

Comparative Study of Alteration in Body Weight and BMI in Paediatric Patient with Epilepsy on Valproate or other Anticonvulsants in Tertiary Care Hospital

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Abstract: background: Epilepsy is a common neurological disorder in children which often require longterm antiepileptic therapy, Valproic acid is widely used antiepileptic drug as it has broad-spectrum activity and its well tolerated. Alteration in body weight and BMI has been reported with valproate and other anticonvulsants on longterm medications, although the real incidence and magnitude of the problem is still controversial, and hardly any comparative study is available in paediatric population. Our study aims to evaluate and compare the changes in bodyweight and BMI, in patients with childhood epilepsy on valproate or other anticonvulsants monotherapy. **method:** 80 children with newly diagnosed epilepsy attended in our hospital from July 2018 to July 2019 were included in our study and divided into two groups comprising 40 each. One group was given valproic acid and another group was given other anticonvulsants (levetiracetam, phenytoin, carbamazepine) monotherapy for at least one year. clinical examination and anthropometric data (height, weight, BMI) was measured, recorded in each visit and was compared at the end of one year. **results:** Significant BMI change noticed among sodium valproate group (45% patients, p value <0.05) compared to others anticonvulsants (12.5%, p value >0.05), but when the patients were categorized according to BMI (underweight, appropriate, overweight, obese), only 12.5% became overweight from baseline 10% for valproate group. 55% patients on valproate gain weight in excess of normal compared to 10% patients on other anticonvulsant in the age group of 3 to 12 years. **Conclusion:** clinically significant weight gain was found among 55% of those taking valproate, on the other hand only 10% with other anticonvulsants caused significant weight gain. patient with valproate only showed statistically significant increase in BMI causing increased overweight patient (12.5%) from baseline of 10% at the end of the year.

Keywords: anticonvulsants, valproate, epilepsy, BMI, W.H.O, growth chart, Z-score, percentile.

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I. Introduction

Pediatric epilepsy is one of the most common nervous system disorder which needs long-term administration of anti-epileptic drugs to control¹. sodium valproate is one of the most commonly used and safer broad-spectrum antiepileptic drug. In the long-term medication process, many cases of adverse reactions appear gradually, of which the most common is the influence of metabolism and endocrine function of children leading to obesity². Weight gain has traditionally been regarded as a characteristic adverse effect of sodium valproate therapy, Reported incidence of it has varied widely ranging from 7.5% to 73.0% in earlier studies^{3,4}. There are reports depicting weight gain in approximately 10% to 44% patients^{4,5}. weight gain was noted in 44 out of the 100 children treated with sodium valproate.⁶ Some risk factors may contribute to sodium valproate-induced weight gain are-(i) Gender: Girls seem to be more prone to weight gain during sodium valproate therapy than boys although very few studies have analysed and compared the patients on valproate or other anticonvulsants monotherapy by gender. (ii) duration: a long duration of therapy has been reported to be associated with significant weight gain. (iii) As far as daily dosage, it has been observed that there is no correlation between the degree of weight gain and daily sodium valproate dosage, as also serum sodium valproate concentration.⁷ (iv) Regarding the type of seizure treated with sodium valproate weight gain problem are more common in psychogenic seizure and generalized seizure⁸. The present study has been taken up to compare change of weight and BMI of patients on sodium valproate against other anticonvulsant monotherapy.

II. Methodology

aims and objectives:To measure and compare the alteration of body weight and B.M.I of children between 3 to 12 years of age with epilepsy after valproate or other anticonvulsants monotherapy for 1 year.

study area: Department of pediatrics, B.S.M.C.H

study population:Children diagnosed with epilepsy as per ILAE definition attending out patient and in patient department of pediatric medicine at B.S.M.C.H,West Bengal aged 3 to 12 years.

sample size: total 80, 40 in both groups.

sample design: The study population is selected satisfying inclusion and exclusion criteria and divided into two groups for receiving valproate or other anticonvulsants as monotherapy

period of study: july 2018 to july 2019

inclusion and exclusion criteria:Children diagnosed with epilepsy between 3-12 years of age and on single anticonvulsant therapy included in the study group. Patient having Thyroid disorder or other endocrinopathies, suffering from protein energy malnutrition and significant underweight, Chronic liver, heart or renal disease, Progressive neurological or psychological illness, Drugs which may alter the body weight and BMI of the patient like insulin, steroid, Receiving multiple anticonvulsants, Recent onset acute illness causing weight loss and drug noncompliant or those haven't given consent.

Study procedure:After obtaining ethical clearance from the Institutional Ethics Committee,study was conducted among the study population after taking informed consent from the guardian /parents. Patients were thoroughly examined and their caregiver/mother were interviewed with predesigned questionnaires. Anthropometric data were obtained, BMI was calculated and were plotted on growth charts and BMI charts for each child.

Outcome definition and parameters: Significant weight gain- various studies have taken significant weight gain as > 0.67 , $+1$, $+2$ increase in Z score after one year of therapy. For convenience of clinical assessment of data compilation , we have taken significant weight gain as $> 1SD$ increase in relation to baseline weight for age, taking WHO 2 to 5 years and 5 to 10 years weight for age standard reference^{11,12}.In the absence of 10 to 12 years WHO reference standards of weight for age, we have also used WHO percentile charts of weight for age, boys and girls, to assess weight gain in excess of normal in both the groups. We have defined "weight gain in excess of normal" as weight after one year crossing one percentile curve above, "normal weight gain" weight after one year does not cross one percentile curve. "Less than normal weight gain" as crossing one percentile curve below.

Children under 5 years of age-Overweight and obesity are weight-for-height greater than 2 standard deviations and 3 standard deviations above WHO Child Growth Standards median. Normal weight that falls weight for height 2 SD below and above WHO weight for height child Growth standard median,¹³ weight for age 2 SD deviation below and above WHO weight for age child growth standard median and BMI 2 SD below and one 1 SD above WHO BMI standard.

Children aged between 5–19 years: overweight is BMI-for-age greater than 1SD above the WHO Growth Reference median; and obesity is greater than 2 SD above the WHO Growth Reference median. Significant BMI gain – increase in BMI z score $+1,+2$ in WHO BMI z score chart for 2 years to 12 years .Normal BMI gain BMI does not crossing $+1$, $+2$ z score above or below WHO BMI z score chart for 2 years to 12 years .Less than significant weight gain- decrease in BMI z score $+1,+2$ in WHO BMI z score chart for 2 years to 12 years

Statistical analysis plan: Data was collected, recorded & compiled on Microsoft Excel data sheet. Statistical methods (mean, standard deviation) and softwares used to analyze the data. Study of significance analyzed by Chi square test for qualitative data and Student t-test for quantitative data. P value <0.05 is considered significant.

III. Results and analysis

Table no1: Categorization of study population according to race, gender and age groups taking valproate and other anticonvulsants.

Racial distribution (n=80)		Gender distribution (n=80)		Age(years)	Valproate (n1=40)		Other anticonvulsants group (n2=40)	
Race	Number(%)	Boys(%)	Girls(%)		Boys(%)	Girls(%)	Boys(%)	Girls(%)
Tribal	20(25)	11(13.75)	9(11.25)	3-<5	5(12.5)	6(15.0)	7(17.5)	5(12.5)
Nontribal	60(75)	42(52.50)	18(22.5)	5-12	20(50.0)	9(22.5)	21(52.5)	7(17.5)
Total	80	53(66.25)	27(33.75)	total	25(62.5)	15(37.5)	28(70.0)	12(30.0)

Mean age is 7.3 years and standard deviation 2.8years for those who are taking valproate, mean age is 7.5 years and standard deviation is 2.9 years for those who are taking other anticonvulsants before commencement of study.Hardly any previous study to compare valproate weight gain below 5 years to 12 years. Salvatore Grosso, Rosa Mostardini, Barbara Piccini¹⁰,Hussein Metwally Abdel Maksoud⁹ study comp-[are weight gain on valprate acording to age and sex.

Tableno2: Comparison among patient taking other anticonvulsants.(levetiracetam,phenytoin, carbamazepine).

age	levetiracetam		phenyton		carbamazepine	
	boys	girls	boys	girls	boys	girls
3-5	4	2	0	2	2	1
5-12	10	4	6	2	6	1
total	14	6	6	4	8	2
	20		10		10	

Table no3: Status of weight of patient on Valproate and other anticonvulsants before and after treatment.

Age (years)	Before treatment started				After completion 1year of treatment			
	Valproate		Other anticonvulsants		Valproate		Other anticonvulsants	
	Normal weight	Overweight	Normal weight	overweight	Normal weight	Overweight	Normal weight	overweight
3-5	12	0	13	0	11	1	13	0
5-12	24	4	27	0	24	4	26	1
total	36	4	40	0	35	5	39	1

Table no 4:-Patients' weight, height and BMI before and after anticonvulsants therapy

parameter	valprote			Other anticonvulsant		
	Before	after	P value	before	After	p-value
Weight (kg)	24.9 ± 8.1	27.48 ± 8.61	< 0.05	25.10 ± 7.86	26.92 ± 7.93	< 0.05
Height(cm)	120.73 ± 15.55	125.36 ± 15.27	< 0.05	122.21 ± 15.07	126.22 ± 15.36	< 0.05
BMI(kg/m ²)	16.53 ± 1.51	16.97 ± 15.28	< 0.05	16.28 ± 1.38	16.48 ± 1.31	> 0.05(0.07)

There is no statistically significant difference in body weight (p-value=0.91,t=0.11) and BMI(p-value=0.44,t=0.77) among these two group before commencement of study.

Tableno5:Weight gain among patient of 3 - 10 years of age taking sodium valproate n other anticonvulsants

AGE (years)	valprote			Other anticonvulsant		
	3-5yrs(%)	5-10yrs(%)	Total(%)	3-5 yrs(%)	5-10yrs(%)	Total(%)
Significant weight gain	6(21.42)	8(28.57)	14(50)	3(10.71)	1(3.57)	4(14.28)
Normal weight gain	5(17.85)	9(32.14)	14(50)	9(32.14)	15(53.57)	24(85.72)

Table no 6: BMI change among patient taking valproate n other anticonvulsants

AGE (YEARS)	valprote			Others anticonvulsants					
	3-5yrs	5-12yrs	total	3-5years	5-12yrs	total	levetiracetam	phenytoin	carbamazepin
Significant BMI gain	5	13	18	3	2	5	3	1	1
Normal BMI change	6	16	22	9	26	35	17	9	9

Table no 7: Weight gain in excess of normal with sodium valproate and other anticonvulsants

AGE (YEARS)	valprote			Others anticonvulsants					
	3-5yrs	5-12yrs	total	3-5years	5-12yrs	total	levetiracetam	phenytoin	carbamazepin
Significant BMI gain	5	13	18	3	2	5	3	1	1
Normal BMI change	6	16	22	9	26	35	17	9	9

To our knowledge there were hardly any study observed comparing weight gain with sodium valproate and other anticonvulsants in pediatric age group, but there were studies comparing weight gain with sodium valproate and other anticonvulsants in adult age group. Torrent *et al*¹⁴, Sudhir Chandra Sarangi³⁶ adult study compared change of weight with sodium valproate with other anticonvulsants (carbamazepine and lamotrigine) have shown that valproic acid causes weight gain not carbamazepine and lamotrigine. We observed there were few study on effect of sodium valproate on weight and BMI. There were few studies comparable to our age group (3 years to 12 years) showing effect of sodium valproate on weight gain i.e Ercan Demir³⁷ study done in 3 years 6 month to 15 years age group, Hussein Metwally *et al*³⁵ study done in 2 years to 14 years age group. To our knowledge there is no study based on tribal population, this study done in Bankura Sammilani medical college & hospital, where a huge amount of patient belongs to tribal population. So we have the opportunity to analyse their weight gain with non tribal patient. In this study, both study groups had mean BMI within the normal range. Significant BMI change noticed among sodium valproate group (45% patients, Mean BMI is increased to 16.97 ± 1.54 , from 16.54 ± 1.51 , p value < 0.04) compared to others anticonvulsants (12.5% patient, mean BMI increased to 16.48 ± 1.31 from 16.28 ± 1.38 , p value > 0.04) which did not shown any significant change. Despite the significant valproic acid-associated increase in BMI, when patients were categorized according to BMI (underweight, appropriate, overweight, obese) the percentage of patients who were overweight rose only to 12.5% (5 patients) from 10% (4 patient) at the end of one year, only 2.5% patient became overweight compared to baseline 0% in other anticonvulsant group. Previous studies of Sahota P *et al*¹⁵, Ayyagari M *et al*¹⁶ and Rauchenzauner M *et al*²⁰ have reported increase in BMI in sodium valproate treated subjects, while de Vries *et al*²³ have reported no increase in BMI after sodium valproate treatment. In this study weight gain noticed in both sodium valproate (p value < 0.04) as well as others anticonvulsant group (p value < 0.05) were statistically significant, but among the patients on sodium valproate 50% patient gain significant weight compared to 14.3% patients on others anticonvulsants gain significant weight at the end of study in the 3-10 years age group and 40% patients on valproate gain in excess of normal weight compared to 10% patients on other anticonvulsant in the age group of 3 to 12 years. Egger J *et al*²⁶, Dinesen H *et al*²⁷, Verity CM *et al*²⁸ and Davidson DLW *et al*²⁹ study shows significant weight gain on valproate therapy. There are not many studies regarding the effect of levetiracetam on body weight. Levetiracetam was found "weight-neutral" by Gidal *et al*²¹ and Briggs DE *et al*²². Levetiracetam in this study is weight neutral. Qiang Yuan *et al*³⁷, comparative study between valproate and levetiracetam found valproate causes significant increase BMI. This study shows carbamazepine and phenytoin is also weight neutral. Among patients on sodium valproate no significant difference in weight gain in excess of normal between 3 to below 5 years (55%) and 5 years to 12 years (53%) age group. When comparing patients on valproate in two sex group 40% patients in both sex gain weight in excess of normal in 3 to 12 years group. So we did not found any significant difference in weight gain in two sex group. An evaluation of adolescent girls suggested that pubertal and postpubertal girls receiving valproic acid treatment have a higher risk of developing weight gain than adults on valproic acid²⁴, that finding was not confirmed by Wirrel²⁵. This study did not shows carbamazepine and phenytoin significantly increase in BMI. There are previous studies demonstrating neutral effect of carbamazepine^{18,19,20} phenytoin^{15,16}. However, many studies reported that women on carbamazepine had a greater BMI when compared with the control group^{31,32}. In this study Levetiracetam does not shows significant BMI change (p value > 0.04). Several studies investigated valproic acid-associated weight gain in populations who range in age from a few months to 18 years^{31,32,33}. To our knowledge, two study (Salvatore Grosso *et al*³⁴, and Hussein Metwally³⁵) evaluating valproic acid-associated weight gain specifically included only young children. Hussein Metwally *et al*³⁵ study shows significant increase in both weight and BMI, while Salvatore Grosso *et al*³⁴ study shows despite significant increase in weight, there is no significant increase in BMI. Our study is in line with Hussein Metwally *et al*³⁵, shows both significant increase in weight and BMI. To our knowledge no previous study done on children with valproate based on tribal population. Non tribal population (55%) shows more weight gain than tribal group (40%) with valproate. However sample size of tribal population is too small for statistical significance.

IV. Conclusion

It can be concluded from our study that sodium valproate causes significant gain in weight and BMI compared to other anticonvulsants. Obesity in children affects growth and development as well as confidence in treatment, so the side effects of sodium valproate treatment should be taken seriously. This study done in Bankura Sammilani Medical College and Hospital with small sample size which may not be representative of population in general, larger sample size could have helped comparison of tribal and non tribal population statistically.

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