APISIO Medika : Jurnal Mahasiswa Kedokteran Universitas Muhammadiyah Malang
Vol. 2, No. 1, February 2024, pp. 13-19

Description of the Use of Antiseizure Medication and Controlled Seizures in Epilepsy Patients at Dr. Soepraoen Army Hospital

Annisa Nurul Arofah[1], Suharto[2], Sekar Asih[3]
[1]Neurology Department Medical Faculty University of Muhammadiyah Malang, East Java, Indonesia
[2]Radiology Department Medical Faculty University of Muhammadiyah Malang, East Java, Indonesia
[3]Medical Faculty University of Muhammadiyah Malang, East Java,Indonesia

Article Info

Article history:

Received August 18, 2024
Revised October 11, 2024
Accepted Jan 21, 2024

Keywords:

Epilepsy
Antiseizure Medication
Controlled Seizure

DOI:
10.22219/apisio.Vol2.AM1.27529.

ABSTRACT

Background: 30% of epilepsy patients had uncontrolled seizures. Antiseizure medication (ASM) is the first-line therapy for seizure control. ASM begins with monotherapy. If it cannot be controlled with monotherapy, polytherapy can be given. **Objective:** To determine the description of the use of ASM and controlled seizures in epilepsy patients at Dr. Soepraoen Hospital in January-December 2019. **Methods:** This research is a descriptive study using medical records of epilepsy patients who received ASM therapy from January-December 2019 who had been receiving routine treatment for the past 1 year. Data analysis using univariate analysis. **Results**: 41 respondents had taken routine treatment for 1 year. The most age of epilepsy patients was 15-34 years (39%). Most were male (68.3%). The onset of seizures was ≥20 years (51.2%). 46.3% used monotherapy, 39% used 2 types of ASM, and 14.6% used ≥3 types of ASM. 65.9% of patients on ASM treatment had seizures controlled. Valproic acid is the most widely used ASM and controls seizures the most. **Conclusion**: Most of the characteristics of epilepsy patients at Dr.Soepraoen Hospital are aged 15-34 years, age of onset of seizures ≥20 years, male sex, monotherapy, and valproic acid. Valproic acid is the most common ASM with controlled seizures.

Corresponding Author:

Annisa Nurul Arofah
Neurology Department Medical Faculty University of Muhammadiyah Malang
Jl. Bendungan Sutami No 188A, Malang, East Java Indonesia

ORCID : https://orcid.org/0000-0003-4250-9609

Email: arofah@umm.ac.id

1. INTRODUCTION

According to The International League Against Epilepsy (ILAE), epilepsy is characterized by at least two unprovoked seizures or reflex arousals that occur for more than 24 hours [1]. Epilepsy occurs due to excessive or abnormal synchronous neuronal activity in the brain. Epilepsy classification is based on seizure type, etiology, and epilepsy syndrome. Types of seizures were made based on seizure semiology and electroencephalography (EEG) images, divided into focal epilepsy and generalized epilepsy. Epileptic seizures can cause emotional, behavioral, and neurological disturbances in patients [2].

Until 2016, around 50 million people worldwide suffer from epilepsy; most come from developing countries. As many as 30% of epilepsy patients have uncontrolled seizures. Low seizure control in developing countries occurs due to the unavailability of antiseizure medication (ASM), the high cost of ASM, and poor adherence to ASM [3]. Older-generation ASMs are frequently used in developing countries because of their availability, lower cost, and good efficacy [4].

ASM is the main therapy for epilepsy [5]. The purpose of giving ASM is to control epileptic seizures [6]. A change in drug type may be necessary because of the initial treatment's lack of efficacy or tolerability [7]. ASM is started with a low dose and then gradually increased to a maintenance dose until optimal effect. Replacement with a second ASM can be given if the first ASM is not effective in controlling seizures. If the second ASM is still not effective in controlling seizures, then a combination of ASM can be given [8]. Sociodemographic, clinical, behavioral, and treatment-related factors play a major role in the outcome of epilepsy treatment [4].

Based on research, found that 86.8% of epilepsy patients could control their seizures for a duration of more than 1 year with monotherapy treatment. 50.5% of seizure control patients with the first ASM given. Each addition of the second and third drug polypharmacy, each addition of the drug will further reduce the percentage of controlled seizures [9].

Based on the background described above, researchers are interested in examining the description of the use of ASM and the control of seizures in people with epilepsy. This research was conducted on all patients with epilepsy who were recorded in the medical records at Dr. Soepraoen Army Hospital in January - December 2019.

2. METHOD

This research is a descriptive study using medical records of epilepsy patients. This research was conducted at Dr. Soepraoen Army Hospital. The sampling technique in this study was total sampling. The inclusion criteria in this study were patients who were diagnosed with epilepsy and had epilepsy treatment for at least one year regularly at Dr. Soepraoen Army Hospital in 2019. Exclusion criteria in this study were patients with unknown types of seizures and patients who were not compliant with epilepsy treatment. Patient data analysis was carried out to determine the characteristics and features of age, sex, age of onset of epilepsy, type of ASM, number of ASM, and control seizures. Data analysis using univariate analysis.

3. RESULTS AND DISCUSSION

A total of 41 epilepsy patients were included in this study and analyzed. The majority of patients were male, 28 people (68.3%), and the most ages were 15-34 years, 16 people (39%). More than half of patients had an age of onset ≥20 years as many as 21 people (51.2%). Most of the patients used monotherapy, 19 people (46.3%) and the most widely used ASM was valproic acid, 12 people (29.3%). The majority of patients, as many as 27 people (65.9%) with controlled seizures (Table 1).

Table 1. Characteristics of the research sample

Variable		Frequency (n)	Percentage (%)
Age			
	0-14 years	8	19,5
	15-34 years	16	39,0
	35-64 years	15	36,6
	≥ 65 years	2	4,9
Sex			
	Male	28	68,3
	Female	13	31,7
Age of Onset			
	<20 years	20	48,8
	≥ 20 years	21	51,2
Number of ASM			
	1	19	46,3
	2	16	39,0
	3	6	14,6
Type of ASM			
	Valproic Acid	12	29,3
	Phenytoin	5	12,2
	Carbamazepine	2	4,9
	Valproic Acid + Phenytoin	2	4,9
	Valproic Acid + Carbamazepine	1	2,4

	Valproic Acid + Clobazam	3	7,3
	Valproic Acid + Gabapentin	2	4,9
	Phenytoin + Clobazam	3	7,3
	Phenytoin + Gabapentin	1	2,4
	Phenytoin + Carbamazepine	2	4,9
	Carbamazepine + Clobazam	2	4,9
	Valproic Acid + Phenytoin + Clobazam	5	12,2
	Valproic Acid + Phenytoin + Gabapentin	1	2,4
Controlled Seizure			
	Controlled	27	65,9
	Uncontrolled	14	34,1

Table 2 An overview of the number of ASM and controlled seizures

No.	Number of ASM	Controlled Seizure		Uncontrolled Seizure		Comparison of Controlled and Uncontrolled (%)
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)	
1.	1	17	62,9	2	14,3	89,5
2.	2	8	29,6	8	57,1	50
3.	3	2	7,4	4	28,6	33,3
	Total	27	100,0	14	100,0	

Table 3 An overview of the type of ASM and controlled seizures

No.	Jenis ASM	Controlled Seizure		Uncontrolled Seizure	
		Frequency (n)	Percentage (%)	Frequency (n)	Percentage (%)
	Valproic Acid	10	37,0	2	14,3
1.	Phenytoin	5	18,5	0	0
2.	Carbamazepine	2	7,4	0	0
3.	Valproic Acid + Phenytoin	1	3,7	1	7,1
4.	Valproic Acid + Carbamazepine	0	0,0	1	7,1
5.	Valproic Acid + Clobazam	3	11,1	0	0
6.	Valproic Acid + Gabapentin	1	3,7	1	7,1
7.	Phenytoin + Clobazam	2	7,4	1	7,1
8.	Phenytoin + Gabapentin	0	0,0	1	7,1
9.	Phenytoin + Carbamazepine	0	0,0	2	14,3
10.	Carbamazepine + Clobazam	1	3,7	1	7,1
11.	Valproic Acid + Phenytoin +	2	7,4	3	21,4
12.	Clobazam	0	0,0	1	7,1
13.	Valproic Acid + Phenytoin + Gabapentin	27	100,0	14	100,0
	Total				

Most of the patients with controlled seizures used monotherapy, 17 people (62.9%). The percentage of controlled seizures gets smaller with each addition of ASM (Table 2). The majority of patients with controlled seizures used valproic acid monotherapy, as many as 10 people (37.0%). While the most uncontrolled seizures, 3 people (21.4%) used a combination of 3 ASMs valproic acid, phenytoin, and clobazam (Table 3).

Of the 41 research subjects (table 1), the highest age results were found at 15-34 years (39.0%). The results of this study are in accordance with research which showed that cases of epilepsy were more common in adults aged 19-64 years, namely 71.4%. This data is supported by research which states that people with epilepsy are more common in the young adult age group [10]. Prevalence is estimated to be lowest in early life, increasing to its highest levels during adolescence and early adulthood [11]. In adulthood, the most common etiology of epilepsy is symptomatic. Symptomatic epilepsy is epilepsy with acquired causes, including cerebral trauma,

cerebral tumors, central nervous system (CNS) infections, stroke, and a history of surgery [12]. In adulthood, a person has a higher risk of getting epilepsy through exposure to hazards at work or daily activities [13].

Based on the results of the study (table 1) it was found that the sex that suffered the most from epilepsy was male, 28 people (68.3%). The results of this study are in accordance with research conducted at Dr. Ramelan Surabaya, which shows that cases of epilepsy are more common in the male sex, namely as many as 60.7% [6]. This research is also in line with research at Prof. Hospital. Dr. R.D. Kandou, Manado, which obtained the results of the study as much as 54.4% male [10]. Genetically and physiologically, brain activity and impulse transfer between synapses are faster in males than in females. This causes men to be more at risk of suffering from epilepsy than women, but no specific biological evidence has been found [14]. According to other studies, the risk of epilepsy in men is higher due to men's work and exposure to risk factors, such as head trauma and alcohol use [15]. Men have a higher rate of head trauma than women, which is one of the causes of epilepsy [13]. In addition, because of societal stigma, women tend to have lower levels of consultation. Women are more likely to hide their epilepsy symptoms for sociocultural reasons [11]. Epilepsy has a significant quality of life and economic impact on healthcare needs and interferes with the work or education of individuals and their families. Several systematic studies have reported that there is a relationship between epilepsy and poverty [15].

From this study (table 1) the results showed that the age of onset of epilepsy was at the age of less than 20 years. Age of onset was categorized to determine the etiological tendency of epilepsy. In patients with age of onset less than 20 years, the most common etiology is idiopathic. [16] Meanwhile, epilepsy patients with an onset age of ≥20 years are generally caused by stroke, CNS infection, metabolic disease, and brain tumors. [17]

From this study (table 1) it was found that the majority of epilepsy patients used monotherapy. This is in accordance with research which showed that the majority of patients, namely as many as 71%, used a single ASM [4]. This is also in line with research that obtained more than half of the patients, namely 55.1%, used monotherapy. The prevalence of epilepsy sufferers is inversely proportional to the number of drugs used. In the polytherapy group, 72.7% used 2 ASMs, 24.4% used 3 ASMs, and 2.9% used ≥ 4 ASMs [18]. Epileptic patients started treatment with monotherapy. Administration of monotherapy in general is able to prevent seizures in 70% of patients [19]. If monotherapy cannot control seizures, they can be replaced with other drugs. If the replacement of drugs is still not controlled, then ASM combination treatment can be given taking into account the profile of the drugs to be combined [8].

From this study (table 1) it was found that the most type of ASM used was valproic acid. These results are in line with research at Al-Ihsan Hospital in Bandung which showed that the majority of subjects, namely 52.86%, received monotherapy with valproic acid, followed by phenytoin and carbamazepine [20]. Valproic acid is generally used as first-line therapy for most types of seizures because of its broad spectrum of activity against almost all types of seizures and epilepsy syndromes, both in pediatric and adult patients [21]. In addition, ASM valproic acid, carbamazepine, and phenytoin are widely used in developing countries because they are easy to obtain and affordable [22]. However, the use of valproic acid should be avoided as much as possible in women of childbearing age and pregnant women, especially in the first trimester. This is due to the teratogenic effect of valproic acid which can cross the placenta and can cause congenital abnormalities in the fetus. The most frequently reported teratogenic effects of valproic acid on the fetus are cardiovascular disorders, orofacial clefts, hypospadias, gastrointestinal atresia, and diaphragmatic hernia [21]. Meanwhile, general side effects that can be received by epileptics with valproic acid therapy are nausea, weight gain, tremors, metabolic disorders, and thrombocytopenia [23].

From this study (Table 1) it was found that the most controlled seizures were controlled seizures, namely 27 people (65.9%). This percentage agrees with that reported in an observational cohort study where the remission rate in patients with newly diagnosed epilepsy was as high as 63.7% [9]. The prognosis of epilepsy can be seen from several factors, including the type of epilepsy, the frequency of initial seizures, medical history, and EEG features. It has been shown that the idiopathic type of epilepsy, a low initial seizure frequency, and a rapid response to therapy are predictors of remission. Patients with a normal EEG on first visit are known to have a higher tendency to achieve remission than patients with epileptiform discharges. Meanwhile, symptomatic epilepsy is a negative predictor of remission. In the symptomatic epilepsy group, patients with encephalitis/meningitis etiology have the worst prognosis compared to other etiologies [12]. Other their research found that seizure remission was associated with a low initial seizure frequency, namely one or two seizures at diagnosis, general type of epilepsy, no psychiatric comorbidities, and treatment using one or two ASMs [24].

From this study (table 2) it was found that seizures were controlled with monotherapy treatment in 17 people (62.9%). The results of this study are in accordance with research which stated that most epilepsy patients experienced remissions on monotherapy with the first or second ASM [19]. This is also in line with research, namely two-thirds of patients with achieving seizure control with the use of a single ASM [4].

From this study it was found that the percentage of controlled seizures was getting smaller with each addition of ASM. The results of this study are in accordance with research where 50.5% of seizure control patients were given the first ASM. If epileptic seizures are difficult to control with monotherapy, then combination therapy can be given. However, the rate of seizure control cannot match or be less than monotherapy [9]. Based on research, several predictors of seizure control, one of which was a lower number of ASM prescribed [19]. The probability of remission decreases with a higher number of ASMs. The likelihood of uncontrolled seizures was 2.5-fold higher in epileptic patients with 2 or more ASMs compared with patients on a single ASM. This can happen because with polytherapy it is possible to have more pill burdens, more drug side effects, and more costs which will affect poor ASM adherence [18]. In other studies it was also stated that polypharmacy causes drug-drug interactions and changes in drug metabolism [4].

From this study (table 3) it was found that seizures were controlled with the use of valproic acid in 10 people (37.0%). The results of this study are in accordance with research conducted at Al-Ihsan Hospital in Bandung which showed that the highest number of epilepsy patients whose seizures were controlled with monotherapy was using valproic acid as much as 83.33% [20]. These results are also in line with research, namely the highest seizure freedom rate for valproic acid, which was 74.5%, followed by carbamazepine and oxcarbazepine, which were 70.1% and 65.7% respectively [25].

Based on research showed that valproic acid is still proven to be effective in controlling seizures in epilepsy patients, both in children and adults [22]. This is because of its broad spectrum of activity against almost all types of seizures and epilepsy syndromes. In particular, valproic acid has been tested in generalized (tonic-clonic, absence, and myoclonic) and focal seizures, and has been found to be effective in Lennox-Gastaut, West, and Dravet syndrome [21]. In research, it was stated that the use of valproic acid has been shown to be effective in treating patients with newly diagnosed epilepsy [25].

From this study, it was found that the combination of carbamazepine and phenytoin was less effective in controlling seizures. The combination of the two ASMs has the same mechanism of action, namely sodium channel blockers. The combined use of several sodium channel blockers is associated with infra-additive anticonvulsant effects and high toxicity [26]. The combination of carbamazepine and valproic acid is also less effective in controlling seizures. Valproic acid may increase carbamazepine toxicity by increasing serum metabolites. Due to the negative pharmacodynamic and pharmacokinetic interactions between carbamazepine and some ASMs, very few drugs can be combined with carbamazepine [26].

The combination of valproic acid and phenytoin shows a synergistic anticonvulsant effect and an additive toxic effect [27]. However, caution must be exercised when valproic acid is combined with sodium channel blockers because it has enzyme inhibitory properties [26]. The combination of gabapentin and valproic acid produces a synergistic anticonvulsant effect [27]. There are no relevant pharmacokinetic interactions between gabapentin and valproic acid. Gabapentin does not undergo oxidative metabolism and is excreted by the kidneys, so it has no pharmacokinetic interactions with other ASMs. Almost all ASMs used as monotherapy, such as valproic acid, carbamazepine, and phenytoin, can be combined with gabapentin [26].

The combination of clobazam and sodium channel blockers, such as carbamazepine and phenytoin, has a synergistic anticonvulsant effect [28]. Combining a sodium channel blocker with GABA-ergic enhancement is more effective than a combination of two drugs with the same mechanism [26]. Clobazam is usually prescribed as an adjunct to ASM because of its ease of administration and ease of use [28].

From this study, the most uncontrolled seizures were obtained with a combination of 3 ASMs of valproic acid, phenytoin, and clobazam, namely 3 people (21.4%). According to theory, the combination of the three ASMs fulfills the principle of rational polytherapy, which combines drugs with different mechanisms of action. Uncontrolled seizures can occur due to poor adherence to medication, lifestyle issues, or DRE [29], [30]. More pill burdens, drug side effects, and costs can lead to non-adherence in treatment [4]. Lifestyle problems such as consuming alcohol, smoking, stress, and lack of sleep are triggers for uncontrolled seizures [30]. DRE is defined when at least two of the appropriate ASM types have been administered at adequate doses but seizures remain uncontrolled [31]. It is necessary to rule out all possible causes of treatment failure, such as nonadherence to medication and lifestyle problems. When pharmacotherapy fails, alternative therapeutic approaches should be used to maximize the patient's quality of life [30]. Non-pharmacological therapies that can be given are the ketogenic diet and resective surgery [32]. The ketogenic diet has been shown to be useful in reducing seizure frequency in resistant patients [33]. The principle of the ketogenic diet is to utilize food composition to produce a metabolic ketogenic state [8]. Resective surgery is an effective treatment for DRE patients [23].

In this study, the majority of epilepsy patients whose seizures were controlled with a monotherapy treatment pattern using valproic acid, as many as 10 people. ASM therapy is initiated with a single drug (monotherapy), starting with a low dose and slowly titrating to the target dose. Giving a single drug will reduce the risk of side effects, avoid drug interactions, increase adherence in treatment, and also be more economical [34]. With effective therapy, 60-70% of epilepsy patients seizures can be stopped with monotherapy [25]. If

monotherapy cannot control seizures, then ASM combination treatment can be given taking into account the profile of the drugs to be combined [8].

The majority of ASMs used in this study were first generation ASMs, such as valproic acid, carbamazepine, and phenytoin. In a study showed that 60-70% of patients who received treatment with the first generation of ASM will achieve remission. Based on the reports of the American Academy of Neurology (AAN) subcommittee in 2004 and 2018, stated that several new generations of ASM have advantages in tolerability and safety, especially in the treatment of elderly patients, fertile women, and pregnant women because of fewer neurotoxic side effects [35]. The existence of a new generation of ASM options allows these drugs to be better suited to the characteristics of each patient [36]. However, the new generation of ASM is no more effective in controlling seizures than the first generation ASM [37].

Appropriate drug combinations exist in drugs with different mechanisms of action, such as the combination of valproic acid with gabapentin, clobazam, or phenytoin, while incompatible combinations exist in drugs with the same mechanism of action, especially the combination of two or more sodium channel blockers, such as carbamazepine and phenytoin. Administration of a combination of ASM with a mechanism of action of increasing GABA-ergic and sodium channel blockers is more effective than a combination of two drugs with the same mechanism [26].

4. CONCLUSION

1. Epilepsy patients at Dr. Soepraoen Army Hospital in January-December 2019 showed most were male, with most ages in the 15-34 year range, and the most onset at the age of ≥20 years.
2. Nearly 2/3 of epilepsy patients treated with ASM have controlled seizures.
3. The majority of epilepsy patients with controlled seizures used valproic acid monotherapy.

5. ACKNOWLEDGEMENTS

The author would like to thank the supervisors, staff from Medical Faculty University of Muhammadiyah Malang, and friends who helped in this research process into drafting the article.

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