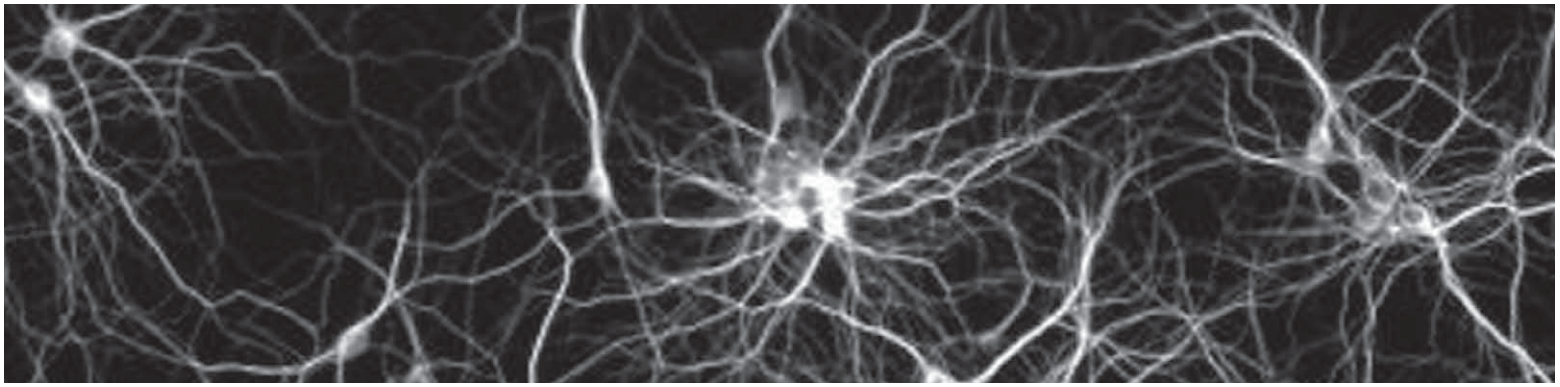

Evaluation of pharmacological treatment efficacy and short-term mortality in patients with status epilepticus at Požega General County Hospital, Požega, Croatia

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ABSTRACT – *Objective:* To determine efficacy of pharmacological treatment and short-term mortality in patients with status epilepticus (SE). *Methods:* This retrospective study included 109 episodes of SE recorded in 102 patients aged 18 years or older admitted to Požega General County Hospital during the period from January 1, 2006 until December 31, 2015. Patients were followed up on day 30 after SE onset to assess their living status. *Results:* Among 102 patients, 52 (51.0%) patients had a history of prior epilepsy. Initial antiepileptic drug was intravenous diazepam in 109 SE episodes. Of these, 97 (89.0%) SE episodes resolved with first- or second-line therapy (diazepam, phenobarbital, levetiracetam). For 12 (11.0%) SE episodes, third-line therapy (midazolam, propofol) was administered. Of these, eight (7.3%) SE were classified as refractory status epilepticus (RSE) and four (3.7%) as super-refractory status epilepticus (super-RSE). Out of 102 patients, nine (8.8%) patients died within 30 days after SE. All patients died during their hospital stay. Five (55.6%) patients died due to the underlying disease and four (44.4%) patients died from clinical complications. Age and negative history of epilepsy were not predictors of mortality (p=0.321 and p=0.191, respectively). *Conclusions:* The SE mortality rate was lower than reported in previous studies and was not related to age and negative history of epilepsy. SE resolved with first- or second-line therapy in nine of ten patients.

Key words: status epilepticus, therapy, mortality rate

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INTRODUCTION

Status epilepticus (SE) is one of the most common neurologic emergencies with significant associated morbidity and mortality, which needs fast diagnosis and therapy to avoid long-term consequences including neuronal injury and neuronal death. SE is defined as an epileptic seizure that shows no clinical signs of arresting after a duration encompassing the great majority of seizures or recurrent seizures without interictal resumption of baseline central nervous system function. Duration of seizures in SE varies from 5 to 30 minutes, depending on the definition (1-6). The Task Force of the International League Against Epilepsy (ILAE) recently defined SE as a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms that lead to abnormally prolonged seizure after five minutes for generalized convulsive SE and 10 minutes for focal SE with impaired consciousness (formerly complex-partial SE), which can have long-term consequences including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures (5-7). In the new classification, non-convulsive SE (NCSE) is divided into NCSE with or without coma (5,7,8).

The incidence of SE varies across studies from 6.2 to 61/100,000 people/year, and in most of the reports from 10 to 41/100,000 people/year. It has been found higher in the United States and lower in central Europe (9-17). The incidence is highest in the elderly and has a second peak in the neonatal period (9,16,18). Generalized convulsive status epilepticus (CSE) is the most common and most serious type of SE, representing 45% to 75% of cases (9,12). The incidence of CSE is 18-28/100,000 people/year (3). In developed countries, the incidence of CSE is 17-23/100,000 people/year (10).

The mortality of SE is around 20%, ranging from 3% to 40%. It may be as high as 40% in the elderly with acute symptomatic SE and comorbidities (13,18-22). Old age, acute symptomatic etiology of seizure, longer duration of SE, coma at presentation, higher rate of comorbidities, refractory SE and negative history of epilepsy were predictors of higher mortality in some studies (10,14,20,22-25). In patients with acute brain infarction and SE, mortality is three times higher than in patients with acute brain infarction without SE (26). Mortality rate was 18% in a meta-analysis of 12 studies in children and adults with SE (3). In a study of SE in French-speaking Switzerland, mortality rate was 7.6% (13). In the study by Classen *et al*. including 85 SE episodes in 74 patients, 21% of the episodes were fatal. Old age and acute symptomatic seizures were predictors of higher mortality (22). In the study by Sokic *et al*. including 920 SE episodes in 750 patients, short-term mortality was 13% (20). In the study by Stelzer *et al*. including 105 patients with epileptic seizures lasting for more than 30 minutes, short-term mortality was 36.2% (21). In the study by Kulkantrakorn *et al*., 13% of patients had refractory SE and 25% died. Advanced age, longer duration of seizure and coma were associated with higher mortality rate (23).

The causes of SE can be divided into acute and chronic. Acute symptomatic causes are associated with higher mortality than chronic ones (10,15,19,27-29). The etiology of SE can be determined in 65%-70% of patients, whereas in the rest the cause remains unknown (9). The most common causes of SE include AED withdrawal and ischemic stroke (23). SE can occur as the first manifestation of epilepsy (14).

There are many types of SE as there are many types of epileptic seizures. The classification based on Gastaut is simplest for clinical practice (2).

Table 1. *Clinical course of convulsive status epilepticus (CSE) divided into four subsequent phases (11,30)*

Early SE: convulsive epileptic activity for more than 5 minutes
Established SE: continuous seizure activity with convulsions or intermittent seizures without regaining consciousness between the seizures for more than 10 and up to 30 minutes
Refractory SE (RES): SE continuous for more than 30 and up to 60 minutes
Superrefractory SE (super-RSE): seizures continue despite maximal treatment with intravenous (IV) anesthetics for more than 24 hours in an intensive care unit

Intravenous (IV) diazepam or lorazepam or intramuscular midazolam are used for initial treatment of early SE (11,31). In established SE, intravenous antiepileptic drugs (AEDs; phenytoin/fosphenytoin, phenobarbital, valproate, levetiracetam) are most commonly used. Refractory SE (RSE) and super-refractory SE (super-RSE) are treated with anesthetics (propofol, midazolam, thiopental) (11).

PATIENTS AND METHODS

This study was designed as a retrospective study and included patients of both genders aged 18

years and older who presented with SE during the period from January 1, 2006 until December 31, 2015 to Department of Neurology, Požega General County Hospital. Upon admission to the hospital, they were transferred to the Neurology Stroke Unit, which is equipped with facilities for vital function monitoring. Only patients with super-RSE and patients with respiratory depression (RD) were dislocated to the Intensive Care Unit (ICU).

Status epilepticus is defined as a condition in which epileptic activity persists for five minutes or longer for CSE (6) and 30 minutes or longer for other forms of SE (7). RSE is defined as absence of clinical and/or EEG control of the seizure for more than 30 minutes and up to 60 minutes (11,21). Super-RSE is defined as SE that continues or recurs 24 hours or more after the onset of anesthetic therapy (30).

According to clinical presentation and EEG features, SE is classified as generalized convulsive SE (CSE), focal motor SE, focal onset evolving into bilateral convulsive SE, epilepsia partialis continua (EPC), myoclonic SE (MSE) and non-convulsive SE (NCSE) (5).

All subjects underwent complete hematologic, metabolic and electrolyte workup, EEG, CT or MRI of the brain. Lumbar puncture was performed as needed. Serial 18-channel electroencephalogram (EEG) (Oxford Instruments, United Kingdom) was obtained following 10-20 International System of electrode placement. We performed first EEG examination within three days of SE occurrence.

The etiology of SE is classified as acute symptomatic (AS), progressive symptomatic (PS), remote symptomatic (RS), or idiopathic/cryptogenic (IC) according to the ILAE recommendations. AS is considered when SE occurs within a week of an acute central nervous system (CNS) or systemic insult (i.e. stroke, meningitis, encephalitis, hepatic encephalopathy, neurotrauma, or alcohol intoxication or withdrawal). PC is considered when SE is related to progressive CNS diseases (i.e. tumors, multiple sclerosis, or degenerative neurologic disease). RS is considered in the presence of a history of CNS insult presumed to result in static encephalopathy associated with an increased risk of epilepsy (i.e. cerebral palsy, stroke, head trauma, encephalitis or meningitis). I/C means that the cause of SE is unknown (32). Short-term mortality is defined as death in the first 30 days following the episode of SE (19).

Patients were treated according to the following protocol: first-line treatment of SE was diazepam 10 mg IV (diluted in 100 mL normal saline/5 minutes). In case of prolonged SE duration, diazepam 20 mg diluted in 500 mL normal saline was administered. If seizures did not resolve, we used second-line drugs, i.e. phenobarbital 10 mg/kg IV (infusion at a maximum dose of 100 mg/min) or levetiracetam 500 mg diluted in normal saline (infused at a maximum dose of 3000 mg/day). If clinical and EEG control was not achieved with first- or second-line therapy (diazepam, phenobarbital or levetiracetam), the patient was considered to have RSE. Patients with RSE and super-RSE were treated with anesthetics, midazolam 0.2 mg/kg as a loading dose, followed by infusion at 0.1-0.4 mg/kg/h or propofol IV 2 mg/kg/h. Patients with super-RSE were dislocated to the ICU. Patients were followed up on day 30 after SE onset.

Statistical analysis was performed using the SPSS for Windows, version 18.0. Differences in quantitative variables were analyzed using χ^2- test with the level of significance less than 5% ($p<0.05$). Descriptive statistics was used and data were presented as mean and standard deviation (SD).

RESULTS

During the study period, we observed 109 episodes of SE in 102 patients. There were 66 (64.7%) male and 36 (35.3%) female patients, yielding the male to female ratio of 1.8:1. The mean patient age was 56.75±18.88 (median 59.5, range 19-94) years. One patient had four SE episodes, four patients had two SE episodes, and 97 (95.1%) patients had a single SE episode. SE started before admission to the hospital in 100 (98.0%) patients and after admission in two (2.0%) patients. Fifty-two (51.0%) patients had a history of prior epilepsy, and they had a mortality rate of 3.8% compared with 14% in those with negative history of epilepsy (p=0.191). The mean duration of hospital stay in all patients with SE was 8.37±4.67 (median 7) days. The mean duration of hospital stay in patients who died was 6.88±7.38 (median 5) days, and in patients who survived 8.50±4.67 (median 8) days (p=0.028).

Status epilepticus was classified as generalized convulsive (CSE) in 50 (45.9%), focal motor in five (4.6%), focal onset evolving to bilateral convulsive SE in 36 (33.0%), epilepsia partialis continua (EPC) in one (0.9%), myoclonic (MSE) in one (0.9%) and non-convulsive (NCSE) in 16 (14.7%) episodes. EEG was performed in seven (6.4%) episodes dur-

Table 2. *Etiology of status epilepticus*

	n	%
Acute symptomatic (AC)	**10**	**9.8**
Acute cerebrovascular accident	5	4.9
Meningitis/encephalitis	2	2
Alcohol withdrawal	3	2.9
Progressive symptomatic (PS)	**15**	**14.7**
Tumors	9	8.8
Multiple sclerosis	3	2.9
Dementia	3	2.9
Remote symptomatic (RS)	**60**	**58.8**
History of cerebrovascular accident	41	40.2
History of head trauma (contusio cerebri, traumatic subarachnoid hemorrhage, epidural/subdural hemorrhage)	11	10.8
History of meningitis/encephalitis	6	5.9
Hydrocephalus	1	1
Mesial temporal sclerosis	1	1
Idiopathic/cryptogenic (I/C)	**17**	**16.7**

Table 3. *Causes of death in patients with status epilepticus*

Diagnosis	n	%
Acute cerebral infarction	3	33.3
Acute meningoencephalitis	1	11.1
Meta cerebri	1	11.1
Pneumonia/respiratory failure	2	22.2
Pneumonia and cardiac decompensation	2	22.2

ing SE and in 92 (84.4%) episodes after termination of SE.

Initial AEDs were IV diazepam in 109 SE episodes. Diazepam IV stopped SE in 81 (74.3%), phenobarbital IV in 13 (11.9%) and levetiracetam IV in three (2.8%) episodes. Third-line therapy was used in 12 (11.0%) SE episodes, i.e. midazolam in 10 (9.2%) and propofol in two (1.8%) episodes. In this group, eight (7.3%) episodes were classified as RSE and four (3.7%) as super-RSE. Intravenous immunoglobulin was used in one (1%) patient who suffered from autoimmune encephalitis. In our study, complications of benzodiazepines (apnea) were recorded in one (1%) patient. Four (3.9%) patients needed artificial ventilation.

During the study period, nine patients died, including seven men and two women. The mortality rate was 8.8%. According to clinical assessment and the course of disease, there are two major causes of death in SE: underlying disease (acute cerebral infarction, acute meningoencephalitis, meta cerebri) and complications (pneumonia, respiratory failure, cardiac decompensation). Five (55.6%) patients died due to the underlying disease and four (44.4%) patients died from complications. Severe clinical complications were pneumonia, respiratory failure and pneumonia, and cardiac decompensation. The mean age of patients who died was 66.44±16.14 (median 72, range 40-84) years and the mean age of patients who survived was 55.81±18.93 (median 58, range 19-94) years. Mortality rate did not differ between genders (p=0.332). Age and negative history of epilepsy were not significant predictors of mortality in our patients (p=0.321, p=0.191).

Table 4. *Factors influencing mortality rate of status epilepticus*

Variable	p value
Sex (female/male)	0.332
Age	0.321
Duration of hospital stay	0.028
Epilepsy history (+/-)	0.191

The patients who died had CSE in three (33.3%) cases, focal onset evolving to bilateral convulsive SE in five (55.6%) cases and epilepsia partialis continua (EPC) in one (11.1%) case. Following clinical and EEG criteria, SE was not stopped until death in one (1%) patient.

DISCUSSION

In our study, SE mortality was similar as in some previous studies (13,33,34) and lower than reported in some other epidemiology studies (3,19-21,24,35). The probable reasons of lower mortality in our research were early treatment, improved treatment, nursing and prevention of complications.

In our investigation, 45.9% of SE episodes were initial and mortality rate was 8.8%. Mortality rate was similar as in an the study from Switzerland where mortality among patients with SE was 7.6%, although 57% of their patients had initial SE (13). In the study by Seltzer *et al*., 52.4% of patients had a history of prior epilepsy, which was similar as in our investigation (21). In other hospital samples, 30%-44% of patients with SE had a history of epilepsy (20,33).

One of the best prognostic factors of SE is etiology, and the highest mortality rates are observed in patients with AS or PS etiology. In earlier investigations, underlying disease was the primary determinant of SE outcome (19,20,28,29,36,37). In our sample, severe underlying disease was the main etiology of death in five (55.6%) patients. In the study of short-term mortality in 750 patients, severe underlying disease was the main etiology of death in 65.8% of patients (20), and in a meta-analysis of 12 studies death was due to severe underlying disease in 89% of cases (3). In our study, respiratory complications occurred in 44.4% of patients who died, which was almost the same as in the study by Sokic *et al*. (20). In our investigation, the presence of a history of CNS insult was the most common cause of SE. Previous studies have reported on advanced age in SE patients as a predictor of higher mortality (14,20), but age was not a significant predictor of mortality in our patients. The length of hospital stay was not a significant predictor of mortality in the study by Moghaddasi *et al*. (24). In our investigation, we found a negative correlation between the length of hospital stay and mortality. Negative history of epilepsy was associated with a significantly higher mortality rate in the study by Mogaddasi *et al*. (24), but not in our study. In the study by Seltzer *et al*., mortality associated with SE was not related to age, specific etiology or SE duration. Mortality was independently related to the occurrence of medical complications (21). A study conducted in an urban public hospital revealed little variation in the etiology of SE over two decades (36). In our study, the etiology of SE was known in 85 (83.3%) patients and the cause remained unknown in 17 (16.7%) patients, which was a greater number of known causes than in the study conducted in Rochester (9). AED withdrawal in previously epileptic patients is typically associated with low mortality (28,33). In our investigation, there was no death in patients with previous epilepsy with low AED levels or AED withdrawal.

In our investigation, IV diazepam effectively controlled SE in 74.3% of episodes, similar to the study performed by Chamberlain *et al*. in a group of pediatric SE patients (38). Phenobarbital and levetiracetam controlled SE in 14.7% of episodes. Ninety-seven (89.0%) patients responded to treatment with first- or second-line therapy, which was similar as in the study by Moghaddasi *et al*., where 84.6% of patients responded to the treatment of tonic-clonic SE (24). In another study, RSE developed in 24% to 43% patients with SE (25), whereas in our study it developed in 11% of patients. In the study by Giovannini *et al*. on 83 SE episodes, third-line therapy was needed in 31% of cases; in this group, 14% were classified as RSE and 17% as super-RSE (25). In our investigation, third-line therapy was needed in 11% of patients, which was similar to the study by Mogaddasi *et al*. (24). In our study, 7.3% of SE were classified as RSE and 3.7% as super-RSE. Propofol and midazolam were used for the treatment of RSE and super-RSE in 11.0%, which was similar to the study by Moghaddasi *et al*. (24). There are no class I data to support recommendations for most AEDs in the treatment of established RSE and super-RSE (11).

In our study, complications of diazepam (apnea) appeared in one (1%) patient. Benzodiazepines may provoke apnea and RD in 3.7%-24% of patients (33). A meta-analysis of the literature indicates that, compared with placebo, after diazepam administration there is a lower risk of requirement for ventilation support and continuation of SE requiring a different drug or general anesthesia with diazepam (39).

In our study, following clinical or EEG criteria, SE was not stopped until death in one (1%) patient, which was similar to the study by Sokic *et al*. (20), and multiply lower than in the study by Seltzer *et al*. (21).

In the London-Innsbruck Status Epilepticus Collegium, major therapeutic advances include the use of benzodiazepines in out-of-hospital situations, especially buccal midazolam and the use of valproate, levetiracetam and lacosamide in the stage of established SE (40). If it is not possible to apply IV therapy in SE patient, intramuscular midazolam is at least as safe and effective as IV lorazepam for pre-hospital seizure cessation (41). Until now, we have no experience with the use of buccal midazolam, IV valproate and IV lacosamide in SE.

CONCLUSION

In our study, mortality rate associated with SE was lower than reported in previous studies. The probable reasons of lower mortality were early treatment, improved treatment and better health care system. Underlying disease and clinical complications influenced the outcome of SE. Age and negative history of epilepsy were not significant predictors of mortality. SE was resolved with first- or second-line therapy in nine of ten patients. For patients with SE, IV diazepam is safe and effective for hospital seizure cessation.

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Praćenje učinkovitosti liječenja i procjena smrtnosti bolesnika s epileptičnim statusom u Općoj županijskoj bolnici Požega

SAŽETAK – *Cilj:* Odrediti uspješnost liječenja i smrtnost kod bolesnika s epileptičnim statusom. *Metode:* Retrospektivna studija obuhvatila je 109 epileptičnih statusa registriranih kod 102 bolesnika u dobi od 18 i više godina koji su liječeni u Općoj županijskoj bolnici Požega od 1. siječnja 2006. do 31. prosinca 2015. godine. Stanje bolesnika procijenjeno je tridesetog dana od početka epileptičnog statusa. *Rezultati:* Od ukupno 102 bolesnika, 52 (51,0 %) su od ranije bolovala od epilepsije. Početna terapija je bio intravenski diazepam kod 109 epileptičnih statusa. Od 109 epileptičnih statusa, u 97 (89 %) slučajeva status je prestao na prvu ili drugu liniju terapije (diazepam, fenobarbital, levetiracetam). Kod 12 (11,0 %) epileptičnih statusa od kojih je osam (7,3 %) bio refraktorni epileptični status, a četiri (3,7 %) superrefraktorni epileptični status, primijenjena je treća linija terapije (midazolam, propofol). Unutar 30 dana od pojave epileptičnog statusa umrlo je devet (8,8 %) bolesnika. Svi bolesnici su umrli tijekom bolničkog liječenja. Uzrok smrti je bila osnovna bolest kod pet (55,6 %), a kliničke komplikacije kod četiri (44,4 %) bolesnika. Dob i negativna osobna anamneza epilepsije nisu bili prediktori smrtnosti (p=0,321, p=0,191). *Zaključak:* Smrtnost uzrokovana epileptičnim statusom bila je niža nego u većini ranijih istraživanja i nije bila povezana s dobi i negativnom osobnom anamnezom epilepsije. Epileptični status je prestao nakon primjene prve ili druge linije terapije kod devet od 10 bolesnika.

Ključne riječi: epileptični status, terapija, smrtnost