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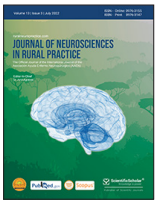

Original Article

Cost-effectiveness of adrenocorticotropic hormone injection and oral prednisolone in patients with West syndrome: A comparative analysis

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ABSTRACT

Objectives: This study aims to compare the cost-effectiveness of oral prednisolone and adrenocorticotropic hormone injection in West syndrome patients, the two most common hormonal therapies used for this condition.

Materials and Methods: In this prospective and observational study, we documented sociodemographic, epilepsy, and development-related variables at baseline and up to 6 months after starting hormonal therapy, in all consecutive eligible patients of WS between August 2019 and June 2021, apart from the direct medical and non-medical costs and indirect health-care costs. We selected cost per quality-adjusted life-year (QALY) gained, per one patient with spasm freedom, one positive responder (>50% reduction in spasms), one relapse-free patient, and one patient with development gain. We determined whether incremental cost-effectiveness ratio for these parameters crossed the threshold value in base-case analysis and alternate scenario analysis.

Results: Out of 52 patients screened, 38 and 13 patients enrolled in ACTH and prednisolone group. On D28, 76% and 71% achieved spasm cessation (P = 0.78) and the total cost of treatment was INR 19783 and 8956 (P = 0.01), in ACTH and prednisolone group respectively. For all pre-specified parameters, the cost/effectiveness ratios including cost/QALY gain were higher in ACTH group and the corresponding ICER values for all these parameters crossed the threshold cost value of INR 148,777 in base-case analysis and also in alternative scenario analysis.

Conclusion: Treatment with oral prednisolone is more cost-effective as compared to ACTH injection for children with WS.

Keywords: West syndrome, Adrenocorticotropic hormone, Quality-adjusted life-year, Cost-effectiveness, Resource-limited setting

INTRODUCTION

West syndrome (WS) is one of the most predominant epileptic encephalopathies in infants and young children in developing countries.[1] The affected patients suffer from epileptic spasms and developmental delay or stagnation, accompanied by hypsarrhythmia in electroencephalogram (EEG).[2] Hormonal therapy with adrenocorticotropic hormone (ACTH) injection or oral prednisolone is considered the first-line treatment in developing countries, although the recent ICISS trial suggests that the addition of vigabatrin might further increase the spasm cessation rate.[3,4] A significant proportion of patients with WS develops drug-resistant epilepsy on long-term follow-up, invariably accompanied by psychomotor retardation and significant financial, social, and emotional burden to caregivers and loss of disability-adjusted life year.[5] Although several trials have compared the efficacy and safety of the above-mentioned treatment options in WS, publications describing the cost-effectiveness of these treatments are scarce in the literature.[6,7] As most caregivers in developing countries belong to the lower socioeconomic status (SES), apart from true efficacy in a trial setting, the cost of medications and other allied health-care expenditures also determine the patient compliance and overall effectiveness of treatment.[8] This study aims to compare the cost-effectiveness of oral prednisolone and ACTH injection in WS patients, the two most common hormonal therapies used for this condition.

MATERIALS AND METHODS

This prospective and observational study was conducted between August 2019 and June 2021 in a tertiary care teaching hospital in the Uttarakhand state of India. The patients

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included were mostly the residents of either Uttarakhand or nearby districts of Uttar Pradesh belonging to rural/semi-urban areas and lower/lower-middle SES. Children with WS (epileptic spasms with/without hypsarrhythmia in EEG) coming to our Pediatric Out Patient Department (OPD) who were started on ACTH or oral prednisolone were enrolled after obtaining institutional ethical approval and detailed informed consent from the caregiver. Those patients who received vigabatrin as first-line treatment or medications other than hormonal therapy or responded only to vitamins like pyridoxine/anti-seizure medications (ASMs) without requiring hormonal therapy, those who already had been started on hormonal therapy before presenting to our center or had contraindications for hormonal therapy were excluded from the study.

Initially, we developed an economic model for the cost-effectiveness analysis in patients with WS.[9] At baseline, the demographic profile of patients and their parents including SES, monthly income, education of parents, area of residence and distance from our hospital, mode of travel, accommodation facilities during outpatient visits/inpatient hospital stay for the caregivers, type of jobs of the parents, loss of wages/working days for the illness of the child/hospital visits, number of siblings, age of onset of epileptic spasms, delay in seeking treatment, number of epileptic spasms per day and other seizures (if any, documented in seizure diaries maintained by caregiver), other ASMs/vitamin cofactors administered previously and co-medications for seizure/other comorbidities such as spasticity/anemia/gastroesophageal reflux/malnutrition, developmental status, etiology of WS, neuroimaging, video EEG, metabolic, genetic, and other investigations were noted. It was noted whether the parents and children were beneficiaries of the Ayushman Bharat Scheme or under the poor free scheme for BPL (below poverty line) families.[10] The economic burden for these patients during inpatient stay was borne by the government, but not the medical and non-medical expenses required for outpatient visits.

Subsequently, we determined the costs incurred for all purposes related to WS, for 6 months after initiating the oral corticosteroid or ACTH. ACTH was offered as the first-line medication for WS if financially and logistically feasible (except for Tuberous sclerosis- associated WS, for which vigabatrin was used instead). But for most cases, financial reasons compelled us to start oral prednisolone instead of ACTH. We used the bottom-up approach for cost analysis and also assumed that all expenditures during the 6 months following corticosteroid/ACTH initiation (including those for the management of uncontrolled seizures, relapse of spasms, adverse events, intercurrent febrile/afebrile illnesses, and addition of vigabatrin/other ASMs) were directly/indirectly related to the corticosteroid/ACTH.

The direct medical costs included the cost of buying the ASMs/vitamin cofactors, outpatient consultation, inpatient hospital admission, investigations for ruling out latent tuberculosis before starting hormonal therapy, blood pressure, blood sugar, and other investigations required for monitoring, ancillary services such as antihypertensives and proton pump inhibitors administered whenever indicated, procuring a refrigerator, medical fees meant for administering daily injections by physicians or paramedical professionals. The regime used for oral prednisolone was as follows: 2 mg/kg/day initially for 1–2 weeks; if the spasms completely stopped between D7 and D14, dose tapered; if >50% reduction in spasm frequency, same dose continued for 2 more weeks; if <50% reduction in daily spasm frequency, dose increased up to 4 mg/kg/day (maximum 60 mg/day). However, for most patients, we started tapering hormonal therapy after 2–4 weeks irrespective of the degree of response. Those chosen for ACTH were given 30–40 IU once-daily subcutaneous injection and gradually increased over the next 7–14 days to a maximum of 60 IU/day. Due to resource-constrained settings, we monitored blood pressure and random blood sugar once weekly. We repeated video EEG in all cases with complete spasm cessation for documenting the electrical resolution of hypsarrhythmia. If the child was already on any ASM before starting hormonal therapy (in most cases valproate, levetiracetam, or benzodiazepine), we continued the same during hormonal therapy too. In those with incomplete cessation/recurrence of spasms, we provided the option of vigabatrin (if financially affordable) or expanded the ASM dose/combination therapy. Treatment was started on outpatient basis, after ruling out latent tuberculosis by Mantoux and chest x-ray. The cost of other investigations such as neuroimaging, EEG, genetic, or metabolic investigations to determine underlying etiology was not excluded in cost-effectiveness analysis. We fixed the unit cost of each of these commodities at the beginning of the study based on the price at our institute and then multiplied it by the number of times the service or product was availed to calculate the total cost. Serious adverse events (SAEs) arising from hormonal therapy were admitted for IP care; other events were managed on OPD basis.

The direct nonmedical costs included expenditures for the travel to and from the hospital, accommodation, and food (on an average two caregivers per patient). We noted the nonmedical cost for each patient at enrollment and then assumed that the pattern will remain the same for all visits during the study period. To increase accuracy, we scrutinized all the medical and non-medical bills incurred at each visit, supplemented by the recall of parents for the missing information. The treating physician decided the scheduling of outpatient clinical visits, but in cases that responded to hormonal therapy, the visits were limited to D7/D14, D28, 3 months and 6 months. The parents were also provided

with a mobile number for access during emergencies. For the Ayushman beneficiaries, the amount of inpatient medical fees (admission charge, medications, and investigations) exempted was collected from the hospital database. The indirect expenditures were calculated using wages lost by the parents, estimated from their monthly income. Caregivers were requested to buy from the pharmacy in the hospital premises to ensure the quality of medications and uniform pricing as far as possible. The expenditure was calculated in INR (Indian rupee), as well as in the United States dollar as of June 30, 2021.

For determining the effectiveness of hormonal therapy, we estimated these parameters: percentage of patients with complete spasm cessation and electrographic resolution of hypsarrhythmia on D28, at least 50% reduction in daily spasm frequency on D28, relapse-freedom from spasms at 6 months and at least 1 point improvement in DQ at 6 months, as compared to baseline. We also determined the number of quality-adjusted life-year (QALYs) gained by first estimating a utility weight from the percentage reduction of spasms on D28 (from this, we subtracted the percentage of days on hormonal therapy/suffered SAEs) and then converting it into decimals (ranging between 0 and 1). We did not consider the spasm reduction at 6 months, as many patients received other ASMs including vigabatrin in both arms. Subsequently, we multiplied the study duration (0.5 years) with the utility weight for an individual patient. We assumed that treatment-emergent adverse events (TEAEs) other than SAEs did not compromise health-related quality of life significantly. In the absence of other definite measures, we used this method to determine the QALYs gained. For those patients lost to follow-up, missing data were filled using various imputation methods (using mean/median available data set for that parameter and Last observation carried forward method).[11]

Based on the outputs of the economic model, which estimated the total costs (combination of direct medical/non-medical and indirect costs), cost-effectiveness was expressed as cost per QALYs gained, cost per spasm free patient, cost per positive responder (at least 50% reduction in spasms), cost per relapse-free patient, and cost per patient with development gain. The cost-effectiveness was determined using incremental cost-effectiveness ratios.[12] The two hormonal therapies were rank-ordered in terms of increasing cost. The costlier strategy was compared with the cheaper one by dividing the additional cost by the additional benefit to determine the ICER. If the costlier strategy provided no additional benefit, it was considered "dominated."[13] Otherwise, the strategy whose ICER was less than the threshold cost/life years was considered the most effective strategy. As per the criteria suggested by the Commission on Macroeconomics and Health, which is also used by the WHO-CHOICE (choosing cost-effective interventions), interventions costing less than the national annual GDP per capita and <3 times, this value for each QALY gained/DALY averted is considered highly cost-effective and cost-effective, respectively.[14,15] Accordingly, as per the data for the Indian population for the economic year 2020-21, we assumed the threshold cost for the more effective hormonal therapy to be considered as highly cost-effective or only cost-effective to be INR 49,592 and INR 148,777, respectively, as we only accounted for expenditure in 6 months (0.5 years).[16] We also performed a deterministic sensitivity analysis to find out the sensitivity of the above analysis (change in result of cost-effectiveness by changing values of input parameters).[17] We varied each parameter, one at a time, beyond the 95% CI or ±25% from base-case values (if 95% CI was not available) to perform these analyses.

RESULTS

During the study period, a total of 52 patients with WS completed at least 6 months of follow-up after starting treatment. Excluding one patient with tuberous sclerosis in whom vigabatrin was started as first-line medication, all were started on hormonal therapy (38-oral prednisolone, 13-ACTH). We had partial missing data for three patients and filled up by imputation methods (two in prednisolone and one in ACTH group – follow-up cost and effectiveness details available only up to 2–3 months). The baseline demographic characteristics as described in [Table 1] showed, ACTH group had more caregivers with higher education, residing in urban areas, with middle/higher SES. However, the baseline clinical, radiological, and electrophysiological profile of these two groups was comparable, as described in [Table 2] (apart from the lead time before initiating hormonal therapy after onset of spasms and the number of patients who were already on ASMs at the time of presentation - favored ACTH group). The clinical and electrophysiological response was slightly better with ACTH, although not reaching the point of statistical significance [Table 3]. The nature and frequency of TEAE and SAEs in both groups have been described in [Table 4]. The ACTH group although had numerically more TEAEs and SAEs, especially hypertension, the difference for any of these did not attain statistical significance.

The median total cost of treatment in 6 months was INR 19,783 and INR 8956, while in the 1st month, it was INR 11,041 and INR 2706, respectively, in ACTH and prednisolone group (P = 0.01 and 0.002, respectively). The cost breakdown showed that the direct medical costs (cost of ACTH and expenditure for its administration by health professional) were the main distinguishing feature (P = 0.008) [Table 5]. One patient in ACTH group had catastrophic health-care expenditure (≥30% total family income during the study period) due to the additional cost of IP care for 1 week of respiratory tract infection and systemic sepsis.

Table 1: Comparison of baseline demographic variables between ACTH and prednisolone groups.

Variables	Prednisolone group (*n*=38) (%)	ACTH group (*n*=13) (%)	*P*-value
Males	23 (60)	8 (61)	0.87
Education of father (graduation or more)	8 (21)	13 (100)	<0.0001
Education of mother (graduation or above)	2 (5)	11 (84)	<0.0001
Socio-economic status (modified Kuppuswamy Scale)			
Lower	29 (76)	0	0.02
Middle	9 (24)	5 (38)	
Higher	0	8 (62)	
Urban residence	7 (18)	13 (100)	<0.0001
Rural residence	31 (82)	0	

ACTH: Adrenocorticotropic hormone

Table 2: Comparison of baseline epilepsy variables and developmental quotient between ACTH and prednisolone groups.

		Prednisolone group (*n*=38)	ACTH group (*n*=13)	*P*-value
Median age at presentation in months (IQR)		7.5 (6–9)	6.5 (5–8)	0.45
Median age at spasm onset in months (IQR)		6 (5–8)	6 (5–7.5)	0.82
Lead time before initiating hormonal therapy after the onset of spasms (median, IQR) (in weeks)		6 (5–8)	3 (2–4)	0.04
Median number of clusters per day at presentation (IQR)		4 (3–6)	4 (3–5)	0.78
Median number of spasms per clusters at presentation (IQR)		5 (3–8)	6 (3–9)	0.71
Number of children already on antiepileptic drugs		8 (21)	7 (53)	0.03
Etiology	Structural	35 (92)	10 (76)	0.16
	Cryptogenic	3 (8)	3 (24)	
EEG	Hypsarrhythmia	15 (39)	5 (38)	0.94
	Hypsarrhythmia variant	23 (61)	8 (62)	
Baseline development quotient (median, IQR)		32 (27–42)	39 (33–48)	0.06
Development quotient on follow-up at 6 months (Median, IQR)		35.5 (30.5–44)	46 (37–53.5)	0.07
Patients with at least 1 point improvement in development quotient		31 (78)	11 (84)	0.78

ACTH: Adrenocorticotropic hormone

For all effectiveness parameters, ACTH group performed numerically slightly better, although the difference was not statistically significant, but for all these parameters, the cost/effectiveness ratios including cost/QALY gain were higher in ACTH group [Table 6]. During decision-making, the ICER value for all these parameters crossed the threshold cost value of INR 148,777. Hence, oral prednisolone was found to be more cost-effective than ACTH, which may be deemed as too expensive over oral prednisolone to provide any clinically meaningful advantage in any effectiveness parameter.

Apart from the above-mentioned base-case analysis (results obtained from running an economic model with the most likely or preferred set of assumptions and input values), in alternative scenario analysis, when model parameters were varied one at a time through a range of values, oral prednisolone still remained the more cost-effective strategy over the 1-month and 6-month time horizons in the deterministic sensitivity analysis. When we adjusted for individual demographic and socio-economic determinants (SES, parental education, gender, etc., as there was a skewed distribution of some parameters), the cost difference was still significant. Similarly, when adjusted for disease-related variables such as etiology, age of onset of spasms, treatment lag, baseline spasm frequency, comedications for seizure, rate of response to primary treatment, relapse rate, and presence of comorbidities, the cost in ACTH group remained significantly higher than in prednisolone group.

DISCUSSION

Our study showed that in the Indian scenario, especially in settings where the demographic scenario of caregivers resembles our center, oral prednisolone is more cost-effective than ACTH injection for patients with WS. Although the success rates for spasm freedom, hypsarrhythmia resolution and relapse-free status are slightly higher for ACTH, it is offset by its price, which is much higher than prednisolone.

The allocation to prednisone and ACTH groups in our study was not randomized and was mainly based on SES/residential status. The caregivers coming from higher SES were likely to spend more for non-medical items such as accommodation, food, and travel in comparison to those from the lower SES.

Table 3: Response of epileptic spasms in low dose and high dose prednisolone groups.

	Prednisolone group (*n*=38)	ACTH group (*n*=13)	*P*-value
Spasm outcome on day 14			
Complete spasm freedom	18 (47)	6 (46)	0.91
>50% spasm reduction but not complete cessation (%)	15 (39)	6 (46)	
<50% spasm reduction (%)	5 (14)	1 (8)	
Normal EEG with complete resolution of hypsarrhythmia	2 (5)	1 (8)	0.74
Resolution of hypsarrhythmia with persistence of background epileptiform discharges	30 (79)	10 (76)	
Persistence of hypsarrhythmia	6 (16)	2 (16)	
Spasm outcome on day 28			
Complete spasm freedom	27 (71)	10 (76)	0.78
>50% spasm reduction but not complete cessation (%)	10 (26)	3 (24)	
<50% spasm reduction (%)	1 (3)	0	
Normal EEG with complete resolution of hypsarrhythmia	5 (13)	3 (24)	0.63
Resolution of hypsarrhythmia with persistence of background epileptiform discharges	32 (84)	10 (76)	
Persistence of hypsarrhythmia	1 (3)	0	
Received vigabatrin	3 (8)	3 (23)	0.16
Number of patients who achieved spasm cessation (at least transiently) at any time during 6 months	31 (81)	12 (92)	0.61
Number of children who remained completely spasm-free at 6-month follow-up	27 (71)	11 (84)	0.56
Number of patients with relapse of spasms after cessation	4 (11)	1 (8)	0.59
Median duration for spasm resolution in patients responding to hormonal therapy (in days) (IQR)	8 (6–10)	6 (5–9)	0.21

ACTH: Adrenocorticotropic hormone

Table 4: Cost breakdown in different subheadings in ACTH and prednisolone group.

Cost of treatment in 6 months (in INR) (median, IQR)	Prednisolone group (*n*=38)	ACTH group (*n*=13)	*P*-value
Total charges	8956 (6174–11259)	19783 (15631–25284)	0.01
Direct medical charges	6811 (91$) (4394–9125)	15286 (204$) (12318–21963)	0.008
Direct non-medical charges	2367 (31$) (1849–2951)	3412 (45$) (2648–4174)	0.34
Travel charges	1948 (26$) (1583–2462)	2738 (36$) (2278–3347)	0.67
Food charges	472 (6$) (313–654)	651 (8$) (497–885)	0.25
Indirect cost (loss of wages)	872 (11$) (531–1029)	1279 (17$) (892–1596)	0.46
Total cost in 1st month	2706 (36$) (1923–3749)	11041 (147$) (8756–15652)	0.002

ACTH: Adrenocorticotropic hormone

Hence, the cost breakdown between the two groups showed that the difference in expenditure was majorly but not entirely due to the price difference of ACTH and prednisolone.

The treatment lag was lower in the ACTH group and more patients had cryptogenic etiology, which is one of the most important prognostic factors for achieving spasm cessation in the previous studies. Thus, if random allocation is adhered to, the slightly better effectiveness parameter might not be reproduced in the future studies from our subcontinent. However, even when adjusted for the skewed variables, the cost difference persisted to be significant.

In our study, inpatient hospitalization solely for the purpose of administering ACTH injection was not provided, adding to the caregivers' expenditure for availing the same from local health professionals and the indirect expenditure incurred from the consequent work absenteeism/loss of pay. In the upcoming years, if pediatricians from secondary care level government/public sector hospitals could prescribe and administer ACTH for WS, cost of therapy could be curtailed. Activities for training pediatricians in district/sub-district level government hospitals in the treatment of difficult to treat epilepsies are a need of the hour to cut down health-

Table 5: Adverse effects in participants of low dose and high dose prednisolone groups.

Variables	Prednisolone group (*n*=38) (%)	ACTH group (*n*=13) (%)	*P*-value
At least one TEAE	31 (81)	12 (92)	0.66
At least one SAE	0	1 (8)	0.25
Weight gain	7 (19)	4 (31)	0.43
Hypertension	5 (13)	5 (38)	0.09
Cushingoid faciess	15 (39)	6 (46)	0.74
Infection requiring hospitalization	0	1 (8)	0.25
Irritability	8 (21)	5 (38)	0.27
Increased Appetite	11 (29)	5 (38)	0.73
Hyperglycemia	4 (10)	2 (16)	0.63

ACTH: Adrenocorticotropic hormone, TEAE: Treatment-emergent adverse events, SAE: Serious adverse events

Table 6: Base-case analysis: Costs, QALYs, and other effective measures for ACTH and prednisolone group.

Treatment group	Cost/ patient (INR)	Percentage reduction in number of spasms	QALYs gained	Cost (INR)/ QALY gained	Cost (INR)/one patients with freedom from spasms	Cost (INR)/ one positive responder	Cost (INR)/ one relapse free patient	Cost (INR)/one patient with developmental gain
ACTH	19783	82	0.410	48251	25717	19783	21431	23379
Prednisolone	8956	79	0.395	22673	12604	9198	12604	10978
ICER (ACTH ranked first and prednisolone ranked second in effectiveness)				222,417/1 QALY gain	262,260/1 more patient with freedom from spasm	352,833/1 more positive responder patient	294,233/1 more patient with relapse free status	206,683/1 more patient with developmental improvement

ACTH: Adrenocorticotropic hormone, QALY: Quality-adjusted life-year

care expenditure in India.[18] With the availability of online meeting platforms, this may not be an impossible dream.

Another notable influence on our cost-effective analysis was the COVID-19 pandemic and government-imposed lockdown measures adding to the difficulties and expenditures – especially in the ACTH group due to the requirement for arranging more logistics. Many caregivers who suffered loss of wages during the pandemic favored oral prednisolone, introducing bias.[19] In non-pandemic times, probably the health expenditure for 1-week hospitalization in a public sector teaching hospital might not have amounted to the catastrophic health expenditure seen in one patient in our ACTH group.

All patients in ACTH group who had a failure of spasm cessation received vigabatrin, whereas some such cases in the prednisolone group still preferred cheaper alternatives such as valproate, levetiracetam, or benzodiazepine. The difference between the two groups might have been lower if only the direct medical and non-medical costs related to healthcare were considered. The results of our study cannot be generalized to the caregivers from the metro cities in India attending corporate hospitals, as the total health expenditure of 6 months in the ACTH group still seems reasonable and within the financial affordability for families belonging to higher SES.

The efficacy of ACTH seems only to be slightly higher than that of oral prednisolone, which was not statistically significant and probably also not clinically meaningful. Moreover, the dose of prednisolone in our study was lower (2 mg/kg/day) than that used in the Western studies. But most Indian studies have used this particular dose,[20] to minimize the adverse effects and intercurrent infections, as intensive regular monitoring is not logistically feasible in resource-constrained settings. The South Asian WS research group and Child Neurology Society had also suggested prednisolone as the preferred first-line treatment for epileptic spasms during the COVID-19 pandemic to minimize health-care visits.[21] In the systematic review by Chang *et al.*[22] including five trials, both high and low-dose steroids were non-inferior to ACTH in terms of hypsarrhythmia resolution, spasm cessation, adverse effects, relapse rate, or subsequent epilepsy rate. However, theoretically, ACTH has an upper hand over prednisolone in controlling epileptic spasms as it suppresses endogenous corticotrophin-releasing hormone (CRH) through a negative feedback pathway. These CRH receptors are abundant in the early part of infancy when epileptic spasms usually develop and excess of CRH

produces more excitant effects on numerous neurons. ACTH is still the preferred first-line treatment for WS in developed countries.

The ICISS trial found that a combination of vigabatrin and hormonal therapy was more efficacious than either tried alone. However, in the Indian setting, financial and logistic difficulties prevent generalization of this result into clinical practice. Another study by Sakpichaisakul *et al*.[23] is also currently recruiting patients of WS for comparing vigabatrin and high dose prednisolone versus vigabatrin alone (NCT04302116). Regarding the comparison of high dose and low dose steroids, the study by Chellamuthu *et al*.[24] favored high dose steroids.

We assumed the threshold cost for determining the cost-effectiveness as half the monthly per capita national GDP, as our center caters to patients from multiple states and in the absence of health insurance, the caregivers had to arrange for rehabilitation measures and non-healthcare expenditures also, which were not accounted for in our study. Comorbidities such as developmental delay and spasticity are significantly higher in patients with WS.[25] In India, even though the public health expenditure is <2% of national GDP, the majority of the public depends on government hospitals for health care.[26] Thus, although intensive and expensive rehabilitation measures are rarely found in the primary and secondary health-care centers in India, most caregivers in our study relied solely on government settings. In this regard, our study provides a relatively accurate picture of the out-of-pocket expenditure of caregivers.

The overall expenditure in our study in the ACTH group was compatible with the other study from North India exploring financial burden in the same cohort by Raithatha *et al*.[27] (INR 27035 yearly). However, it is significantly higher than the cost in the oral prednisolone group, which might be because the majority of patients received ACTH as first-line medication in their study (probably due to better financial status of attending caregivers). In this study also, direct medical expenses contributed toward two-third of the total expenditure and ASMs were major contributors among direct medical costs even in those receiving prednisolone, like in our study. As the number of ASMs at baseline and number of patients requiring additional, ASMs were comparable and there was no cross-over between the two groups, coexisting ASMs was unlikely to be a confounding factor for effectiveness estimation. Moreover, the economic model considered all these input variables, and changing these input variables in the deterministic sensitivity analysis did not change the direction of the cost-effectiveness analysis result. In the study by Raithatha *et al*.[27] also, the cost in ACTH group was significantly higher than prednisolone group and ACTH was preferred mainly by parents belonging to higher SES. Due to better health-care awareness, they were more likely to report early, which is an important prognostic factor for achieving spasm freedom, and were likely to have better compliance with advised treatment. This could have explained some proportion of effectiveness difference between two groups.

Hypertension was more in the ACTH group in ours, as it was in a recent study by McGarry *et al*.,[28] although the difference was not statistically significant in either. Moreover, only rarely did any of these patients develop long-term hypertension according to McGarry *et al*.[28] and none developed cardiomyopathy. The overall spasm cessation rate in our study is compatible with the previous studies from India by Raithatha *et al*.[27] and Chellamuthu *et al*.,[24] but lower than the cohorts reported from developed countries. This is probably due to the preponderance of structural etiologies such as hypoxic-ischemic encephalopathy, neonatal hypoglycemia, or meningoencephalitis sequelae, which are less likely to have spasm cessation compared to cryptogenic WS.

Other limitations of our study were small sample size (especially in ACTH group), shorter follow-up duration (unable to determine long-term epilepsy incidence), missing data in three patients (overcome to some extent by imputation methods), and lack of control over the commercial brand of medications the caregivers were affording and less reliability of cost details maintained by caregivers with the lower SES (especially for non-medical costs such as travel and food more in the prednisolone group). The response rate in our study is relatively higher, but it could be because at 6 months, many patients received a combination of hormonal therapy, vigabatrin as well as other ASMs and 6 months is a relatively short period for determining the relapse rate of epileptic spasms. Finally, there is no valid objective parameter for determining QALY in infants with WS. We considered the percentage of spasm reduction as the most objective and meaningful proxy for QALY in WS patients, although the number of spasms maintained in seizure diaries by parents might not be fully accurate, especially for parents belonging to the lower SES and when the number of spasms is as high as >100/day. Despite these limitations, this was the first study to compare the cost-effectiveness of these two hormonal therapies in a resource-constrained setting and is likely to help public health policymakers in taking accurate decisions and ameliorating measures to cut down the out-of-pocket expenditure of caregivers.

CONCLUSION

Treatment with oral prednisolone is more cost-effective than ACTH injection for children with WS. Nevertheless, long-term data from patients prescribed with these two hormonal therapies allocated randomly in non-pandemic times with a larger sample size will be more helpful in determining a more accurate measure of cost-effectiveness.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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