VITAMIN B6 & TREATMENT OF INFANTILE SPASMS: A COMPARISON WITH STANDARD STEROID THERAPY

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Abstract:
Background:
Considering the inadequacies of current therapeutic regimens for infantile spasms (IS), and the frequent and serious side effects of Some regimens, the ongoing search for more enhanced protocols is understandable.
Materials and Methods:
We have compared the therapeutic and adverse effects of vitamin B6 given in high doses with those of prednisolone in a randomized controlled clinical trial. Vitamin B6 (40mg/kg/24hr) and prednisolone (1.5mg/kg/day) were given to in 22 and 15 patients respectively, and the patients were followed for at least 6 months.
Results:
Response to treatment was slightly better in the prednisolone group but the difference was not significant (p = 0.4). On the other hand adverse effects were also seen more frequently with prednisolone.
Conclusion:
We conclude that high dose vitamin B6 should be considered as an alternative method of treatment; it seems that it can be safely used where there is contraindication to use other antiepileptic drugs or where they have failed; even in newly diagnosed cases of IS.
Keywords: Vitamin B6, prednisolone, infantile spasm

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Introduction

Infantile spasms (IS), one of the most serious epileptic syndromes of infancy, responds poorly to most conventional treatments, with the outcome being frequently unfavorable in terms of seizure control and cognitive development (1-5). Many antiepileptic drugs have been tried (2). The indisputable role of corticosteroids in treatment of IS has been recognized many years; in fact, since Sorel (6) reported the first favourable response with the use of ACTH in 1958, steroids in the form of natural ACTH, synthetic ACTH, tetracosactide, prednisolone, and hydrocortisone have remained the first line of treatment for IS. Nevertheless, frequent and serious side effects of steroids have always urged researchers to look for less hazardous therapeutic methods (7-9). Beside steroids which are still considered as the cornerstone of the treatment, nitrazepam, vigabatrin, sodium valproate, vitamin B6, and zonisamide are among the alternatives; felbamate, lamotrigine, and

Topiramate, used as second line therapeutic agents (10-13); unfortunately however, most of the other aforementioned antiepileptics also have well known adverse effects which restrict their safe use (1,2,14,15). Among the more recently recommended therapeutic regimens, high dose vitamin B6 is one of the most popular (16,17). Vitamin B6 (pyridoxine) exerts its antiepileptic effect by increasing the concentration of GABA in the CNS. Pyridoxal phosphate, the active metabolite of vitamin B6, is the coenzyme for glutamate decarboxylase and GABA transaminase, the enzymes necessary for the production and metabolism of the central nervous system GABA (18, 19).

In the present study we have tried to evaluate vitamin B6 as a treatment for IS in comparison to prednisolone, the generally accepted standard therapy for the condition.

Patients and Methods

Our study was a randomized, clinical trial in which we used a variety of techniques and modalities including interview, history taking, physical exam, and data processing software.

All of the patients presenting to our center between August 2002 and Aug 2003 with syndrome of infantile spasms (IS), were enrolled, their past medical history, in particular their perinatal history, was reviewed and a thorough physical and neurological exam was performed. Weight, head circumference, and vital signs were recorded. The patients' age, duration of symptoms, sex, and frequency of seizures were recorded in specifically designed questionnaires, as were any other unusual observations.

Biochemical studies including serum electrolytes, blood sugar, and liver function tests were performed, as were other metabolic and serologic investigations, including, blood gas, amino acids and TORCH studies, to uncover the underlying disorder. In addition to the above, brain CT scan and EEG were obtained; the EEG was analyzed for abnormal patterns, although having hypsarrhytmia was not a prerequisite for subject enrollment in this study.

After completing the above investigations, treatment was started by either vitamin B6 or prednisolone. Each patient was randomly placed in either the "test" (treated by vitamin B6) or the "control" (treated by prednisolone) group. Vitamin B6 was given at a dose of 40mg/kg/24hr, and prednisolone at.1.5mg/kg/24hr, each being divided into 3 doses/day for at least two weeks. At the end of this period, subjects were assessed for decrease in seizure frequency, improvement in alertness, and developmental scale. The criteria of "response to treatment" were: 1. Interruption of seizures or a decrease of over 50% in their frequency, and 2. Improvement in the neurological exam, including alertness and developmental status. The patients were closely observed for appearance of drug side effects; to this end, blood pressure was checked and urine was tested for glucose daily; blood was drawn for electrolytes every 3 days; patients were weighed at the end of the 1st and 2nd weeks of therapy; they were also observed for any clues to infections. Patients were evaluated for therapeutic response after 2 weeks and were followed after discharge by outpatient visits on a monthly basis at least for 6 months.

For one year 38 patients were studied, at the end of which 8 patients were excluded, 7 owing to insufficient follow-up, and 1 due to suspicious investigations and doubtful diagnosis. Of the 30 patients remaining in the study group, 15 received vitamin B6, 8 were given prednisolone, and the other 7 patients received both drugs at different times; in fact these last seven patients were assessed twice, as they participated both once in the "test" and again in the "control" groups. As a result, vitamin B6 was totally tested in 22 and prednisolone in 15 patients. Although not many ethical considerations called for attention in this study, nevertheless, some were taken into account.All of the potential adverse effects were explained to the parents before the onset of the treatment and informed consent was obtained. Also all information concerning the patients was kept secret.

Results

The study group comprised 37 patients (age range 1.5 to 24 months), with nearly half of them, (18) aged between 6 and 12 months. The patients were predominantly male (26 out of 37(70.3%) and 11 patients (29.7%) were female. "Flexion" type of IS was observed in 17(45.9%) of patients, 8 had "extension" type (21.6%), and finally 12 patients had the "mixed" type.

Etiologically, a clear underlying cause was identified in 20 of the patients (symptomatic group). Of the remaining 17 patients, 7 had apparently normal neurological development prior to onset of the seizures (idiopathic group), and the other 10 patients reported developmental

tdelay before appearance of the spasms (cryptogenic group). Among the patients, with a specific known etiology (symptomatic group), 6 had history of different perinatal problems including: asphyxia, major infections, hypoglycemia, or respiratory distress and acidosis. CNS dysgenesis, tuberous sclerosis, and inborn errors of metabolism, were each observed in 3 patients; and lastly congenital rubella syndrome and postnatal herpes encephalitis were each detected in one case. Eighteen of the patients showed hypsarrhythmia in their EEG, 15 had other nonspecific abnormal patterns specially HVSW (high voltage slow waves); EEG did not reveal significant findings in the other 4.

No significant difference existed between the "test" and "control" groups in terms of age, sex, clinical form of seizure (flexion, extension, or mixed type), etiology, and EEG findings.

Patients who received prednisolone showed a more pronounced decrease in seizure frequency, but the difference not significant (p=0.4) (table1). A decrease more than 50% in seizures was considered as the cut-off point for response to treatment. Based on this, 66.7% of the patients in the prednisolone group and 36.3% of the patients in the vitamin B6 group showed therapeutic response.

Difference was even more negligible in terms of improvement in developmental status, and "Fischer" test did not reveal any significant differences between the two groups (table 2). A remarkable improvement was detected in 13.7% of patients receiving vitamin B6 and 20% of patients in the prednisolone group; it needs to be mentioned that one patient taking vitamin B6 recovered completely, whereas not a single such case was seen in the prednisolone group.

Of 7 cases who had received both drugs separately, 3 had no response to either of them; in three others vitamin B6 failed, while prednisolone showed relative success; in the last case vitamin B6 was successful, contrary to results with prednisolone.The reason for starting the second drug was lack of success with the first drug in 5 cases,and infections following prednisolone in the other 2. Regarding untoward effects, in particular the major ones leading to discontinuation of the drug, these were seen more commonly in the prednisolone group (infection and hypertension in each in three patients, liver dysfunction in two) (table 3).

Discussion

Seki and Takayamu(20) in 1996 tried a combination therapy of high dose Pyridoxal phosphate and low dose corticotropin for treatment of infantile spasms (IS) in an attempt to reduce side effects of corticotherapy, and they achieved favorable results.

Many authors -especially the Japanese- have tried vitamin B6 with high doses as the mono-therapy for IS in recent years (21-27); the reported range of success has been relatively wide. Through a meta-analysis in 2000, Ito et al reviewed the status of the treatments undertaken for IS in Japanese institutions and observed that vitamin B6 was the preferred first line drug for treatment (28), in

Table 1- Rate of seizure reduction after treatment

Therapeutic Group	Rate of Seizure Reduction	Complete Cessation	Reduction >90%	Reduction 50-90%	Reduction <50%	None	Total
Prednisolone	Number	4	4	2	1	4	15
	Percent	26.7%	26.7%	13.3%	6.6%	26.7%	100%
Vitamin B_6	Number	4	1	3	6	8	22
	Percent	18.2%	4.5%	13.6%	27.3%	36.4%	100%
Total	Number	8	5	5	7	12	37
	Percent	21.6%	13.5%	13.5%	19%	32.4%	100%

χ^2=2.17, P=0.14, df=1, There is no significant difference between the two groups

contrast to the US where ACTH is the drug most used by child neurologists (24). At most of the institutions, vitamin B6 was started at a dosage of 10 to 50 mg/kg/day and then was increased by 10 mg/kg/day every 3 to 5 days up to a dosage of 40-50mg/kg/day. Fourteen institutions prescribed fixed dosages. Altogether high-dose vitamin B6 therapy resulted in complete cessation of the spasms in 13% to 29% of patients [28).

We used the fixed dosage (40mg/kg/day) schedule in our study and found our results were similar to those of Ito et al's success rate for seizure control. Although in our study prednisolone controlled the seizures better than vitamin B6 did, but the difference was not statistically significant (table1). The difference between the two drugs was even narrower in terms of improving the developmental state of the patients, with the two agents having very similar effects (table2).

Table 2- Rate of improvement in developmental state after treatment

Therapeutic Groups	Developmental Improvement Rate	Complete Recovery	Remarkable Improve-ment	Slight improve-ment	No Improve-ment	Total
Prednisolone	Number	0	3	8	4	15
	Percent	0%	20%	53.3%	26.7%	100%
Vitamin B_6	Number	1	3	5	13	22
	Percent	4.5%	13.7%	22.7%	59.1%	100%
Total	Number	1	6	13	17	37
	Percent	2.7%	16.2%	35.1%	46%	100%

Fischer test did not reveal significant difference between the two groups

After intravenous B6 administration, apnea, lethargy, pallor, decreased responsiveness, and hypotonia may occur and persist for several hours (29, 30). These reactions have been also reported less frequently after intramuscular administration (31), and the initial oral dose (32). Believed to result from a massive initial release of GABA (32), these symptoms are usually mild but on rare occasions have necessitated intubation and assisted ventilation (33). Loss of appetite, periods of restlessness and crying, vomiting, and apathy have been reported during therapy for infantile spasms with high doses of vitamin B6 (17)

Table 3- Frequency of side effects observed with treatment

Side Effects		Prednisolone	VitaminB_6
Arterial Hypertension		3	1
Infection		3	0
Vomiting		0	2
Liver Dysfunction		2	0
Electrolyte Imbalance		0	0
Glucosuria		0	0
Weight Gain	<5%	1	2
	5-10%	4	2
	>10%	3	0

Fisher test did not reveal significant difference between the two groups

We used the oral route of administration and, in two cases only, encountered vomiting severe enough to need attention (smaller, more frequent meals). There were almost no other remarkable side effects seen in patients receiving vitamin B6. The four patients who showed weight gain with vitamin B6 administration, were dehydrated and emaciated infants at presentation whose general condition improved later following hydration and they regained their normal weight, in contrast to the patients in prednisolone group whose weight gain was due to development of cushingoid features. The treatment of infantile spasms seems to be far from ideal, considering the significant side effects seen in present medical therapeutics believed to be effective. Also, further blinded randomized clinical trials are needed to assess the long-term social and cognitive outcomes. At the same time, considering the above therapeutic results and especially the rare adverse reactions of high-dose vitamin B6, we conclude that this is a treatment well worth trying; it seems that high-dose vitamin B6 can safely be used where there are contraindications to use other antiepileptic drugs or where they have failed; this applies to their use in freshly diagnosed IS cases as well.

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