Sodium valproate vs phenytoin in status epilepticus: A pilot study

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Abstract—Sixty-eight patients with convulsive status epilepticus (SE) were randomly assigned to two groups to study the efficacy of sodium valproate (VPA) and phenytoin (PHT). Seizures were aborted in 66% in the VPA group and 42% in the PHT group. As a second choice in refractory patients, VPA was effective in 79% and PHT was effective in 25%. The side effects in the two groups did not differ. Sodium valproate may be preferred in convulsive SE because of its higher efficacy.

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Intravenous phenytoin (PHT) is used in status epilepticus (SE) but is associated with high cardiovascular toxicity.[1] Sodium valproate (VPA) does not have such side effects, and its reported efficacy in SE is 58% to 83%.[2,3] We performed a randomized controlled trial to compare the efficacy of VPA and PHT in convulsive SE.

Methods. Consecutive patients with convulsive SE were recruited after approval from the local ethics committee. SE was defined as two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsive seizures lasting for more than 10 minutes.[4] Patients with nonconvulsive and subtle SE, hypotension, cardiac arrhythmia, congestive heart failure, pregnancy, pancreatitis, and drug allergy and those requiring immediate neurosurgery were excluded. The patients were randomized using random table numbers into VPA and PHT groups. The VPA group received sodium valproate 30 mg/kg in 100 mL saline infused over 15 minutes. The PHT group received phenytoin sodium 18 mg/kg in 100 mL saline infused immediately at a rate of 50 mg/minute. Lack of seizure control after infusion was treated with the other study drug. Subsequent failure was treated by diazepam or lorazepam. During infusion respiration, pulse and blood pressure were monitored. Liver function tests were performed after 24 and 72 hours of treatment. In patients with liver dysfunction, serum ammonia was also measured. The patients received general care, fluid, electrolytes, calories, antipyretic for fever, and antibiotics for infection.

Primary outcome was defined as clinical seizure cessation after infusion and secondary outcome as seizure freedom at 24 hours. EEG was performed 1 hour after clinical control of convulsion if the consciousness did not improve.

The sample size was calculated keeping Type I error (α) = 0.05 and Type II error (β) = 0.1, using a Z test for proportion. The critical difference in the response between the study drugs was considered as 20%. Considering the efficacy of PHT as 40% based on reported literature,[4] the sample size was calculated to be 85, with the power of the test as 90%. It was possible to recruit 68 patients only, which reduced the power of the test to 71%. The power calculation was based on a one-sided test. Fisher exact, chi-square, and independent *t* tests were used for statistical analysis.

Results. Eighty-two patients with SE were recruited; 14 were excluded: liver failure in 4, nonconvulsive SE in 5, epilepsia partialis continua in 1, and premedication in 4. Therefore, our results are based on 68 patients (age range 1 to 85 years; 27 females). The etiology of SE was CNS infection in 38, stroke in 9, metabolic-toxic encephalopathy in 16, drug withdrawal in 2, and idiopathic in 3 patients. CT scan was performed in 49 patients, and MRI was performed in 25 patients; the CT scan was abnormal in 23 patients (47%), and MRI was abnormal in 17 patients (68%). As initial therapy, 35 patients received VPA, and 33 received PHT. The baseline features in two groups were comparable (table 1).

Effect of therapy. The SE was aborted by VPA in 23 (66%) and by PHT in 14 (42%), and the difference was significant (one-sided *p* value = 0.046, Fisher exact test). In refractory patients, as a second choice, VPA was effective in 15 of 19 patients (79%), whereas PHT was effective in 3 of 12 patients (25%) (one-sided *p* value = 0.004, Fisher exact test). Twenty-four–hour seizure freedom was achieved in 29 of 55 patients, of whom 8 achieved control with PHT, 10 achieved control with VPA, and 11 achieved control with a combination, which was insignificant (table 2). Thirteen patients did not respond to either of these drugs and required other drugs. None of the patients died within 24 hours of SE. However, 19 patients died during their hospital stay: 11 in the first week, 6 in the second week, and 2 in the third week. Six of these patients had metabolic encephalopathy, 16 had CNS infection, and 3 had stroke.

After therapy, hypotension occurred in 4, liver dysfunction occurred in 12 (increased SGPT in 12, serum bilirubin in 2), and respiratory depression occurred in 12 patients, 5 of whom needed artificial ventilation. The frequency of respiratory dysfunction, however, was higher in combination therapy but was not significant (table 3).

Discussion. In our study, VPA was more effective than PHT in controlling convulsive SE, both as the first (66% vs 42%) and as the second choice (79% vs 25%). In a study on SE, PHT was effective in 43.6%, diazepam was effective in 55.8%, lorazepam was effective in 64.9%, and phenobarbitone was effective in 58.2%.[4] Efficacy of PHT in our study is in agreement with these results. In another study of 13 elderly patients with SE, VPA was effective in 4.[5] In a retrospective analysis of 41 children, VPA terminated SE in 78% who were refractory to diazepam, phenobarbitone, and PHT.[6] In our study also, VPA as a second choice terminated SE more frequently (79%) than PHT (25%), which is in agreement with the reported

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Table 1 *Baseline clinical, laboratory, and radiologic variables in status epilepticus patients receiving VPA and PHT therapy*

Variable	VPA (n = 35)	PHT (n = 33)	*p* Value
Age			0.20*
Children (≤15 y)	8	4	
Adults (>15 y)	27	29	
Sex			0.12*
Male	24	17	
Female	11	16	
Seizure duration, hours	1.76 ± 0.49	1.70 ± 0.47	0.56
GCS score, mean ± SD	5.2 ± 0.9	5.2 ± 1.2	1.00
Etiology			0.35*
Primary injuries	24	23	
CNS infection	21	17	
CVA	3	6	
Secondary injuries			
Metabolic	10	6	
Drug withdrawal	0	2	
Unknown	1	2	
Associated medical illness (diabetes, hypertension, renal failure, cardiac, etc.)			0.46*
Present	12	10	
Absent	23	23	
Serum albumin, mean ± SD	3.29 ± 0.70	3.53 ± 0.66	0.37
Cranial imaging			0.41*
Positive	19	16	
Negative	16	17	

* One-sided *p* value.

VPA = valproate; PHT = phenytoin; GCS = Glasgow Coma Scale; CVA = cerebrovascular accident.

Table 2 *Clinical seizure cessation after infusion and 24-hour seizure freedom in patients with status epilepticus after VPA, PHT, VPA-PHT, and PHT-VPA*

Primary outcome	Status aborted	Status not aborted	SE	One-sided *p* value
VPA	23 (65.7%)	12 (34.3%)	0.08	0.046
PHT	14 (42%)	19 (58%)	0.09	
VPA-PHT	3 (25%)	9 (75%)	0.12	0.004
PHT-VPA	15 (79%)	4 (21%)	0.09	
Secondary outcome	**24-h seizure freedom**	**Recurrence within 24 h**		
VPA	8 (57%)	6 (43%)	0.13	0.32
PHT	10 (43.4%)	13 (56.6%)	0.10	
Combination	11 (61%)	7 (39%)	0.11	

VPA = valproate; PHT = phenytoin; VPA-PHT = valproate followed by phenytoin; PHT-VPA = phenytoin followed by valproate.

efficacy of VPA as second, third, or even fourth choice. The higher efficacy of VPA has been attributed to its synergistic effect with previously administered antiepileptic drugs; however, a delayed effect of PHT cannot be ruled out.[7] It is also possible that VPA may displace PHT from albumin, thus increasing the level of free PHT. In our study, however, serum albumin levels were comparable between the two groups. The reported side effects of PHT in SE are hypotension (27%), respiratory depression (9.9%), and cardiac arrhythmia (6.9%).[4] In our study, PHT resulted in hypotension and respiratory depression in 2 patients each and cardiac arrhythmia in none. As opposed to this, VPA monotherapy was not associated with hypotension in any patient; respiratory suppression in 1; and liver dysfunction, which was easily managed, in 3. The side effects, however, were not significantly different between the groups, which may be due to small sample size. The safety and tolerability of VPA were reported, and up to 6 mg/kg/minute could be administered to a total loading dose of 45 mg/kg.[7,8] We, however, used VPA in a dose of 30 mg/kg and kept the infusion rate up to 2 mg/kg/minute.

Our SE patients had a high proportion of acute symptomatic epilepsy due to CNS infection, stroke, and systemic disorders as opposed to other studies.[4,7] This difference may be due to the higher prevalence of infections and infestations in the tropics.

To avoid bias, randomization was performed by one and evaluation was performed by another investigator, both of who were unaware of the treatment protocol. The identities of the drugs were not masked, which may have introduced some bias. Our results are also based on a small sample size, and antiepileptic drug levels were not measured. We re-

Table 3 *Side effects of drugs in patients with status epilepticus*

	Single drug			Multiple drugs		
Side effect	Phenytoin (n = 14)	Valproate (n = 23)	*p* Value	Phenytoin→valproate (n = 19)	Valproate→phenytoin (n = 12)	One-sided *p* value
Cardiac			0.14			0.49
Present	2	0		1	1	
Absent	12	23		18	11	
Respiratory			0.27			0.29
Present	2	1		5	4	
Absent	12	22		14	8	
Liver dysfunction			0.37			0.18
Present	2	3		3	4	
Absent	12	20		16	8	

corded EEG 1 hour after cessation of convulsion if the consciousness did not improve. The limitation of EEG in convulsive SE is well known because of technical difficulty and artifacts; however, EEG is invaluable in differentiating altered sensorium due to continued seizure from drug overdose.[9] Our results need confirmation in a larger study.

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