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Treatment of infantile spasms in resource limited settings: A randomized controlled trial

Huda Sardar[1], **Ashfa Ameer Khan**[2], **Tipu Sultan**[2]
[1]Faculty of Health Sciences, McMaster University, Hamilton, Canada, [2]The Children's Hospital and Institute of Child Health, Lahore, Pakistan

Corresponding author: Tipu Sultan;598-D, Johar Town, Lahore, Pakistan; Email: tipusultanmalik@hotmail.com; Tel: +88-0171-5254283.
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Abstract

Objective: To compare the outcome of adrenocorticotropic hormone (ACTH) with oral prednisolone for treatment of infantile spasms (IS).
Methodology: This randomized controlled trial was conducted at the Department of Pediatric Neurology, The Children's Hospital in Lahore, Pakistan, from January 1st, 2014 to December 31st, 2017. Seventy patients with infantile spasms who met the selection criteria were randomized into two equal groups of 35 patients using a lottery method. Patients in group A received prednisolone, and in group B received ACTH. The two groups were compared to determine spasm-free outcome. Non-probability purposive sampling was used, inclusion criterion was children up to the age of one year with infantile spasms, and exclusion criteria consisted of children who had been previously treated with steroids or ACTH. History was taken by a pediatric neurology fellow, and informed consent was obtained from parents. Data was collected on a specially designed proforma and ethics approval was sought through the hospital's institutional review board.
Results: In group A, 29(83%) patients were spasm-free, while in group B, 31(88%) patients were spasm-free.
Conclusion: Prednisolone is as effective as ACTH for control of IS and far more cost-effective, accessible and easier to administer. Developing countries should consider this treatment option as a first line therapy.

Keywords: epilepsy; infantile spasms; ACTH; Prednisolone; randomized controlled trial; hypsarrhythmia

Introduction

Infantile spasms (IS) is a unique seizure disorder that occurs almost exclusively in infants [1][2]. It was first described by WJ West in 1841 in his own son; the triad of infantile spasms, hypsarrhythmia on electroencephalogram (EEG) and mental retardation is called West syndrome [3]. If left untreated, IS is associated with devastating neurological defecits [4]. Diagnosis, evaluation and management of IS continues to pose many challenges to pediatricians. A recent IS working group of pediatric neurologists who reviewed the medical literature determined that early recognition of IS and prompt treatment may improve developmental and cognitive outcomes in children [5]. As a result, educating pediatricians and general physicians about IS is crucial. The disorder manifests itself as myoclonic-tonic seizures (spasms) that may be characterized by flexor, extensor, or mixed movements, a distinct EEG pattern of hypsarrhythmia (Figure 1) or/and psychomotor delay [6]. The incidence of IS ranges from 2 to 3.5 in 10,000 live births, with onset during the first year of life in 90% of those affected. The peak age of onset is between 3 and 7 months; onset after 18 months is rare, though onset up to 4 years of age has been reported. Spasms usually cease by five years of age, but other seizure types are reported in as many as 60% of children with IS even after cessation of spasms [7]. IS contributes to 10% of all mental retardation and more than 50% evolve to different epilepsy syndromes [8]. In addition, the disorder occurs in children from all ethnic groups, and boys are affected slightly more often than girls (ratio of 60:40) [9][10]. IS is divided into two groups: cryptogenic (or idiopathic) and symptomatic. Apparent neurological deficit is not identified in the cryptogenic group (10-15%), while patients in the symptomatic group (85-90%) have some underlying disorder of brain [11][12]. The EEG findings (hypsarrhythmia) accompany-

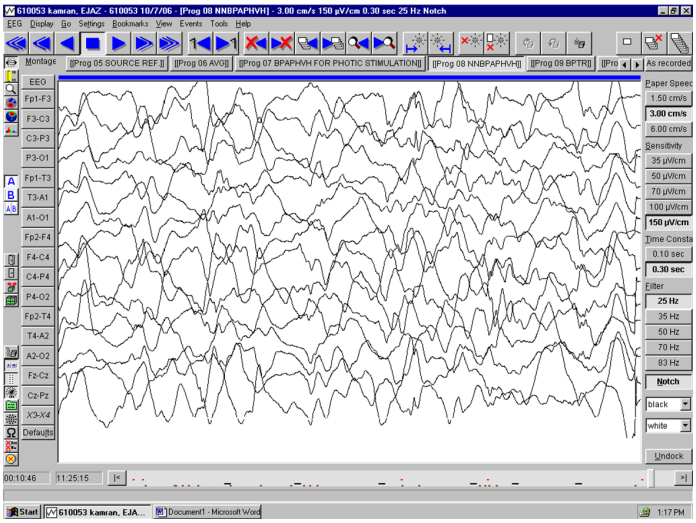

Figure 1 Hypsarrhythmia in a male aged 9 months

ing IS are typically chaotic or disorganized background activity, consisting of high amplitude slow waves mixed with spikes and polyspikes (Figure 1) [13]. Furthermore, IS is associated with significant long-term complications, including psychomotor delay, development of other seizure types, impaired cognitive and psychosocial functioning, and mortality in a small but signicant number of patients [14].

Notably, the treatment of IS has been a challenge as many patients appear to be resistant to conventional antiepileptic drugs. Agents that have been employed in the treatment of IS include benzodiazepine, sodium valproate, vigabatrin, corticosteroids, adrenocorticotropic hormone (ACTH), ketogenic diet, vitamin B6, intravenous immunoglobulins, topiramate, and zonisamide. However, there is little consensus with regards to the definitive dose, efficacy and duration of treatment of these agents in comparison to each other [15]. In a recent clinical trial by Kossof EH et al., ACTH was compared with oral prednisolone. More children with infantile syndrome were spasm-free with oral prednisolone (83% versus 43%). Oral prednisolone was also shown to be less expensive than ACTH [16]. Many patients in Pakistan are socioeconomically disadvantaged; the high cost of ACTH, the lack of its availability, and the need to administer treatment via intramuscular injection are factors that pose significant barriers in terms of patient access to care. Contrary to that, prednisolone is easily available, orally-administered, and more economical. Keeping in view the aforementioned considerations, this study was planned to determine the better option between oral prednisolone and ACTH in the management of IS, particularly from a clinical perspective.

Methods

A randomized controlled trial was conducted at the Department of Pediatric Neurology, The Children's Hospital, and Institute of Child Health in Lahore, Pakistan from January 1st, 2014 to December 31st, 2017, with approval from the institutional review board. The study aimed to compare the outcome of oral prednisolone with ACTH for treatment of infantile spasms. The operational definition used to identify infantile spasms was the presence of characteristic seizures (exor or extensor spasms, alone or in combination). This was confirmed on EEG, which showed hypsarrhythmia. The outcome was measured in terms of spasm-free status defined as the absence of seizure activity characteristic of infantile spasms with disappearance of hypsarrhythmia on EEG within four weeks of stopping the medication. The seizure activity was witnessed and reported by the parents.

Inclusion criteria was children up to age of one year with infantile spasms (as per operational definition), although some patients up to 2 years of age were also enrolled. In addition, patients were excluded if they had been previously treated with steroids or ACTH. Seventy eligible patients (both males and females) who met the selection criteria were registered and subsequently divided into two equal groups randomly using the non-probability purposive sampling technique. Thirty-five patients in group A received oral prednisolone (2 mg/kg/day for a period of four weeks and then tapered gradually over next four weeks). Thirty-five patients in group B received intramuscular injection of ACTH (150 IU/m/day initially daily for two weeks and then slowly tapered over the next six weeks). History was taken by a pediatric neurology fellow and informed consent was obtained from parents prior to enrollment. Thirty five patients each thus received oral prednisolone and intramuscular ACTH in Group A and Group B respectively. Patient data was collected on a specially designed proforma, entered into SPSS version 20 and analyzed. The two groups were compared for statistical significance using a Chi-squared(χ^2) test.

Results

The age of the 70 patients among both groups is outlined in Table 1. There was no significant difference between the two groups. Patients were also distributed according to sex.

Table 1 Distribution of patients by age n=70

Age in months	Group A		Group II	
	No. of patients (n)	Percentage (%)	No. of patients (n)	Percentage (%)
< 2	16	43	21	60
02-Mar	11	29	8	23
03-Jun	4	12	3	8.6
06-Sep	3	8.6	2	5.7
09-Dec	1	3	1	3
Mean ± SD	2.11 ± 1.30		1.69±1.05	
Range	1 – 5		1 – 5	
P value	0.633			

In group A, there were 9 (25.7%) female patients, while 26 (74.3%) patients were male. Female to male ratio was 1:2.9 (Table 2). In group B, there were 7 (20%) female patients, while 28 (80%) patients were male. Female to male ratio was 1:4. Again, there was no statistically significant difference between the two groups (Table 2). In group A,

Table 2 Distribution of patients by sex

Age in years	Group A No. of patients (n)	Percentage (%)	Group B No. of patients (n)	Percentage (%)
Female	9	25.7	7	20
Male	26	74.3	28	80
P value	0.569			

29 (83%) patients were spasm-free, while 6 (17%) patients were not. In group B, 31 (88%) patients were spasm-free and 4 (12%) patients were not (Table 3).

Table 3 Spasm-free children n=70

Spasm-free	Group A		Group B		*P* value*
	n	%	n	%	
Yes	29	83	31	88	0.022*
No	6	17	4	12	
Total	100	100	100	100	

*chi-square(χ^2)statistic

Discussion

IS is a seizure disorder of infancy not frequently seen in routine practice. In the medical literature, efforts are ongoing to determine which treatment is the better of the two [10]. To further this aim, our study compared the efficacy of two treatment modalities, ACTH and prednisolone, in making children spasm-free. The results of this randomized controlled trial were in favor of the prednisolone group due to its low cost and good control of seizures. We included seventy children with infantile spasms. The mean age of the children affected with infantile spasms was 2.11±1.30 years and 1.69 ±1.05 years. Although, we included a broader age group of up to 2 years, the majority of patients (approximately 87%) were less than one year of age. In a study by Noureen N et al., the majority of patients (approximately 66%) were of age < 3 years [17]. Mean age of the patients was 6.5±3.35 months (age range 3 months to 1.5 years). In our study, infantile spasms were seen more frequently in males. This observation is also supported by Western literature, which indicates high incidence of infantile spasms in males [10]. Other clinical trials have also compared the two drugs, producing variable results. Kossof EH et al. showed that more patients were spasm-free after prednisolone [16]. Advantage of oral prednisolone discussed in this study included the marked difference in the cost of the full course treatment. Moreover, the study highlighted that prednisolone is given orally as compared to injectable ACTH, making it a more convenient therapy [16]. The results are also congruent with more local literature. In a study from Multan, the male population constituted approximately 68% of the total sample size and only 32% were females [17].

In this study, it was found that study participants given prednisolone were spasm-free post-treatment. This reflects that prednisolone produced better clinical results amongst patients. In another study by Hrachovy et al., twenty-four patients with infantile spasms were entered in a double-blind, placebo-controlled, crossover study to compare the effectiveness of ACTH (20 to 30 units/day) with that of prednisolone (2 mg/kg/day) [18]. Response to therapy was determined by utilizing a comprehensive monitoring system and was defined as a complete cessation of spasms and disappearance of the hypsarrhythmic EEG pattern. A major difference between the effectiveness of ACTH and that of prednisone in stopping the spasms and improving the EEG pattern was not demonstrated. Furthermore, in Azam B et al., the mean age of the patients was 11 months, with an age range of 2 months to 3 years [19]. These results also validate the Western literature, which reveals that the incidence of infantile spasms is highest between the age of 4-6 months of age [19].

However, another double-blind study showed a 100% response rate in ACTH versus 59% response to prednisolone (dose 3 mg/kg body weight which was equal to the dose used in Kossoff EH et al., in 15 to 20-kilogram child) [16]. In addition, a US consensus report, Pellok (2010), showed 70% response to prednisolone, so there is a lot of controversy [20]. A clinical trial from Pakistan, Azam M et al. concluded that there is no difference in treatment of ACTH or oral steroid among patients with infantile spasms. They claimed that the overall spasm-free outcome was similar in both groups. Regardless, the cost of ACTH injection was shown to be more than 100 times the cost of oral prednisolone, suggesting that a low-cost drug (i.e., oral steroid) should be preferred[19]. Baram TC et al., conducted a study among 28 patients with IS. Out of 15 infants randomized to ACTH, 13 were spasm-free (86.6%)[21]. In this study, four of the 14 patients given prednisolone were spasm-free (28.6%).

The above discussion highlights that the current medical literature presents mixed results on the clinical effectiveness of ACTH in comparison to prednisolone. In a developing country like Pakistan, where resources are limited, and the majority of the population belongs to low-income groups, oral prednisolone appears to be more useful as compared to ACTH with the advantages of easy availability and administration, less monitoring, and low cost with good control of seizures.

Limitations

This study had some limitations. It was not feasible to design a double-blind trial, considering that ACTH is administered as an injection while prednisolone is given via an oral dose. Nevertheless, randomization was used to reduce selection bias. This was a single center study consisting of a limited population of patients presenting to one tertiary care unit. Therefore, the results were not the representative of the whole population, a consideration that impacts

its external validity.

Conclusion

The study concluded that the number of patients treated with prednisolone were almost equal to the group treated with ACTH. Thus, it is recommended that patients with IS receive prednisolone as first-line therapy in developing countries due to its very low cost. Finally, there is a need for more randomized clinical trials to produce general consensus.

Abbreviations

ACTH Adrenocorticotropic Hormone
IS Infantile spasms

Acknowledgments

Ethical approval was obtained from the Institute of Child Health, Lahore institutional review board.

Competing interests

The authors have declared that they have no competing interests.

Authors' contributions

All the authors contributed to data collection and also critically reviewed the manuscript. The final version of the manuscript was approved by all the authors.

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References

[1] Lerner JT, Salamon N, Sankar R. Clinical profile of vigabatrin as monotherapy for treatment of infantile spasms. Neuropsychiatric disease and treatment. 2010 nov;6:731–40. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21127692http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2987507.

[2] Shields WD. Infantile spasms: little seizures, BIG consequences. Epilepsy currents;6(3):63–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16761063http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1464162.

[3] Riikonen R. Epidemiological data of West syndrome in Finland. Brain & development. 2001 nov;23(7):539–41. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11701251.

[4] Wanigasinghe J. Diagnosis and treatment of infantile spasms. Sri Lanka Journal of Child Health. 2010 dec;39(4):141. Available from: https://sljch.sljol.info/article/10.4038/sljch.v39i4.2480/.

[5] Workshop on Infantile Spasms. Epilepsia. 1992 jan;33(1):195–195. Available from: http://doi.wiley.com/10.1111/j.1528-1157.1992.tb02306.x.

[6] J Piña-Garza. Fenichel's Clinical Pediatric Neurology. 7th ed. Saunders Elsevier; 2013.

[7] Bonkowsky JL, Filloux FM, Byington CL. Herpes simplex virus central nervous system relapse during treatment of infantile spasms with corticotropin. Pediatrics. 2006 may;117(5):e1045–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16606680.

[8] Vinters HV. Histopathology of brain tissue from patients with infantile spasms. International review of neurobiology. 2002;49:63–76. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12040906.

[9] Infantile spasms (West syndrome). In: Sankar R, Koh S, Wu J, Menkes JH In: Menkes JH, Sernat HB MB, editor. Child neurology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2006. p. 877–880.

[10] Johnston MV. Infantile spasms. In: Behrman RE, Kliegman RM, Jenson HB SB, editor. Nelson text book of paediatrics. W. B. Saunders; 2007. p. 2463–2464.

[11] Gupta R, Appleton R. Corticosteroids in the management of the paediatric epilepsies. Archives of disease in childhood. 2005 apr;90(4):379–84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15781928http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC1720348.

[12] Carmant L. Vigabatrin therapy for infantile spasms: review of major trials in Europe, Canada, and the United States; and recommendations for dosing. Acta neurologica Scandinavica Supplementum. 2011;(192):36–47. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22061179.

[13] Stafstrom CE, Holmes GL. Can preventative antiepileptic therapy alter outcome in infants with tuberous sclerosis complex? Epilepsia. 2007 aug;48(8):1632–4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17692053.

[14] Ibrahim S, Gulab S, Ishaque S, Saleem T. Clinical profile and treatment of infantile spasms using vigabatrin and ACTH–a developing country perspective. BMC pediatrics. 2010 jan;10:1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20078871http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2820464.

[15] Tsao CY. Current trends in the treatment of infantile spasms. Neuropsychiatric disease and treatment. 2009;5:289–99. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19557123http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC2695218.

[16] Kossoff EH, Hartman AL, Rubenstein JE, Vining EPG. High-dose oral prednisolone for infantile spasms: an effective and less expensive alternative to ACTH. Epilepsy & behavior : E&B. 2009 apr;14(4):674–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19435579.

[17] Noureen N, Rana MT. Clinical profile and response to oral prednisolone in infantile spasm. Journal of the College of Physicians and Surgeons–Pakistan : JCPSP. 2010 mar;20(3):186–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20392382.

[18] Hrachovy RA FJ. Severe encephalopathic epilepsy in infants: infantile spasmss (West syndrome). In: Pellock JM, Bourgeois BF, Dodson WE, Nordli DR Jr SR, editor. Pediatric Epilepsy: Diagnosis and Therapy. New York, NY: Demos Medical Publishing; 2008. p. 249–268.

[19] Azam M, Bhatti N, Krishin J. Use of ACTH and prednisolone in infantile spasms: Experience from a developing country. Seizure. 2005;14(8):552–556.

[20] Pellock JM, Hrachovy R, Shinnar S, Baram TZ, Bettis D, Dlugos DJ, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010 oct;51(10):2175–89. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20608959.

[21] Baram TZ, Mitchell WG, Tournay A, Snead OC, Hanson RA, Horton EJ. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics. 1996 mar;97(3):375–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/8604274http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC3100715.