Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.60, No.1(2020). p. 13-7; doi: http://dx.doi.org/10.14238/pi60.1.2020.13-7

Original Article

Platelet counts in epileptic children receiving valproic acid

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Abstract

Background Epileptic seizures are a transient occurrence resulting from abnormal, excessive, or synchronous neural activity in the brain. Epilepsy requires long-term treatment, increasingly larger doses, and combination therapy. Anti-epileptic drugs (AEDs), especially valproic acid (VPA), are the main treatment of choice. Thrombocytopenia is the most common adverse event from AEDs.

Objective To evaluate platelet counts in epileptic children receiving valproic acid monotherapy vs. polytherapy.

Methods This analytic, observational, retrospective cohort study was conducted in children with epilepsy below 18 years of age and treated in Dr. Moewardi Hospital, Surakarta, Central Java. Subjects had received VPA treatment for at least 6 months, either as monotherapy or polytherapy. There were 40 subjects in each group (VPA monotherapy vs. VPA polytherapy). The exclusion criteria were patients who had thrombocytopenia and did not take valproic acid regularly. The data was taken from laboratory and the outcome assessed was decreasing of platelet count.

Results Administration of VPA as monotherapy *vs.* polytherapy was not significantly associated with incidence of thrombocytopenia. However, duration of VPA use > 2 years was associated with significantly greater proportion of thrombocytopenia, with OR 33.0 (95%CI 4.157 to 261.962; P=0.001) compared to VPA use < 2 years. Similarly, VPA dose of >30 mg/kg/day was significantly associated with greater proportion of thrombocytopenia, with OR 4.081 (95%CI 1.337 to 12.458; P=0.013) compared to <30 mg/kg/day dosage.

Conclusion Incidence of thrombocytopenia is not significantly different between VPA as a monotherapy and polytherapy. However, higher VPA dose and longer VPA duration are associated with higher proportion of thrombocytopenia. **[Paediatr Indones. 2020;60:13-7; doi: http://dx.doi.org/10.14238/pi60.1.2020.13-7]**.

Keywords: *valproic acid; monotherapy; polytherapy; platelets; epileptic; epilepsy*

Epileptic seizure is defined as a transient occurrence of signs and/or symptoms resulting from an abnormal, excessive, or synchronous neural activity in the brain.[1] Cipto Mangunkusumo Hospital, Jakarta reported that of 1,700 patients in 2009 and 2010, 218 generalized epilepsy and 71 focal epilepsy patients were newly-diagnosed annually.[2]

Epilepsy often requires a long period of treatment, progressively higher doses, and combined therapy. Adverse events of long-term anti-epileptic drugs (AEDs) include hepatotoxicity, as well as behavioral and memory disorders. They may also affect the hematologic and endocrine systems, bone density, and lipid profiles.[3]

Close hematologic monitoring must be done in patients using carbamazepine, phenytoin, and VPA. Thrombocytopenia is the most common side effect of AEDs, especially VPA. Its mechanism is

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Submitted September 3, 2019. Accepted January 28, 2020.

unclear, though VPA is thought to have a direct toxic effect on bone marrow, as well as trigger the production of autoantibodies against platelets.[4] To our knowledge, no study to date has been conducted on thrombocytopenia incidence in children with epilepsy receiving long-term VPA in Dr. Moewardi Hospital, Surakarta. Therefore, we aimed to evaluate platelet counts in patients receiving either VPA monotherapy or polytherapy.

Methods

This retrospective, observational, cohort study was performed in Dr. Moewardi Hospital, Surakarta, Central Java, from July 2018 to January 2019. The study subjects were pediatric patients below 18 years of age receiving VPA monotherapy or VPA with other AEDs (polytherapy) for at least 6 months. Patients who did not take AEDs regularly, had underlying thrombocytopenia (i. e. idiopathic thrombocytopenic purpura/ITP, dengue haemorhagic fever/DHF) were excluded. Parents or guardians provided written informed consent. We assessed decreasing of platelet count and thrombocytopenia incidence.

The sampling technique using an unpaired numeric analysis led to an estimated minimum required number of 40 subjects for each group (monotherapy *vs.* polytherapy). Platelet counts were performed by the clinical laboratory using venous blood specimens. A platelet cut-off of <150,000/uL was used to classify patients as thrombocytopenic. Statistical analyses were unpaired T-test, Mann-Whitney, and Chi-square tests. Results with P values <0.05 were considered to be statistically significant. This study was approved by Ethics Committee of Health Studies, Dr. Moewardi Hospital/Universitas Sebelas Maret Medical School, Surakarta.

Results

There were 80 pediatric epileptic patients aged < 18 years who fulfilled our inclusion criteria. The basic characteristics of subjects were sex, age, and the length of VPA use. The majority of subjects were male in both groups. Mann Whitney test revealed no significant difference in the mean age of patients between the monotherapy and polytherapy groups. Length of VPA use was significantly shorter in the monotherapy group [30.33 (SD 18.38) months] than in the polytherapy group [52.28 (SD 41.45) months] (P=0.023). The characteristics of subjects are shown in **Table 1**.

Table 1. Subjects' characteristics

Characteristics	Valproic acid		P value
	Monotherapy (n=40)	Polytherapy (n=40)	
Sex, n (%)			0.818*
Male	24 (60.0)	25 (62.5)	
Female	16 (40.0)	15 (37.5)	
Mean age (SD), months	53.13 (35.67)	73.80 (49.70)	0.070#
Mean length of VPA use (SD), months	30.33 (18.32)	52.28 (41.45)	0.023#

Note: *Chi-square test, #Mann-Whitney test

The mean platelet count of the VAP monotherapy and polytherapy groups were 218.45 (SD 88.81) K/dL and 241.92 (SD 84.74) K/dL, respectively. Fifteen (37.5%) patients in the monotherapy group and 9 (22.5%) patients in the polytherapy group had platelet counts ≤150,000/dL. The incidences of thrombocytopenia in VPA monotherapy and polytherapy are shown in **Table 2**.

Table 2. Type of VPA therapy and platelet count mean by groups

Platelet count	Type of VPA therapy	
	Monotherapy (n=40)	Polytherapy (n=40)
≤150,000/µL (n=24)	15	9
>150,000/µL (n=56)	25	31
Mean (SD), k/dL	218.45 (88.81)	241.92 (84.74)

Further statistical analyses of possible associations between VPA monotherapy and polytherapy, length of VPA use, as well as VPA dose on thrombocytopenia were conducted. Chi-square test revealed no significant differences in the percentages of patients receiving either monotherapy or polytherapy between the platelet count groups (P=0.143). The length of VPA use significantly affected the decrease of platelet

count in which the administration of VAP for more than two years increased the incidence of the decline in platelet count (P<0.001). High dose of VAP was statistically significant affect the decrease of platelet count (P=0.01) (**Table 3**).

Table 3. Analysis of platelet count groups with type of VPA therapy, length of use, as well as dose

Variables	Platelet		P value
	≤150,000/µL (n=24)	>150,000/µL (n=56)	
Valproic acid, n			
Monotherapy	15	25	0.143
Polytherapy	9	31	
Length of use, n			
≤ 2 years	1	33	<0.001*
> 2 years	23	23	
Dose, n			
≤ 30 mg/kg/day	5	29	0.010*
>30 mg/kg/day	19	27	

*Chi-square test

Multivariate analysis demonstrated that patients who received VPA therapy for more than two years would have a 33 times higher risk of having a platelet count of ≤150,000u/L compared to those who received the therapy for less than two years (OR 33.0; 95%CI 4.157 to 261.962; P=0.001). In addition, VPA dose of >30mg/kg BW/day increased the risk of platelet decline by 4.081 compared to a dose of ≤30mg/kg BW/day (OR 4.081; 95%CI 1.337 to 12.458; P=0.013) (**Table 4**).

Discussion

In our study, 37.5% patients receiving VPA monotherapy and 22.5% patients with polytherapy had platelet count ≤150,000/dL. Decrease in platelet count may be associated with VPA therapy, whether monotherapy or in combination with other AEDs and the length of VPA use. In our study, VPA was mostly commonly combined with carbamazepine. The length of VPA use was in line with epilepsy therapy protocol. Typically, only VPA is administered, but if its maximum dose does not prevent seizures then other AEDs would be added. Thus, patients receiving polytherapy use VPA longer than those in monotherapy.[5]

Chi-square test revealed no significant difference in thrombocytopenia between the monotherapy and polytherapy groups. However, we found a significant association between thrombocytopenia and length of VPA use. This difference was then analyzed further with multivariate analysis revealing an OR of 33.0 (95%CI 4.157 to 261.962; P=0.001). An estimated 6-33% of patients taking VPA experience thrombocytopenia.[6] Therefore, it can be considered that not all VPA use will couse thrombocytopenia. A study noted that thrombocytopenia occurs more frequently in patients receiving monotherapy.[9] Another previous study also reported that thrombocytopenia occurred in 26.4% of patient using VPA monotherapy and 15.8% of

Table 4. Multivariate analysis of platelet count groups with type of VPA therapy, length of use, and dose

Variables	Platelet		OR (95% CI)	P value
	≤150,000/µL (n=24)	>150,000/µL (n=56)		
Valproic acid, n				
Monotherapy	15	25	0.484 (0.182 to 1.289)	0.147
Polytherapy	9	31		
Length of use, n				
≤ 2 years	1	33	33.0 (4.157 to 261.962)	0.001*
> 2 years	23	23		
Dose, n			4.081 (1.337 to 12.458)	0.013*
≤ 30 mg/kg/day	5	29		
>30 mg/kg/day	19	27		

patients using VPA polytherapy.[11] Although the VPA mechanism of action is unclear, it suggested that carbamazepine, the most common drug used in polytherapy, can lower VPA level so that thrombocytopenia incidence decreases.[10,11]

We found that the VPA dose of >30 mg/kg BW/day had a 4-fold probability for platelet count ≤150,000/dL. This finding was in agreement with a 2014 study where 1/5 of children taking VPA monotherapy for more than 6 months at a dose of 30 mg/kg BW/day experienced decreased platelet count.[12] Other studies showed that decreased platelet count was related to VPA dose and depended on the serum level of VPA (>100 mg/L).[12,13] However, we did not check serum VPA level, so we could not evaluate for its association to lower platelet count in our subjects.

In our study, the multivariate analysis revealed that the use of VPA for two years or less reduced thrombocytopenia incidence significantly. Type of VPA, whether monotherapy or polytherapy, was not associated with platelet count but increased length of VPA use correlated with thrombocytopenia. Generally, long-term VPA therapy in children with epilepsy leads to hematologic system disorders, one of which is thrombocytopenia.[6]

Our study had several limitations. The blood specimen collection was done randomly, so we could not evaluate for a trend in platelet count decrease. Also, we did not include subjects with similar length of VPA use, thus we could not accurately assess for differences of platelet count decline. In conclusion, there is no difference in incidence of thrombocytopenia in children with epilepsy receiving either valproic acid as monotherapy compared to polytherapy. However, significantly more subjects with longer VPA use and higher VPA dose are in the low platelet group.

Conflict of interest

None declared.

Funding Acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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