Effect of Using Valproate Acid Monotherapy on Color Perception of Children with Epilepsy in Universitas Sumatera Utara Hospital and Network Hospital

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Background
The medical management for epilepsy sufferers is to control generated seizures therefore not repeatedly occur using long-term anti-seizure medicines. Long-term treatment of epilepsy will potentially cause side effects, one of which is often used is valproate acid (VPA). It is known that VPA has ocular effects such as color perception disorders.

Methods
This study was prospective, observational analytic using cross sectional study method. Subjects were girl patients with a diagnosis of pediatric epilepsy who received VPA monotherapy at Universitas Sumatera Utara Hospital and Network Hospital.

Results
From 35 subjects with average age of 11 years old, using wilcoxon signed rank test, found the significance value 0,0001* therefore there was effect significantly on subjects on color perception disorder. The most type of color perception disorders found was tritan with slightly severity. Based on the duration of VPA, using fisher's exact test, the significance value was 0.021* so that there was a significant effect of color perception disorders. Based on the doses of VPA, using fisher's exact test, the significance value was 0.334 so that there was no effect between the dose of VPA and color perception disorder.

Conclusion
There was a significant effect between the duration of VPA used on color perception disorders, there was no significant effect between the dose of VPA on color perception disorders, and the most type of color perception disorders was tritan.

Keywords : Valproate acid, Epilepsy, Color Perception

I. INTRODUCTION

Epilepsy is a chronic condition on nervous system characterized by recurrent seizures. Seizures occur when an abnormal electrical activity in the brain causes an involuntary change of body movement and function, sensation, awareness, and behavior.[1] Effects of epilepsy on children are broader than adults. Long-term effects will occur in both children physical health and daily life.

The medical management for epilepsy sufferers is to control generated seizures therefore not repeatedly occur using long-term anti-seizure medicines. Long-term treatment of epilepsy will potentially cause side effects, one of which is often used is valproate acid (VPA). It is known that VPA has ocular effects such as color perception disorders.[2-4]

A study conducted by Verroti et al in 2004 suggested that patients aged 11-18 years who used VPA and carbamazepine experienced a blue-yellow perception impairment.[2] A study by Sorri et al in 2005 showed that VPA could lead to color perception abnormalities in adults epilepsy sufferers.[3] Hilton et al in 2003 found that gabapentin and carbamazepine strongly influenced the process of decreasing color perception and contrast sensitivity in adults.[4]

II. METHODS

This is an observational analytic prospective using a cross-sectional study and has been approved by the Ethics Committee of the Faculty of Medicine, University of Sumatera Utara. The subjects were girl patients with a diagnosis of pediatric epilepsy who received VPA monotherapy at University of Sumatera utara Hospital and Network Hospital from May to November 2018. The number of samples was 35 subjects aged 7-18 years. The inclusion criteria were subjects who had received VPA monotherapy ≥6 months and willing to participate. The exclusion criteria were subjects who had ocular abnormalities before the use of VPA, congenital color blindness, other systemic diseases, and subjects who were not disciplined on taking VPA medication regularly.

The dependent variables were color perception outcome and the severity of color perception disorders; the independent variables were the dose and duration of VPA used in children with epilepsy. To obtain data in this study, first we examined the visual acuity of subjects using snellen chart, and then color perception was examined using farnsworth munsell D-15 monocular in both eyes. The data obtained are presented in tabulation form and described, which then performed analytical statistical techniques using the non parametric test type of Wilcoxon signed rank test and fisher's exact test.

III. RESULTS

The following obtained data included the characteristics of subjects based on age:

Table 3.1 The Characteristics of Subjects Based on Age

Age (years)	Frequency
≥7 - ≤9	11
>9 - ≤12	16
≥12 - ≤15	6
≥15 - ≤18	2
Total	35

In table 3.1 showed the subjects were 35 girl epilepsy patients aged ≥7 - ≤18 years with the highest frequency ranged >9 - ≤12 years. The average age of the overall study subjects was 11 years old. Subsequent, a table of dose characteristics and duration of VPA used daily, the outcome and severity of subjects.

Table 3.2 Characteristics of Dose and Duration of VPA Used Daily, The outcome and Severity of Subjects

	Frequency	Percentage
Dose (mg)		
≤ 500	22	62,9%
> 500	13	37,1%
Total	35	100%
Duration of Used Daily (Months)		
> 6 - ≤ 12	7	20,0%
> 12	28	80,0%
Total	35	100%
Outcome		
No Color Blind	11	31,5%
Deutan	4	11,4%
Protan	2	5,7%
Tritan	18	51,4%
Total	35	100%
Severity		
Normal	11	31,4%
Slightly	24	68,6%
Total	35	100%

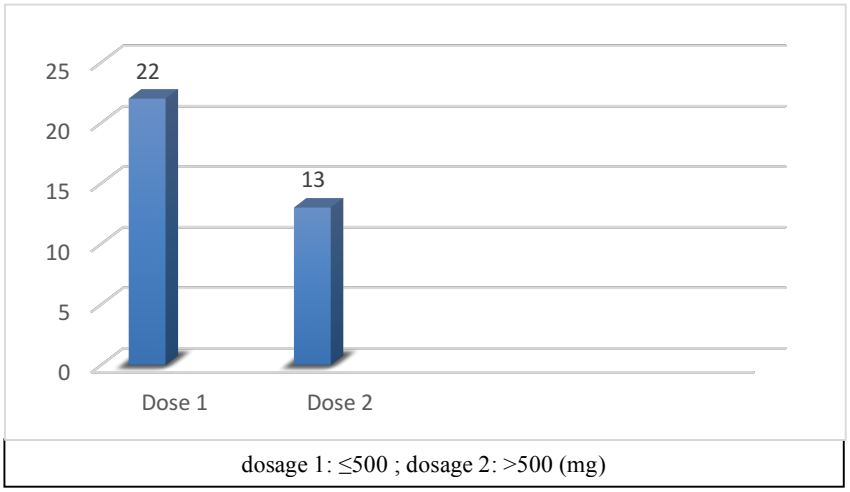
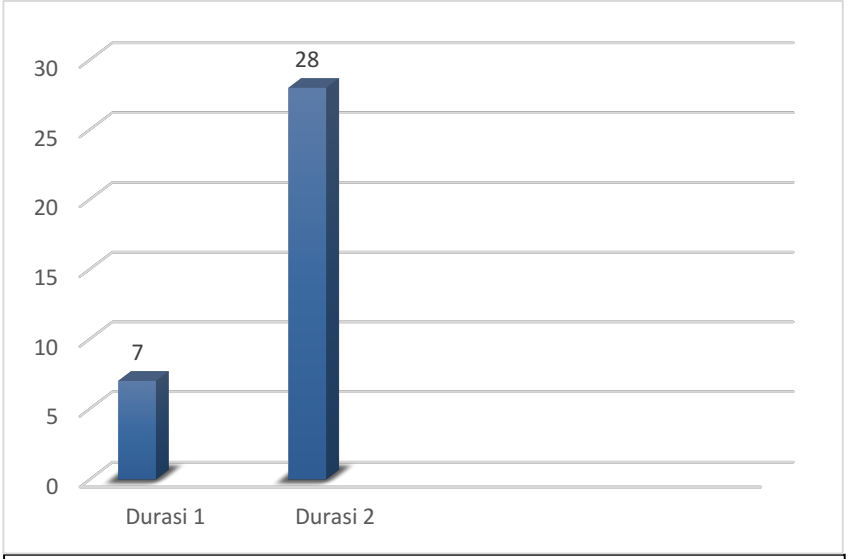


Figure 3.1 Subjects Consumed a Doses of VPA a Daily

Table 3.2 and Figure 3.1 showed that 22 of 35 subjects consumed a doses of VPA < 500mg daily, and 13 of 35 subjects consumed a dose of VPA > 500mg per day.



duration 1: > 6 - ≤12; duration 2: > 12 (months)

Figure 3.2 Duration of VPA Used Daily.

Table 3.2 and Figure 3.2 showed that 7 of 35 subjects consumed VPA during > 6 - ≤12 months, and 28 of 35 subjects consumed VPA during >12 months.

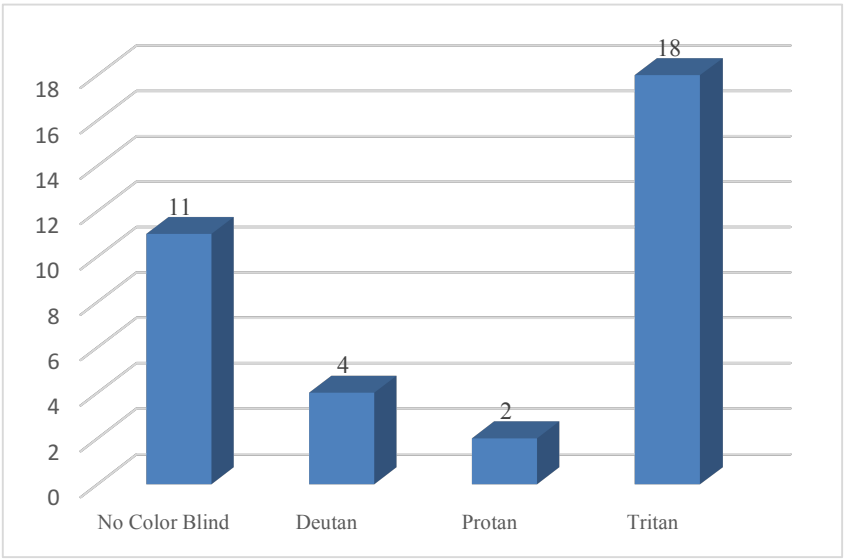


Figure 3.3 Results of Subjects Interpretation Using Fansworth Munsell D-15 test

In Table 3.2 and Figure 3.3, the results of subjects interpretation using Fansworth Munsell D-15 test showed 11 out of 35 subjects are no color blind, 4 of 35 subjects suffered deutan, 2 of 35 subjects suffered protan, and 18 of 35 subjects suffered tritan.

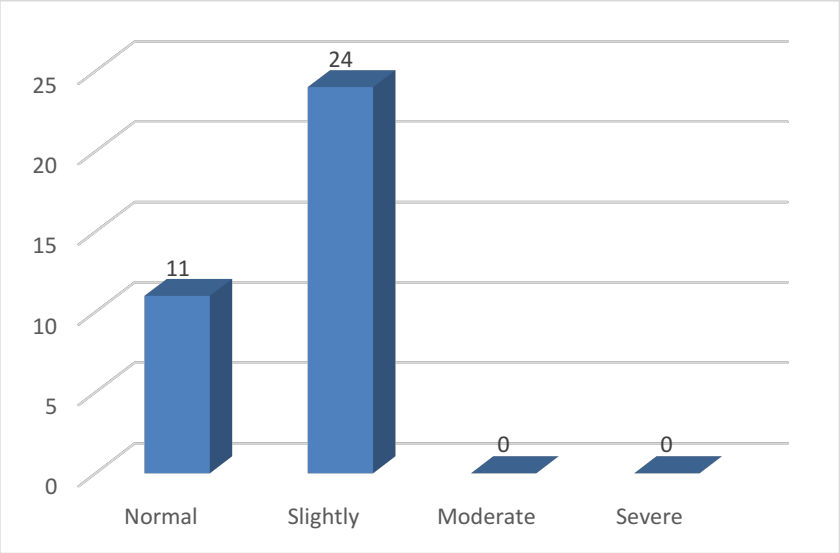


Figure 3.4 Severity of Color Perception Disorder

In Table 3.2 and Figure 3.4, the results of severity of color perception disorder showed 11 out of 35 subjects are normal and 24 of 35 subjects are slightly. Below, result of the non-parametric test used, i.e. Wilcoxon signed rank test to determine changes in color perception after consuming VPA.

Table 3.3 Changes in Color Perception After Consuming VPA

Variable	Rasio		Change in Differences		*p.*
	Before	After			
	N	N		n	
Category					
- NCL	35	11	Negative Differences	0	
- Deutan	0	4	Positive Differences	24	0,0001*
- Protan	0	2	Ties	11	
- Tritan	0	18			

In table 3.3 showed that the statistical using wilcoxon signed rank test obtained p value < 0,050 or significance value of 0,0001*, therefore it can be concluded that there was a significant effect of changes in color perception after consuming VPA on children with epilepsy. Below, result of the non-parametric test used, i.e. fisher's exact test to determine changes in color perception after consuming VPA based on duration.

Table 3.4 Changes in Color Perception After Consuming VPA Based on Duration

Duration	Color Perception After consuming VPA				Total		P	fisher's exact test
	NCL		Deutan/Protan/Tritan					
	N	%	N	%	N	%		
>6 - ≤12 months	5	45,5	2	8,3	7	20,0	0,050	0,021*
> 12 months	6	54,5	22	91,7	28	80,0		

In table 3.4 showed that the statistical using fisher's exact test obtained p value <0.050 or significance value of 0.021*, therefore it can be concluded that there was a significant effect between the duration of VPA used and color perception disorders on girl epilepsy patients. Below, result of the non-parametric test used, i.e. fisher's exact test to determine changes in color perception after consuming VPA based on dose daily.

Table 3.5 Changes in Color Perception After Consuming VPA Based on Doses

Doses	Color Perception After Consuming VPA				Total		*P*	*fisher's exact test*
	NCL		Deutan/Protan/Tritan					
	N	%	N	%	N	%		
≤ 500 mg	8	72,7	14	58,3	22	62,9	0,050	0,334
> 500 mg	3	27,3	10	41,7	13	37,1		

In table 3.5 showed that the statistical using fisher's exact test obtained p value < 0.050 or a significance value of 0.334, therefore it can be concluded that there was no significant effect between doses of VPA used and color perception disorders on girl epilepsy patients.

IV. DISCUSSION

This study used Farnsworth Munsell D-15 test because it is applicative, fast, and precise in detecting color perception disorders.[6-8] Farnsworth Munsell D-15 test can also distinguish color perception disorders caused by drug exposure or due to congenital color perception disorders.[6-9] The Farnsworth Munsell D-15 test is known to have a sensitivity level of 90% and a specificity level of 96%.[10-13] VPA is known to induce short-term color vision abnormalities.[3,14,15] It occurs because of VPA could lead to retinal function changes visually.[16] A study by Iraha et al in 2016 suggested that the subjects who consumed VPA as much as 55% experienced impaired color perception and when the VPA used was stopped, it was reported that 7% remained difficult to distinguish colors.[17] Color perception due to the effects of long-term VPA usage was reversible, but in some other studies still in debate.[16]

VPA can significantly reduce the number of available photoreceptors.[16,18] VPA can affect the GABAergic system which results in shorter-wave length which has a high sensitivity to the incidence of color perception disorders.[19] In some previous studies, VPA could result ocular side effects such as transient tritanopia without affecting retinal function.[14] VPA can cause color perception disorders, especially blue. This is due to a defect of the perception or transmission of sensory nerve signals[20]

The interpretation of tritan color perception disorders arises because VPA interferes with shorter-wavelength production. However, it is undeniable that VPA can also cause protan or deutan color perception disorders but not common. It is known that tritan is very rare due to genetics, but is usually found due to exposure to certain drugs.[19,20]

V. CONCLUSION

There was a significant effect between the duration of VPA used on color perception disorders, there was no significant effect between the dose of VPA on color perception disorders, and the most type of color perception disorders was tritan

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