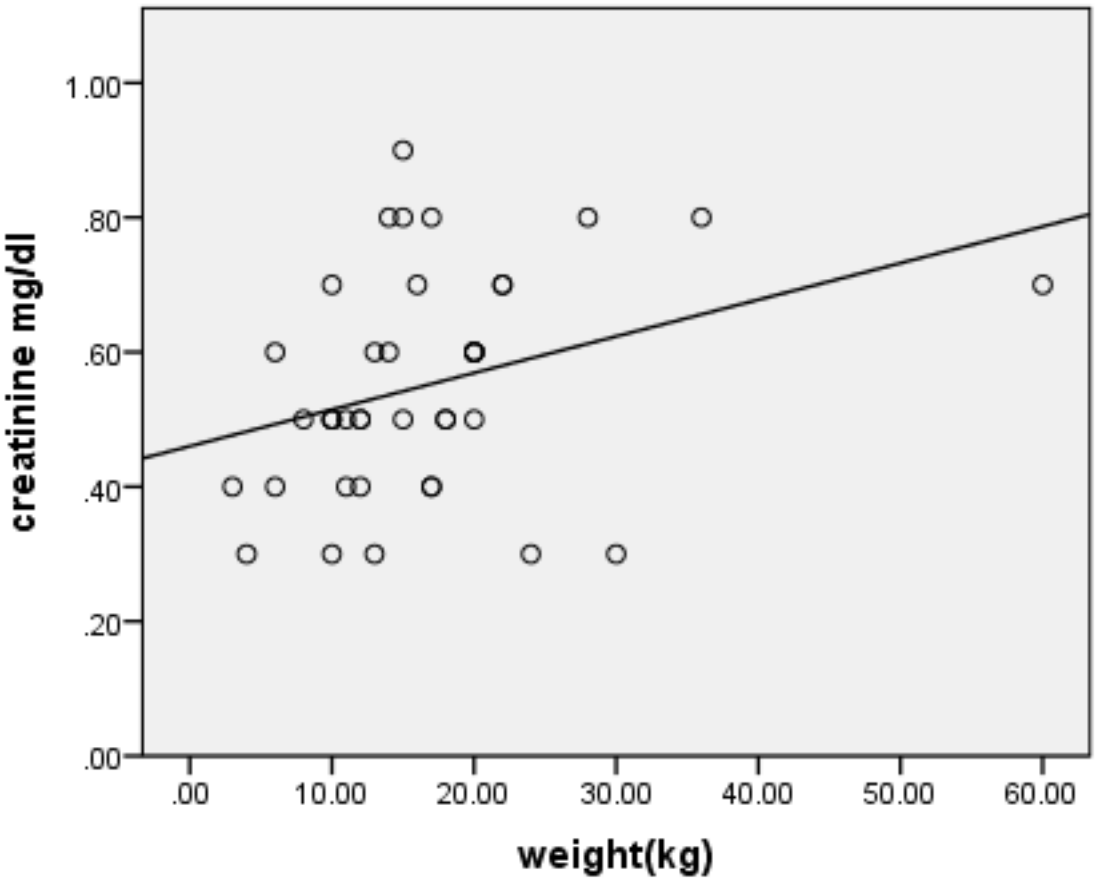

Figure (4.6): A scatter plot show significant positive correlation between creatinine and body weight in cases group. r= (0.40*), p- value (0.04).

5. Discussion, Conclusion and Recommendations

5.1 Discussion

Nearly one third of patients with epilepsy need life-long treatment with one or more antiepileptic drugs (AEDs) (Hamed., 2017). Valproate and carbamazepine are effective and widely used antiepileptic drugs for the treatment of many types of epilepsy in children (Havali et al., 2014). In this study, 40 child using antiepileptic drugs and 40 healthy children were enrolled to asses plasma urea and creatinine levels.

Study showed a significant increase in means of both plasma urea and creatinine levels in case group when compared to control groups p- value 0.00, This result ties well with previous studies whom found increase in the levels of plasma urea and creatinine in children treated with valproate and carbamazepine (Unay et al .,2006).

According to types of treatment there was increase of plasma urea in patients received valproate when compared with those taken carbamazepine, the result indicated valproate may affect kidney function more than carbamazepine this result agree with previous study Valproate had adverse effect of kidney more than carbamazepine (havali et al., 2014), also this was consistent with what has been found in previous study the mean value of urea was numerically higher in patient take valproate (janjuna et al., 1994).also show increase of plasma creatinine in patient received carbamazepine when compared with those taken valproate, this result agree with (Cagnon., et al 2007) shows valproate treatment cause elevations of urinary creatine and guanidinoacetate which corroborating disturbed creatine metabolism.

Also study showed that no correlation between plasma urea and duration of carbamazepine or valproate treatment, this may be urea levels affect by duration of treatment and drug dosage.

Significant positive correlation between plasma Creatinine Level and duration of valproate or carbamazepine treatment similar pattern of results was obtained in (Hamed et al., 2018) showing that significant higher concentration of serum creatinine in patient received VPA or CBZ.

5.2 Conclusion

Sudanese children with epilepsy used antiepileptic drugs (VPA, CBZ) treatment**,** had higher increase in plasma urea and creatinine levels, and creatinine level positively correlate with duration of treatment.

5.3 Recommendations

- Monitoring the effect of antiepileptic drugs on kidney functions for epileptic patient by measurement of electrolyte, urine protein excretion and creatinine clearance.
- Assessment of renal tubular function by 24hour urine protein excretion, and assessment of Fanconi's syndrome by detection of urinary low molecular weight protein, glucose and uric acid.
- Further study with another study design cohort study.

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