The Effectiveness Comparison of Valproic Acid 500 mg and Amitriptyline 15 mg in Reducing the Frequency of Headache Attack in Patients with Tension-Type Headache

Elsa Susanti[1], Isti Suharjanti[1]

[1]Departement of Neurology, Faculty of Medicine Universitas Airlangga, Surabaya (60131), Indonesia

Abstract

Background: Tension-type headache (TTH) is the most common headache. Continuous analgesic use can develop into headache caused by drug abuse (medication overused headache); thus, the preventive therapy is necessary. Amitriptyline and valproic acid are drugs reported to reduce the frequency of headache in TTH patients.

Objective: To analyze the effectiveness of valproic acid 500 mg and amitriptyline 15 mg in reducing the frequency of headache attack in patients with tension-type headache.

Methods: The study applied a Double Blind Randomized Clinical Trial involving 50 TTH patients. The subjects were divided into two groups: amitriptyline 15 mg and valproate acid 500 mg. The period of drug administration was 6 weeks. The variables that were compared were the decreasing frequency of headache and the intensity of the pain.

Results: There was no significant difference in the decrease of headache frequency ($p = 0.730$) and pain intensity ($p = 0.430$) between the amitriptyline group and valproate acid group. However, each drug effectively decreased the frequency of headache and pain intensity in TTH patients ($p = 0.000$).

Conclusion: There was no significant difference between the effectiveness of valproic acid 500 mg and amitriptyline 15 mg in reducing the frequency of headache in patients with TTH.

Keywords: *valproic acid, amitriptyline, pain, tension-type headache*

Introduction

Tension type headache (TTH), previously called muscle contraction headache, is the most common headache where most people consider it a normal headache, compared with migraine. This is a complex disorder in which various heterogeneous mechanisms play a role. TTH often occurs daily. The prevalence of chronic TTH in one year in the general population ranges from 3% in females and 1.5% in males [1]. Previous studies have suggested that the prevalence of headache is 78% in a population-based study in Denmark; however, episodic TTH (one day per month or less) is the most common that does not require special medical treatment. However, 24% to 37% experience headache several times per month, 10% experience pain per week, and 2% to 3% of the population experience chronic TTH that lasts for a longer period of time in their lives [2].

Chronic TTH is a risk factor for the occurrence of analgesic abuse that will develop into headache. Persistent headache and psychiatric comorbidity often cause this chronic TTH to be overcome. Although TTH is common, pathophysiology and mechanisms remain unclear. Pathophysiology is thought to be multifactorial, involving factors of central and peripheral nervous system as well as environmental factors [3]. The vagueness

Corresponding author:
Isti Suharjanti:
Corresponding author's address: Departement of Neurology, Faculty of Medicine Universitas Airlangga, Surabaya (60131), Indonesia,
E-mail: suharjantii@gmail.com, (+6231) 5020251

of this pathogenesis is reflected in the variation of available prophylactic drugs. The most commonly used prophylactic drugs are tricyclic antidepressants (TCA), other classes of antidepressants and muscle relaxants, but benzodiazepines and vasodilator agents are also prescribed [4]. To obtain effective treatment, it was conducted a study comparing valproic acid 500 mg and amitriptyline 15 mg in reducing the frequency of headache attacks in patients with tension-type headache[5].

Method

Subjects in this study were tension type headache patients who were treated at the Neurological Outpatient Unit of Dr. Soetomo General Hospital Surabaya, Indonesia that have fulfilled the criteria of inclusion and exclusion [6]. Inclusion criteria included chronic and frequent episodic tension type headache that fulfilled the criteria based on the National Consensus III Study Group Headache Perdossi 2010 and aged 18-50 years old. Exclusion criteria included secondary headache patients based on the National Consensus III of the Study Group of Headache Pain in 2010, patients with a history of allergy or contra indication of the administered drug, and pregnant women, mental illness or severe illness such as malignancy. Patients who were willing to participate in the research had to fill out the informed consent sheet [7].

The study protocol was approved by the Ethical Commission to conduct basic science/clinical research in Dr. Soetomo General Hospital Surabaya. Subsequently, the subjects were divided into two groups, the group receiving amitriptyline 15 mg and the group receiving valproic acid 500 mg. Both drugs were put into capsule packs of the same color and size; thus, the researchers and the study subjects could not distinguish the contents of the capsule. This drug was given to the patients for six weeks [8]. The patients were given an explanation of the headache diary that must be filled by the patients every day during the study. After the examination, the patients were sent back with a headache diary, and medicine. The patients were given 14 capsules of medicine to drink 1x1 for two weeks either while experiencing headache or no. The patients were also given analgesic of 10 tablets and consumed only if there was a headache attack. The patients were asked to return for control, handed over a headache diary and took medication every two weeks for six weeks [9].

The collected data was processed by statistical tests using SPSS 16.0 software (SPSS, Inc., Chicago, IL). The statistical test used in this study was paired t-test and independent t-test if the data was distributed normal. If the data was distributed abnormal, it was examined by wilcoxon test continued with mann withney test. Furthermore, chi square test was conducted to know the success of treatment on each group with $p < 0.05$ [10].

Result

Table 1. The Characteristics of Research Subjects

Characteristics	Amitriptyline (%)	Valproic Acid	p
Gender Male Female	 18 (36.00) 7 (14.00)	 18 (36.00) 7 (14.00)	1.000
Education JHS SHS University	 10 (20.00) 9 (18.00) 6 (12.00)	 9 (18.00) 11 (22.00) 5 (10.00)	0.840
Occupation Employed Unemployed	 12 (24.00) 13 (26.00)	 9 (18.00) 16 (32.00)	0.390
Coffee drinkers Yes No	 3 (6.00) 22 (44.00)	 2 (4.00) 23 (46.00)	1.000
Stressor Yes No	 2 (4.00) 23 (46.00)	 1 (2.00) 24 (48.00)	1.000

The number of samples at the beginning of the study were 50 respondents. Most of the subjects were females of 36% in the amitriptyline group and 36% in the valproic acid group. Senior High School students were 18% in amitriptyline group and 22% in the valproic acid group. Employed subjects were 26% in the amitriptyline group and 32% in the valproic acid group. The subjects who did not consume coffee were 44% in the amitriptyline group and 46% in the valproic acid group. The subjects who did not have stressor were 46% in the amitriptyline group and 48% in the valproic acid group.

Table 2. Frequency and intensity of pain of research subjects

	Amitriptyline		**p**	**Valproic Acid**		**p**
	Median (Min- Max)	**Mean±SD**		**Median (Min- Max)**	**Mean±SD**	
TTH1 TTH2	3.75 (1.17-750) 2.00 (0.00-5.66)		0.000	*5.00 (1.75-7.5)* *2.66 (0.50-6.33)*		0.000
VAS1 VAS2		6.07±1.38 3.17±2.18	0.000		5.54±1.08 2.17±1.38	0.000

The result of statistical analysis obtained the frequency of headache before and after treatment using amitriptyline with p = 0.000. In addition, valproic acid group obtained p = 0.000. The results of statistical analysis on the intensity of headache before and after taking amitriptyline obtained p = 0.000. The same condition was found in the subjects consuming valproic acid with p = 0.000.

Table 3. Frequency of pain, intensity of headache, and treatment success

	Amitriptyline		**Valproic Acid**		**P**
	Mean±SD	**n (%)**	**Mean±SD**	**n (%)**	
Delta mean TTH Delta Vas	2.18±1.24 2.90±2.57		2.32±1.40 3.36±1.45		0.720 0.430
Successful Unsuccessful		13 (26.00) 12 (24.00)		11 (22.00) 14 (28.00)	

*Odds ratio of treatment success = 1.37

The success of preventive treatment was assessed by a decrease in the frequency of headache attacks at the end of the study at week six. The improvement of the frequency of headache attacks after treatment was the difference between the frequency of headache before treatment (mean TTH1) and the frequency of attacks after-treatment (mean TTH2), reported as delta mean TTH. Improvement in pain intensity was assessed by the difference between the value of pain intensity before treatment (VAS1) with pain intensity after treatment (VAS2), reported as delta VAS.

The success rate of treatment in both groups where the drug was considered effective if it successfully reduced the frequency of headache attacks as much as ≥ 50%. The treatment success rate was higher in the amitriptyline group than in the valproic acid group.

Odds Ratio obtained 1.37 with 95% confidence interval. The results of statistical analysis showed that there was no significant difference between success rate in both groups with p = 0.570.

Discussion

The effectiveness of amitriptyline as a chronic TTH preventive therapy is quite common. A randomized study compared amitriptyline with citalopram as a chronic TTH preventive therapy. They found that amitriptyline was more effective than citalopram in reducing headache attacks. Various publications also concluded that amitriptyline significantly reduces chronic TTH attacks compared with placebo [11].

Meanwhile, other studies have observed that amitriptyline may also reduce pain in the palpation of the pericranial muscles. But they also found that undesirable side effects were high in the amitriptyline group compared to other drugs. Randomized controlled clinical trials on TTH management with TCA conducted stress management therapy and a combination of both 187 patients. It was revealed that 78 (80%) of 97 patients receiving amitriptyline reported unwanted side effects such as dry mouth, drowsiness, weight gain, sweating, constipation, abdominal pain, nervousness, and increased appetite [11].

A systematic review and meta-analysis of the use of tricyclic antidepressants and headache involving 37 studies (30 studies using amitriptyline) showed that tricyclic antidepressants reduced the number of days of headache attacks in TTH patients and the number of headache attacks in migraine patients [12]. However, side effects that arise are also quite a lot like dry mouth, drowsiness and stomach upset. The dose of amitriptyline used varies from 10 mg-150 mg per day. Because of this side-effect profile, amitriptyline is not an appropriate therapy for patients with multiple contraindications and elderly [13].

Several studies have examined the use of valproic acid as a preventive therapy for headache. A reserach studied the efficacy and safety of sodium valproate for long-term therapy in patients with chronic headaches. The study involved 642 patients undergoing treatment with sodium valproate, in which 138 patients received only sodium valproate. The results of this study received an average improvement of 47%, 50% decrease in the frequency of headache attacks in patients who obtained only sodium valproate (93 of 138 patients). Almost 75% of patients experienced a decrease in frequency of headache attacks by 50%. Drug side effects occured in about 35% of patients but no serious side effects, and hepatotoxicity is also not found during treatment up to 6 years [14].

Previous research conducted an open-label trial of 30 patients using sodium divalproate at a dose of between 1000 mg and 2000 mg per day. Based on the index of weekly headache, pain-free days and dysfuctional days, general well-being rating and physicians global assessment of patients increased significantly in two-thirds of patients. In another study, the researchers consecutively studied 75 patients with intractable headache syndrome, dividing them into 3 groups of migraine frequency, transformed migraine, TTH and treating all patients with sodium divalproate 500 mg twice daily. Thirty-six patients (48%) reported a decrease in headache frequency by 50% or more.

A randomized double blind trial with placebo controlled enrolled 70 patients with chronic headaches. Twenty-nine migraine patients and 41 chronic TTH patients were divided into groups of valproic acid and placebo. Visual Analog Scale (VAS) and frequency of pain are used as evaluation. The initial dose used in this study was 500 mg per day given for 3 months. In this study, there was a decrease in the maximum pain of VAS and frequency of pain in the valproic acid group at the end of the study (p = 0.000). The incidence of rare, somnolent and tremor-like side effects was found in one patient, impotence occurred in one patient and hair loss occurred in one patient. This was in line with the results of our study, which also resulted in decreased frequency of pain and pain intensity (VAS) in the valproic acid group at the end of the study (p = 0.000).

The use of amitriptyline and valproic acid in this study is as preventive action. With the reduced frequency of headache attacks, the less the intensity of pain was experienced by the patient [15]. This is probably due to the high levels of neurotransmitter inhibitors such as serotonin and GABA; thus, it suppresses the acute pain impulse that appears.This explains that prevention of headache attacks on TTH and efforts to find effective preventive drugs is still a challenge in medicine and this is closely related to the many factors involved in the pathogenesis of this headache. A previously published review shows that the average preventive therapy is less effective [16].

Conclusion

There was no significant difference between the effectiveness of valproic acid 500 mg and amitriptyline 15 mg in reducing the frequency of headache in patients with frequent episodic and chronic TTH.

Ethical Clearance: This research process involves participants in the survey using a questionnaire that was accordant with the ethical research principle based on the regulation of research ethic committee. The present study was carried out in accordance with the research principles. This study implemented the basic principle ethics of respect, beneficence, nonmaleficence, and justice.

Conflict of Interest: The author reports no conflict of interest of this work.

Source of Funding: This study is done with individual funding.

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