Aishwari S Kumar et al /J. Pharm. Sci. & Res. Vol. 9(3), 2017, 302-306

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Early Detection of Seizures in Epilepsy Using Point of Care (POC) Systems

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Abstract

In epileptic patients recurrence of seizure is a concern and its prognosis is important. Getting seizure freedom is necessary for the patients to maintain a normal risk free life. Even though, the pharmacological treatment provides 60-70% reduction in seizures over prolonged treatment, the concerns of recurrence remains. In this review we are analysing the common psychological and physiological complications associated with epilepsy. Also analysing the use of point of care (POC) systems for seizure prognosis. In addition, the future possibilities for developing indigenous affordable and accessible technologies for seizure prognosis are analysed.

INTRODUCTION

As per a recent survey on campaign program against epilepsy by WHO, globally, 50million people around the world are affected by epilepsy. [1] It sums up to 1% of global burden of disease (BOD), in that 80% is in developing world, and in some regions patients have no access for treatment (80-90%). [1, 2] Epileptic shock happens due to fast submission and receiving of nerve impulses in the brain, that causes seizures and unconsciousness. The epileptic seizures are generally violent and uncontrolled depending upon the stage of the disease. [3, 4] To the patients, the aberrant onset of seizure cause secondary distress, mood shifts, depression, lethal accidents to even death. The recurrence of seizure and related events creates fear and depression in patients. Depression has negative socio-economic implications. It affects large number of people worldwide without much discrimination for age, sex, or race and can cause sudden unexpected death. [5] Even though, the pharmacological treatment provides 60-70% reduction in seizures [6] over prolonged treatment, the concerns of seizure recurrence remain. The point of care (POC) systems are aimed for early management of events to reduce consequences, such as fire alarm and glucose test kits. POCs are generally used with minimum assistance. If the onset of a seizure can be detected (prognosis), or pre-treated early enough using point of care (POC) systems that can reduce the fear and depression as well as help in better management of epilepsy.

I. COMMON COMPLICATIONS ASSOCIATED WITH RECURRENT EPILEPTIC SIEZURES

SUDDEN UNEXPECTED DEATH IN EPILEPTIC PATIENTS (SUDEP)

Rarely it is found that people die out of seizure, but it is reported. Sudden Unexpected Death in Epileptic Patients (SUDEP) is the most common cause of lethality related to epilepsy. Stopping of medication prescribed is one of the risk factor for SUDEP. [5, 7] Recent reports have accounted for 1.16 cases out of 1,000 people for SUDEP in people with epilepsy. [8, 9] For an uncontrolled seizure during SUDEP the risk of death are even more at 1 in 150, the characteristics are occurrence of seizure and die in bed lying face down. [10, 11] There is no correct evidence of cause of death in SUDEP. Recent study publishes that the person affected may suffocate from impaired breathing and fluid in the lungs. [2]

MOOD SHIFTS

The mood shifts or mood disorders experienced by epileptic patients is now known for more than 2,000 years. However, the relation between the mood swing and epilepsy is not understood until recent. [12, 13] The mood disorders may be exhibited most of the time, or appear just before, during, or after a seizure and it affects their sleep, appetite, and sexual desires. These mood shifts are individual dependent; some show prolonged mood shifts, while others show irritancy. [12] The most commonly exhibited mood shift is anxiety. It generally affects all age, can happen in childhood; where it is equal in both boys and girls. In adolescents and older individual, anxiety can lead to depression and is more frequent in women, due to hormonal changes. [14] To go in detail, anxiety is sometimes denoted to be a different group of common illness and the patients generally respond to treatment.

DEPRESSION

Depression is a commonly found co-morbidity of epilepsy, with typical behavioural manifestations. [15] Upto 30% of epileptic patients suffers from depression. [16] One-third of epileptic patient have shown involvement of various areas of brain in the pathogenesis of depression. [17] Depression is mood disorder with clinically relevant symptoms for at least two weeks with differential changes in physical, mental and social behaviour. Depression does not allow one to think positive and lead a simple, enjoyable, and happy life. It affects the individual himself along with the people attached to. Patients suffer from depression share common features as anhedonia, loss of concentration, fatigue, retardation, gain or loss of weight and recurrent ideas of death. [18] Given the common complications associated with epilepsy the differential regulation of complications associated with seizures are analysed; such as neuronal regulation, brain involvement, body involvement and gender differences.

II. The Differential Regulation Of Epileptic Siezures And Complications

NEURONAL FUNCTIONS ON EPILEPSY

Nervous system works by molecular events depending upon the action potential. The excitability of neurons happens due to action potential. The action potential induces release of neurotransmitter on the axon terminal as a result of neuronal membrane depolarization. [19] This excitability can be occurred inside the neurons (intrinsic) or in the extracellular space (extrinsic). The incoming of seizure is mainly due to two reasons (1) A sudden burst of action potential causing high frequency neurotransmitter release or due to (2) Disordered synchronization of neurons. [20] Given the neuronal functions associated with epilepsy, organ level functions are set to analyse. .

BRAIN FUNCTIONS ON EPILEPSY

At organ level, in the brain, parasympathetic tone is modulated by left hemisphere, whereas, the sympathetic tone is modulated by the right hemisphere. Sympathetic nerve response is more predominant during epilepsy, which alters functions of various systems and can cause tachycardia, tachypnea, and increase in blood pressure. [21] The effect on effector organs such as heart and other glandular organs depends on the site of epileptic foci and that cannot be generalised. [22] In adults mainly temporal lobe epilepsy occurs, which results in vomiting, urinary urge and so on.

BODY RELATED REGULATION OF EPILEPSY

The exact factor for the cause of epileptic seizure is not well understood; in particular, multiple systems in the body are involving in its onset. [23] Medication error, illness or lack of sleep, drugs as cocaine and alcohol consumption also pave the way for epileptic seizures. The eating habits, dehydration, nutritional deficiency as well influence the onset. For women, hormonal changes along with abnormal menstrual cycle enhance the upcoming seizures. [24] From these discussions, it is apparent that, the recurrence of seizure is grossly regulated by the body. The body is influenced by mental, physical and social events. Thus, an overall control in the involvement of physical, mental and social events can produce control over recurrence of seizures.

GENDER VARIATIONS IN RECOURRENCE OF SIEZURES

According to a recent study males are more prone to epilepsy than female; 49 out of 1,00,000 males as compared to 41 out of 1,00,000 female are involved. [25] There are many predisposing factors for increasing recurrence of seizure in males such as alcohol consumption, poor nutritional availability and so on. Since men are more prone to such circumstances than females the incidents are high. [26]

WOMEN FACES ADDITIONAL CHALLENGES DUE TO EPILEPTIC SIEZURES

Women with pregnancy face additional challenge in child bearing years. [27] During pregnancy increased chances of medication non-adherence is reported. [22] This is because of the concerns of antiepileptic drugs crossing the placenta and affecting the baby. [22] The decreased intake of drug leads to increased chances of seizures during carrying, [22] Physiological changes in mother during pregnancy alter seizure threshold and pharmacokinetics due to variations in gastric motility, increased hormone release and increased volume of distribution. [22] The metabolism of the foetus is also inadequate to metabolize the drug passing through the placenta. [28]

The volume of distribution (V_D) is also a factor governing the chances of fetal malformation during pregnancy. Increased V_D enhances the crossing of drugs to maternal milk. [29, 30] Protein binding of the drug influences the drug migration to breast milk. The concentration of Anti-epileptic drugs (highly protein bound) is low in breast milk but for the antiepileptic drugs with no protein – bound are in equal concentration in serum as well as in milk. [31] Breast feeding is very important for both maternal and the child. [32] Mother-baby bonding is established through the milk feeding (as believed in Indian culture), which also helps the baby to fight against invading microbes. [33, 34] The treatment associated complications cause concerns for the mother of losing bonding with child that is leading to mood shifts and depression.

On the other hand, adherence to medication leads to increased risks of congenital malformations (cleft lip) particularly with valproate (4-6%). Valproate in first 28 days causes defects in neuronal tube and lack of spinal tube closure. It also causes children with low IQ and autism. [35] Analysing the complications associated with seizures the available point of care systems (POCs) for the prognosis of seizure is set to analyse.

III. Point Of Care Systems To Address The Complications Associated With Recurrent Siezures In Epilepsy

Point of care systems (POC)s are technologies used for the early detection, diagnosis or treatment of a disease condition to get desired beneficial effect. The POCs are generally light, portable kits that can be carried by the patient and for self-use. [36] Examples for such systems are blood pressure (BP) apparatus, thermometer and glucose testing kit for diabetes. Epileptic seizure occurs suddenly without any symptoms. If a POC is available, for early diagnosis of the forthcoming seizure that can help the patient to take necessary precautions. People with epilepsy are much prone to accidental injuries than the normal population, thus, necessary precautions to avoid such secondary injuries can be put up. By which the patients get the mental confidence to freely move around, that improves overall mental status. [37] Researchers have introduced several devices that help in prognosis and treatment of seizure, some of them are:-

EPIWATCH

The Epiwatch helps to collect the data of seizure before, after and during occurrence.[38] This application designed by John Hopkins University, can be used in Apple watches and in smart phone. [38] It also has the options for studying the physiological changes, altered responses and also behaviour pattern during and before seizures. This device help to keep a track on what is happening to the patient during an occurrence of seizures (aura). [2, 3] Using the

system, multiple indications during seizure is simultaneously recorded has a detector and an app for collection of data and interpretation [2, 3]. This system has provided relief and care about 2.5m people residing in United States. This detector app also accesses to accelerometer (detects the movement) and gyroscope (determines the orientation in spaces). [39]

WEMU SMART CLOTHING SYSTEM

WEMU smart clothing system provides prognosis from siezure and protection while providing freedom to move. [40] This clothing is comfortable and highly accepted for indoor and outdoor purposes. This clothing is connected to the Smartphone app that allows the doctor to investigate the details of data recorded. [41] This kind of smart systems may help people to avoid long queues and take appointment in hospitals.

INVASIVE AND NON-INVASIVE VAGUS NERVE STIMULATOR

Vagus nerve stimulation (VNS) helps to prevent seizures. [42-46] The Vagus Nerve Stimulation (VNS) device supplies small electrical pulse to the brain via the vagus nerve. [47] The vagus nerve is the, X^{th} cranial nerve covers the neck and travels between the chest and abdomen and also the lower part of body. This is the longest cranial nerve that controls the involuntary actions of heart rate and many other involuntary functions. This is sometimes referred to as the "pacemaker for the brain". The gammaCore a non-invasive VNS device is a handheld device produces an electrical signal that non-invasively stimulates the cervical branch of vagus nerve. A conductive gel is applied on the surface of device which is coming in contact with the stimulation site on neck and electrical pulse is given in one or two doses. [48] The implantable devices are placed subcutaneously on the upper part of the chest under skin during general anaesthesia. [49] This is an implantable device placed on left side of the chest under skin. [50]

ELECTROENCEPHALOGRAM (EEG)

Electroencephalogram (EEG) is helpful as it is capable of sending warning to both patients and the observers during and before the shock. EEG is a painless test that records the electrical activity of the brain. [51] The electrode captures these continuous electrical signals and displayed as a graph. There are many types of EEG with varying ease of application. In standard EEG, the graphs are collected while the patient is sitting or lying down. This is generally done to outpatients at the hospital. In sleep EEG tests; the sketching is done while the patients are asleep or drowsy. [48] The standard EEG tests are collected when the patient is awake but this may not produce any sort of unusual variations in EEG print thus less informative about the recurrence of seizure, whereas the sleep EEG shows unusual electrical activity reflecting upcoming seizure activity. [48] In sleep deprived EEG, the EEG is collected in sleep deprived condition, as it provides random changes in brain electrical activity. This test is non-compliant to many patients. [52] To improve the EEG accessibility during movement, ambulatory EEG tests are done. [53]This is highly successful for improving the health care to the rural side. This procedure may take few hours, days or even weeks, ensures better chances of picking up the electrical activity of the brain during movement. [54] As the body is engaged in any means of work, whether it be walking, moping or any job that really sets the brain to work passively and relevant signals can be recorded. [53, 54] Ambulatory EEG reduces hospitalisation. A diary of the patient's activity such as eating, sleeping, so on is maintained during the period. This information is matched with the test results for finding reasons for seizure reoccurrence. [48] Video-EEG [55] helps to collect the EEG as well as the video and audio of the patient at the same time. This helps the doctors to distinguish the type of the EEG, for surgical intervention. This test requires hospitalization.

The analysis of the POCs indicates that, it is focusing only on the seizure prognosis, not assisting the patients in comorbidity management. Further, other safety concerns associated with comorbidity management is analysed.

IV. PRECAUTIONS TO BE TAKEN FOR EPILEPTIC PATIENTS

There are several safety measures for the patient affected with epilepsy to take care in every circumstances and places. Some of such safety measures are discussed below.

WATER SAFETY

Generally, epileptic patients during swimming need to take care of drowning due to seizure and unconsciousness. [56] Unexpected seizure reoccurrence causes concerns for patients interested in swimming. The patient should never be alone. In case of bathing, showers are recommended instead of bathing in tub or river side. As seizure is an abnormal account of signal transmission the patient may tend to fall into water. Thus a flexible shower hose is recommended.

FIRE SAFETY

As per reports, there are seizure free period between 3 to 12 months. But in case of uncontrolled seizures, the person should be very careful with heat and flames. [50] Use of microwaves is recommended as the exposure to heat may cause suffocation and dehydration to patients that can lead to seizure reoccurrence.

ENVIRONMENT SAFETY

It is necessary to keep the house, study area or work area to be free from harmful substances. For example, it is necessary to remove the edgy items around the house so that the patient doesn't hit themselves on it and get injured during seizure. If the patient closes the door of the room/house make sure that the neighbour has a key to help out in emergency. [11] Carpets protect the patient from hitting directly onto floor leading to head injuries. Sharp edges should be covered and glass tables should be avoided so as to prevent unexpected injury. [50]

Given the siezure associated complications, POCs and required safety aspects for co-morbidity management; the future course of POC design is analysed further.

V. FUTURE DIRECTIONS

More than 40yrs researchers thought that seizures onset is abrupt just before clinical attack. However, studies of long digital cranial EEG readings shown that seizures begin even minutes to hours before. [7] A recent survey on seizure prediction methods has shown that there is a high

patient interest for developing such methods. [57] The expectations are (1) short prediction time windows and (2) indications on seizure prone periods. [57] If a portable system that can indicate the epileptic attack earlier enough, and which is affordable and works based on non-invasive simple principles is developed; that will be beneficial for both the patients and epileptic clinics. Such technologies need to be developed keeping larger spectrum of the society including economically backward in mind. [2] As per Indian scenario affordability of currently available sophisticated devices seems to be inaccessible. One significant observation regarding seizure related symptoms is that there is extensive autonomic stimulation during seizure leading to extensive salivary secretion as well as variations in blood pressure. If these glandular, cardiovascular variations [58], cerebral blood flow monitoring [59] can be correlated to neuronal activity a simple algorithm could be devised for the early detection of seizure in epileptic patients. [2, 3] A recent study has shown that, patient specific automatic seizure detection out performed generic setup. [60] Many reports have notified about anxiety, mood swings and depression in patients. These multiple factors can be correlated and developed as a decision tree to identify a possible epileptic attack. Future research direction by combining the physiological and psychological factors can lead to newer technologies that are affordable and accessible. Basically, prognosis and protection need to be combined in future technologies for increasing its reachabilty to the rural countryside.

ACKNOWLEDGEMENT

Dr. Kaladhar wanted to thank Dr. Sabitha M, Principal, Amrita School of Pharmacy, Amrita University, Prof. Shanti V. Nair, Dean, Amrita University and Prof. Chandra P Sharma (Formerly Head, BST Division, BMT Wing and acting Head BMT Wing, SCTIMST) for the kind support.

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