Oiginal Articles

The role of oral prednisolone in the management of infantile spasms in resource-limited countries: experience from Sudan

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Abstract

Background: Infantile spasms; one of the commonest childhood epileptic encephalopathies, is usually associated with a characteristic electroencephalographic (EEG) pattern known as hypsarrhythmia. In the past, numerous clinical trials have investigated the role of different treatment regimens; yet it is one of the most notorious childhood epilepsies. This study aims to assess the role of oral Prednisolone in the management of Infantile Spasms (IS) among our patients.

Methods: This is a cross sectional, prospective, hospital based study conducted in 2013, at the two main pediatric epilepsy outpatient clinics in Khartoum State, Sudan. All patients received oral prednisolone in usual dose (2 mg/kg/day) for the first six weeks and then tapered over another four to six weeks. It included 54 patients who were interviewed using a designated questionnaire before starting the prednisolone and reassessed at 6-8 weeks for seizure frequency, duration and side effects of steroids. The EEG was done at presentation and repeated at 10-12 weeks post treatment. Other investigations were requested as deemed appropriate.

Results: The peak age at onset of the seizure was between 6 -12 months. Thirty-two patients (59.3%) showed complete clinical cessation of the spasms and 22(40.7%) patients showed reduction in the spasm frequency in 6-8 weeks duration. The EEG was repeated at 10-12 weeks after treatment, and out of 43 patients with typical hypsarrhythmia 36(83.7%) patients showed complete disappearance of the hypsarrhythmia compared to 6(54.5%) of those with polyspikes and waves. Fourteen patients (25.9 %) had experienced side effects of Prednisolone.

Conclusion: Oral Prednisolone is effective in the initial management of IS, associated with clinical and electrographic remission in our population. Because of its availability and low cost, it can be considered as the drug of choice in developing countries like ours.

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Background

The term infantile spasm has been used to describe a seizure semiology that is age-related epilepsy syndrome and is usually associated with a characteristic electroencephalographic (EEG) pattern known as hypsarrhythmia. Many children go on to develop other forms of severe epilepsy, and most (80% -90%) have psychomotor retardation(1). In the past, numerous clinical trials investigated different treatment regimens yet it remains one of the most childhood refractory seizures. Although ACTH is recommended as the drug of choice in most recent guidelines, many use oral prednisolone as it is easily available, less costly and has few side effects.(2) This study aims to assess the role of oral prednisolone in the management of patients with Infantile Spasms (IS).

Patients and Methods

This is a retrospective, observational, hospital based study. It includes children with new onset infantile spasm, attending the outpatient clinics for childhood epilepsies and neurodisabilities at Gaffer Ibn Auf Specialized Hospital for Children and Saad Abu Alella Khartoum University Teaching Hospital. The study was conducted over six month's duration (October 2012-March 2013). The study included patients whose age was between 3 months and 3years who presented for the first time with Infantile Spasm (IS). The diagnosis of IS was based on history (seizure semiology), clinical examination and EEG findings. Using seizure semiology, they were further classified into flexors, extensors and mixed types. One hundred and five patients with infantile spasms were seen during this period, 56(53.3%) patients fulfilled the inclusion criteria. Patients' families were interviewed using a designated questionnaire on day one before starting the prednisolone treatment and reassessed at 6-8 weeks following treatment for the seizures frequency, duration and side effect of steroids. The dose regimen for oral prednisolone was 2mg/kg/day given for 6 weeks and tapered over 4weeks time, during which patients were observed for side effects of steroid; blood pressure and Random Blood Glucose (RBG) were measured weekly and if abnormal, the (RBG) was measured daily. The EEG was performed initially upon diagnosis and repeated 10-12 weeks post treatment for evidence of persistence of hypsarrhythmia or any other EEG abnormalities. Other investigations were requested as deemed appropriate.

Ethical approval was obtained from the Research Committee, Sudan Medical Specialization Board and a verbal consent was taken from parents and/or caregivers after explaining the aims of the study in simple Arabic language. Data were analyzed using SSPS version1, Chai squire test was used and p -value was considered as significant if less than 0.05.

Results

Fifty-six patients fulfilled the inclusion criteria; two of them missed their follow up appointments and were excluded. Their age ranged between 3 months and 3 years. The peak age at onset of the seizure was between 6 -12 months. The male to female ratio was 2:1.

The commonest seizure semiology was the flexion spasms noted in 22 (40.7 %) patients, followed by extensor spasms in 13 (24.1 %) and 19 (35.2 %) had a mixed type (flexor and extensor).

Thirty-nine patients (72.3 %) had developmental impairment compared to 15(27.7%) with normal developmental milestones.

Forty nine patients (90.7 %) had MRI and/or CT of the brain, of whom 17(34.7%) had generalized brain atrophy, 14(28.6%) congenital brain anomalies, 5(10.2%) leukodystrophy, 4(8.2%) Basal ganglion lesion, 2(4.0%) intracranial calcifications (Tuberous Sclerosis) and 7(14.3%) had normal brain images as shown in Table 1.

EEG was done to all patients before starting treatment, forty-three patients (79.6 %) displayed typical hypsarrhythmias, while 11(20.4%) showed polyspike and wave pattern.

Thirty-two patients (59.3%) showed complete clinical cessation of the spasms following prednisolone treatment. Out of 29(53.7%) patients who had uncountable spasms per day; 16(55.2%) showed complete disappearance of the spasms; while in 13(44.8%) the spasms decreased in frequency; there was no statistically significant difference regarding response to treatment between patients with uncountable spasms per day and those with less frequent spasms (p-value= 0.824) as shown in Table 2.

Twenty-two (40.7%) patients showed reduction in the seizures duration. Out of 40 patients in whom the spasms took few seconds, spasms disappeared completely in 25(62.5%) patients, while in 4 out of 7 patients in whom spasms occurred in clusters, the spasms disappeared completely following

Prednisolone treatments. The difference, regarding response to treatment, between patients with clusters of spasms per day and those with brief spasms was not statistically significant (p-value= 0.0821) Table 3.

Out of 39(72.3%) patients with global developmental impairment 17(43.5%) showed complete spasm cessation as compared to 100% spasms disappearance in patients with normal development, this was found to be statistically significant (P- value = 0.031)

The EEG was repeated at 10-12 weeks after treatment, and out of 43 patients with typical hypsarrhythmia, 36(83.7%) patients showed complete disappearance of the hypsarrhythmia compared to 6(54.5%) of those with polyspikes and waves; there is no statistical significant difference regarding EEG response between patients with typical hypsarrhythmia and those with polyspikes and waves (p-value= 0.091) as shown in Table 4.

Fourteen patients (25.9 %) had experienced side effects of prednisolone, 12(85.7 %) had Cushinoid features and two patients (14.3 %) developed high blood pressure.

Table1. Brain image (MRI/CT) findings among the study group (n=49)

Brain image (MRI/CT) findings	**Number (%)**
Generalized brain atrophy	17(34.7)
Congenital brain anomalies	14(28.6)
Leukodystrophy	05(10.2)
Basal ganglion lesions	04(8.2)
Intracranial calcifications	02(04.0)
Normal brain	07(14.3)
Total	**49(100)**

Table 2. Frequency of spasms per day before and after treatment with oral prednisolone (n=54)

Frequency of spasms /day	**Before treatment n(%)**	**After treatment(6-8 weeks)**	
		Disappeared n (%)	Decreased in frequency n (%)
Uncountable	29(53.7%)	16 (55.2)	13(44.8%)
10-20	16(29.6)	10(62.5)	06(37.5%)
Less than 10	09(16.7)	06(66.7)	03(33.3%)
Total	**54(100)**	**32(59.3)**	**22(40.7)**

P- Value=0.824

Table 3. Duration of spasm/ day before and after oral prednisolone (n=54)

Frequency of spasms /day	Before treatment n(%)	After treatment(6-8 weeks	
		Disappeared n (%)	Decreased in frequency n (%)
Few seconds	40(75.0)	25 (62.5)	15(37.5)
One minute	05(9.2)	02(40.0)	03(60.0)
One- two minutes	02(3.7)	01(50)	01(50)
Clusters(more than 2 minutes)	07(13.0)	04(57.1)	03(42.9)
Total	**54(100)**	**32(59.3)**	**22(40.7)**

P- Value=0.0821

Table 4. EEG finding before and after oral prednisolone (n=54)

EEG changes	Before treatment	After treatment(10- 12 weeks)	
		Normal EEG n (%)	Abnormal EEG n (%)
Typical hypsarrhythmia	43(79.6)	36 (83.7)	7(16.3)
Atypical hypsarrhythmia (Polyspikes and waves)	11(20.4)	6(54.5)	5(45.5)
Total	**54(100)**	**42(77.8)**	**12(22.2)**

P- Value=0.0821

Discussion

Infantile Spasms, also known as salaam attacks, were first described by Doctor West J, a 19th century neurologist who described the syndrome in his own son in a letter he wrote to the Lancet in 1841.[3] It is a syndrome that includes a peculiar type of seizure, a high risk of psychomotor retardation, and usually a characteristic electroencephalographic (EEG) pattern known as hypsarrhythmia.[1,2,3] Infantile spasms are believed to reflect abnormal interactions between the cortex and brainstem structures. Focal lesions early in life may secondarily affect other sites in the brain, and hypsarrhythmia may represent this abnormal activity arising from multiple brain sites. The frequent onset of infantile spasms in infancy suggests that an immature central nervous system (CNS) may be important in the syndrome's pathogenesis.[4]

Treatment of IS has been evaluated in a 2004 and a 2012 American Academy of Neurology (AAN) practice parameter,[5,6] as well as in the United States consensus report in 2010[7]. Conclusions were limited by the overall poor methodology of the available studies. Lack of adherence to standardized case definitions and outcome measures is one problem with many studies. Another problem is that

inclusion of a control group is critical, as the natural history of the disease is that clinical spasms subside and electroencephalogram patterns evolve without therapy, yet many clinicians would be reluctant not to treat, as there is some observational data to suggest that delayed therapy may worsen prognosis[7]. As a result, many questions remain regarding the mechanism, optimal drug, dose, duration of therapy, and the importance of prompt initiation of treatment after the appearance of spasms.

The mainstay of medical treatment of (IS) is hormonal therapy with corticotrophin.[8] The mechanism of action of ACTH (adrenocorticotrophin hormone) and corticosteroids is not known. Administration of ACTH can control spasms in patients with adrenal suppression, suggesting that the effect is independent of adrenal corticosteroid release. Corticotrophins may have direct anticonvulsant effects, perhaps via suppression of corticotrophin releasing hormone (CRH), an endogenous neuropeptide that may provoke convulsions in immature brain[9-10]. Significant side effects may occur with ACTH including hypertension, immune suppression, electrolyte imbalance, gastrointestinal disturbances, ocular opacities, hypertrophic cardiomyopathy, and growth impairment.[11,12] A transient Cushinoid appearance, hirsutism, irritability, and sleep disorders are also seen.[13] Oral Prednisolone is less costly, easier-to-administer and has fewer side effects especially in our settings with high risk of infection and it has been suggested as a potential effective alternative to ACTH[12]. However, most consensus and guideline groups have found the data regarding corticosteroids to be insufficient to recommend their use as first line treatment[9].

Since September 2007, the ACTH was replaced with high-dose oral prednisolone (40-60 mg/day) according to the 2004 United Kingdom Infantile Spasms Study (UKISS)[5]. Ten of 15 infants with new-onset and previously treated infantile spasms became spasm free within 2 weeks and 4 had later recurred. In our study none of our patients received ACTH as it is not always available in Sudan, has a high side effect profile and the need for injections (and hence hospitalization) adds a further financial load on families.

We used oral prednisolone in the usual dose of (2 mg/kg/ day) for 6 weeks and tapered it over 4-6 weeks. Thirty-two patients (59.2 %) had complete cessation of spasms following oral prednisolone. Twenty-two patients (40.8 %) had a decrease in frequency and duration of spasms in 4-6 weeks. These results suggest that prednisolone therapy is effective in the initial management of infantile spasms. This was similar to the results that had been mentioned by Kossoff*, et al*.[14] In contrast, many studies found no sufficient evidence to support a recommendation for prednisolone [15-17] and there is no consensus on the dosage of prednisolone required for the treatment of infantile spasms.[18] Recent data have shown that a high dose (4 mg/kg/day) may be more efficacious than the usual dose (2 mg/kg/day) [19]. However, there are no randomized controlled trials comparing these doses[20]. Azam, *et al* in their report from Islamabad showed that 59.3 % of their patients were clinically free from spasms and had normal EEG following steroid treatment[21] .

In this study, more children with normal development were spasm free than those with developmental impairment, (P=0.03) which is similar to reports in the literature[19-21].

Among our study group 14 patients (25.9 %) had experienced side effects of prednisolone; mainly Cushingoid appearance and high blood pressure; a result similar to what had been mentioned by *Partikian et al*[22].Fortunately none of our patients developed sepsis or other severe complications that necessitated discontinuation of therapy.

Conclusion

Oral prednisolone in the usual dose of 2mg/kg/day was effective in the initial management of infantile spasms. It is cheap, locally produced and is included in the health insurance coverage; so it can be considered as the drug of choice in countries with similar health facilities and working environments. However, there is a need for long-term follow up to assess prednisolone efficiency on long-term management and rate of seizure recurrence.

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