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Cost-effective analysis of dual therapy in epilepsy, a study from India

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Abstract

Background and Objective: For improving overall care in epileptic patients, careful evaluation of pharmacotherapy, seizure control, quality of life (QOL) and cost effectiveness are helpful but such data are relatively meagre from developing countries. The present study was undertaken to audit all these said factors with different drug combinations comparing older with newer drugs in the setting of a tertiary care epilepsy hospital in India. *Methods:* Forty patients were divided into four treatment groups, of ten each which were valproic acid + lamotrigine (Group-I), valproic acid+ clonazepam (Group-II), oxcarbazepine + clobazam (Group-III) and phenobarbitone + phenytoin (Group-IV), based on most commonly used dual therapy in local clinical practice. The patients were followed at monthly intervals for six months. Efficacy was assessed by reduction in seizure frequency, QOL was assessed by using an adapted version of 31- items questionnaire QOLIE-31 (quality of life in epilepsy) and cost effectiveness was calculated as ratio of direct cost of medicine and improvement in quality of life. *Results:* There was a significant reduction in seizure frequency and improvement in QOL in all four groups at 2nd and 6th months. Cost-effectiveness analysis at the end showed that group-IV paid the least for same improvement in QOL.
Conclusion: Older drugs are equally efficacious as compared to newer in controlling seizure frequency and improving QOL, but are more cost effective.

INTRODUCTION

Epilepsy is a common neurological disease affecting almost 50 million people worldwide.[1] It is defined as a chronic neurological condition whose cardinal feature is a predisposition to recurrent unprovoked seizures.[2] Approximately, 85% of people affected with epilepsy live in developing countries. In India alone, there are an estimated 5 million people affected with epilepsy.[3] About 20% of all epileptics on earth reside in India. Patients with epilepsy are prone to have poorer self-esteem and higher levels of anxiety, depression and problems with social interaction and involvement. At the same time, the concept of quality of life (QOL) assessment has led to development of generic and disease- specific questionnaires to evaluate areas of concern to patients. So, the ultimate goal in the management of epilepsy is not only cessation of seizures with minimal side effects but also an improvement in the patient's overall quality of life.[4]

Economy plays a very important role in managing these epileptic burden of epilepsy in developing countries is avoidable by the routine availability of low-cost anti-epileptic drugs (AEDs).[6] The annual economic burden of epilepsy in India is 88.2% of GNP per capita and 0.5% of the GNP.[5] A significant proportion of the current Economic concerns are increasingly important in health system design, provider payment, and research funding decisions. Cost estimates are needed to provide insight into where the potential opportunities for cost-savings lie and to lay the groundwork for research to determine how to treat the disorder more effectively. The methods used to measure the QOL and costs of epilepsy are reviewed and results from studies in different countries are being discussed. From India, there are few studies from southern part of country. Most of the studies have discussed about mono-therapy (single drug) or poly-therapy (multiple drugs) while discussing cost of epilepsy treatment or their impact on QOL. But the issue

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of dual therapy (two drugs) with QOL and cost of epilepsy has not been specifically discussed. Dual therapy for epilepsy is a common practice in our Centre, especially in patients not responding to monotherapy. Therefore, this study was planned to find out the efficacy of dual AEDs at a tertiary care hospital with QOL and cost-effective analysis for their seizure control.

METHODS

It was an observational prospective follow-up study of outdoor patients of epilepsy attending the neurology department of Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand, India. A total of forty patients, with history of one or more episodes of unprovoked seizures and who had completed titration phase of 4-6 weeks of their respective combination drug regimens were included. Patients less than 10 years of age, or having epileptic encephalopathy, mental retardation, focal neurological deficit or serious co-morbid illness were not included. The patients were divided into four groups of ten patients each receiving combination treatment as following: Group I: valproic acid (VPA 600mg) + lamotrigine (LTG 50mg); Group II: valproic acid (600mg) + clonazepam (CZP 0.5mg); Group III: oxcarbazepine (OXC 900mg) + clobazam (CLB 20mg); Group IV: phenobarbitone (PB 75mg) + phenytoin (PHT 200mg). The choice of the four combinations for study was based on the common clinical practice, as they were the commonly used dual AED therapy in our Centre.

Seizure types and epileptic syndromes were classified according to ILAE (International league against epilepsy guidelines). Parameters under study were recorded as follows:

Efficacy: Efficacy was assessed by reduction in seizure frequency after monthly follow-up. Mean numbers of seizures per months was calculated at baseline and at the end of 2nd and 6th months.

Quality of life (QOL)**:** By using 31 items questionnaire, (QOLIE-31) in quality of life in epilepsy was measured at 0, 2 and 6 months during follow-up. This questionnaire was developed and recommended for epilepsy cases evaluation.[7] QOLIE-31 has one visual analogue scale of overall quality of life and 30 questions pertaining to diverse aspects and the range score for that aspect were as follows:- seizure worry (5, 0-8), overall QOL (2, 0-14), emotional well being (5, 0-15), energy or fatigue (4, 0-12), cognitive performance (6,0-27), medication effects (3, 0-3) and social function (5, 0-21), total score (30, 0-100). A lower score indicated poor QOL and a higher score indicated better QOL.

Safety: Safety of various treatment groups was assessed by monitoring of adverse drug reaction and change in cognitive function score at 2nd and 6th months. Haematology and blood chemistry were also done at baseline, 2 and 6 months. Adverse reactions with different drug were asked according to checklist available at the time of interview. Mini-mental state examination (MMSE) was used to assess the cognitive function in all patients.

Cost effectiveness: It was calculated as ratio of cost of treatment and improvement in quality of life with every combination. The direct medication cost was calculated in Indian national rupees (INR). Retail price of each drug as per Indian drug regulation in current time was recorded.

Statistical analysis: Statistical analysis was done using paired "t test" for intra-group comparison. The value of $p < 0.05$ was considered statistically significant.

RESULTS

General characteristics

Mean age was 25.7 ± 1.9 years of these 40 patients and 27 (67.5%) were males and 13 (32.5%) were females. 70% of respondents had generalized tonic-clonic type of seizures and remaining 30% had partial type of seizures. The mean duration of disease in Group-I was 47.6±13.5 months, 52.9±28.1 months in Group-II, 58.3±29.1 months in Group-III, and 60.1±34.8 months in Group-IV. Overall mean duration of seizures was 59.6± 12.5 months.

Change in seizure frequency (Table 1)

The efficacy of the four combination drug regimens was assessed by reduction in seizure frequency. There was significant reduction in seizure frequency in all four groups at 2 months and at 6 months as compared to baseline. All the four groups were not comparable at the time of inclusion in terms of seizure frequency. Mean seizure frequency per month at entry and reduction during follow-up are given in Table 1. There was no statistical difference in the outcome of all the groups at the end of the study. None of the patients showed status epilepticus or seizure exacerbations.

Table 1: Efficacy profile with changes in seizure frequency / month (Mean ± S.E) in each study group

Time interval	Group I VPA + LTG (n = 10)	Group II VPA+CZP (n = 10)	Group III OXC+CLB (n = 10)	Group IV PB+PHT (n = 10)
0 day	1.80 ± 0.48	0.79 ± 0.30*	3.15 ± 0.71	1.05 ± 0.36#
2 months	0.45 ± 0.15	0.10 ± 0.10∞	1.10 ± 0.3	0.30 ± 0.13
6 months	0.02 ± 0.025	0.00 ± 0.00	0.20 ± 0.13	0.04 ± 0.02

VPA: Valproic acid, LTG: Lamotrigine, CZP: Clonazepam, OXP: Oxcarbazepine, CLB: clobazam, PB: Phenobarbitone, PHT: Phenytoin.
* P 0.01 vs corresponding OXC+CLB at 0 day.
# P 0.03 vs corresponding OXC+CLB at 0 day.
∞ P 0.02 vs corresponding OXC+CLB at 2 months.
The p-value of each group when compared before and after treatment was <0.001.

Change in quality of life (QOL) (Table 2)

The QOL was comparable in all the groups at the beginning. There was significant improvement in QOL in all four groups after 2nd and 6th months. Only Group IV (PHT+PB) had significant change in QOL at the end of 2 months (p=0.02). However, there was no significant difference in QOL among four groups at the end of 6 months.

Safety assessment

As per checklist, the most common adverse reaction was somnolence, acne, anorexia and irritability was found in 4 patients of PHT+PB group, weight gain and anal fissure in three patients of VPA+LTG group, poor memory and somnolence each in 1 patient of VPA+CZP and OXC+CLB group respectively. Though the adverse reaction was most common in PHT+PB group and necessitated dose adjustment, none required discontinuation of medicine. There was no effect on QOL due to these adverse effects and none of the patients withdrew from the study due to adverse effect.

Majority of the patients had MMSE score of 30 at baseline except 2 patients in VPA+CZP group whose scores were 26 and 25 respectively and 2 patients in PHT+PB group had scores of 28 and 20. There was no significant change in cognitive function in all patients at 2 and 6 months follow-up.

Cost effectiveness of the treatment (Table 3)

At the end of 6 months, mean total cost paid by patients was INR 2293.05 ± 331.12 in VPA+LTG (Group-I), INR 1629.31 ± 43.06 in VPA+CZP (Group-II), INR 3139.32 ± 433.17 in OXC+CLB (Group-III), INR and INR 685.15 ± 85.54 in PHT+PB (Group-IV), respectively.

Cost-effectiveness at the end of analysis was 179.14 in Group-I, 107.40 in Group-II 231.00 in Group-III and 42.27 in Group-IV. This shows that the Group-IV paid least and Group-II paid maximum for same improvement in QOL (p=0.01).

Table 2: Change in QOL at different time intervals

Time interval	Group I VPA + LMT (n = 10)	Group II VPA+CZP (n = 10)	Group III OXC+CLB (n = 10)	Group IV PB+PHT (n = 10)
0 day	48.71 ± 1.42	47.22 ± 2.29	50.51 ± 2.44	49.48 ± 2.22
2 months	52.01 ± 1.59	54.03 ± 2.32	54.161 ± 2.51	59.39 ± 2.28*
6 months	61.51 ± 2.08	62.39 ± 2.73	64.10 ± 2.66	65.69 ± 3.49

VPA: Valproic acid, LTG: Lamotrigine, CZP: Clonazepam, OXP: Oxcarbazepine, CLB: clobazam, PB: Phenobarbitone, PHT: Phenytoin.
* P = 0.02 vs corresponding VPA + LMT at 2 months
The p-value of each group when compared before and after treatment (6 months) was <0.001.

Table 3: Cost effective analysis of the different dual therapy regime at 6 months.

Treatment Groups	Direct medication cost in Indian Rupees. Mean ± S.D	Cost effectiveness
VPA + LTG	2293.05 ± 331.12	179.14
VPA + CZP	1629.31 ± 43.06	107.40
OXC + CLB	3139.32 ± 433.17	231.00
PB + PHT	685.15 ± 85.54	42.27

VPA: Valproic acid, LTG: Lamotrigine, CZP: Clonazepam, OXP: Oxcarbazepine, CLB: clobazam, PB: Phenobarbitone, PHT: Phenytoin.
Cost effectiveness = total cost in rupees / total improvement in quality of life
I USD = 49 Indian Rupees

DISCUSSION

Epilepsy is a chronic disease that may require AED therapy for many years. The goal of AED therapy is to achieve a seizure-free state and to improve the QOL.[8] The AED treatment that effectively prevents the occurrence of seizures, with minimum drug related side effects, provide the best QOL and ensure patient satisfaction.[9-11] Medical treatment data suggest that most of the patients have seizures remission on single antiepileptic drug and small fraction requires second antiepileptic drug to control seizures.[12-13] This has evolved the concept of rationale poly-therapy in epilepsy.[14-15] There is a long debate about the good and bad aspects of various combinations of antiepileptic medication.

In our study, it was observed that the health related QOL in all groups improved with the decrease in seizure frequency, there by establishing a negative relationship between seizure frequency and QOL. The finding is in accordance with an earlier report in literature, which showed that seizure remission is the key factor in reducing the stigma and feeling of handicap associated with epilepsy.[16] In an one-year observational study on patients of generalized tonic-clonic (GTCS) and partial seizures, the patients on mono-therapy had high QOL than on poly-therapy.[17] In our study, dual-therapy did not worsen QOL, rather improved it. It could be explained due to improvement in seizure frequency without much change in neurotoxicity.

There are many variations for combining two AEDs. Our choice of the study combination was based on most commonly used dual therapy in our local clinical practice. It is important to consider various pharmacokinetic and toxic effects of combining the two AEDs. VPA compounds can be rationally combined with LTG[18], carbamazepine[19,20], CZP[21,22], vigabatrin[14] and PHT.[23] Combination of VPA+LTG has synergistic effect of co-medication, single bed time dose schedule for better drug compliance and its usefulness in broad spectrum of generalized, partial and unclassified epileptic disorders.[24] The relative disadvantages are high cost and increased reported risk of cutaneous reaction.[25] Though we have not analyzed in detail, but risk of skin allergy was not very high in our experience but cost was the second highest in the four dual therapies studied. CZP or LTG with VPA are effective combinations in once a day dosing schedule for patients of primary generalized epilepsy with poor control on VPA mono-therapy.[22,26]

Next combination was OXC with CLB. CLB is good add-on AED for short duration in partial epilepsy cases.[27] There may be selection bias to prescribe this combination when patients require short duration treatment like in acute symptomatic seizures. This was the most costly combination in our study with the same improvement in QOL. A combination of CLB with carbamazepine may reduce the cost of therapy without sacrificing potency.

The combination of PB with PHT has long been commonly prescribed in India. This combination is found to have good potency without increase in neurotoxicity.[28,29] In our study this was found to be the cheapest and effective combination. This combination has been recommended, for the treatment of generalised tonic- clonic and partial seizures.[30] Burgeois[31] similarly reported a positive result in combining PHT and PB, while examining the antiepileptic and neurotoxic effects of combining older AEDs.

AEDs with short half life requires 2-3 daily

doses and frequently results in break through seizures even when single day dose is missed by patients.[32] One unexplored advantage of addition of PB to PHT or carbamazepine and CZP or LTG to VPA is prolongation in half life of the combined formulation. So, in patients with history of breakthrough seizures due to frequent missed doses, it is better to use mono or dual-therapy with longer half life.

The disadvantage of combinations is additive neurotoxic side effects of AEDs. The combinations used in our study did not show any such effects in the short follow-up. However, there toxicity may develop later with prolonged treatment. Our study had shortcomings of being observational, of short duration, and limited number of study subjects. However, we believe the study is important as there are scanty data available on the cost-benefit analysis including QOL of the dual-therapy regimes, especially in the developing countries where cost is often crucial.

In conclusion, our study showed that PHT and PB is a more cost effective combination therapy than other combinations involving newer AEDs.

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