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Effect of Sodium Valproate in Children with Epilepsy under 2 Years of Age: Study in a Tertiary Care Hospital, Rajshahi, Bangladesh

Fazlur Rahman[1*], Md. Mosharrof Hossain[1], Md. Ruhul Amin[1], Masuda Parvin[2], Md. Mostafizur Rahman[3]

[1]Assistant Professor, Department of Pediatrics, Rajshahi Medical College, Rajshahi, Bangladesh. *Corresponding author

[2]Assistant Professor, Department of Pediatrics, Kushtia Medical College, Kushtia, Bangladesh.

[3]Assistant Professor, Department of Dermatology &Venereology, Rajshahi Medical College, Rajshahi, Bangladesh.

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Abstract

Background: Sodium valproate is proposed for addition to the Model List of Essential Medicines for use in the management of epilepsy in children. This is effective in treating many seizure types, like a generalized tonic-clonic seizure, myoclonic seizure, absence seizure and in other epilepsy syndromes like infantile spasms, Landau-Kleffner syndrome (LKS), etc. **Aim of the study:** This study aimed to observe the side effects caused by sodium valproate in children with epilepsy below 2 years of age. **Methods:** An observational study was conducted in the Department of Pediatrics, Rajshahi Medical College Hospital, Rajshahi, Bangladesh during the period from January 2020 to December 2020. Fifty (50) children below 2 years of age with epilepsy were enrolled in this study. Enrolment was done after informed verbal consent from the mother or the attendant. A detailed history was taken about demographic factors which include children's age, age at onset of seizure, height, weight. Data were collected in a pre-designed questionnaire. The data was processed and analyzed by the application of SPSS version-22. **Results:** Male was dominating in the gender distribution and were 54% and female were 46%. A maximum of 46% of patients was diagnosed with epilepsy between 6-12 months. Out of the total studied patients, the maximum 44% started sodium valproate at ages between 7-12 months. Among the total studied patients 40% took 26-30mg/kg/day sodium valproate as their treatment regime. A total of 16% had anemia among the studied patients, whereas for the rest 84% of patients, no other symptoms were found during their general examination. Among the total studied patients, the most dominating side effect of the patients was vomiting which resulted in 1/5th (20%) of all side effects. The side effects of both hair loss and loss of appetite show the same result of 10% for each whereas, only 4% and 2% had abdominal pain and weight gain respectively. **Conclusion:** In this study, vomiting was found as the most significant side effect, which was similar to other different studies. These findings may be helpful in further research. It was a single-centered study with a small-sized sample.

Keywords: Effect, Epilepsy, Sodium Valproate.

INTRODUCTION

Sodium valproate is effective in controlling tonic-clonic seizures, particularly in primary generalized epilepsy. It is used to control seizures (fits) in most types of epilepsy. Sodium valproate may be used alone or in combination with another anticonvulsant for the treatment of epilepsy. Sodium valproate may take several days to show an initial effect and in some cases may take two to six weeks for the maximum effect. Treatment is started with low doses and may be increased over a couple of

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weeks according to the response. This is effective in treating many seizure types, like a generalized tonic-clonic seizure(GTCS), other types of generalized epilepsy like a myoclonic seizure, absence seizure, in other epilepsy syndromes like an infantile spasm, severe myoclonic epilepsy (SME), Landau –Kleffner syndrome (LKS), myoclonic-astatic epilepsy (MAE), etc. Sodium valproate has rare but severe side effects on the liver, bone marrow, and pancreas.[1] Most Sodium valproate hepatotoxicity occurred in children younger than 2 years who had pre-existing neurological or other physical defects.[2] Special precaution should be needed for its use in children below 2 years of age and children treated with multiple anti-epileptic drugs (AEDs). Sodium valproate is an anticonvulsant. Epilepsy is a neurological disorder that demands immediate medical attention and might even require long-term therapy. Sodium valproate is one of the most potent drugs with a broad spectrum anticonvulsant effect for the management of many seizure types, including generalized tonic-clonic seizure,[3] In cases where other potential anticonvulsants are not available or costly, sodium valproate is often used. This includes West Syndrome, severe myoclonic epilepsy, myoclonic-astatic epilepsy (MAE). There is a need of monitoring the drug level continuously in the high-risk group (e.g. infants under 3 years of age receiving polytherapy) which exhibited the highest between-subject as well as within-patient variability.[4] But in this study, drug level of sodium valproate is not monitored, because children received this drug at a maximum dose of 40 mg/kg/day which is usually tolerable. Due to its wide range of effectiveness, availability, and cost-effectiveness, sodium valproate has been used for a long time in countries like ours. Sodium valproate achieved a high degree of seizure control with 75% of patients having at least 12 months of freedom from seizures.[6] The current study attempted to analyze the various patterns of side effects resulting from using the Sodium valproate in children younger than 2 years of age with epilepsy and their impact on the continuation of Sodium valproate therapy. Epilepsy is a common neurological disorder that demands immediate medical attention and often long-term therapy. A high prevalence of epilepsy in children is a common occurrence in developing countries.[5] There are situations where Sodium valproate is absolutely indicated where other potential anticonvulsants are not available or costly that includes West Syndrome, severe myoclonic epilepsy, myoclonic-astatic epilepsy (MAE). Sodium valproate achieved a high degree of seizure control with 75% of patients having at least 12 months of freedom from seizures.[7]

Objectives

To observe the effect of using Sodium valproate in children with epilepsy below 2 years of age.

MATERIALS AND METHODS

An observational study was conducted in the Department of Pediatrics,

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Rajshahi Medical College Hospital, Rajshahi, Bangladesh during the period from January 2020 to December 2020. Fifty (50) children below 2 years of age with epilepsy were enrolled in this study. Enrollment was done after informed verbal consent from the mother or the attendant. A detailed history was taken about demographic factors which include children's age, age at onset of seizure, height, weight. Data were collected in a pre-designed questionnaire. The data was processed and analyzed by the application of SPSS version-22.

Inclusion criteria:

Children with epilepsy of both sexes under 2 years of age group, who were prescribed Sodium valproate by the attending physician of the study center.

Exclusion criteria:

Children with status epileptics and seizures associated with acute conditions like stroke are excluded. Patients with pre-existing hepatic impairment, bone marrow abnormalities, and neuro-metabolic diseases were also excluded.

RESULTS

Sodium valproate is rarely used in cases of epilepsy below 2 years of age. That is why the target group was small in size and only 50 children having epilepsy were seen and investigated in the data-gathering period. In this study, the proportion and pattern of side effects were observed in 50 cases of children with epilepsy who were prescribed sodium valproate by the attending physician of the study center. Study results have shown below in the tabulated and graphic form.

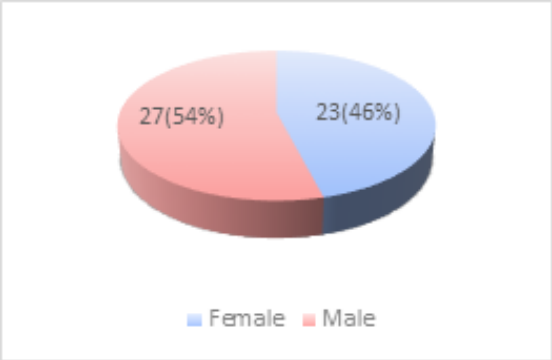

Figure 1: Sex of the patients(N=50)

Table 1: Descriptive statistics of some demographic characteristics of the patients (N=50)

Demographic characteristics	Minimum	Maximum	Mean	SD
Age of the patients (months)	6	36	15.88	6.81
Age at onset of seizure (month)	2	20	8.3	4.99
Weight (Kg)	7	14	10.26	1.66
Height (cm)	65	93	76.82	7.02

Table 2: Distribution according to age at diagnosis (N=50)

Age at diagnosis	Frequency	Percentage (%)
< 6 months	14	28.00
6-12 months	23	46.00
12-24 months	13	26.00
Total	50	100.0

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Table 3: Distribution of the patients by the dose of sodium valproate (N=50)

Dose (mg/kg)	Frequency	Percentage (%)
20-25 mg	16	32.00
26-30 mg	20	40.0
31-35 mg	10	20.0
36-40 mg	4	8.00
Total	50	100.0

Table 4: Distribution of the patients by types of epilepsy (N=50)

Types of epilepsy	Frequency	Percentage (%)
GTCS	37	74
Infantile spasm	7	14
Myoclonic epilepsy	6	12
Total	50	100.0

[Table 1] showed that among the total studied patients, the minimum and maximum age of them was 6 months and 36 months respectively, the mean±SD age was 15.88±6.81 months. In relation to the onset of a seizure, the minimum and maximum age of the patients were 2 and 20 months respectively and their mean±SD age was 8.3±4.99 months. It also revealed that the minimum and maximum weights of the study participants were 7 kg and 14 kg respectively, the mean±SD weight was 10.26±1.66 kg. The study also revealed that the minimum and maximum height of the patients was 65 cm and 93 cm respectively and the mean±SD height was 76.82±7.02 cm. The sex composition of the study patients was presented in figure I. Results revealed that 54% of the population was male and 46% was female. [Table 2] showed the age at diagnosis of the patients, which points out that the maximum 46% of patients were diagnosed between 6-12 months, 28% patients below 6 months, and the rest 26% patients were range between 12-24 months. [Table 3] showed the dose of Sodium valproate among studied patients. Among the total studied patients 40% took 26-30mg/kg/day of Sodium valproate, 32% patients took 20-25 mg/kg/day, 20% took 31-35 mg/kg/day of Sodium valproate and only 8% took 36-40 mg/kg/day of Sodium valproate. [Table 4] illustrated that out of the total 50 patients 74% had GTCS, 12%, and 14% had Myoclonic epilepsy and infantile spasm respectively. [Table 5] illustrated the type of investigations done for the patients. Out of the total studied patients, the minimum and maximum percentages for Hb were 9% and 12.2% respectively, whereas their mean percentage for Hb was 11.18±0.70. Regarding the ESR the minimum and maximum investigations were 6 mm in 1st hour and 25 mm in 1st hour respectively, whereas their mean investigation for ESR was 12.54±4.26. The investigation for TC of WBC showed that the minimum and maximum count were $5.5X10^9/L$ and $13X10^9/L$ respectively, whereas the mean count for TC of WBC was 7.77 ±1.58. In relation to the percentage for Neutrophil illustrated that the minimum and maximum percentages were 22% and 59% respectively, whereas their mean percentage for Neutrophil was 46.4±6.45. The investigation for Lymphocytes showed that the minimum and maximum

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percentages were 40% and 60% respectively, whereas the mean percentage for lymphocytes was 49.82±4.9. In regard to the Monocyte, the maximum percentage was 10%, whereas there was no minimum result for Monocyte percentage and their mean percentage for Monocyte was 2.54±1.86. The percentage for Eosinophil showed that the minimum and maximum percentage among the total respondents were 2% and 7% respectively, whereas their mean percentage for Eosinophil was 3.13±1.81. In regard to the Platelet, the minimum and maximum count among the 49 studied patients out of 50 were 210X10^9 /L and 410 X10^9 /L respectively, whereas the mean number for Platelet was 287.14±35.92. This table also revealed that the investigation for Serum ammonia among the total patients results that the minimum and maximum levels were 21 micromole/L and 63micromole/L respectively, whereas the mean level for Serum ammonia was 43.1±9.68. The level for Serum SGPT showed that the minimum and maximum levels were 15 U/L and 35 U/L respectively, whereas their mean level for Serum SGPT was 25.08±5.29. Table VI showed the side effect of the Sodium valproate of the studied patients. Among the total studied patients, the most common side effect was vomiting which resulted in 1/5th (20%) of all side effects. The side effects of both hair loss and loss of appetite showed the same result of 10% for each whereas, only 4% and 2% had abdominal pain and weight gain respectively. No patient had clinical, serological, or sonological evidence of pancreatitis and hepatic impairment. [Table 7] showed the association between side effects of sodium valproate with a type of epilepsy. Among the total studied patients, 20% had vomiting which is a common side effect in all types of epilepsy. The trend of this result is almost the same for both hair loss and loss of appetite of 10% for each side effect that holds all types of epilepsy. In addition, this table also revealed that the side effects of both weight gain and abdominal pain were contained by only one type of epilepsy out of three i.e. infantile spasm for weight gain, whereas GTCS for abdominal pain. The 2 cases of abdominal pain were further evaluated by USG of hepatobiliary system.

Table 5: Descriptive statistics of different types of Investigations sought by the patients (N=50)

Investigations	N	Minimum	Maximum	Mean	Std. Deviation
Hb (%)	60	9.00	12.20	11.18	0.70
ESR (mm in 1st hour)	60	6.00	25.00	12.54	4.26
TC of WBC (10^9 /L)	60	5.50	13.00	7.77	1.58
Neutrophil (%)	60	22.00	59.00	46.40	6.45
Lymphocyte (%)	60	40.00	60.00	49.82	4.90
Monocyte (%)	60	0.0	10.00	2.54	1.86
Eosinophil (%)	9	2.00	7.00	3.13	1.81
Platelet (10^9 /L)	59	210.00	410.00	287.14	35.92
Serum ammonia (micromole/L)	60	21.00	63.00	43.10	9.68
Serum SGPT (U/L)	60	15.00	35.00	25.08	5.29

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Table 6: Distribution according to side effects of the patients (N=50)

Side effects	Frequency	Percentage (%)
Vomiting	10	20.0
Hair loss	5	10.0
Weight gain	1	2
Abdominal pain	2	4
Loss of appetite	5	10
No side effects	28	56

Table 7: Association of side effects of Sodium valproate with types of epilepsy (N=50)

Side effects	Types of epilepsy			Total
	GTCS	Infantile spasm	Myoclonic epilepsy	
Vomiting	5(10.0%)	1(2.0%)	4(8.0%)	12(20%)
Hair loss	3(6.00%)	1(2.0%)	1(2%)	6(10.0%)
Weight gain	0	1(2.0%)	0	1(2.00%)
Abdominal pain	2(4.00%)	0	0	2(4.00%)
Loss of appetite	3(6.00%)	1(2.0%)	1(2%)	5(10.0%)

DISCUSSION

Seizures have been found to have a higher incidence in younger children with a decreasing frequency in the older age group.[8,9] In childhood epilepsy, the common age at diagnosis is 1 month to 5 years observed in a study,[10] but in this study, epilepsy has been frequently found at the age of 6months to 1 year. In this study, male was dominating in the gender distribution and were 54% and female were 46%. In many other studies, seizures were found to be more common in males also.[8,9] To control the seizures, maximum dose used here was 40mg/kg/day of Sodium valproate whereas a maximum dose of 30mg/kg/day was received by patients in other similar studies.[13] There was another study that showed the daily dosage of Sodium valproate was 30-50 mg/kg body weight in childhood epilepsy.[11] There are different types of epilepsy found in different age groups. In this study, most of the patients presented with GTCS (74%), and the second most was infantile spasm (14%). On the other hand, generalized tonic-clonic (62%), focal seizure (32%), and miscellaneous seizures (6%) were found in other studies. It was observed that GTCS is the most common type of epilepsy in childhood.[13] Thrombocytopenia is one of the side effects of valproate therapy.[14] In some studies, it was observed that thrombocytopenia occurred in the study populations (15 patients had thrombocytopenia out of 45 patients). Thus, immune-mediated thrombocytopenia may be a common occurrence at the administration of valproic acid, but the pathogenesis of this phenomenon remains to be explored.[14] However, this study didn't observe any case of thrombocytopenia with valproate therapy. Regarding metabolic disturbances, oftentimes a

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consequence of increased renal production of ammonia or inhibition of nitrogen elimination or both hyperammonemia is seen with valproic acid (VPA) therapy.[16,17]Enhanced hyperammonemia is seen with VPA therapy in the presence of poly-therapy hyperammonemia.[18,19] However, this study didn't observe any case of hyperammonemia with valproate therapy. Along with some rare side effects, there are some common side effects in valproate therapy. In this study, among 50 patients, there were some milder side effects found such as vomiting (n=10), weight gain (n=1), hair loss (n=5), and loss of appetite (n=5). Similarly, another study conducted a retrospective analysis of 100 children with epilepsy treated with Sodium valproate and found some milder but troublesome side effects which were increased weight gain (n=44), gastrointestinal disturbances (n=20), transient hair loss (n=6).[11] During the course of a therapy, where 211 epileptic patients were given Sodium valproate as single-drug treatment, six cases of hair loss were found between Sodium valproate users.[7] Though the studies had different sample sizes, the findings were quite similar, especially the gastrointestinal disturbances and hair loss. Hepatotoxicity is a rare but very serious side effect in valproate therapy. High incidence of valproate hepatotoxicity in infants may relate to familial metabolic defects and the incidence of fatal hepatic failure associated with valproic acid (VPA) therapy is found to be the highest in children under the age of three years, particularly in those with developmental delay. Moreover, most cases of VPA hepatotoxicity occurred in children younger than 2 years who had pre-existing neurologic or other physical defects. Many were developmentally delayed. A precipitating illness, possibly viral, occurred in many children.[20] However, this study did not find any cases of valproate hepatotoxicity among the studied children. Acute pancreatitis is another known serious side effect of valproate therapy. In this study, no cases of acute pancreatitis were observed. Similarly, another study found a definitive association between valproate therapy and acute pancreatitis. Their study found only 2 cases of Valproate-associated pancreatitis described below 2 years of age. Even though the definite association between valproate and acute pancreatitis has been reported, the underlying etiology is still unknown.[21] Considering the various studies around the use of Sodium Valproate including the current, one has stated that there was no significant incidence of side effects with the exception of patients who developed vomiting, hair loss, loss of appetite, and weight gain. No hepatic and pancreatic impairment was found due to the use of Sodium valproate in treating epilepsy of children under 2 years of age. The average annual incidence of epilepsy in developed countries is 40-70 per 100,000 of the general population. In developing countries, this figure is much higher at around 100-190 per 100,000 of the general population per year.[22] The possibility that

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malnutrition might lower the seizure threshold hasn't been examined in detail yet. This review suggests potential biochemical mechanisms that could adversely affect seizure threshold, particularly the effect of malnutrition on inhibitory neurotransmitters and electrolyte imbalance.[19] Most cases of Sodium Valproate hepatotoxicity occurred in children less than 2 years old who had preexisting neurological or other physical defects. Special precaution should be needed for its use in children below 2 years of age and children treated with multiple anti-epileptic drugs (AEDs).[19] Various clinical studies over the last decades have demonstrated that valproic acid (VPA) is effective in the treatment of many seizure types, including absence, tonic-clonic, and partial seizures. Both as add-on therapy and as monotherapy, VPA is well-established as a first-line drug. In addition, it is also used to treat infantile spasms (West Syndrome), Lennox-Gastaut syndrome, febrile seizures, and status epilepticus.[1] A micro-dialysis study demonstrated the pharmaco-kinetic rationale for acute treatment with VPA. It is based on the rapid distribution of VPA to the brain.[2] A recent study performed a meta-analysis that compared VPA with carbamazepine in the monotherapy of epilepsy. The investigators concluded that there was no reason for the preference of VPA for generalized-onset seizures, while the preference for carbamazepine was supported in the case of partial-onset seizures.[21] Gastrointestinal side effects, e.g., nausea, vomiting, and gastrointestinal distress have been reported to occur in up to 25% of the patients, probably less with enteric-coated formulation.[1] Weight gain is a frequent problem and an increase in body weight and body mass index following VPA treatment has recently been studied. These studies show that weight gain occurs within the first ten weeks of treatment and is in the order of six kilograms.[22] Weight gain during VPA therapy is associated with metabolic changes like a decrease in Beta-oxidation of fatty acids,[23] increased insulin and insulin/glucose ratios, and increased leptin and insulin levels.[18] The problem appears to be more common in females, it is not necessarily eliminated by caloric restriction and it may lead to discontinuation of VPA therapy.[23]

CONCLUSION

In this study, vomiting was found as the most significant side effect which was similar to other different studies also.

These findings may be helpful for future researchers in further research. In fact, it was a single-centered study with a small-sized sample. So the findings of this study may not reflect the exact scenario of the whole country.

Recommendations

We would like to recommend more studies focusing on epilepsy in children under the age of 2 years with a larger sized sample for getting appropriate findings.

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