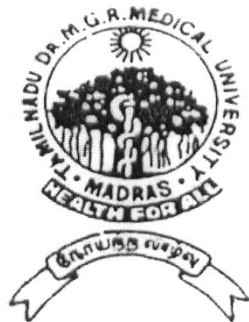


**A DISSERTATION  
ON  
PROSPECTIVE COHORT STUDY OF ONE HUNDRED  
CASES OF FIRST UNPROVOKED SEIZURE**

*Submitted in partial fulfillment  
of requirements for*

**BRANCH - I D.M. NEUROLOGY**  
of

**THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY  
CHENNAI**



**GOVERNMENT STANLEY MEDICAL COLLEGE**

**CHENNAI – 600 001.**

**AUGUST 2007**

## CERTIFICATE

This is to certify that this dissertation entitled  
“A PROSPECTIVE COHORT STUDY OF ONE HUNDRED CASES OF FIRST  
UNPROVOKED SEIZURE” submitted by  
Dr. V. CHANDRAMOULEESWARAN appearing for D.M. Neurology degree  
examination in August 2007 is a bonafide record of work done by him under my direct  
guidance and supervision in partial fulfillment of regulations of The Tamil Nadu Dr.  
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## **DECLARATION**

I, solemnly declare that the dissertation titled “**A PROSPECTIVE COHORT STUDY OF ONE HUNDRED CASES OF FIRST UNPROVOKED SEIZURE**” is done by me in the Department of Neurology, Government Stanley Medical College and Hospital, Chennai during 2004 – 2007 under the guidance of **Prof. Dr. M. DHANARAJ** and **Prof. Dr. A. MURUGESAN**.

The dissertation is submitted to The Tamil Nadu Dr. MGR Medical University towards the partial fulfillment of requirements for the award of **D.M. Degree in Neurology**.

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## INTRODUCTION

Seizures have been recognized since ancient days. One of the earliest descriptions of generalized tonic-clonic seizure was recorded over 3000 years ago in Mesopotamia and it was attributed to the God of the Moon. Epileptic seizures were also described in ancient cultures of India, China and Egypt.

The word seizure is derived from Latin word "sacire", meaning, "to take possession of" indicating that the person having a seizure is possessed or at least out of control.

A seizure is a paroxysmal self limited event caused by an excessive electrical discharge of central nervous system. Epilepsy is a disorder characterized by recurrent seizures. A First Unprovoked Seizure (FUS) is a first seizure episode occurring in an individual without an identified proximate precipitant and it excludes seizures occurring after

an acute insult to the central nervous system or with generalised systemic metabolic disturbance of the body<sup>1</sup>. Unprovoked seizures can be further classified into: Remote symptomatic seizure (associated with stroke, head injury, tumour, infection etc) and idiopathic seizures (without history of neurological insult or a neurological deficit presumed to be present from birth) <sup>1</sup>.

A first seizure is a frightening event for families and friends. But the patients may have a certain degree of confusion and reluctance to seek attention. The consequences of a diagnosis of “epilepsy” are serious both for the patients and their families. In the management of epilepsy, it is important to humanely guide and counsel the anxious patients. The consequences of a diagnosis and treatment must outweigh the risks of seizures recurrence<sup>2</sup>.

The incidence of single seizure is 5% in a general population<sup>3, 4</sup>. Until recently, the long term anti epileptic drug therapy was started soon after a single seizure of any type based on the belief that all seizures



were likely to recur and that seizures could be dangerous and could cause brain damage.

The antiepileptic drugs were also thought to be safer and effective in prevention of further episodes of seizures and thereby altering the long term prognosis after the single seizure.

Through various studies it was found that FUS had a recurrence rate of only 30-40% in 3 to 5 years<sup>1, 5, 6</sup>. But once the patient had a second seizure, the risk of third seizure would be 73% and the risk of fourth would be 76% after a third seizure<sup>5</sup>. So it is implied that once a patient has more than one seizure episode, the risk of having subsequent seizures are quite high and hence patients should be treated after the second seizure<sup>7,9</sup>.

**Many clinical trials on FUS revealed the following facts :**

- 1) Anti epileptic drugs are potentially toxic producing physical, cognitive, psychological and teratogenic manifestations<sup>2</sup>.
  
- 2) The initiation of anti epileptic drugs immediately after the FUS might not alter the long term prognosis of seizure recurrence<sup>8</sup>.
  
- 3) The initiation of the Anti Epileptic drugs after FUS may reduce the incidence of seizure recurrence in the first 3 months after the initial seizure episode<sup>8</sup>.

- 4) So following a FUS, initiation of anti epileptic drug therapy is highly controversial and it must be based on a risk benefit assessment that outweighs the risk of seizure recurrence against the side effects of long term anti epileptic therapy<sup>2</sup>.

The decision regarding initiation of anti epileptic drug therapy is highly controversial in view of the variable recurrence rate, potential side effects of anti epileptic drugs and non alteration of long term prognosis, as well as social stigma of long term medication for this chronic illness which can have profound negative effect on self esteem, social opportunities and elimination from occupation, restriction of recreational activities. Occurrence of seizure during work involving handling of heavy machineries, constructional work or deep sea water fishing may not only cause grievous injury but also endanger the life of the individual himself.

In the management of FUS, a few authors preferred to start anti epileptic drug therapy immediately after the first seizure, others preferred to wait for the occurrence of a second seizure. But none of the authors had taken into consideration the patients' or their family members' opinion. Hence this present study analyses patients' preferences towards immediate anti epileptic drug therapy following first attack of unprovoked generalised tonic clonic seizure and the reasons for their preferences were studied with a one year follow up to confirm the validity of their decision. The preferences of the patients with relevance to their occupation, education and gender were assessed. The role of family members and appropriate counselling by the neurologist in the decision making process were also assessed. In this study, the recurrence rate in those patients who preferred as well as deferred anti epileptic drug therapy were followed up for a period of one year.

Patients with family history of seizures, localization related seizures, myoclonic seizures, EEG and imaging abnormalities were excluded from this study and started on appropriate drug therapy without waiting for the second seizure, since the recurrence rate is higher among them<sup>6</sup>.

## REVIEW OF LITERATURE

An epileptic seizure is defined as a sudden transitory event of motor, sensory, autonomic or psychic nature assumed to be the result of transient excessive discharge of a hyper excitable population of neurons in the brain<sup>10</sup>.

An unprovoked seizure is defined as seizure occurring without an identified proximate precipitant, which excluded seizures associated with an acute insult to the central nervous system or with systemic metabolic disturbance<sup>11</sup>.

Epilepsy is defined as at least two episodes of unprovoked seizures occurring 24 hours apart<sup>11</sup>.

First Unprovoked Seizure is a seizure episode without any proximal precipitating event occurring for the first time. A clear history from the patient and an eyewitness if possible, is crucial in determining whether or not the episode was epileptic.

Incidence of single seizure in general population was about 5%<sup>3, 12</sup> and the incidence of epilepsy is about 1-2 %<sup>12</sup>. The recurrence rate after first seizure is highly variable from 17 -81%<sup>40, 41</sup>. The reason for this variation was mainly a selection bias in the patient population chosen for study. The majority of hospital based study estimates have fallen in the lower end of the range, while estimates from population based studies and studies in which patients were enrolled within 24 hrs of seizure fall at the top. So the population based study was more reliable<sup>15</sup>. The recurrence was much higher in the initial few weeks or first 3 months after an initial attack<sup>14</sup>.

Until recently, it was a common practice for physicians to begin long term AED therapy immediately after a single seizure based on the belief that seizures were likely to recur, could be dangerous and could cause further brain damage which in turn could cause recurrence. They assumed that AED were safe, had few side effects and were effective in prevention of seizure recurrence. These concepts have undergone substantial changes due to various studies conducted on people with FUS.

The cumulative risk of seizure recurrence was studied by various authors. The conclusion of Elwes et al on the course of untreated epilepsy predicted a recurrence rate of 27% at the end of 5 years<sup>14</sup>.

The study conducted by Hauser et al in 1982, put the recurrence rate at 16%, 21% and 27% at the end of first, second and third years respectively after the index seizure. His study revealed that the recurrence rate in idiopathic group was 17% in 20 months and 26% in 36 months. He further observed that if the patients were seizure free for



36 months, then it was unlikely to recur later. Age at index seizure, sex, seizure type, status epilepticus or abnormality on neurological examination did not affect the seizure recurrence<sup>5</sup>. While Annegers et al in 1986 arrived at a recurrence rate of 36%, 48% and 56% at first, third and fifth years respectively from the index seizure<sup>16</sup>. Shinnar et al configured in 1996 a recurrence rate of 29%, 37%, 42% and 44% at the end of first, second, fifth and eighth years respectively<sup>17</sup>.

Gowers, way back in 1881, in a follow up study on 160 patients found the recurrence rate to be around 33% in one month, 50% in 3 months and 87% in one year. He further said that after a second seizure, the intervals between successive seizures tended to decrease and concluded that “seizures beget seizures” (i.e. once a major attack has occurred, the brain might more readily undergo further attacks)<sup>36</sup>. This was also been substantiated by various studies. A study by Elwes et al showed the recurrence rate to be 33% in the first month and 50% in first three months and 87% in one year<sup>14</sup> thus, agreed on many aspects of the observations and views expressed by Gower<sup>36</sup>.

Hausser et al arrived at a recurrence rate of 32% in three months, 41% in 6 months, 57% in one year, 73% in 4 years. Patients who did not have a recurrence in 4 years, had no further seizures for additional 3 years<sup>15</sup>.

In a study conducted by Shinnar et al, median time to seizure recurrence was 6.2 months, the cumulative risk of seizure recurrence was 66% at end of first year, 70% at the end of third year and 81% at the end of fifth year. Majority of seizures occurred in the first 6 months with most of the attacks occurring in the initial 3 months. So AEDs if at all given were useful only in the first six months<sup>8</sup>.

In a multicentered randomized study conducted by Musico et al, the chance of achieving one year remission was 82% in patients treated at first seizure, 84% in patients treated at the time of seizure relapse. Similarly the chance of achieving 2 year remission was 60 % in patients treated at first seizure and 59% in patients treated at the time of seizure relapse<sup>26</sup>. These findings were confirmed by various other studies in

which untreated patients tended to achieve seizure remission similar to those under treatment immediately after the seizure.

The risk of recurrence after a first single unprovoked seizure was more or less similar in treated as well as untreated cases. In a randomized multi centric study of immediate and deferred anti epileptic drug treatment in 1847 patients with single seizures, Marson et al concluded after a 5 year follow up, 76% of patients in the immediate treatment group and 77% of those in the deferred treatment group were seizure free between 3 and 5 years after randomization. The patients in both the groups did not differ with respect to quality of life outcomes or serious complications<sup>18</sup>. Similarly studies conducted by Shinnar et al, Wolf and Bulloch et al showed no difference between the preferred and deferred treatment groups<sup>19, 20, 21</sup>.

Ettore Beghi in a study of treatment of single seizures observed that the chance of achieving one year remission was 82% in patients treated at the first seizure and 84% in patients treated after seizure

relapse. Similarly the chance of achieving 2 year remission was 60% and 59%<sup>1</sup>. The First Seizure Trial Group after a study on treatment of first tonic clonic seizures observed that the relapse rate is 87% and 68% in the first and second year in the treated group and 83% and 60% respectively in the untreated group<sup>22</sup>. Also in a study conducted at NIMHANS in 1993, the cumulative risk of recurrence in the treated group was 23%, 30%, 32%, 33% and 33% as compared to 28%, 36%, 40%, 43% and 45% at 1, 6, 12, 24 and 36 months respectively in the untreated group<sup>24</sup>.

Study conducted by Camfield et al in 1989 concluded that one year of daily treatment with carbamazepine significantly reduced the recurrence rate after a first afebrile seizure in children compared with the untreated group, in a randomized open trial. The same authors concluded in June 2002 after a 15 year follow up study that long term outcome was unchanged and subsequent clinical course, remission rate were not improved in comparison with the untreated group and suggested that diagnosis and treatment of epilepsy must be delayed until there have been at least two unprovoked seizures<sup>7</sup>.

Similar views were expressed by Musico M et al after a multi-centered randomized open trial. They concluded that patients treated after the first seizure and those treated after seizure relapse had the same time dependant probability of achieving 1 and 2 seizure free years<sup>43</sup>.

Duchowny M et al also believed that AED therapy reduced the risk of recurrence for the first 3 months only and was not associated with a significant benefit after more than 3 months. They also concluded that the benefit of early medical therapy was short lived since there was no evidence that immediate treatment induces earlier or sustained remission<sup>46</sup>.

Marson A et al of MESS study group on immediate vs deferred AED therapy concluded after a 5 year follow up study that 43% of patients in the treated group and 53% of patients in the deferred group had seizures. The rate of remission was similar in both the groups. The study concluded that little was lost in the long run by deferring treatment in a patient who presented with a first seizure<sup>18</sup>.

From the above studies on FUS it was concluded that untreated patients tend to achieve seizure remission in proportions similar to those of patients who were immediately treated after the index seizure. Further the delayed initiation of treatment after the occurrence of second seizure episode had the same long term prognosis as that of early initiation of treatment. Hence we inferred that patients treated after the first seizure and those treated after the seizure relapse had the same time dependant probability of achieving 1 and 2 seizure free years.

In a study conducted by Hausser, it was found that once the patient developed second seizure, the risk of having a third unprovoked seizure was 32% at three months, 41% at 6 months, 57% at one year and 73% at end of 4 years. Patients who did not have a recurrence within four years after a second seizure would have no further seizures for additional 3 years. The risk of fourth unprovoked seizure after the third was 31% at three months, 48% at six months, 61% at one year and 76% at three years<sup>5</sup>. Thus when compared with the risk of seizure recurrence after first unprovoked seizure which stands at 30 – 40% in five years, the risk of seizure recurrence after second and third unprovoked seizures was quite high warranting the initiation of the AED therapy after the

second unprovoked seizure.

According to Shinnar et al, the risk of subsequent seizures after two unprovoked seizures rose to about 70%. The cumulative risk of additional seizures after a third seizure was 66%, 70%, 81% respectively at the end of first, second and fifth years respectively<sup>8,17</sup>.

In a prospective study conducted by collaborative group for the study of epilepsy, it was concluded that the probability of achieving one year remission (expressed as relative risk) was 0.76 in patients treated after two or more seizures, in comparison with those treated after first seizure. Similarly the corresponding figures for second and third year remissions were 0.67 and 0.66 respectively. The risk of relapse of a first seizure was inherently lower than that of any further seizure (38% by 2 years). After the second seizure, the risk of relapse increased to about 79-96%. The second year risk of recurrence varied significantly according to the presence of recognized etiology of the seizure and of an abnormal EEG<sup>42</sup>.

Studies also concluded that 90% of newly diagnosed patients with epilepsy tended to achieve prolonged seizure remission and about 40-60% of these enter remission as soon as treatment was initiated. Though the AED therapy reduced the risk of seizure recurrence during the active phase (first 3 months), it did not alter the long term prognosis. The risk was lowest (24%) in patients with idiopathic or cryptogenic seizure and normal EEG, intermediate (48%) in those with symptomatic seizures or abnormal EEGs, and highest (65%) in those with symptomatic seizures and abnormal EEGs<sup>7, 16, 17</sup>. Presence of initial prolonged seizure, seizure during sleep and family history of seizure, increased the risk of recurrence.

Studies on the predictive value of EEG concerning the risk of seizure recurrence had shown contradictory results in various studies. In a study conducted by Gilbert DL et al, the specificity, sensitivity, positive and negative predictive values were studied. His conclusion was that the expected information from EEG was too low to affect the treatment recommendation in most of the patients. So EEG should be ordered selectively and not routinely after first unprovoked seizure<sup>30</sup>. The diagnostic aid of routine EEG findings in patients presenting with



first unprovoked seizure had more relevance only if the EEG was recorded close in time with the event<sup>31</sup>. EEG was more useful to make a diagnosis of focal non epileptic and epileptic abnormalities of a first seizure<sup>32</sup>. EEG could be helpful in supporting the diagnosis in older patients but should not be used to exclude diagnosis of epilepsy. EEG was useful in defining seizure types, quantifying risk of recurrence and quantifying likelihood of finding diagnostic abnormalities. EEG with epileptiform abnormalities tended to have 1.5 – 3.0 fold increase in the risk of seizure recurrence. EEG had up to 4% false positive rate, a relatively low sensitivity, a positive predict value of 2% - 3% and did not have any role in initial seizure management<sup>3</sup>.

According to Beghi et al, adverse reactions were reported in about a third of ambulatory patients receiving chronic AED therapy. The incidence of adverse effects tended to increase with increasing dosage. It was commonly accepted that currently available AEDs would have an adverse influence on mental and behavioral functions particularly in infants and elderly<sup>1</sup>. The side effects of AED were systemic reactions such as hepatic, bone marrow toxicity or Steven Johnson syndrome, behavioral, cognitive effects and teratogenicity in pregnant women<sup>1, 2</sup>.

Hence the decision about the nature and timing of therapy with anti seizure medication should be individualized considering the risk of recurrence and the likelihood of side effects of the medication in a particular patient.

Madhusudanan M et al in their article observed that actual decision whether or not to treat patients who presented with initial seizure must be individualized and dependant on probability of having a recurrence and on the perceived risk benefit ratio of treatment <sup>13</sup>. But AED therapy was indicated in patients doing risky occupations like driving or operating dangerous machinery. The above findings were of considerable importance because up to 30% of the patients treated with AED therapy experience moderate to severe side effects leading on to drug non compliance in 20% <sup>28,43</sup>.

Among people with only single seizure, the proportion in whom serious side effects of continuous anti seizure medication would occur, generally exceeds the proportion who would have an additional seizure

in the ensuing few years. On the other hand, among those with two or more unprovoked seizures, the risk of additional seizures was higher than the risk of side effects of medication. So people with two or more unprovoked seizures should be treated. Further the decision to treat seizures carries with it the change in the patient's life style along with driving and occupational restrictions, social stigma and economic burden related to the cost of medications and adverse side effects usually occurring within 30 days of AED therapy. The clinical course and remission rates of first seizure were similar in treated and non treated cases<sup>29</sup>.

Hermann ST observed that decisions regarding treatment of single unprovoked seizures must balance the seizure recurrence risk, the potential impact of a recurrent seizure, the likelihood of adverse effects of treatment and the patient preference<sup>6</sup>.

Greenwood RS et al suggested that physician and family should weigh the risks and benefits of treatment against withholding and

stopping therapy for providing a better quality of life for the patient. They advocated withholding of AED therapy until a second seizure<sup>9</sup>.

The American Academy of Neurology in their recommendation suggested that the treatment option must be individualized based on risk benefit assessment that outweighed the risk of another seizure against the risk of chronic anti epileptic therapy after taking into account both medical issues and patient and family preference. The following recommendations were made for children and adolescents who experienced a first seizure

1. Treatment with AED was not indicated for the prevention of the development of epilepsy.
2. Treatment with AED should be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial side effects<sup>2</sup>.

The clinical review by Say RE et al, suggested the involvement of patients and their relatives in treatment decision recognising the patients as experts with a unique knowledge of their own health and their preferences for treatments, health states and outcomes. Increased patient involvement, a result of various sociopolitical changes was an important part of quality improvement since it was associated with improved health outcome and enables doctors to be more accountable to the public<sup>34</sup>.

The SIGN guidelines provided evidence based recommendation on the diagnosis and treatment of epilepsy<sup>45</sup>. The recommendations were

1. Ultimate judgement regarding treatment plan must be made by the doctor following discussion of the options with the patient, in light of the diagnostic and treatment choices available.
  
2. Diagnosis of epilepsy should be made by a neurologist or other epilepsy specialist.
  
3. A clear history from the patient and an eye witness to the attack could give the most important diagnostic information and should be the main stay of diagnosis.

4. EEG is not routinely indicated and should not be performed to exclude a diagnosis of epilepsy.
  
5. The decision to start AED therapy should be made by the patient and doctor. Anti epileptic drug therapy should be given if patient considers the risk of recurrence unacceptable.
  
6. Patient should be warned of potential side effects and given clear instructions to seek medical attention in case of any side effects arising.
  
7. Dietary and other life style advice should be given.

8. Advice and information on epilepsy should be given to the understanding of the patient making suitable adjustments for different socio cultural contexts. The doctor should be approachable, communicative, knowledgeable and receptive.



## **AIMS OF THE STUDY**

- a) To study the patients' preference towards anti epileptic therapy following first attack of generalized tonic clonic seizure.
  
- b) To categorize their preferences based on sex, education and occupational status of the patients.
  
- c) To follow up the preferred and deferred group of patients for a period of one year and to assess the recurrence of seizure and their drug compliance level.
  
- d) To give a final conclusion regarding the initiation of anti epileptic drug therapy based on the above said observations after adequate counselling of the patient and their family members.

## **MATERIALS AND METHODS**

This study was conducted in the Department of Neurology, Government Stanley Medical College Hospital, a tertiary care center located in north Chennai in Tamil Nadu, a state in south India. This hospital caters primarily to the lower socio economic group. Unprovoked Generalized Tonic clonic Seizure (GTCS) was defined as a generalized tonic clonic seizure occurring without any clear precipitating event and witnessed by a person. Prospectively all the patients with first attack of unprovoked GTCS who attended the outpatient department from September 2004 to December 2005 were enrolled and relevant demographic data such as age, gender, education, occupation and economic status were recorded. History regarding any injury during the seizure was also recorded.

**INCLUSION CRITERIA** \_\_\_\_\_ :

The inclusion criteria adopted were:

- a) First attack of unprovoked GTCS
- b) Age between 18 to 60 years
- c) Normal CT brain
- d) Time from the onset of the seizure to registration less than 30 days.

**EXCLUSION CRITERIA:** The exclusion criteria were

- a) Patients with positive family history of seizures or epilepsy
- b) Seizure cluster within 24 hours
- c) Pregnant women
- d) Focal neurological deficit
- e) Abnormal CT brain.
- f) Alcohol related seizures

EEG was done in all the patients but the results were not considered while including the patients in the study. Patients and the family members were counselled between the 8<sup>th</sup> and 30<sup>th</sup> day of seizure. Patients seen within 7 days of onset of seizure were put on tablet Clobazam 10 mg twice a day for 7 days before enrolling for the study. Patients and their family members were explained clearly about the following facts:

- a) First attack of unprovoked Generalized Tonic Clonic Seizure was not epilepsy (GTCS).
  
- b) The chance of recurrence rate of seizure was about 30%- 40% in three to five years period
  
- c) If anti epileptic drug therapy (AED) was preferred it should be taken for five seizure free years without missing even a single

day

- d) Long term AED therapy was associated with some adverse effects
  
- e) Early initiation of AED therapy would not alter the long term prognosis
  
- f) All those patients who deferred AED treatment initially would be given the drug by the hospital, in case of recurrence of seizure.

All patients belonging to both preferred and deferred group were given the relevant general information regarding education, marriage, work environment (related to driving, fishing, working in heights or near machineries, handling sharp instruments etc).

After adequate counselling and clarifying the doubts, the patients were asked about their preferences and reasons for their preferences for AED therapy. If a patient was indecisive, he/she was encouraged to discuss with the family members and take the appropriate decision on the next visit. Those who preferred AED were started on tablet Phenytoin 200mg once a day and were instructed to collect the drug periodically once in two weeks from the hospital.

A seizure diary was maintained. Patients in both the groups were regularly followed up once in 2 months in the outpatient department. During follow-up visits, drug compliance, any recurrence of seizure, and adverse drug events were documented.

At the end of one year all the patients were asked to comment about their earlier decision regarding the initiation of AED.

## \_\_\_\_\_**STATISTICAL ANALYSIS**

Demographic characteristics of patients with first unprovoked GTCS were given in frequencies and their percentages. Age, sex, educational status and occupation of patients who preferred or deferred AED therapy were analyzed using Pearson's Chi-square test and Yates corrected Chi-square test. Odds ratio were given with 95% confidence interval (CI).

Reasons given by the patients for preferring or deferring AED therapy were given in frequencies and their percentages. In the process of decision making, the decider's (patient's or their relative's) proportional differences on preferring or deferring AED were analyzed using Pearson's Chi-square test. Odds ratio was given with 95% CI.

P value less than 0.05 was taken as statistically significant.

## **RESULTS**

A total of 100 patients satisfied our inclusion criteria and were taken up for the study. The results are given in the following tables with relevant graphic representations.

**TABLE 1.1**

**DEMOGRAPHIC PROFILE OF THE PATIENTS  
- AGE GROUP ( n = 100 )**

The study population consisted of 100 patients, 47(47%) were in the age group of under 20 years, 25(25%) were in the age group between 21 – 30 years, 21(21%) were in the age group between 31 – 40 years and 7(7%) were in the age group above 40years. Maximum number of patients were below twenty years.



**TABLE 1.2**  
**DEMOGRAPHIC PROFILE OF THE PATIENTS**  
**- SEX DISTRIBUTION**

<b>Gender</b>	<b>No. of patients</b>	<b>%</b>
Male	76	76
Female	24	24

In the study population, 76(76%) were males and 24(24%) were females. There was a male preponderance in the study population.

**TABLE 1.3**  
**DEMOGRAPHIC PROFILE OF THE PATIENTS**  
**- EDUCATIONAL STATUS**

<b>Literacy</b>	<b>No. of patients</b>	<b>%</b>
Primary	26	26
Middle school and above	74	74

The educational status of the 100 patients revealed that 26(26%) were educated up to primary school level and the rest 74(74%) were educated up to middle school and above.

**TABLE 1.4**  
**DEMOGRAPHIC PROFILE OF THE PATIENTS**  
**- OCCUPATIONAL STATUS**

Most of our study population consisted of manual laborers 62(62%) and rest of them were house wives 17(17%) and students 21(21%).

**TABLE 2**  
**FACTORS INFLUENCING PREFERENCES OF**  
**AED THERAPY - AGE (n=100)**

<b>Age Group</b>	<b>Preferred Group (n=56)</b>	<b>Deferred Group (n=44)</b>	<b>Odds Ratio (95%CI)</b>	<b>P-Value</b>
<20	27(48.2%)	20(45.5%)	1.00	$X^2 = 0.01$ $P = 0.95$
21-30	14(25%)	11(25%)	0.94	
31-40	10(17.9%)	11(25%)	0.67	
>40	5(8.9%)	2(4.5%)	1.85	

<sup>a</sup> Test of significance was Pearson chi-square test/Yates corrected chi-square test

<sup>b</sup> Odds ratio with 95% Confidence Interval

The factors influencing preferences of AED therapy revealed that younger age group of less than 30 years dominated both preferred and

deferred group. Out of them 27(48%) in the preferred and 20(45%) in deferred group, were below 20 years.

**TABLE 3**  
**FACTORS INFLUENCING PREFERENCES OF**  
**AED THERAPY – SEX (n=100)**

<b>Sex</b>	<b>Preferred Group (n=56)</b>	<b>Deferred Group (n=44)</b>	<b>Odds Ratio (95%CI)<sup>b</sup></b>	<b>P-value<sup>a</sup></b>
Male	48(85.7%)	28(63.6%)	3.4(1.2-10.1)	X <sup>2</sup> =6.58
Female	8(14.3%)	16(36.4%)		P=0.01

<sup>a</sup> Test of significance was Pearson chi-square test/Yates corrected chi-square test

<sup>b</sup> Odds ratio with 95% Confidence Interval

Most of the males in the study population 48(63%) opted for AED and while the majority of the females 16(66%) did not opt for AED.

**TABLE 4**  
**FACTORS INFLUENCING PREFERENCES OF**  
**AED THERAPY – EDUCATION (n=100)**

<b>Education</b>	<b>Preferred Group(n=56)</b>	<b>Deferred Group(n=44)</b>	<b>Odds Ratio (95%CI)<sup>b</sup></b>	<b>P-value<sup>a</sup></b>
Primary	20(35.7%)	6(13.6%)	3.5(1.2-11.1)	X <sup>2</sup> =6.24 P=0.01
Middle School	36(64.8%)	38(86.4%)		
And above				

<sup>a</sup> Test of significance was Pearson chi-square test/Yates corrected chi-square test

<sup>b</sup> Odds ratio with 95% Confidence Interval

The bearing of educational back ground on initial choice of AED therapy indicate that people with lesser education (up to primary level) i.e 20(77%) preferred to undergo therapy when compared with better educated people (middle school and above) 38(52%) who deferred the AED.

**TABLE 5**  
**FACTORS INFLUENCING PREFERENCES OF**  
**AED THERAPY N - OCCUPATION (n=100)**

<b>Occupation</b>	<b>Preferred Group(n=56)</b>	<b>Deferred Group(n=44)</b>	<b>Odds Ratio (95%CI)<sup>b</sup></b>	<b>P-value<sup>a</sup></b>
House Wife	5(8.9%)	12(27.3%)	3.8(1.1-13.9)	X <sup>2</sup> =5.9 P=0.01
Student	11(19.6%)	10(22.7%)	0.8(0.3-2.4)	X <sup>2</sup> =0.1 P=0.71
Manual Labourer	40(71.4%)	22(50%)	2.5(1.1-6.2)	X <sup>2</sup> =4.8 P=0.03

<sup>a</sup> Test of significance was Pearson chi-square test/Yates corrected chi-square test

<sup>b</sup> Odds ratio with 95% Confidence Interval

Manual laborers had a preference for AED therapy while the majority of house wives and students deferred the therapy.

**TABLE 6**

**FACTORS INFLUENCING PREFERENCES OF**  
**AED THERAPY – DECIDER (PATIENT / RELATIVE) (n=100)**

<b>Decider to take AED therapy</b>	<b>Preferred Group (n=56)</b>	<b>Deferred Group (n=44)</b>	<b>Odds Ratio (95%CI)<sup>b</sup></b>	<b>P-value<sup>a</sup></b>
Patients	38(67.9%)	20(45.5%)	2.5(1.2-6.2)	X <sup>2</sup> =5.1  P=0.02
Patients and Relatives	18(32.5%)	24(54.5%)		

<sup>a</sup> Test of significance was Pearson chi-square test/Yates corrected chi-square test

<sup>b</sup> Odds ratio with 95% Confidence Interval

Majority of the patients themselves were categorical in initiation of AED therapy in preferred group (68%). While in the deferred group, 55% of the patients were influenced by their relatives to defer therapy.

**TABLE 7**  
**AED THERAPY PREFERENCES AND**  
**REASONS (n = 56)**

<b>Reasons for AED preference</b>	<b>Number of patients</b>	<b>%</b>
Fear of injury	6	10
Occupational Risk	20	36
Do not want a recurrence at any cost	30	54

In the preferred group, majority of the patients (54%) wanted to under go AED therapy since they did not want recurrence of attack at any cost since they were either living alone or could not avail medical help at times of emergency. They also feared loss of employment. Most of the males who preferred therapy were the lesser educated and manual laborers involved in masonry work, fishing or electrical works. They feared not only injuries during seizure episode but also risk to their life itself. Hence they were interested in undergoing AED therapy.



**TABLE 8**  
**AED THERAPY DEFERENCES AND**  
**REASONS (n = 44)**

<b>Reasons</b>	<b>Number of patients</b>	<b>%</b>
Fear of adverse effects	25	56
Wait for the second attack	19	44

In the deferred group, most of the patients (56%) had a fear of adverse effects of AED therapy, hence deferred the treatment.

**TABLE 9**  
**ONE YEAR FOLLOW-UP (n=84)**

<b>Category</b>	<b>No. of patients</b>	<b>%</b>
Preferred group	44	52
Deferred group	40	48

One year follow up was carried out in 84 patients. Out of them 44(52%) were from preferred group and the rest were from the deferred group.

**TABLE 10**  
**RECURRENCE RATE (One year)**

<b>Category</b>	<b>No. of patients</b>	<b>Recurrence</b>	<b>%</b>
Preferred group	44	6	14
Deferred group	40	8	20

Among them 6(14%) in the preferred group and 8(20%) in the deferred group experienced recurrence of seizure. 4 patients (66%) in the preferred and 6 patients (75%) in the deferred group, experienced seizure within the first three months.

**TABLE 11**  
**EEG ABNORMALITIES AND RECURRENCES (n = 84)**

<b>Category</b>	<b>No. of patients</b>	<b>EEG abnormality</b>	<b>%</b>	<b>Recurrence</b>	<b>%</b>
Preferred group	44	13	30	4	31
Deferred group	40	11	27	3	27

EEG were abnormal in 13(30%) in the preferred group and 11(24%) in the deferred group. 4 patients (31%) in the preferred group and 3 patients (27%) had experienced seizure relapse.

## DISCUSSION

The present study was conducted in Department of Neurology, Government Stanley medical college Hospital not only with the sole purpose of studying patient's attitude towards AED therapy after a first unprovoked GTCS but also to study the recurrence rate after a one year follow up. A total of one hundred new cases were included in the study after applying appropriate inclusion and exclusion criteria.

Among the study population, 76% were males. In both preferred and deferred groups, males outnumbered females. This is probably because of a selection bias in a hospital based study in a developing country where more males report to hospitals than females because of socioeconomic reasons. The same conclusion was drawn by Hausser WA et al<sup>15</sup>, Shinnar A et al<sup>8, 17</sup> and in a CAROLE study by Jallon P et al<sup>36</sup>.

The median age group of patients with FUS was less than 20 years. Out of the study population 34(46%) were below 20 years, drawing a parallel with studies conducted earlier as in a CAROLE study by Jallon P et al<sup>36</sup>, Das CP et al<sup>12</sup>.

Most of the study population consisted of manual laborers with

education up to primary level. The choice of anti epileptic therapy was influenced by the educational status, occupation and gender. As reported in the present study, males with lower education doing manual jobs had more preference for AED therapy when compared with their higher educated counterparts. The decision was based mainly on the fear of injury, the occupational risk involved there in and avoidance of seizure recurrence for obvious reasons.

In the management of single seizures, after the initial evaluation was complete, the main decision was whether to prescribe treatment. (or)to wait for the recurrence. Although the medical literatures on this subject were controversial, several factors should be considered.

In 1881 Gowers suggested that “seizures beget seizures” and cause more and more brain damage with each episode, which if correct, would suggest that all patients should be treated<sup>33</sup>. But later studies revealed the variable recurrence rate after first seizure and the side effects and social stigma involved in the long term anti epileptic drug therapy.

In the absence of risk factors such as underlying neurological abnormalities, the recurrence following first attack of unprovoked GTCS was about 30 – 40%<sup>3</sup> in three to five years.

The recurrence rate given by various studies at end of one year coincided with our study on FUS conducted at Govt. Stanley Hospital.

In a study conducted by Hausser et al the recurrence rate at the end of one year was found to be 20%<sup>15</sup>. In a study conducted in NIMHANS, Bangalore by Gupta SK et al, the recurrence rate stood at 23%<sup>24</sup>. In a prospective study conducted by Wolf P, Mara KI, the recurrence rate in the first year follow up was 17.4%<sup>44</sup>. In our present study the recurrence rate was about 17% at the end of one year. The recurrence rate among the preferred and deferred group were 14% and 20% respectively.

The recurrence was found to be the greatest in the initial 3 to 6 months after the index seizure and falls to less than 10% after 2 years<sup>8</sup>. In the present study also the maximum number of recurrences occurred in the initial 3 to 6 months period in the preferred group. In the deferred group, most of the recurrence occurred within first 3 months, as shown by Shinnar S et al in one of their studies<sup>35</sup>. In our study the recurrence rate was comparatively lower in the initial 3 months in the preferred group.

The probability of achieving one year remission, the preferred and deferred group of AED therapy was given by various studies. One

year remission achieved in a study conducted by Beghi E et al of first trial group were 83% and 87%<sup>1</sup>. In the NIMHANS study by Gupta SK et al, the remission achieved were 77% and 72% in the preferred and deferred group respectively<sup>24</sup>. In a multicentered randomized trial by Musico M et al comparing the treatment of FUS with that of recurrence showed that the long term effects of the two strategies were approximately similar<sup>43</sup>. In the present study, the probabilities of achieving one year remission among the preferred and deferred groups were 86% and 80% respectively.

EEG abnormalities were reported in 13 and 11 patients of preferred and deferred groups out of which 4 and 3 reported recurrence of seizure during follow up. Studies had been inconclusive on the effect of EEG abnormalities on seizure recurrence. Gilbert DL concluded and recommended that EEG should not be done routinely after first unprovoked seizure since the quantity of expected information from the EEG was too low to affect the treatment recommendations<sup>30</sup>. SIGN guidelines also did not advocate routine EEG after a first seizure<sup>45</sup>. In our study also even though routine EEG was done in all patients, the results were not taken into consideration while planning the treatment approach.



However recent well conducted unbiased studies of prognosis following a FUS have also demonstrated that a significant percentage of patients did not have further seizures even without anti epileptic drug therapy. It seems intuitive that treating patients with antiepileptic medication, thereby preventing further seizures, should be better than not treating them. Treatment did appear to reduce risk of recurrent seizures in many but not all the treated patients.

Hence several neurologists felt that in the management of single seizure the risk benefit ratio must be weighed before initiating AED therapy. But who should assess it? The clinician or the affected person? Obviously the patient's spouse, close relatives were more concerned about the health and welfare of the affected person and they could take a better decision suitable to the patient provided, if they were informed about the relevant scientific information about first seizure by the neurologist. Such a decision would be more relevant and practical from the patient's perspective and help to improve the health care.

The importance of patient's preference in treatment decision was stressed by Say RE in his study<sup>34</sup>. SIGN guidelines also suggested that ultimate judgment regarding treatment plan must be made by the doctor following discussion of the options with the patient, in light of the

diagnostic and treatment choices available<sup>45</sup>.

This concept was proved correct in the present study also as evidenced by the similar recurrence rates in both preferred and deferred group after one year follow up.

In the present study, one of the most important reasons for immediate preference of AED therapy was certain risky jobs the patients were involved in. Those patients who were involved in fishing, construction work, welding, driving, handling sharp instruments as in carpentry feared that an attack while on work could endanger their life itself and hence never risked a recurrence. Another major group of patients never wanted to risk any more attack at all. Even though few patients expressed that they were living alone and there would be none to offer any medical help at the time of emergency, most of them could not offer any other specific reasons. It could be the fear of seizure itself and the social stigma attached to it. Those who sustained major injuries during the first attack also feared similar injuries during recurrence and preferred immediate anti epileptic therapy. Thus fear of seizure, seizure related injuries and probably the stigma attached to epilepsy were also the major causes for preferring AED drug therapy.

Most of the patients who deferred immediate AED therapy were

better educated females who were not involved in physical labour. An equal number of patients, mostly better educated housewives deferred the drug therapy and the reasons were

- a. Fear of adverse effects of long term AED therapy. These patients were more concerned about the adverse effects of long term AED therapy and preferred to wait for the second attack.
- b. Willing to wait for the second attack, as the recurrence might not occur in 50% of patients.

The study had shown that following first attack of unprovoked GTCS, approximately one half of the patients, mostly males preferred AED therapy because of

- (a) An 'attack' while at work, might harm their life
- (b) Fear of major seizure-related injuries
- (c) Other reasons such as living alone etc.

Some could not give specific reasons for preferring but it might have been due to fear of seizure itself and the stigma attached to it.

In the present study, the effect of the patient's involvement in the treatment decision was studied. All the patients were happy in getting

themselves involved in the decision making of preferring or deferring anti epileptic drug from their own perspective. At the end of first year, they felt their initial decision was correct and relevant. Those who had recurrence of seizure in the first year follow up in the deferred group voluntarily came up for the treatment and those who had recurrence in the preferred group due to defective compliance felt guilty and promised to be regular. Active participation of the patients helped to improve the drug compliance of the patient. The drug compliance rate among the patients attending regular epileptic clinic at Neurology Department, Government Stanley Medical College Hospital, was only 62%<sup>25</sup>. But in our study, drug compliance among the preferred group was 85%. The above said observations confirm the importance of involving the patients and their relatives in the process of decision making regarding initiation of AED therapy. Further, such a self decision could avert any unwanted legal complications which might arise following the unilateral decision of the clinician.

## CONCLUSIONS

1. Following an attack of first unprovoked seizure, lower educated male laborers preferred AED therapy for the fear of injury, loss of job or their life itself.
2. Recurrence rate in the treated and untreated group after a one year follow up stood at 14% and 20% respectively.
3. Most of the recurrence in the preferred group occurred between the third to sixth months and in the deferred within 3 months, inferring that the AED therapy did not have any role in preventing seizure recurrence beyond three months.
4. Effective counseling resulted in better compliance rate (85%).

## MESSAGE

Following a first attack of unprovoked seizure **the decision regarding AED therapy may be taken by the affected patients and their close family members after adequate counselling by the physician.** Such a decision will be more relevant and suitable from the patients' perspective and increases the patient's compliance to treatment.

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## **ANNEXURES**

### **PROFORMA**

Name: \_\_\_\_\_ SerialNo: \_\_\_\_\_

Age: \_\_\_\_\_ Neuro No: \_\_\_\_\_

EEG No : \_\_\_\_\_

Sex: \_\_\_\_\_ Date of registration: \_\_\_\_\_

Address: \_\_\_\_\_

Education: \_\_\_\_\_

Occupation: \_\_\_\_\_ Income: \_\_\_\_\_

Education of the relative: \_\_\_\_\_

Date of first seizures: \_\_\_\_\_

Time of occurrence: \_\_\_\_\_ day time \_\_\_\_\_ sleep

EEG: \_\_\_\_\_

CT scan \_\_\_\_\_

Time taken to decide about treatment: \_\_\_\_\_ days

Decided to \_\_\_\_\_ start treatment

\_\_\_\_\_ not willing for treatment

Decision taken by \_\_\_\_\_ patient \_\_\_\_\_ relative.....

Reason to start/not willing for treatment: \_\_\_\_\_

### **Reviews:**

