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Journal of Neurological Disorders & Stroke

Research Article

Comparison the Effects of Phenytoin, Phenobarbital, Topiramate, Carbamazepine and Sodiumvalproate on Sensory Nerve Conduction Velocity (SNCV) in Children under Treatment of Seizure

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Submitted: 08 October 2018

Accepted: 28 October 2018

Published: 30 September 2018

Keywords

- Seizure
- Anticonvulsant drug
- Nerve conduction velocity
- Epilepsy

Abstract

The aim of this study was to investigate the effect of antiepileptic drugs (phenytoin, phenobarbital, Topiramate, carbamazepine and valproate) on sensory nerve conduction velocity (SNCV) in children under treatment of Seizure. 125 known patients with seizure were randomly categorized into 5 groups of 25, and each group received phenytoin, phenobarbital, Topiramate, valproate and carbamazepine. We used a group of 25 patients with febrile convulsion as a control group. We followed patients for 6 months and sensory and motor neural conduction velocity was recorded from each measured patient. Collected data analyzed by statistical methods in SPSS version 19.Anticonvulsant drugs all reduced the sensory nervous conduction velocity in patients and compared with drugs, the general drugs had a similar effect, but phenobarbital lowered the neurotransmission rate than the rest, and phenytoin had neuropathic complications more than other drugs. The changes mentioned were not related to the age and gender of the patients. Results showed that all of the anticonvulsants such as phenytoin, phenobarbital, Topiramate, and sodium valproate could be reduced the sensory neural conduction velocity in patients and the impact was similar between drugs.

INTRODUCTION

Carbamazepine, phenobarbital, phenytoin, Topiramate and sodium valproate are the most widely used antiepileptic drugs for the treatment of seizure disorders. These drugs have been moderately effective in managing seizures; each has undesirable side effects. Recent studies have shown that optimal use of single-drug therapy is often as effective as the use of two or more drugs and is frequently less toxic. So, an understanding of the appropriate use of the available drugs is of great importance. About one percent of the world general population had epilepsy. Epilepsy attacks after stroke are the second most common neurological disorder. Today standard treatments have managed to control nearly 80% of patients. Seizures are short term episodes as a result of abnormal discharge of brain neurons. Various causes of infections to neoplasm or trauma may play a role in causing these attacks [1]. Almost 4-10% of children experience at least one seizure. The prevalence of epilepsy in children is about1-2%. The purpose of the onset of treatment is to maintain optimal functional status. Almost in60% of children the seizure controlled with an appropriate primary drug and the results is satisfactory [2]. Seizure is one of the most common diseases in children's age group which is controlled by the availability of anticonvulsants,due to the effects of anticonvulsants it seems that these medications can be affect Sensory Nerve Conduction Velocity (SNCV) [3-6]. Of course, in the poisoning with some medications such as phenytoin the NCV has decreased. On the other one of the effective factors on the NCV was temperature while some anticonvulsants can increase fever in body [7-10]. Consumers of anticonvulsants in neurological examinations showed clinging deep reflexes [11]. Phenytoin, Phenobarbital, Carbamazepine and Valproate are antiepileptic drugs used to treat epilepsy due to their proper and economic effects which are used extensively against new drugs. Of course

this group of old medicines is not free of complications and has a variety of adverse effects either dangerous or unprotected and reversible. Decreasing the NCV is a mild complication. NCV is weekly common side effects which are among all anticonvulsants and if this complication is severe among children had clinical importance that needs to pay attention to the clinical use of these drugs by the doctor. The aim of this study was to investigate the effects of phenytoin, phenobarbital, Topiramate, carbamazepine and sodiumvalproate on the SNCV in treated seizure children.

METHODS

This study was a semi-experimental study. In this study, children aged 2-15 years with one of generalized or partial seizures requiring anticonvulsant drugs (Phenytoin, phenobarbital, Topiramate, carbamazepine, sodium valproate) selected and randomly divided into 5 groups each with 25 patients and each group received a drug. Children were excluded from the study if they had any effective disruption to NCV. A group of 25 other children with seizure fever which did not receive anticonvulsants and were considered as control group. At baseline NCV is performed that during this test, nerve is stimulated by the electrodes attached to the skin by the skin patch. Two electrodes are placed on the nerve pathway in the skin in this case the compound muscle action potential is recorded by the recipient electrode based on that NCS moves is interpreted as a nerve strip and in this study the NCV in the upper limb is measured in the median and ulna nerves and in the lower extremity of Peroneal and sural by the EMG-NCV, Micromed device made in Italy and 6 months later measurement of the patients was performed and the data were analyzed. After collecting NCV information from patients and control group at the beginning and end of the study, they were entered into SPSS along with information on age, sex and drug use and the results were evaluated during the 6months of use of the drug and compared to the control group and finally compared with the normal disturbances neurodegeneration speed entered into the reference of the neurology books was deduced.

Inclusion criteria

Children suffering from one type of tonic – colonic seizure, partial seizures, partial seizures with secondary generalization and other types (tonic, colonic, young Myoclonic Epilepsy and etc) that are diagnosed based on clinical examination and EEG and secondary causes of seizure such as trauma and tumors and electrolyte disturbance and etc. based on imaging methods and laboratory studies were included in the study.

Exclusion criteria

Children with any disruptive agent in the NCV include alcohol consumption neurological drugs (such as muscle relaxants, tranquilizers, psychotropic drugs)diabetes, hypothyroidism, systemic diseases, heart pacemakers and seizures due to secondary causes including brain tumors, traumas, electrolyte imbalance were excluded from the study. In this study parents of children were informed and the consent form was obtained.

RESULTS

The average age of children was 5.5 ± 2.9 with an age range of 1 to 11 .68 (45.2%) were boyand82 (54.8%) were girls. All of drugs studied compared to the control group reduces sensory and motor NCV ofupper and lower limbs nerves.

Results showed that the phenytoin as an anti-seizure drug significantly reduces the mean of NCV in the upper and lower limbs at baseline and after six months in compare with the control groupin median nerve was significant (Table1).

Results showed that phenobarbital as an anti-seizure drug has significant effect on the mean of NCV at the baseline and six months late in compare with control group in sural nerve was significant (Table 2).

Results showed that topiramate as an anticonvulsant drug significantly reduced the SNCV of Median, Ulnar, Sural and Peroneal nerves at baseline in compared with the control group and after six months follow treatment the significant difference were seen in the median and sural nerves in compare with control group (Table 3).

Results showed that sodium valproate as an anticonvulsant drug significantly decreased the sensory NCV of median nerve at baseline and six months late in compared with the control group (Table 4).

Studies have shown that Carbamazepine as an anticonvulsant drug at baseline in compared with the control group significantly decreased the SNCV of the upper and lower extremities of median, ulnar and peroneal nerves but after six months the significant difference was seen only in median nerve (Table 5).

After six months' follow-up treatment by drugs in median nerve the mean of NCV after six months in compare to baseline was significant in drug sodium valproate ($p=0.001$) and Carbamazepine ($p=0.001$). Also in Sural nerve the significant difference in the mean of NCV was seen only in drug Phenobarbital ($p=0.001$). The effect of anticonvulsant drugs on the sensory and motor NCV of the upper and lower extremities was not related to the gender and age of the patients. We could say that all groups were matched by age and gender difference during study.

By comparing the effect of phenytoin and phenobarbital on NCV, we showed that phenytoin reduced the mean of NCV in the median nerve more than phenobarbital and this difference was statistically significant. Comparing the effect of drugs on the NCV at the beginning of treatment and 6 months late the difference in the effect of phenytoin and carbamazepine was significantly different at 6 months while there was no significant difference in other drugs. Comparing the effect of Phenobarbital and topiramate on NCV, we see that to primate reduced the NCV in the median nerve more than Phenobarbital and this difference was statistically significant. Comparing the effect of Phenobarbital and valproate on NCV, we see that valproate sodium reduces NCV in median nerve more than Phenobarbital and this difference was statistically significant. Comparing the effect of Phenobarbital and carbamazepine on NCV we see that carbamazepine reduced the NCV in the median nerve more than phenobarbital and this difference was statistically significant. Results showed that the mean of NCV among all antiepileptic drugs by type of nerve hadn't significant difference and the effect of all drugs on NCV change was similar.

Table 1: Compare the mean of NCV in treated patients with phenytoin by type of nerve.

Type of nerve	Drugs	Mean	p-value
Median	Phenytoin in Baseline	52	0.001
	Control	58.7	
Median	Control	58.7	0.001
	Phenytoin 6 month late	51.6	
Ulnar	Phenytoin in Baseline	52.4	1
	Control	52.4	
Ulnar	Control	52.4	0.22
	Phenytoin 6 month late	50.6	
Sural	Phenytoin in Baseline	47.76	0.16
	Control	50.64	
Sural	Control	50.64	0.043
	Phenytoin 6 month late	47.2	
Peroneal	Phenytoin in Baseline	47.8	0.005
	Control	52.4	
Peroneal	Control	52.4	0.27
	Phenytoin 6 month late	42.9	

Table 2. Compare the mean of NCV in treated patients with phenobarbital by type of nerves.

Type of nerve	Drugs	Mean	p-value
Median	Phenobarbital in baseline	56.04	0.28
	Control	58.7	
Median	Control	58.7	0.055
	phenobarbital six month late	55.4	
Ulnar	phenobarbital in baseline	52.4	1
	Control	52.4	
Ulnar	Control	52.4	0.34
	phenobarbitalsix month late	53.2	
Sural	phenobarbital in Baseline	45.2	0.001
	Control	50.64	
Sural	Control	50.64	0.001
	phenobarbitalsix month late	43.8	
Peroneal	phenobarbital in baseline	45.2	0.001
	Control	52.4	
Peroneal	Control	52.4	0.002
	phenobarbitalsix month late	41.2	

Table 3: Compare the mean of NCV in treated patients with topiramate by type of nerves.

Type of nerve	Drugs	Mean	p-value
Median	topiramate in baseline	52.36	0.001
	Control	58.7	
Median	Control	58.7	0.001
	topiramate six month late	52.4	
Ulnar	topiramate in baseline	58.72	0.001
	Control	52.4	
Ulnar	Control	52.4	0.27
	topiramate six month late	50.1	
Sural	topiramate in Baseline	46.76	0.019
	Control	50.64	
Sural	Control	50.64	0.003
	topiramate six month late	46.2	
Peroneal	topiramate in baseline	46.8	0.001
	Control	52.4	
Peroneal	Control	52.4	0.06
	topiramate six month late	43.02	

Table 4. Compare the mean of NCV in treated patients with sodium valproate by type of nerves.

Type of nerve	Drugs	Mean	p-value
Median	sodium valproate in baseline	52.4	0.001
	Control	58.7	
Median	Control	58.7	0.001
	sodium valproate six month late	53.3	
Ulnar	sodium valproate in baseline	52	1
	Control	52.4	
Ulnar	Control	52.4	0.41
	sodium valproate six month late	50.08	
Sural	sodium valproate in Baseline	47.56	0.11
	Control	50.64	
Sural	Control	50.64	0.18
	sodium valproate six month late	47.8	
Peroneal	sodium valproate in baseline	52	1
	Control	52.4	
Peroneal	Control	52.4	0.047
	sodium valproate six month late	46.75	

Table 5. Compare the mean of NCV in treated patients with Carbamazepine by type of nerves.

Type of nerves	Drugs	Mean	p-value
Median	Carbamazepine in baseline	52.4	0.001
	Control	58.7	
Median	Control	58.7	0.001
	Carbamazepine six month late	50.6	
Ulnar	Carbamazepine in baseline	56.04	0.0046
	Control	52.4	
Ulnar	Control	52.4	0.47
	Carbamazepine six month late	48.7	
Sural	Carbamazepine in Baseline	48.12	0.26
	Control	50.64	
Sural	Control	50.64	0.23
	Carbamazepine six month late	48.04	
Peroneal	Carbamazepine in baseline	56.04	0.049
	Control	52.4	
Peroneal	Control	52.4	0.35
	Carbamazepine six month late	46.3	

DISCUSSION

In this study the main object was to investigate the impact of antiepileptic drugs on NCV in patients with seizure and our study results showed that the mean of NCV in all nerves reduced in compare with control group but after six months follow treatment the significant differences in median nerve were seen in sodium valproate (p=0.001) and Carbamazepine drugs (p=0.001). Also in Sural nerve the significant difference after six months in compared with baseline only seen in phenobarbital drug (p=0.001). In compare the rate of reduction between drugs results showed that among all nerves the trend of changes and difference were significant and all of drug had significant and similar impact on the NCV. Also the results showed that Carbamazepine and phenytoin are most likely to be successful overall when used for the treatment of seizures in children in compare to the other drugs. Carbamazepine might be preferable in children, adolescents or women that confirmed by results of this study. In a similar study in 1990 Krause et al suggested that anticonvulsants reduced the NCV in the median and peroneal nerve [3].A review by Danner and et al found that carbamazepine as an anti-seizure drug more than phenytoin reduced the NCV [12]. According to the results of Freeman et al research on the subject of polyneuropathy treatment the mean decrease in NCV in control group was higher than topiramate. Secondary measurements showed that the NCV was not reduced for topiramate treated patients [13]. Swift and et al in a study showed that there was no relationship between phenobarbital or phenytoin levels and the duration of their use and abnormal electrical findings as well as environmental neuropathy [14]. According to research by Chokroverty et al., the NCV in the posteriortibial nerve was significantly reduced in patients who had been treated with phenytoin for more than 10 years or those who had a drug level of more than 20 mg / ml in their blood [15]. In a study by Danner and et al the results showed that carbamazepine could reduce the NCV during 4 weeks after treatment [16]. The results of Danner and et al study showed a significant decrease in the

mean of NCV in seizure patients who receiving anticonvulsants [17]. In research by Castro et al, the NCV in patients receiving anticonvulsants is significantly reduced in comparison to the control group which includes healthy subjects [18]. According to research by Ramirez et al, long term use of phenytoin causes the destruction of their neurons and demyelination and reduces NCV and 16months after the drug cut, the neural cells are restored [19]. Study by Traccis and et al showed that long term treatment with carbamazepine reduces the sensory and motor NCV of the environmental nerves [20]. Zebrowska and et al concluded in their research that if you take 300 - 400 mg of phenytoin every day, NCV in the environmental nerves will not decrease [21]. Also Boylu and et al in a study showed that Sodium valproate, Carbamazepine and topiramate have not significant impact on the NCV which wasn't in line with our study results because we showed that these drug effective in the reduction rate of NCV in seizure patients [6].

The present study showed that all of the anticonvulsants used in this study reduced the sensory NCV of the upper and lower limb nerves. This difference was statistically significant for each drug at baseline compared to the control group. About Phenytoin and carbamazepine results showed that the difference in NCV in baseline and six months late was significant (p=0.001).

Geraldini and Taylor in their study showed that gender was not related to the effect of anticonvulsant drugs on NCV inpatients [5,22]. Krause and et al in their study showed that the gender of patients was ineffective in the sensory NCV of median and perineal sensory and motor NCV. The NCV in the median nerve in men was lower than women [3]. Boylu and Shorvon and Encinoza in their research stated that the gender of the patients did not affect the NCV which was in line with our study results [4,6,23].

The findings of this study were in line with other studies which showed that the gender of patients did not affect the sensory and motor NCV in patients treated with anticonvulsant. Boylu and Shorvon and Encinoza in their research showed that age of the patients did not affect the NCV and the results of this study similar to other studies, showed that there was no correlation between the age of patients and the reduction rate of sensory and motor NCV when taking anticonvulsant drugs [4,6,23].

Danner and et al found that anticonvulsant medications reduce NCV but carbamazepine reduces NCV more than phenytoin [12]. The results of Mervaala et al study showed that the effects of phenytoin and carbamazepine on the NCV were similar to other studies and the effect of sodium valproate on reducing NCV is less than the other two drugs [24]. Zafeiridou and et al in their study showed that phenytoin even at below concentrations has not neurological complications [25]. Hamed and et al showed that among the anti-seizure drugs, phenytoin had the most complications of neuropathy. Environmental neuropathy is almost reportedin carbamazepine treatment and environmental neuropathy also common in the administration of other anticonvulsants such as sodium valproate and topiramate [26]. Uemura and et al in a study showed that the decreasing rate of NCV in phenytoin is higher than carbamazepine [27]. According to Ay et al study, both of carbamazepine and valproate sodium cause environmental neuropathy and there was no significant difference in the side effects of neuropathy between two drugs [28]. In this study similar to previous studies, phenobarbital was decreased the rate of NCV more than other drugs and phenytoin more than other drugs. But differences in the results of the effects of carbamazepine can be due to the variability of its blood level and previous studies have been carried out to evaluate the blood levels of drugs and starting an anticonvulsant medication as a first line of treatment may also be involved. Also the racial and age differences in response to drugs should not be overlooked and this topic due to neurological complications especially in children is very important.

CONCLUSION

All of the anticonvulsants used in the study, reduced the motorsensory NCV of the upper and lower extremities of the all nerves in compared with control group and so for understanding of the appropriate use of more drugs replace one drug on treatment of seizure we could select the better choice of each drug for treatment of seizure patients without pay attention to the sex and age of patients. Because of the importance of this topic among children cases and also due to more studies in adults, it is suggested that studies be conducted on the basis of the blood levels of drugs in the future specialty among children.

LIMITATION

In this study we only investigated the impact of antiepileptic drugs on NCV in children treated for seizure and the quality of treatment and rate of improvement of patients not discussed in the study. Also due to lake of study about this topic in the country among children we couldn't have more detail about topic and compare with other internal studies.

FINANCIALLY SUPPORT

This study results of a Medical Doctoral thesis which approved by Ardabil University of Medical Science and author would like to thanks all patients participated in the study.

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Cite this article

Ahmadabadi F, Fattahzadeh GH, Atalu A, Badihi P (2018) Comparison the Effects of Phenytoin, Phenobarbital, Topiramate, Carbamazepine and Sodiumvalproate on Sensory Nerve Conduction Velocity (SNCV) in Children under Treatment of Seizure. J Neurol Disord Stroke 6(3): 1146.