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*Full Length Research Paper*

# The number of seizure episodes in patients presenting with refractory status epilepticus. Causes and modes of management

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**It is not well documented in the literature of the total number of status epilepticus (SE) episodes in patients presenting with the diagnosis of refractory status epilepticus (RSE) regardless of the cause. It is not well known of what is the right management protocol that should be initiated to control such repeated episodes. We retrospectively evaluated patients presenting with refractory status epilepticus to find out what is the frequency of seizure episodes at their admission. We also evaluated the management protocol at our center. All data were obtained in patients presenting between July 2014-July 2015. 121 status epilepticus episodes were documented in 29 patients who carry the diagnosis of refractory status epilepticus. More than half of the group was male, 17/29 (58.6%). The majority carried the diagnosis of vascular disorder as the cause of their refractory status epilepticus and the majority was started on levetiracetam as the first drug of choice. We document the high frequency of repeated episodes of seizures once the patient presents with refractory status epilepticus for the first time. The majority of those individuals had the diagnosis of vascular disorder as a cause for the seizures.**

**Keywords:** Epilepticus, seizure, episodes in patients

## INTRODUCTION

### Background

The definition of SE has varied over the years from vague terminology without time specification until 1999 when the definition was agreed upon to be any generalized convulsive seizure that last for more than 5 minutes of (Gastaut, 1973) continuous seizure or (Roger et al., 1974) two or more discrete seizures between which there is incomplete recovery of consciousness (Gastaut, 1973; Roger et al., 1974; Meldrum and Horton, 1973; Treatment of convulsive status epilepticus, 1993; Guidelines for epidemiologic studies on epilepsy, 1993; DeLorenzo et

al., 1999; Lowenstein et al., 1999). Recently, the definition was further modified to the following:

SE is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms which lead to abnormally prolonged seizures (after time point t1). It is a condition that can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (Eugen et al., 2015).

RSE is defined as continuous seizures of more 30-60 minutes despite treatments and Super refractory status epilepticus (SRSE) is defined as having seizures for more than 24 hours despite anesthetics use.

The exact agent that should be used and the duration of its use is not well established. It is agreed that either midazolam, propofol, or phenobarbital to be used as the initial anesthetic drug of choice (Rossetti and Lowenstein, 2011; Rossetti, 2007).

In general, midazolam has fewer side effects on the degree of hypotension and phenobarbital has more side effect profile but better control of seizures (Claassen et al., 2002).

The duration and the intensity that these drugs should be maintained for is not well known, but generally agreed to be maintained for at least 24-48 hours of electrographic seizure control and then followed by slow withdrawal and maintaining the long term medications (Legriel et al., 2008; Drislane et al., 2009; Holtkamp et al., 2005; Rossetti et al., 2011; Cooper et al., 2009)

## METHODS

We collected data on adult patients above the age of 18 years presenting to the intensive care unit (ICU) between July 2014-July 2015.

All cases defined as RSE and SRSE based on the international definitions of a seizure disorder that lasted more than 30 minutes despite appropriate use of medications at each stage of the development of status epilepticus and needed the use of intravenous (IV) infusions of anesthetic antiepileptic drugs.

The IV drugs chosen was based on the discretion of the treating physician and the hemodynamic properties of the patient. In general, the use of midazolam was started if the patient was hemodynamically unstable and was on shock state so there wont be major effect on the patients' blood pressure or perfusion. Shock state was defined as the presence of low cardiac output measured by the mean arterial pressure of less than 60mm Hg or if there is systemic evidence of low perfusion to vital organs such as the kidneys and the brain.

All patients were intubated and mechanically ventilated at the time of enrollment. We ran a descriptive analysis on all variables of baseline characteristics and an SPSS 20 program used to calculate the mean and median of variables as well as significance. We defined an episode of status epilepticus in each individual if the patient was successfully treated and maintained free of clinical and electrographic seizure. Electroencephalography (EEG) was obtained on all patients having a clinical diagnosis of seizure and was done at the time seen appropriate by the treating physician that the seizure episode has already stopped. Maintenance of EEG clearance was also obtained later if the patient level of consciousness was

not improving despite the stop on intravenous sedation and anesthesia. Clinical evidence of seizure was suspected if the patient has clear generalized or focal tonic and or clonic movements of the upper of lower extremities, focal myoclonic movements, ocular twitches, and or palatal rhythmic movements.

## RESULTS

A total of 121 episodes of refractory status epilepticus were found in 29 patients in the accrual period. The youngest patient was 19 years old and the oldest was 95 years. The mean age was calculated to be 64.4 years.

58.6% (17 patients) were male and the rest were female gender.

14 (48.2%) had a vascular etiology as the main cause of their seizures and the rest of the group carried the diagnosis of metabolic, infectious, genetic, trauma, and respiratory failure.

Among the 121 episodes of status epilepticus, 65 (53.7%) had midazolam infusion as their first choice of intravenous drug, and the rest were treated with propofol infusion to control their seizure episode.

The number of status epilepticus varied significantly among the whole group between one episode to as high as 18 episodes with a mean of 5.3 episodes in the group and a median of 4 episodes.

There was no significant correlation between the underlying cause of status epilepticus and the total number of episodes of status. One patient with 17 episodes of status had the diagnosis of vascular disorder as the primary cause and another patient with 18 episodes had metabolic cause as the primary cause for his status. The majority of the patients received levetiracetam as their first choice of antiepileptic drug and only 6 patients had used phenytoin as the first choice. 11 (37.9%) patients had only one enteral drug used as the maintenance therapy. The rest of the group received a second drug that was variable between, levetiracetam, phenytoin, topiramate, and sodium valproate.

## DISCUSSION

The data we are presenting is to stress on the point that patients presenting with refractory and super refractory status epilepticus may develop repeated episodes of seizures necessitating the use of intravenous infusions of anesthetics.

As seen in our cohort, despite the intensive treatment of each episode with appropriate medications, patients continue to have repeated episodes of status despite reaching freedom from their seizures. It is not known and there is no clear correlation between the cause of the seizure and the risk of recurrence over time as

elaborated in our results.

It is postulated that once the patient carries the diagnosis of refractory status epilepticus at the time of presentation, it is very common for patients to have repeated spells of seizures when they are still admitted in the hospital. It is by nature, that status epilepticus is resistant to treatment sometimes and that as long as the patient is in the ICU, he or she may have the risk of recurrence. There are many factors that are in play when it comes to the risk of recurrence. Sepsis and repeated infection is one of the possible causes that patients easily can acquire during their ICU stay. Infection is a major factor that lowers seizure threshold and pushes patients easily into repeated status episodes. As well, metabolic derangements and electrolytes disturbances are very common in the ICU that also lowers seizure thresholds. Renal failure is also a major cause of why patients may develop repeated episodes of status epilepticus. It is unfortunate that in our data, we could not extract of which of these variables were playing a major factor in pushing patients into repeated episodes of status epilepticus and its very important in future researches to extract such an important information. From our data, the use of maintenance therapy was limited to only two medications at maximum and one may think that we should be more aggressive in adding more medications as maintenance to maintain seizure freedom in such cases.

In the literature, there is still debate about the duration of anesthetic drugs in patients with RSE and SRSE and the exact definition of freedom from a status episode. It is generally agreed that we should keep the infusions for at least 24-48 hours after clinical and electrographic freedom from seizure. We suggest from our data that this duration to be reconsidered based on the notion that the majority of our patients had repeated episodes of status epilepticus despite appropriate treatment.

This opens the discussion for the need of future research to properly establish the duration and the choice of intravenous as well as maintenance therapy to prevent such episodes from happening again and again

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