RESEARCH ARTICLE

COMPARATIVE EFFECTS OF NITRAZEPAM AND ACTH ON THE TREATMENT OF INFANTILE SPASM

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Abstract:

Objective

Infantile spasms (IS) or West syndrome is a convulsive disease characterized by brief, symmetric axial muscle contractions (neck, trunk, and/or extremities). The therapy universally recognized as most effective in the treatment of IS, is treatment with the adrenocorticotropic hormone (ACTH) or oral corticosteroids. This therapy however has important side effects. Many studies have sought to find alternative therapies with fewer side effects. Nitrazepam, it has been proven, can be as effective as ACTH in controlling infantile spasms. The aim of this study was to evaluate and compare the efficacy of Nitrazepam and ACTH on the treatment of infantile spasms.

Materials & Methods

This randomized controlled clinical trial, enrolled sixty patients with newly diagnosed and previously untreated IS; diagnosis was made based on the criteria of The International Classification of Epilepsies of the International League Against Epilepsy (ILAE). Prior to treatment, all patients underwent Electro encephalo graphs (EEGs) and CT scans. Patients were randomized to receive 0.5-1 mg/kg Nitrazpam (NZP) in three daily doses or 40 IU Depot ACTH in a single morning dose. Complete cessation of spasms was considered to be as optimal response.

Results

Of the sixty patients studied, 24 (40%) were girls and 36(60%) were boys. All patients in the both groups were matched for age and sex.There were no differences between the both groups regarding age and sex (non-significant). Following treatments, at the end of the 6-week duration therapy, optimal response (Cessation of spasms) was obtained in 19 (63%) patients of NZP group and 9 (30%) patients of ACTH group, ($P < 0.05$). ACTH side effects were more pronounced than those of NZP; Most patients in ACTH group, developed cushingoid features (moon face 93%, weight gain 100%)($P < 0.05$); a few patients,all from the ACTH group, developed hypertension ($P < 0.05$). The side effects of nitrazepam were drowsiness 33%, hypotonia 10%, infection 20%, and hypersalivation 93%. EEG anomalies had disappeared in 47% of NZP patients and in 30% of ACTH patients ($P > 0.05$).

Conclusion

This study supports the belief that NZP offers an effective and possibly safer therapy than ACTH, for the management of IS and that the therapeutic response, if imminent, can be detected within 4-6 weeks of treatment. Clinicians should consider using NZP as a first-line therapy for IS.

Keywords: Corticotropin /Spasms, Infantile / Nitrazepam

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Introduction

Infantile spasms (IS), a type of seizure that was first described by West in 1841, who witnessed the epileptic phenomenon in his own son(1). Infantile spasms or the West syndrome is a convulsive disease that is characterized by brief, symmetric axial muscle contractions (neck, trunk, and/or extremities). Most cases involve flexors and extensors, but either of the two may be involved independently(2). IS, as the name implies, occurs most often during the first year of life, affecting one in every 2000-4000 infants(3-5). The condition responds poorly to most conventional treatments, with the outcome being frequently unfavorable in terms of seizure control and cognitive development (6-10). Most, but not all, patients with this disorder show severe EEG abnormalities; this pattern was originally referred to as hypsarrhythmia by Gibbs and Gibbs(11). Cases with known etiology or signs of brain damage preceding the spasms are classified as symptomatic; those without known etiology or signs of brain damage are considered cryptogenic. Prognosis is generally poor. The therapy universally recognized as most effective in the treatment of IS, is the adrenocorticotropic hormone (ACTH) or oral corticosteroids(12). Steroids in the form of natural ACTH, synthetic ACTH, tetracosactide, prednisolone, and hydrocortisone have remained the first line of treatment for IS(13-15). However, this therapy has important side effects and cannot be continued for >40-60 days. Many studies have sought to find alternative therapies with fewer side effects(16-23). Hormone therapy is not effective in newborns with neurologic disorders and congenital cerebral anomalies. It has been shown that Na-Valporate (100mg/kg/day) although effective in about 70% patients, may cause liver damage(7). Nitrazepam (NZP), clonazepam, chlorazepate, and clobazam are the benzodiazepines that have been known to have efficacy in infantile spasms. In 1973, Vasella et al(24) reported that 38% of patients on clonazepam had reduced spasms; however, no efficacy was demonstrated in the study by Mimaki et al(25). Also, no effects of clobazam were found in another study conducted in 1986(19). The only drug known to have been as effective as ACTH in controlling infantile spasms, is nitrazepam(17). The aim of this study was to evaluate and compare the efficacies of Nitrazepam and ACTH in the treatment of infantile spasms.

Materials & Methods

In this randomized controlled clinical trial, sixty patients, aged between 2 and 24 months (at onset of symptoms), with newly diagnosed and previously untreated IS, were enrolled between 1999 and 2000. This study was not designed as a double blind clinical trial because ACTH was a parentral and NZP was an oral agent. Diagnosis was made based on the criteria of The International Classification of Epilepsies of the International League Against Epilepsy (ILAE)(22). All patients underwent EEG recording and brain CT scan at initiation of treatment. Patients were randomized into 2 groups, to receive 0.5-1 mg/kg NZP in three daily doses or 40 IU Depot ACTH in a single morning dose. If after 14 days of therapy, spasms did not disappear, or if intolerance was present, the therapy was discontinued. Complete cessation of spasms was considered to be an optimal response (complete treatment). Basic workup included CBC diff (Complete Blood Count), BS (Blood Sugar), UA, (Urine Analysis), serum amino acids, and thyroid function tests. Metabolic evaluation and sepsis workup were also done for all patients. Blood pressure, drowsiness, and any other adverse drug effects were recorded on the first day of admission, and also at 4th and 6th weeks of therapy.

Results

Of the sixty patients studied, 24 (40%) were girls and 36(60%) were boys. There were no differences between the two groups regarding sex and age ($P>0.05$)(Table 1). Of the thirty infants in each group, 6 (20%) had spasms classified as cryptogenic. In the remaining 24 (80%) patients, spasms were symptomatic. The clinical forms of convulsion included flexion (58%), extension (10%), and mixed (32%). Main causes of symptomatic IS types were hypoxic ischemic encephalopathy, brain malformation (cortical dysplegia, migration disorder, fetal infection, tuberous sclerosis, etc. Computed Tomography (CT) scan was abnormal in 49 (82%) patients (Table 1).

At the end of the 6th week of therapy, an optimal response (cessation of spasms) was obtained in 19 (63%) patients of the NZP group and 9 (30%) patients of the ACTH group ($P<0.05$) (Table 2).

Overall side effects were drowsiness (25%), weight gain (53.3%), moon face (46.7%), infection (21.7%), hypertension (11.7%), and hypotonia (6.7%).

The side effects seen in ACTH patients were more pronounced than those of the NZP group. Most ACTH patients developed cushingoid features (moon face 93%, weight gain 100%) (P<0.05), and a few in this group also developed hypertension (P<0.05) (Table 3). EEG variations were analyzed after 6 weeks of therapy in both groups, showing that in 47% of NZP patients and in 30% of ACTH patients, these abnormalities had disappeared (P>0.05)(Tables 4,5).

Table 1: Comparison of sex, age, type of convulsion, CT Scan findings, hypsarrhythmia, and type of IS in NZP and ACTH groups

		Treatment Groups		*P.Value*
		NZP (N=30)	*ACTH (N=30)*	
Sex	Boy	20(77%)	16(54%)	P=0.42 df=1 Chi2=0.62 Non-Significant
	Girl	10(33%)	14(46%)	
Age (month)	(Mean +/- SD)	9.55 +/- 4.63	11.63 +/- 5.4	P=0.11 t=1.60 Non-Significant
Type of Convulsion	Flexion	17(57%)	18(60%)	----
	Extension	2 (6%)	4 (13%)	
	Mixed	11 (37%)	8 (27%)	
CT Scan Findings	Normal	5(17%)	6(20%)	----
	Abnormal	25 (83%)	24 (80%)	
Hypsarrhythmia	Mild to Moderate	4(14%)	6(20%)	----
	Sever	26 (86%)	24 (80%)	
IS Types	Cryptogenic	*6(20%)*	*6(20%)*	----
	Symptomatic	*24 (80%)*	*24 (80%)*	

IS: Infantile Spasm NZP:Nitrazepam ACTH: Adrenocorticotropic Hormone

Table 2: Treatment response at 2nd, 4th, and 6th weeks of treatment period in NZP and ACTH groups

Time of Treatment		*Treatment Response*			*P Value*
		Cessation of Spasms	*Reduced episodes up to 50%*	*No Response*	
2nd Week	*NZP (N=30)*	*13(43%)*	*15(50%)*	*2(7%)*	P=0.31 df=1 Chi2=1.00 Non-Significant
	ACTH (N=30)	*8(26%)*	*19(63%)*	*3(11%)*	
4th Week	*NZP (N=30)*	*15(50%)*	*12(40%)*	*3(10%)*	P=0.33 df=1 Chi2=0.94 Non-Significant
	ACTH (N=30)	*10(33%)*	*16(53%)*	*4(14%)*	
6th Week	*NZP (N=30)*	*19(63%)*	*8(27%)*	*3(10%)*	P=0.01 df=1 Chi2=4.86 Significant
	ACTH (N=30)	*9(30%)*	*16(53%)*	*5(17%)*	

NZP:Nitrazepam ACTH: Adrenocorticotropic Hormone

Table 3: Comparison of the side effects of NZP and ACTH in the 2 groups

Side Effects	***Treatment Groups***		***P.Value***
	NZP *(N=30)*	***ACTH*** *(N=30)*	
Drowsiness	*10(33%)*	*5(17%)*	*P=0.23 df=1 Chi2=1.42 Non-Significant*
Weight Gain	*2(7%)*	*30(100%)*	*P=0.00 df=1 Chi2=48.8 Significant*
Moon Face	--	*28 (93%)*	*P=0.00 df=1 Chi2=48.8 Significant*
Infection	*6(20%)*	*7(24%)*	*P=0.75 df=1 Chi2=0.098 Non-Significant*
Hypertension	--	*7(24%)*	*P=0.00 Significant (Fisher's Exact Test)*
Hypotonia	*3(10%)*	*1(3%)*	*P=0.61 Non-Significant (Fisher's Exact Test)*
Hypersalivation	*28 (95%)*	--	*P=0.00 df=1 Chi2=48.8 Significant*

Table 4: Electroencephalographic status in the ACTH and NZP groups before treatment

	Electroencephalogram		
	Hypsarrythmia	Moderately abnormal	Mildly abnormal or within normal limits
NZP (N=30)	12(40%)	10(33%)	8(27%)
ACTH (N=30)	13(43%)	11(35%)	6(22%)

Table 5: Disappearance of EEG abnormalities after treatment

	Disappearance of EEG abnormalities			***P.Value***
	Complete	***Relative (>50%)***	***No Changes***	
NZP (N=30)	*14(47%)*	*7(23%)*	*9(30%)*	*P=0.36 df=2 Chi2=2.02 Non-Significant*
ACTH (N=30)	*9(30%)*	*11(37%)*	*10(33%)*	

Discussion

The treatment of infantile spasms is, at best, empirical because the underlying pathophysiology of the disorder and the precise mechanisms of action of drugs used for it, are not fully understood(2). Steroids and ACTH have been known to be effective in the treatment of infantile spasms for more than 40 years(4,5,26,27). The role of surgical treatment for IS has not been fully defined(28).

In a recent extensive review, Snead and Chiron(12) confirmed that therapy with ACTH and steroids is the most effective in treating infantile spasms, with success rates varying from 50% to 90%. Corticosteroids are also effective. Prednisolone (2 to 10 mg/kg per day), dexamethasone (0.3 to 0.5 mg/kg per day) and hydrocortisone (5 to 20 mg/kg per day) are most commonly recommended(29). The percentages vary among different patient series depending on the//in relation to etiology (with better response among cryptogenic cases), dosage and duration of treatment, and side effects.

A major disadvantage of treatment with ACTH and steroids is the relatively high incidence of side effects (37% in our patients) such as irritability, agitation, increased blood pressure, increased body weight, diarrhea, and susceptibility to infections; moreover, because of the risk of adverse effects, these drugs should be used only for relatively short periods of time(2). Many other antiepileptic drugs have been used to treat IS, and with the possible exception of BZDs and valproic acid (VPA), results have been poor(19-22). Vigabatrin is especially useful when the spasms are caused by tuberous sclerosis(30). Nitrazepam, clonazepam, chlorazepate, and clobazam are the benzodiazepines that have demonstrated efficacy in infantile spasms. In 1973, Vasella et al(24) reported that 38% of patients on clonazepam had reduced spasms; however the study by Mimaki et al, showed no such efficacy(25). Also, in another study conducted in 1986, no effects using clobazam were found(19). In a double-blind, controlled study, only nitrazepam was proved to be as effective as ACTH in controlling infantile spasms(17). We conducted this randomized study to compare using NZP and ACTH as first-line treatments for IS. Patients were selected randomly, and the two groups-one treated with NZP and the other with ACTH-were sufficiently similar/carefully matched. The success rate (complete disappearance of spasms) of the NZP group was higher than that seen in the ACTH group (63% VS 30%); NZP also produced fewer side-effects. Most patients in the ACTH group, developed cushingoid features (moon face 93%, weight gain 100%). NZP side effects were drowsiness 10 (33%), hypotonia 3 (10%), infection 6 (20%), and hypersalivation 28 (95%). In a study conducted by Dreifuss F et al fifty-two patients were enrolled in a four-week randomized multicenter study comparing nitrazepam and corticotropin in the treatment of infantile spasms; results of both treatments despite significantly reducing spasm frequency from that documented at baseline, showed more qualitatively severe adverse effects encountered among the patients treated with corticotrophin(17).

Conclusion

In conclusion, this study supports the belief that NZP offers an effective and possibly safer therapy for the management of IS than does ACTH, and that a therapeutic response, if imminent, can be detected within 4-6 weeks of treatment. It is recommended that clinicians should consider using NZP as a first-line therapy for IS.

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