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Use of ACTH and prednisolone in infantile spasms: Experience from a developing country☆,☆☆

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KEYWORDS
Infantile spasms;
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Summary

Background : Adrenocorticotrophic hormone (ACTH) and prednisone are both used to treat infantile spasms (IS) in West syndrome. In many countries, ACTH is expensive and difficult to obtain whereas, prednisone or prednisolone are cheap, given orally and easily available.
Aims : The purpose of this retrospective data analysis was to compare the efficacy and cost of ACTH and prednisolone in the treatment of IS from the perspective of a developing country.
Methods : Patients admitted with West syndrome in Children's Hospital, Islamabad, between January 1995 and December 2001 were included in the analysis. The diagnosis was made after eliciting a history of characteristic seizures and detecting hypsarrhythmia on the EEG. Parents were offered the use of either ACTH administered by intramuscular injection or prednisolone given orally. ACTH was expensive and difficult to obtain whereas prednisolone was cheap and easily available.
Results : One hundred and five children were included in the study. Sixty-three were boys and their age ranged from 2 months to 3 years with a mean of 11 months. Thirty-three children received ACTH injections; 27 showed improvement and 11 remained spasms free after discontinuation of injections. Seventy-two patients were given oral prednisolone, 51 responded and 17 remained spasms free after oral steroids were stopped. Overall outcome was similar in both groups. The cost of ACTH injection was more than 100 times the cost of oral prednisolone.
Conclusion : No significant difference was seen in the final outcome in both treatment groups. Since prednisolone is inexpensive, easily available and given orally, it is the preferred mode of therapy.

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Introduction

Infantile spasms (IS) is a rare age-specific type of seizure, which occurs in West syndrome. A characteristic EEG appearance called hypsarrhythmia and a high risk of severe developmental delay are other features of the syndrome. There are a variety of predisposing genetic, perinatal and postnatal aetiologies.[1] Onset is typically seen in the first year of life, often between the ages of 3 and 8 months.[2] The seizures are difficult to treat and long-term outcome for seizure control and development remains poor. Because of the poor response rate, a wide variety of drugs are used to treat IS the world over. However, two commonly used forms of therapy are adrenocorticotrophic hormone (ACTH) and prednisolone (or prednisone). More than 40 years ago, ACTH was used empirically to treat these seizures with some success and later on oral steroids were tried as well.[3] In the last decade, vigabatrin has been shown to be the first anticonvulsant to have a significant response rate for infantile spasms but serious visual field defect has been found in approximately one-third of treated adults and is known to occur in children.[4,5] Vigabatrin is available in Europe but not readily in many countries including Pakistan.

There is some evidence that excess of corticotrophin releasing hormone (CRH) may be the common pathway for the development of seizures in the developing brain.[6] Initially, it was thought that prednisone was as effective as ACTH.[7,8] More recently, it has been shown that ACTH is superior to 2 mg/kg/day prednisone and high dose is no better than low-dose ACTH.[9] The 2 mg/kg/day dose of prednisone has been suggested to be too low in the Cochrane review.[10] ACTH is expensive, given parenterally and may be difficult to obtain in some countries: synthetic ACTH (tetracosactide) is beginning to replace the natural product. Prednisolone, on the other hand, is inexpensive, given orally and is easily available. When choosing between different therapies, determining factors are not only the efficacy and side effects but also their cost and availability especially in developing countries. For these reasons, data were collected on patients receiving ACTH or prednisolone to compare their efficacy, cost and long-term outcome.

Methods

Many children with poorly controlled seizures are referred to the neurology section of The Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad. Data were reviewed retrospectively from January 1995 to December 2001. The diagnosis of IS was made when child presented with characteristic seizures (flexor or extensor spasms, eye deviation alone or in combination) and in addition EEG showed hypsarrhythmia or one of its variants.[11,12] Patients were included in the study if the initial presentation age was less than 3 years and they had not received ACTH or prednisolone previously. Whenever possible, repeat EEG and neuroimaging studies were performed. Twenty-four hour EEG monitoring facilities were not available in the hospital. Once the EEG report was received, parents were informed about both modes of therapy including cost, availability, painful injection and relative superiority of ACTH. Then parents were allowed to choose either ACTH injection or oral prednisolone. Parents had to obtain the drug from private pharmacy and pay the price. ACTH (tetracosactide-synthetic preparation) was given as single intramuscular injection, 20 units for children weighing less than 10 kg and 40 units for 10 or more than 10 kg. Those parents reluctant for outpatient treatment were admitted. Blood glucose and blood pressure were monitored twice weekly in admitted and once weekly in outpatients. Children receiving oral prednisolone (2—3 mg/kg/day in two divided doses) were treated as outpatients. They were seen at 2-week intervals in Paediatric Neurology clinic. Blood sugar, urine analysis and stool for occult blood were performed whenever indicated. A response was defined as either complete cessation or 50% or more reduction in the frequency of spasms as judged by the parents. EEG confirmation was not required.

Results

One hundred and five children were included in the study. Sixty-three (60%) were boys and age ranged from 2 months to 3 years with a mean of 11 months. Underlying aetiology was comparable in groups and included cerebral palsy, inherited brain disorders and unknown (Table 1). Seventy children had typical hypsarrhythmia on EEG and 35 had one of its variants.[11] Computed tomography (CT) of the brain was performed on 25 patients and magnetic resonance imaging (MRI) on six patients. The most common abnormality was cerebral atrophy seen in seventeen children. Other abnormalities detected were intracranial calcification or tubers or both (five cases), neuronal migrational disorders (three cases) and six were reported as normal. Total duration of follow-up was from 6 to 10 months.

Thirty-three (31%) children were treated with ACTH and 27 (82%) responded either becoming fit free or seizure frequency reduced by 50% or more. In

Table 1 Children with infantile spasms had the following underlying conditions

	ACTH group (%)	Prednisolone group (%)
Cerebral palsy	5 (15)	17 (24)
Neurodegenerative disorders	4 (12)	16 (22)
Microcephaly	1 (3)	5 (7)
Tuberous sclerosis	3 (9)	2 (3)
Meningoencephalitis	1 (3)	4 (6)
Dysgenesis	3 (9)	0 (0)
Congenital infections	0 (0)	2 (3)
Unknown	16 (48)	26 (36)

most children ACTH injections were given for 4 weeks in full dose and tapered over 2 weeks. The maximum duration of treatment was 6 weeks including tapering phase. Eleven (33%) children remained free of spasms after stopping the ACTH injections. Seventy-two (69%) patients were given oral prednisolone; 51 (71%) showed response. Prednisolone was tapered more slowly and in majority of children the duration of treatment varied from 6 to 8 weeks. Fifteen children were given prednisolone for longer duration, 12—14 weeks including the last 2 weeks of alternate day therapy. Seventeen (24%) patients remained spasms free until final follow up after discontinuation of the drug. However, difference between ACTH and prednisolone was not statistically significant ($p = 041$). No difference was seen between short (6—8 weeks) and long duration (12—14 weeks) prednisolone therapy. In a 10 kg child, the cost of 4 weeks' prednisolone (2 mg/kg/day) treatment was approximately one US$ whereas ACTH (20 units) treatment for 4 weeks costs 100 US$.

Major side effects in both groups were increased appetite and weight gain, which were more frequent in the ACTH than the prednisolone group. Most of the parents complained about painful ACTH injections, nevertheless, none asked to modify the treatment. Nine patients died but long after ACTH (2) or prednisolone (7) was stopped. All were severely neurologically compromised and repeated chest infections were considered the cause of death. In none was it thought that ACTH or prednisolone were the cause of death. Some children developed hyperglycemia, hypertension and infections, which were treated symptomatically. In none was dosage of either ACTH or prednisolone reduced because of side effects.

Subsequently, 80 (76%) patients (23/33 ACTH and 57/72 prednisolone group) developed epilepsy and in the majority it remained poorly controlled despite two or more antiepileptic drugs (sodium valproate, clonazepam, phenytoin, carbamazepine and vigabatrin). All but vigabatrin were on occasion given before ACTH or prednisolone. Twenty-five children were either fit free or had occasional seizures. Psychomotor retardation was seen in 102 (97%) children. Three children remained normal or had minimal delay, one from ACTH and two from prednisolone group.

Discussion

Basically this was a retrospective hospital-based clinical audit where infants and children from large parts of northern areas of the country with complicated neurological disorders are referred. It was possible to study a significant number of patients in a relatively short time. Difficulties were lack of 24-h EEG monitoring, repeat EEG or neuroimaging studies. Despite these limitations this is an important study. Selection of a particular mode of therapy is based on its efficacy and side effects as compared to other alternatives. Cost of treatment is usually not an important factor. This is because in most developed countries provision of healthcare is responsibility of the state. That is not the case in most developing countries including Pakistan. Delivery of healthcare in poor countries is a serious problem. With respect to the care of epileptic patients, drug treatment is very poor in many developing countries and antiepileptic agents are not always available to those who need them most.[13] The purchase of expensive drugs can put significant constraints on already limited family income and may lead to poor compliance. Therefore, the cost of the drug selected for the child with epilepsy is an important determining factor. In the present study the selection of therapy was based not only on its reported effectiveness and side effects but also on cost and availability. Parents were given the option to choose between ACTH and prednisolone. Not surprisingly, two-third of the parents opted for oral prednisolone and the remaining one-third used ACTH. Four-week prednisolone treatment in a 10 kg child would cost only one US$ whereas ACTH in the same child would cost 100 US$ or more. Moreover, prednisolone was easily available, inexpensive and could be given orally, ACTH was difficult

to get (ACTH gel was not available). Problems with availability and affordability of ACTH are not limited to one country and have been reported from other developing countries.[14]

Though ACTH and prednisolone are the most effective available agents in controlling IS, no universal standard exists for treating IS. ACTH is used more selectively in European countries in comparison to prednisolone,[15] whereas about 88% of paediatric neurologists in United States use ACTH as the first choice.[16] Results of studies on the efficacy of ACTH and prednisone are not uniform. In some studies ACTH was far superior to prednisone,[9] and in others prednisone was as effective as ACTH.[7] In present study ACTH was marginally better than prednisolone but difference was not statistically significant. Thirty-three percent in the ACTH and 24% in the prednisolone group remained spasm free after these drugs were stopped; overall prognosis was very poor in both groups.

During the past several decades, a large volume of literature has appeared on the epidemiology, pathophysiology, treatment, side effects and long-term prognosis of IS. Hancock et al.,[10] have recently reviewed the subject. They selected randomized controlled studies published between 1960 and 2000. They did not find reliable evidence that any of the treatments were better than others including ACTH versus prednisone. In a similar review of published data, ACTH and prednisone were the most frequently used therapies to treat IS.[17] Again opinions differed regarding relative efficacy of ACTH and steroids. Kalra et al.,[18] found prednisolone as effective in controlling spasms as ACTH. Vigabatrin, one of the newer antiepileptic agent has also been used to treat the IS and some consider vigabatrin as drug of choice for IS in tuberous sclerosis.[19] But irreversible visual field constrictions limit the use of vigabatrin in IS especially in young child.[5] We did not use vigabatrin and other antiepileptics such as phenobarbitone, sodium valproate, pyridoxine and lorazepam as initial therapy for infantile spasms. Some children were given one or more of these drugs (but not vigabatrin) before the diagnosis of IS was established.

Fifty-six percent patients belonged to symptomatic group and common underlying pathologies were cerebral palsy (21%) and degenerative brain disorders (19%). The diagnosis was primarily based on history and neurological examination. Identification of seizures was clinical and by the parents. It is known that parental observations are generally unreliable.[7] Forty-two percent of the patients remained in unknown group because of lack of comprehensive laboratory workup and neuroimaging studies. The spectrum of underlying pathologies in the present study was similar to other studies. In a large study, one-third of symptomatic patients had birth related aetiology and 20% had tuberous sclerosis.[20] In another study, hypoxic-ischemic encephalopathy was the commonest underlying aetiology (51%) followed by brain anomalies (21%) and neurocutaneous syndromes (9%).[21] With advances in laboratory and neuroimaging techniques, more and more underlying pathologies are identified in children with IS.[22]

Overall prognosis in our study was extremely poor. Ninety-seven percent of children had psychomotor retardation and 80% had epilepsy. Most patients were referred from other centres and may be considered difficult cases. Cases, which responded to treatment, will not have been referred. This may be a possible explanation for the poor outcome in our study. Most of the reports from other countries also have poor outcome especially in symptomatic IS.[23]

Twenty years ago, the justification of using ACTH instead of oral steroids was questioned.[18] Today we have similar reservations that both drugs have comparable efficacy and relapse rates but huge difference in the availability and cost of the drugs. An important aspect which has been highlighted by other researchers is the fact that successful treatment of IS with a particular therapy does not improve the long-term prognosis.[24] Therefore, at present, the significance of selection of one or the other drug to treat IS can be questioned.

Despite all the advances in understanding the pathophysiology and some favourable reports, IS remains a disease that is relatively easy to diagnose but difficult to treat and overall prognosis remains dismal. An ideal drug would be one which is not only effective in controlling spasms, has minimal side effects, improves long-term outcome but also affordable by most of the patients and easily available. Till the time an effective therapy is developed or ACTH becomes easily available and is cost-effective, prednisolone will remain an attractive alternative for IS, at least in developing countries. Moreover, it would be helpful to know the best dose and duration of treatment for both prednisolone and ACTH, in order to maximize response rate while minimizing side effects.

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