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Gabapentin as monotherapy for post stroke epilepsy

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Abstract
Background: Stroke is one of the most devastating neurological disease with dire complications. One of the complications of stroke is post stroke epilepsy. The mortality of post stroke epilepsy is higher (3, 4 % - 4%) compared to other complications of stroke. The Preffered treatment for post stroke epilepsy is monotherapy, which is effective in 88% of the case. Although effective, the current established treatment for post stroke epilepsy such as carbamazepine or lamotigrine shows higher side effects.
Discussion: Gabapentin is one of the approved drugs for epilepsy. Although the mechanism of action is unknown, gabapentin is effective in treating epilepsy with patients receiving 900 mg/day dose and 1,800 mg/day dose stayed longer in the study compared to placebo. Gabapentin also shows lower side effect compared to establish treatment such as carbamazepine with gabapentin treated patient showed 60% adverse events and carbamazepine 84% adverse events.
Conclusion: Gabapentin could be the potential drug for post stroke epilepsy which is safe, effective, and has lower side effects.

Keywords: gabapentin, monotherapy, post stroke epilepsy, post stroke seizure, stroke

Introduction

Stroke is a devastating neurological disease. Generally, stroke is classified into two types. The first type is ischemic stroke, consists of 85% of stroke. And the second type is hemorhagic stroke, consist of 15% of all stroke. However this disease could not be seen as black and white because this stroke is a syndrome with dire complications. The etiology of ischemic stroke consists of many causes such as cardioembolic, arteroembolic, lacunar, and other causes that varies between populations. The severity and clinical manifestatsions of troke could varies from patient to patient. The severity ranges from mild to evere stroke, with possible similar underlying cause (Tupuwa.D. *et al.*, 2015) [7].

Epidemiology of Stroke

Stroke is one of the major cause in disability. Worldwide, there are more than 20 million people who sufferr from stroke and more than 6, millions death happened because of stroke. Majority of this morbidity come from third wold countries which consists of 75.2 of all stroke related death. In Asia where there are many developed countries, stroke is a major health problem. The mortality is higher compared to other continents such as Europe and America, except in ome countries like Japan. The lowest incidens rate rate of stroke was found in Malaysia (67/100.000 person-years) (Venketasubramanian *et al.*, 2017) [8].

Post Stroke Epilepsy Definition

Post stroke epilepsy or sometimes also known as post stroke seizure is a post stroke complication characterized by epilepsy or seizures. The difference is that a post stroke seizure is a single or recurrent seizure that is associated with a state of reversible or irreversible damage due to a stroke that occurs in the early stages of a stroke. Meanwhile, post stroke epilepsy is defined as a confirmed diagnosis of epilepsy that occurs after a stroke event. The diagnosis of epilepsy can decrease the quality of life as well as increase the mortality of the patient. In patients suffering from post-stroke epilepsy, it was found that the mortality rate was higher, around 3.4% - 4% compared to other stroke complications (Myint, Staufenberg and Sabanathan, 2006) [4]. Another literature by (Jungehulsing *et al.*, 2013) [3]. Defines a patient with post-stroke epilepsy if a patient suffers from one post-stroke seizure, 2 years after the stroke.

Ischemia can cause irreversible damage to the brain and can cause disruption of electrical activity in the brain. According to (Sarecka-Hujar and Kopyta, 2019) [6] post stroke seizures can be divided into early post stroke seizures and late post stroke seizures. Early post stroke seizures are defined as seizures that occur from the time of stroke to seven days after the attack, whereas late post stroke seizures are seizures that occur from seven days to the second day after the stroke. Meanwhile, epilepsy is defined as the occurrence of two seizures without provocation which have a ≥60% probability of the occurrence of further seizures for the next 10 years (Sarecka-Hujar and Kopyta, 2019) [6]

Epidemiology of Post Stroke Epilepsy

It was found that 11.5% of patients who had a stroke had a risk of suffering complications in the form of seizures both early onset and late onset. According to a study that followed stroke patients 5 years after the attack, it was found that 5% - 20% of patients will have seizures at a later date, but only a proportion of patients will have epilepsy characterized by recurrent seizures without provocation. (Myint, Staufenberg and Sabanathan, 2006) [4].

The prevalence of post-stroke epilepsy in adults suffering from stroke is found to be around 2% to 4%. In various studies in different countries, this figure is the closest to the prevalence of these findings. France found that 6.9% of patients who had suffered a stroke had a late post stroke seizure. Meanwhile, Finland recorded the figures of 3.5% and 4.2%. Meanwhile, in Rajasthan, there was an early post stroke seizure rate of 54% and a late post stroke seizure of 46%. As for post stroke epilepsy, in Germany it was 8.2% prevalence, while the prevalence of post stroke epilepsy in Taiwan was 1.6% (Sarecka-Hujar and Kopyta, 2019) [6]

Whereas data in the UK shows that the prevalence of early post stroke seizures is 2.2% - 33% while late post stroke seizures are 3% to 67% with a fairly repetitive pattern, namely seizures generally occur 24 hours after a stroke, and a second seizure occurs. about six to twelve months after a stroke (Xu, 2019) [9]

Risk Factors

The risk factors for post stroke epilepsy and post stroke seizure depend on various factors. In adults, common risk factors are type of stroke, size of infarction, location of stroke, and severity of ischemia (Jungehulsing *et al.*, 2013) [3]. Found that hypertension and stroke severity can be predictors of post-stroke epilepsy. However, in this literature there was no finding between metabolic factors and the incidence of seizures.

Meanwhile, according to (Roivainen *et al.*, 2013) [5]smoking, drinking alcohol and the incidence of infection before stroke is more often found in patients who have late post stroke seizures when compared to early post stroke seizures.

Another factor that can increase the risk of post stroke seizures is the volume of the infarction, the greater the volume of an infarct, the more susceptible a person is to suffer from seizures. While the most important risk factor is cortical involvement, cortical involvement is often associated with late post stroke seizures (Sarecka-Hujar and Kopyta, 2019) [6].

According to a study conducted (Jungehulsing *et al.*, 2013) [3] there are several risk factors that can be identified from post-stroke epilepsy. For the age group, it was found that the age group 65-74 years suffered the most from post stroke epilepsy with 29%. Women were also found to be more vulnerable than men. As for the type of stroke, which contributed the greatest number was cerebral infarction (82%) followed by intracerebral hemorrhage with (13%) and subarachnoic bleeding (4.8%). For comorbid factors, the most common cause of post stroke epilepsy was artrial hypertension (79.8%) then diabetes mellitus (28.1%). To predict the risk of post-stroke epilepsy there is a scale that can be used. The bigger the score, the more susceptible a patient is to suffer from post-stroke epilepsy.

Table 1: *Post Stroke Epilepsy Risk Scale* (Xu, 2019).

Variable	Score
Supratentorial stroke	2
Intraserebral bleeding in cortical area	2
Ischemia with neurological deficit	1
Ischemia affecting cortical area or subcortical area	1
Seizure under 14 days after the incident of stroke	1
Seizure after 15 days after the incident of stroke	2

Patophysiology

There are several causes for early onset seizures after ischemic stroke. Increased intracellular calcium and sodium ions lead to a decrease in the threshold for depolariasiation, glutamate excitotoxicity, hypoxia, metabolic dysfunction, global hypoperfusion, and hypoperfusion trauma, which have been widely suggested to be neurofunctional etiologies. Seizures after a bleeding stroke result from irritation caused by the products of blood metabolism. It is suspected that the ischemic area caused by bleeding plays an important role in this process. Meanwhile, late onset seizures are often associated with changes in neuronal excitability and glyotic scarring. In addition, hemosiderin is also associated with bleeding strokes (Myint, Staufenberg and Sabanathan, 2006) [4].

In the early onset of the seizure beside the increased intracellular calcium and sodium that cause depolrarisation of transmembrane potential and resulted in decrease of seizures threshold, there is also excitotoxicity in acute ischemia. This start with the increase concentration of glutamate. Glutamate is a neurotransmitter which has exicitatory properties. The incease of this neurotransmitter is associated with secondary neurolar injury. The focus of seizure activity that were found in some animal studies is called the “ischaemic penumbra”. This area is a viable tissues that are close to the focus of the infract and this area contains of electrically irritable tissue (Boovalingam *et al.*, 2012) [1]. According to the International League against Epilepsy classification post stroke seizures can present as focal seizures with or without loss of consciousness, with or without motor disturbances, or may present as bilateral tonic-clonic seizures. Several types of post stroke seizures also present as mild clinical symptoms such as eye deviation, nystagmus, facial twitching, motoric deficits, speech disturbances and fluctuating improvement in stroke conditions. Meanwhile, for some patients, there are sometimes no motor or senosrik symptoms at all, only impaired consciousness and behavior. For patients like this, it can only be detected by electroencephalogram (EEG). The diagnosis of post stroke seizure or post stroke epilepsy can be confirmed from the clinical symptoms with the classification described above. However, if clinical symptoms are atypical, electroencephalogram can be done to make the diagnosis. EEG examination is intended for those with clinical symptoms that are not clear enough (Xu, 2019) [9].

Current Treatment Perspectives

The therapy of post stroke seizures is divided into two categories, prophylactic and symptomatic prevention. In general, experts through the American Heart Association and the European Stroke Organization say that porphylaxis therapy uses anti-epileptic drugs (OAE) to prevent seizures in stroke patients. There is insufficient evidence to support administration of OAE as prophylaxis. Besides that, OAE can also cause various side effects that cannot be ignored. Routine use of OAE can lead to poor outcomes for stroke patients. However, this can be avoided by using the new generation of OAE (Xu, 2019) [9]

As for sympathetic therapy, it can be given if the post stroke seizure diagnosis is upright. There is a general opinion among experts that when the second seizure occurs without provocation, OAE should be given immediately because the risk of second seizure is very high, around 57% for the first 1 year and 73% in the second 4 years. So in general, post stroke epilepsy should be

treated with OAE. Meanwhile, for post stroke seizures, OAE is not routinely administered, because patients who had seizures without provocation only once, most rarely experienced a second seizure (60%). So that OAE therapy is only intended for recurrent seizures, and should be postponed if the seizures have not recurred (Xu, 2019) [9].

Discussion

Literature that compares antiepileptic drugs for stroke patients are in short amount. The accepted view is to treat post stroke epilepsy with monotherapy anti-epileptic drug. This course of treatment are proven effective in controllong seizures in 88 percent of the patients. The most common drug used for post stroke epilepsy is carbamazepine. Lamotrigine is also another drug of choice and is better tolerated in elderly patient because it prevents seizure in longer duration. Benzodiazepine is the preffered treatment for ongoing seizures (Boovalingam *et al.*, 2012) [1].

Management of post stroke epilepsy by prescribing Anti-Epileptic Drugs (AEDs) should follow the usual standard similar principlis when treating patient with epilepsy. Monotherapy is the preferred course, but when it fails, it is recommended to redo the workup and considering other diagnosis. When this happens, the second line AED should be prescribed. The changes of doses and medication should be done in careful way condisering the withdrawal period. The last principle states that combination therapy could be prescribed to some patients only when it is necessary, but side effects and drug interactions must be monitored. (Boovalingam *et al.*, 2012) [1].

Gabapentin is one of the AEDs that was approved to be prescribed for epilepsy. Gabapentin works through a neurotransmitter called gammaaminobutyric acid or GABA. The exact mechanism is still mostly unkown, but from *in vivo* and human studies it's found that this drug is not metabolise into GABA or GABA against, and also does not inhibit GABA reuptake or degredation. Gabapentin have high affinity to the α2δ sub unit of voltage-activated calcium channels in *in vitro* studies (Ziganshina, Gamirova and Abakumova, 2017) [10].

The International League against Epilepsy only recommends gabapentin as monotherapy for newly diagnosed, fofcal seizures in adults and in elderly. For children this drug is only recommended for focal epilepsy in children. The American Academy of Neurology alaso recommends gabapentin as adjuvant therapy for epilepsy. The Russian Government also recommends this drug as monotherapy for partial seizures with or without secondary generalisation in adults and adolescents aged 12 years and above (Ziganshina, Gamirova and Abakumova, 2017) [10].

In a double blind randomized trial, gabapeentin in the dosis of 900 and 1,800 mg/day is proven safe, effective, and well tolerated with minimal side effects as monotherapy for epilepsy. Compared to patients that that receive 300 mg/day (placebo dose), patients with doses of 900 mg/day and 1,800 mg/day stayed in the study longer, thus prove the efficacy of gabapentin as monotherapy. Adverse events in gabapentin were also lower compared to the established treatment of crbamazepine. In carbamazepine treated patients, they report 84 percent of adverse events compared to 60 percent who received gabapentin as monotherapy. (Chadwick *et al.*, 1998) [2].

Conclusion

Gabapentin is not the established treatment of epilepsy and post stroke epilepsy. Although the mechanism is unknown, gabapentin shows good efficacy and lower adverse events as monotherapy compared to other established drugs such as carbamazepine. More research is definitely needed, but available data shows that gabapentin could be the potential of being the next monotherapy drugs for post stroke epilepsy.

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