Study of profile of status Epilepticus in a sample of Egyptian patients treated in Al-Azhar university hospitals

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Background: Status epilepticus (SE) is a medical emergency that can lead to serious sequelae if left untreated, SE was defined as an ongoing seizure lasting more than 5 minutes, or by repeated seizure without complete recovery in between. Identification of clinical parameters and etiological factors for SE can be used for early diagnosis, management and improve outcome. **Objective:** evaluate the clinical parameters and etiological factors of status epilepticus in a sample of Egyptian patients admitted at Al-Azhar university hospitals. Methods: Data on all consecutive patients with status epilepticus of all etiologies admitted to Al Azhar university hospitals included detailed medical and neurological history, detailed history of epilepsy (type of seizure, frequency of seizure, anti-epileptic drugs use and etiology of epilepsy), history of status epilepticus (Type, etiology, trigger factors, duration of SE, recurrent SE or not, Anti-epileptic drugs for treatment of SE and outcome), after neurologic evaluation. Patients were subjected to relevant laboratory, neuroimaging and electroencephalographic studies and incase of nonconvulsive status epilepticus, EEG criteria were used. Etiological factors and detailed clinical data about SE and detailed clinical data about history of epilepsy in epileptic patients had been documented and all these data tabulated and statistically managed. **Results:** The most common cause of SE in epileptic patients was poor compliance to AED and the cause of SE in non-epileptic was vascular cause. Marital status and family support had an important role in compliance on AED, commonest cause of death wasvascular cause and commonest cause of disability was CNS infection. Drug abuse precipitate recurrence of SE. Patients with history of recurrent SE develop SE needs longer time and more drugs to be controlled. Mortality rate due to SE was 12.5%, idiopathic etiology offered the best chance for good clinical outcome. Conclusion: Status epilepticus is a complex clinical syndrome that requires immediate and careful evaluation. SE caused by a variety of diseases of different outcomes, so cases of SE should be investigated thoroughly and need urgent evaluation. Social and family support plays an important role in drug compliance and development of SE.

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Key words: Status epilepticus; profile; Egyptian patients; drug compliance; family support.

Introduction

Status epilepticus is defined as an epileptic state of a prolonged seizure (lasting for more than 5 minutes) or repeating seizures without regaining consciousness between them 1 .

Non-convulsive status epilepticus (NCSE) may be defined as "an enduring epileptic condition with reduced or altered consciousness, behavioral and vegetative abnormalities, or merely subjective symptoms without major convulsive movements" ².

Status epilepticus (SE) is a life threatening condition of ongoing or repetitive seizures, which carries high mortality and severe disability³. The incidence of status epilepticus is 6.8 to 41 cases per 100,000 persons annually ⁴.

Status Epilepticus may be classified broadly as convulsive SE and nonconvulsive SE. Convulsive SE (CSE) can be further classified into (a) tonicclonic, (b) tonic, (c) clonic and (d) myoclonic. Generalized tonic-clonic SE is the most common form. Nonconvulsive SE (NCSE) refers to continuous generalized electrical seizure activity lasting for at least 30 min, but without physical convulsions. CSE may evolve into the nonconvulsive form after treatment or NCSE may arise de novo. NCSE is characterized by abnormal mental status, unresponsiveness, ocular motor abnormalities, persistent electrographic seizures, and possible response to anticonvulsants. All patients with prolonged postictal confusion or unexplained coma should undergo EEG monitoring for confirmation.

NCSE has long been divided into two main categories: absence SE (ASE) and complex partial SE (CPSE)⁵.

Outcome in refractory status epilepticus is poor; mortality is almost 50%, and only a minority of patients (primarily those with preexisting epilepsy and no acute brain process) return to their premorbid functional baseline ⁶.

The aim of this study is to evaluate the clinical parameters and etiological factors of status epilepticus in a sample of Egyptian patients admitted at Al- Azhar university hospitals.

PATIENTS AND METHODS:

The present study was conducted on 40 patients with status epilepticus (SE) between beginning of January 2016 to end of June 2016 who admitted at general and neurology intensive care units at Al-Azhar university hospitals (Al-Hussein and Bab Al-Sharea). All patients presented with status epilepticus included in the present study. All patients were subjected to the following procedures:

(I) Detailed medical and neurological history including personal history, family history including history of epilepsy and social history.

(II) Detailed history of epilepsy:

The history taking included: -

(1) Type of seizures. (Generalized, Partial and Polymorphic)

(2) Frequency of seizures: (frequent or infrequent)

(3) Anti-epileptic drugs use: (number of drugs and serum drug level).

(4) Etiology of epilepsy such as: History suggestive of CNS infection, head trauma, stroke.

(III) Detailed history of status epilepticus:

(a) Type of SE: (convulsive or non-convulsive)

(b) Etiology of SE:

Idiopathic, vascular, CNS infection, metabolic & electrolyte disturbance, tumor, traumatic brain injury and febrile convulsion.

(c) Trigger factors for SE: (poor compliance, infection and fever, drug abuse, trauma, metabolic and electrolyte disturbance, sleep deprivation or unknown).

(d) Duration of SE:(less than 60 minutes, 60 minutes to 24 hours, more than 24 hours)

(e) Recurrent SE or not.

(f) Anti-Epileptic Drugs for treatment of Status Epilepticus (diazepam and phenytoin or combination of AED (diazepam, phenytoin, midazolam, Propofol and thiopental)

(g) Outcome of patient at hospital discharge (dead, disability and good outcome)

(IV) Full general and neurological examination.(V) Routine blood investigations: -

-Complete blood count, blood glucose levels, serum electrolytes, liver and kidney function tests, arterial blood gas. Lumbar puncture (LP) and CSF analysis were performed in patients presented with symptoms and signs suggesting CNS infection. Other relevant investigations performed when needed.

(VI) Serum levels of conventional antiepileptic drugs.

(VII) Neurophysiological assessment by using conventional Electro-encephalography (EEG) after SE management.

(VIII) Brain Magnetic Resonance Imaging (MRI) and/or CT Brain: for detection of any structural abnormalities.

(IX) Treatment paradigm for status epilepticus:

All patients were subjected to a standard treatment protocol according to duration of seizures⁷.

(X) Statistics: All data tabulated and statistically managed. Statistical presentation and analysis of the study results were conducted, using the mean and Chi-square by statistical package for social science (SPSS version, 17).

3. Results

In the present study, a total of 40 patients with Status epilepticus were seen and managed at Al-Azhar University Hospitals (Al-Hussein and Bab Al-Sharea) between beginning of January 2016 to end of June 2016.

In the present study, as regarding age, their ages ranged from 3 to 67 years. As regarding sex, 16 (40.0 %) patients were females and 24 (60.0%) were males. As regarding residency, 36 (90.0%) were living in urban areas and 4 (10.0%) were living in rural areas. As regarding marital history and sexual relationships, 17(42.5%) were married and had legal sexual relationships except 1 (2.5%) had extra-marital relationship and 23 (57.5%) patients were not. As regarding drug abuse, three (7.5%) patients had a history of drug abuse. As regarding income, 16 (40.0%) patients had good income. Twenty-three (57.5%) patients were epileptic. Twenty (50.0%) patients had normal neurological examination. As regard MRI brain, 19 (47.5%) patients had normal findings.

As regarding clinical profile of known epileptic patients, there were 14(60.9%) patients had

generalized tonic clonic seizures, 6 (26.1%) had partial type, 3 (13.0%) had polymorphic type. As regarding cause of epilepsy, 13 (56.5%) had idiopathic causes, 3(13.0%) had CNS infection, 3(13.0%) had vascular causes, 3(13.0%) had brain tumor and finally 1(4.3%) had history of trauma. As regarding the serum drug level, 12 (52.2%) had low serum level, 2 (8.7%) had AED level within therapeutic range but serum drug level couldn't be assessed in 9 (39.1%) patients. Nine (39.1%) patients were treated by one anti-epileptic drug (AED), 4(17.4%) were treated by 2 AEDs and 9 (39.1%) were treated by more than 2 AEDs. Seizures were frequent in 17 (73.9%) patients but they weren't in 6 (26.1%).

Table (1): Demographic data, social history, examination, MRI brain and history of epilepsy in studied patients:

		Total no. = 40 pts
A 30	Mean ±SD	34.99 ± 19.17
Age	Range	3 - 67
Sex	Females	16 (40.0%)
Sex	Males	24 (60.0%)
Residence	Rural	4 (10.0%)
Residence	Urban	36 (90.0%)
Morriago	No	23 (57.5%)
Marriage	Yes	17 (42.5%)
	No	37 (92.5%)
Drug abuse	Yes	3 (7.5%)
	Multiple partner	1 (2.5%)
Sexual history	No	23 (57.5%)
	Within marriage	16 (40.0%)
Income	Good	16 (40.0%)
Income	Low	24 (60.0%)
Examination	Abnormal	20 (50.0%)
Examination	Normal	20 (50.0%)
MRI brain	Abnormal	21 (52.5%)
IVIKI UFAIN	Normal	19 (47.5%)
Listom, of spilopar	No	17 (42.5%)
History of epilepsy	Yes	23 (57.5%)

As regarding clinical profile of all patients who developed SE, 13 (32.5%) patients had idiopathic cause and it is the most common cause, 10 (25.0%) had vascular causes. Six (15.0%) patients had CNS infection, 4 (10.0%) had metabolic & electrolyte disturbance, 3(7.50%) had brain tumor, 2(5.0%) had febrile convulsion and 2(5.0%) had traumatic brain injury. As regarding type of SE, 36 (90%) patients had convulsive SE. As regarding SE duration, 18 (45.0%) patients had SE lasted less than 60 minutes, 13 (32.5%) had SE lasted 60 minutes to 24 hours but SE duration was more than 24 hours in 9(22.5%). Studied patients treated with diazepam and phenytoin in 18(45.0%) patients and patients treated by combination of AED (Diazepam, phenytoin, midazolam, propofol, and general anesthesia) were22 (55.0%) patients. As regarding trigger factors for developing SE, 15 (37.50%) patients had poor compliance and it was the commonest trigger factor.

In the current study, five (12.5%) patients died, 6 (15.0%) had disability and 29 (72.5%) had good outcome. As regarding EEG findings,6(15.0%) patients had abnormal epileptiform discharge, 29 (72.5%) had normal findings and cannot be assessed in 5 (12.5%) patients.

There was high statistically significant difference between epileptic and non-epileptic patients as regarding idiopathic cause of SE and Poor compliance as a trigger for SE (P-value 0.000).

There was statistically significant difference between epileptic and non-epileptic patients as regarding marital history, SE etiology (idiopathic causes and vascular causes), trigger factors (poor compliance to AED and infection and fever), SE duration and Outcome of SE patients(P-value < 0.05).

Table (2) :	Clinical	data o	i epner	osy niste	ory:
				No.	%

		No.	%
	Generalized	14	60.9%
Type of seizure	Polymorphic	3	13.0%
	Partial	6	26.1%
	Mono	9	39.1%
AED	Two	4	17.4%
AED	Poly	9	39.1%
	Untreated	1	4.3%
	Therapeutic	2	8.7%
Drug level	Sub therapeutic	12	52.2%
	Cannot be assessed	9	39.1%
	Idiopathic	13	56.5%
	CNS infection	3	13.0%
Cause	Vascular	3	13.0%
	Tumor	3	13.0%
	Trauma	1	4.3%
Frequency of	Infrequent	6	26.1%
seizures before SE	res before SE Frequent		73.9%

 Table (3): Clinical data of status epilepticus

		No.	%
Tune CE	Convulsive	36	90.0%
Type SE	Non convulsive	4	10.0%
	Idiopathic	13	32.5%
	Vascular	10	25.0%
	CNS infection	6	15.0%
Cause SE	Metabolic & electrolyte		
Cause SE	disturbance	4	10.0%
	Tumor	3	7.50%
	Febrile convulsion	2	5.0%
	Trauma	2	5.0%
	Ischemia	1	2.50%
	Sleep deprivation	2	5.00%
	Trauma	2	5.00%
	Drug abuse	3	7.50%
Trigger factors	Metabolic and electrolyte		
	disturbance	5	12.50%
	Unknown	5	12.50%
	Infection & fever	7	17.50%
	Poor compliance	15	37.50%
Recurrent SE	No	32	80.0%
Recurrent SE	Yes	8	20.0%
	<60 m	18	45.0%
SE duration	60m -24hours	13	32.5%
	> 24 hours	9	22.5%
AEDs for SE	combination	22	55.0%
treatment	Diazepam & phenytoin	18	45.0%

There was statistically significant relation between recurrence of SE and the following parameters: history of epilepsy, drug abuse, SE duration, AEDs used for treatment of SE, EEG findings and frequency of seizures (P-value < 0.05).

There was statistically significant relation between cause of SE and SE duration (P-value <0.05).

		nd non-epileptic patie No history of epilepsy		Positive history of epilepsy		Chi-square test	
		No.	%	No.	%	X ²	P-value
Tuno SE	Convulsive	16	94.1%	20	87.0%	0.557	0.455
Type SE	non convulsive	1	5.9%	3	13.0%		
	Idiopathic	0	0.0%	13	56.5%	14.235	0.000
	Vascular	7	41.2%	3	13.0%	4.126	0.042
	CNS infection	4	23.5%	2	8.7%	1.687	0.194
Cause SE	Metabolic & electrolyte disturbance	3	17.6%	1	4.3%	1.921	0.166
	Tumor	0	0.0%	3	13.0%	3.285	0.070
	Febrile convulsion	2	11.8%	0	0.0%	2.848	0.091
	Trauma	1	5.9%	1	4.3%	1.388	0.239
	Drug abuse	0	0.0%	3	13.0%	2.397	0.122
	Poor compliance	0	0.0%	15	65.2%	17.739	0.000
	Infection & fever	6	35.3%	1	4.3%	6.484	0.011
Trigger factors	Ischemia	1	5.9%	0	0.0%	1.388	0.239
	Metabolic and electrolyte disturbance	4	23.5%	1	4.3%	3.288	0.070
	Sleep deprivation	0	0.0%	2	8.7%	1.556	0.212
	Trauma	2	11.8%	0	0.0%	2.848	0.091
	Unknown	4	23.5%	1	4.3%	3.288	0.070

Dead Disability Good

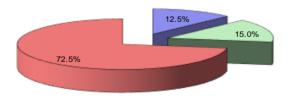


Figure (1):Outcome of SE in studied patients.

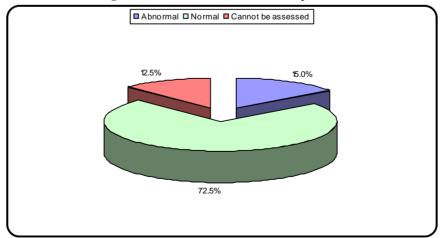
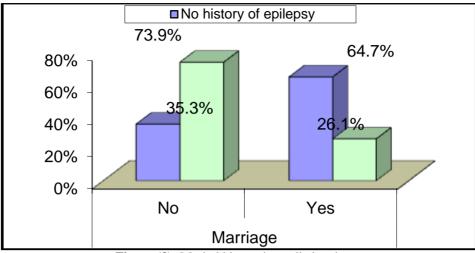


Figure (2):EEG findings in studied patients.





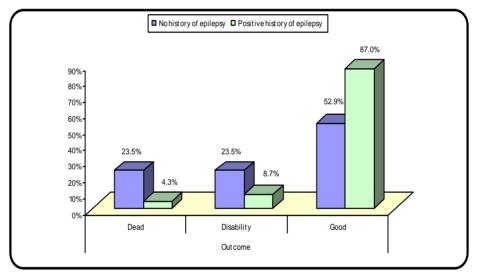


Figure (4): Outcome of epileptic and non-epileptic patients.

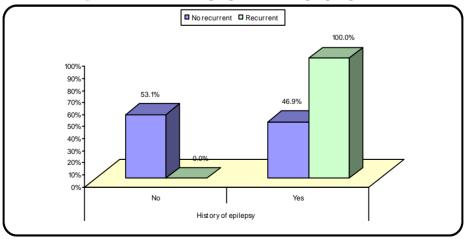


Figure (5): Recurrence of SE in epileptic and non-epileptic patients.

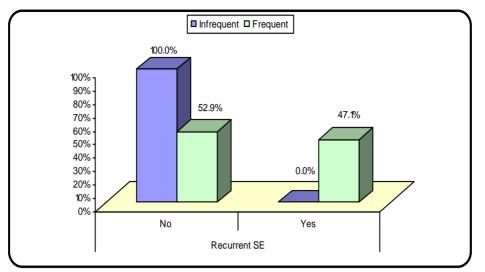


Figure (6): Relation between history of frequency of seizures and history of recurrence of SE:

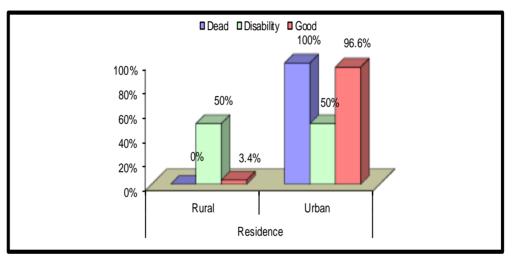


Figure (7): Relation between residence and outcome of SE.

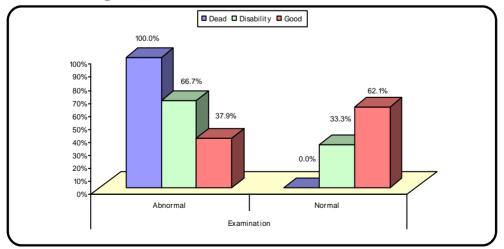


Figure (8):Relation between neurological examination and outcome.

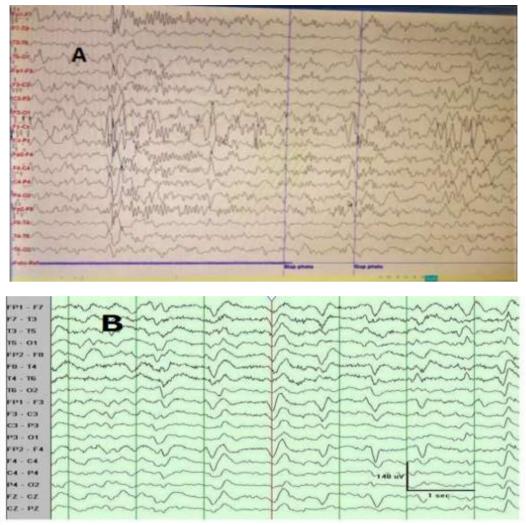


Figure (9): male child 3 years old presented with status epilepticus due to febrile convulsion (A), male patient 55 years old presented with hepatic encephalopathy, EEG shows triphasic waves (B).

4. Discussion

In the current study, it was found that SE was more common in males. This is in agreement with number of studies, notably in *Koubeissi and Alshekhlee 2007 and in* a prospective populationbased study from Switzerland^{8,9}.

In the study of *Coeyetaux et al. 2000* from Switzerland, the age-adjusted rate for status epilepticus was 7.8/100,000 for females and 12.1/100,000 for males. That the greater incidence of status epilepticus in men could be partially explained by (1) the fact that men are at greater risk of acute symptomatic and remote symptomatic insults (cerebrovascular disease, head trauma, alcoholism, CNS infections) than women ^{10,11}. (2) The gender difference in seizure threshold possibly mediated by the GABA-sensitive substantia nigra, which is under the influence of sex hormones, and which may be involved in the expression of seizures.

Mean age in the present study was 34.99 ± 19.17 but in a large US study done by *Koubeissi and Alshekhlee 2007*, they found that mean age was 39 ± 25.6 years⁸.

In the current study, the incidence rate of SE was higher in urban areas going with *Coeytaux et al.,2000*. We noticed that the urban recruitment was higher than rural recruitment because Al-Azhar university hospitals serve urban areas and the cost of transference from rural areas are high and consume a lot of time that can be used for urgent treatment of SE in nearby hospitals I^0 .

There was significant difference between epileptic and non-epileptic patients as regard marital history as we found that 17 (73.9%) of epileptic patients weren't married (P-value<0.05) and this may suggest a relation between marital history and poor compliance in development of SE in epileptic patients. According to *Choi et al., 2003,* they found that social and family life dissatisfaction affect compliance of drugs. Also they can explain the incidence of marital state by those people consider that epilepsy is an inherited disorder and that marriage with those patients should be avoided. In addition, they consider epilepsy as an untreatable disease I^2 .

In the current study, as regarding causes of SE, 13 (32.5%) patients had idiopathic cause and it is the most common cause. 10 (25.0%) had vascular causes. Six (15.0%) had CNS infection, 4 (10.0%) had metabolic & electrolyte disturbance, 3(7.50%) had brain tumor, 2(5.0%) had febrile convulsion and 2(5.0%) had traumatic brain injury. As regarding trigger factors for developing SE, 15 (37.50%) patients had poor compliance and it was the commonest trigger factor. But this is not going with Hui et al., 2003, Vignatelli et al., 2003, Vignatelli et al., 2005.Koubeissi and Alshekhlee 2007. Canouï Poitrine et al., 2011, Sánchez and Rincon 2016 they found that major etiologies of SE were cerebrovascular events, withdrawal or changes in AEDs, as well as remote symptomatic epilepsy. The differences in their results may be due to availability of AED and health awareness of epilepsy and SE in developed countries play an important role in drug compliance, so epileptic patients are less vulnerable to develop SE and other causes are more common to produce SE 13,14,15,8,16,17

In the current study, as regarding causes of SE, the results are going with a prospective study in Sao Paolo, Brazil, recollected data from 102 patients with SE admitted to a local hospital emergency department. Patients were subdivided into two groups: A, consisting of epileptic patients, and B, individuals with no previous history of epilepsy. In Group A, the main causes of SE were non-compliance with AEDs (31.8%) and undetermined etiology (39%) (p < 0.05). In Group B, three etiologies predominated: CNS infection (26.6%), stroke (24.4%) and metabolic disturbances (17.7%) (p < 0.05) ¹⁸, and other studies from Central and South America ¹⁹.Sadarangani et al., 2008 reported in their cohort study of Kenyan children, found that 71% of SE cases had an infectious cause, 53% attributed to malaria. Likewise ²⁰, Amare et al. 2008 described CNS infections as the primary source of SE episodes in 119 Ethiopian patients aged 13 or older. The specific etiologies for these CNS infections were cerebral toxoplasmosis and meningitis 21.

These results can be explained by the patients with status epilepticus in developing countries encounter several significant barriers to adequate treatment. These include poor health care infrastructure, nonavailability of injectable formulations of antiepileptic drugs, and lack of personnel with neurologic expertise who can recognize and appropriately treat patients with status epilepticus. In spite of these limitations, the mortality related to status epilepticus is quite comparable to that reported in developed countries.

Rossetti et al. 2006 reported that etiology has repeatedly been proven to be the major determinant of SE outcome. In the present series. idiopathic/cryptogenic etiological group carried the best results towards good neurological and functional outcome²². A study reported by Amare et al 2008 supported the current data. Idiopathic group almost always includes non-evident etiologically fatal causes and mostly comprises patients non-compliant on antiepileptic drugs which has been suggested to carry excellent outcome.

In the current study, no significance association between sex, age marital history drug abuse, sexual relations, income, type of SE and outcome of SE, and this is in agreement with *Moghaddasi et al.*, 2015 cleared that age, sex were not associated with mortality ²³.

In the present study, poor outcome was significant associated with symptomatic SE, vascular and traumatic brain injury cause death while CNS infection associated with disability in agreement with *Joyalakshmi et al. 2014; Kang et al. 2014; Kumar et al. 2014, Vooturi et al., 2014and Tsetsou et al. 2015,* theyshowed thatpoor SE outcome associated with encephalitis and stroke being the most frequent causes and according to *Dhakar et al. 2015,* reported that generalized convulsive SE (GCSE) in traumatic brain injury (TBI) patients was associated with worse outcome. These results can be explained by certain etiologies might be a direct determinant of the natural duration of SE and influence the relative resistance of status epilepticus to treatment ^{24,25,26,27,1,28}.

In the present study, epileptic patients who developed SE had good outcome, this is in agreement with *Moghaddasi et al. 2015*, they cleared that those with negative history of epilepsy had higher mortality rate. Furthermore, from another aspect they found that patients with negative history of epilepsy had significant higher mortality rate that may be explained by refractory SE and its sequelae are may be because of an underlying cause ²³.

In the present study, patients with prolonged SE duration showed poor outcome in contrast to **Moghaddasi et al. 2015**, they cleared that duration of SE was not associated with poor outcome. In the other hand, patients who needed more drugs to control SE showed poor outcome, this is in agreement with **Treiman et al. 1998**, they stated that mortality rate was significantly less in patients who responded to less treatment^{23,29}.

In the present study, etiology of SE played an important role in determining SE duration, response to AED and outcome of patients and this is in agreement with, *Treiman et al. 1998, Joyalakshmi et al. 2014; Kang et al., 2014; Kumar et al., 2014, Vooturi et al. 2014, Moghaddasi et al, 2015 and Tsetsou et al. 2015, ^{29,24,25,26,27,23,1}.*

Longer duration of SE is unlikely to be a positive prognostic factor, but proving that it is a significant negative prognostic factor independent of etiology is very difficult. The etiology is still by far the most important prognostic factor. Patients with exacerbations of earlier epilepsy do better, and those with anoxia almost always die. Type of seizure are correlated with outcome but probably related to etiology as well. After the first several hours, there is no substantial drop-off in survival with any particular duration of SE and, once etiology is accounted for, there is no major effect of duration on outcome in SE. When the etiology is considered at least permissive of a reasonable recovery, some patients with particularly long durations of SE can still be treated successfully.

In the current study, five (12.5%) patients died according to *Rossetti et al. 2006*, they found Mortality rate was 15.6% and range between 7.6% and 39% and in the study of **Koubeissiet** *al. 2007*, female patients had significantly greater mortality rate. In the study of **Moghaddasi et al. 2015**, total mortality rate was 16.9% and slightly higher in females; however, the difference was not statistically significant 8,23 .

In the present study, drug abuse had significant association with development of SE, this is in agreement with **Thundiyil et al. 2007**, they demonstrated the role of drug abuse in developing seizures and SE. Many of these drugs are widely available, used extensively and induce brain seizures as many studies have determined that up to 9% of cases of status epilepticus presenting to the emergency department may result from drug toxicity(*Lowenstein D and Alldredge B, 1993*).^{30,31}.

Eight (20.0%) of studied patients had history of recurrent SE. Recurrent SE more common with idiopathic epilepsy, vascular causes, CNS infection and brain tumors, so those patients with different causes more refractory to treatment and showed failure of response to AED, Study reported by *Tsetsou et al.* 2015, showed some points of disagreement with our study as they reported that SE recurrences involve 32% of patients over 4-year study and this also similar to another study that reported which retrospectively found a recurrence of 32% over 10 years and these important differences probably related to different methodologies ¹.

Also *Tsetsou et al. 2015*, reported that survival was higher among patients with recurrent SE episodes and this is in agreement with our study as outcome not

significantly associated with recurrent SE, so we can conclude that mortality and morbidity following SE are related to the underlying clinical profile of the patient, but not SE recurrence itself¹.

5. Conclusion:

Status epilepticus is a complex clinical syndrome that requires immediate and careful evaluation. SE caused by variety of diseases of different outcomes, so cases of SE should be investigated thoroughly and need urgent evaluation. Social and family support plays an important role in drug compliance and development of SE.

Recommendations:

Educational programs for both medical staff and general populations about importance of early diagnosis, rapid and proper management of patients with SE and it is critical for physicians to diagnose the cause of status epilepticus as soon as possible, for effective treatment. More studies should be done about non convulsive SE and more studies should be done about relation between substance abuse and SE.

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