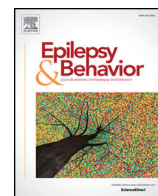




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Incidence and mortality of super-refractory status epilepticus in adults

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ABSTRACT

Objectives: Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that continues or recurs 24 h or more after the onset of anesthetic therapy. We defined the incidence and outcome of SRSE in adults in Finland.

Methods: We analyzed retrospectively the Finnish Intensive Care Consortium database in order to identify adult patients with SRSE treated in ICUs in Finland during a three-year period (2010–2012). The database consists of admissions to all 20 Finnish hospitals treating refractory SE (RSE) with general anesthesia in the intensive care unit (ICU). We included consecutive adult (16 years or older) patients with RSE and identified those who had SRSE. Patients with postanoxic etiologies were excluded.

Results: All five university hospitals and 10/15 of the central hospitals participated. The adult referral population of the study hospitals is 3.9 million, representing 91% of the total adult population of Finland. We identified 395 patients with ICU-treated RSE, 87 (22%) of whom were classified as having SRSE. This corresponds to an annual incidence of SRSE of 0.7/100,000 (95% confidence interval [CI]: 0.6–0.9). The one-year mortality rates were 36% (95% CI: 26–46%) for patients with SRSE and 22% (95% CI: 17–27%) for patients with RSE. Mortality was highest (63%) in patients with SRSE aged over 75 years.

Conclusions: Approximately 20% of patients with RSE treated in Finnish ICUs progressed to having SRSE. The incidence of SRSE, 0.7/100,000, is about 5–10% of the incidence of SE. The mortality of patients with SRSE, 36%, was comparable to earlier studies and twofold higher than the mortality of patients with RSE.

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1. Introduction

Status epilepticus (SE) is an important neurological emergency associated with significant mortality and morbidity. Status epilepticus is considered refractory (RSE) if the first- and second-line treatments with antiepileptic drugs fail and the patient is treated with general anesthesia in the intensive care unit (ICU). Status epilepticus is defined as super-refractory (SRSE) if it continues 24 h or more after the onset of anesthesia, including those cases in which the SE recurs on the reduction or withdrawal of anesthesia [1]. Approximately 12–43% of all those

presenting to the hospital with SE progress to having RSE and 10–15% to SRSE [1,2]. In most studies assessing SE, persistence or recurrence of seizures beyond 24 h of anesthetic treatment is not documented. The incidence of SRSE is not known [3]. The prognosis of SRSE is rather poor, and long-term mortality rates between 30 and 50% have been reported [4]. A recent hospital-based series of SRSE reported a one-year mortality of 58% [5].

Most previous SRSE studies are hospital-based case series. There are no population-based studies of SRSE [4]. Based on previous data, the three main prognostic factors of SE are the duration of SE, the patient's age, and the underlying cause [1,6]. According to a review about the outcome of patients with RSE, including those with SRSE, roughly one-third of patients die, one-third survive with mild or severe neurological deficits, and one-third recover to their baseline health [4]. Elderly patients

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seem to have a worse prognosis. In addition, elderly patients are more sensitive to the harmful side effects of antiepileptic drugs (AEDs) and anesthetics used [7]. The etiology spectrum of SRSE differs from the etiologies of SE. Refractory seizures are more likely to develop as a result of severe brain injury due to trauma, infection, immunological disease, or stroke or as new-onset refractory epilepsy. The seizure types vary from convulsive to nonconvulsive [3]. The aim of the treatment is to prevent damage to the cerebral cortex by controlling the epileptic activity while treating the cause of SRSE at the same time [1,3].

This study was conducted to assess the incidence and mortality of SRSE in the adult population in Finland. We wanted also to determine how well the Finnish current care guidelines [8], recommendations on diagnostic EEG, and continuous EEG monitoring in RSE are being followed.

2. Material and methods

We analyzed retrospectively the Finnish Intensive Care Consortium database in order to identify patients with RSE and SRSE treated in ICUs in Finland during a three-year period (2010–2012). Finland is divided into 20 hospital districts that have 15 central hospitals and 5 university hospitals that provide all the secondary and tertiary care, ICUs, and neurological services for their referral population. The Finnish Intensive Care Consortium is a body coordinating a national benchmarking program in intensive care. The Consortium database collects data from every ICU admission from all general adult ICUs in Finnish hospitals. The information on clinical characteristics, severity of illness, and outcome is validated in each ICU by local physicians [9]. We searched the database by using the ICD-10 codes for epilepsy, SE, and convulsions (G40.X, G41.X, R56.8) as well as the Acute Physiology and Chronic Health Evaluation (APACHE) II [10] diagnostic group “seizure” to identify all patients treated in an ICU for seizure disorders and included the patients that had been treated in the ICU for at least 48 h (minimum duration of treatment for patients treated with general anesthesia in ICUs). Intensive care unit physicians in each participating hospital reevaluated the patient charts to identify patients with RSE and SRSE according to the criteria. We included consecutive adult (16 years or older) patients with RSE that had seizures that failed to improve with the first- and second-line treatments with AEDs and were treated with general anesthesia in the ICU, and among this population with RSE, we identified the patients meeting the criteria for SRSE (SE continuing or recurring 24 h after the onset of the first general anesthesia). Patients with postanoxic etiologies were excluded. The statistical analyses were made with SPSS 21.0. We conducted a retrospective observational study based on a national ICU registry. The Finnish Intensive Care Consortium board granted us access to its database. These registry data are anonymous. Local hospital registry permissions were obtained.

3. Results

3.1. Study population and incidence

All five university hospitals and 10 out of the 15 central hospitals participated in this study (Fig. 1). The total adult referral population of these hospitals is 3.9 million inhabitants, representing 91% of the total adult population of Finland. During the study period, altogether 56,427 patients were treated in the study ICUs. We identified 395 patients with RSE, and 87 (22%) of them were classified as having SRSE. This corresponds to an annual incidence of SRSE of 0.7/100,000 (95% CI: 0.6–0.9). The median age of patients with SRSE was 57 years (range: 17–84 years). There were 44 males (51%) and 43 females (49%).

3.2. Diagnosis and treatment

Sixty-three (72%) patients had a diagnostic EEG performed before the first intravenous anesthetic treatment was started in the ICU,

whereas in 28% of the patients, the diagnosis was based on clinical judgment alone. Seventy-four (85%) patients had continuous EEG monitoring during the treatment. Eighty-four (96%) patients had EEG and clinical evaluation combined when weaning from the anesthesia. Results for treatment characteristics are shown in Table 1.

3.3. Mortality and long-term outcome

In the group with SRSE, the one-year mortality was 36% (95% CI: 26–46%). When discharged from the hospital, 55% of the patients with SRSE went to primary care, 17% to specialist level care, and 17% home. Detailed outcome data are shown in Table 2.

4. Discussion

This study reveals the relatively low incidence and high mortality of SRSE in a population-based setting. Diagnostic EEG and continuous EEG monitoring were widely used in this group of patients.

4.1. Incidence and mortality

To our knowledge, this is the first population-based study describing the incidence and long-term mortality of SRSE. The incidence of SRSE was 0.7/100,000. The annual incidence of SE was estimated earlier at about 10–20/100,000 [11]. A rough approximation has shown that 10–15% of all SE becomes super-refractory [1–3]. In a recent hospital-based study from Switzerland by Marchi et al., 50/467 (11%) of patients with SE needed general anesthesia, but the duration of the therapy was not indicated [12]. We may estimate that 1–3 patients per 100,000 annually need ICU treatment and anesthesia because of their RSE, but not all of them have seizures that progress into SRSE. Approximately one in every five of our patients with RSE had seizures that became super-refractory. We do not have the exact incidence of SE from our area from the same time point, but we can estimate that 5–10% of all SE becomes SRSE.

The hospital mortality (10%) of patients with SRSE in our study is low compared to other studies that have reported hospital mortalities of up to 42% [4,5,13,14]. However, the hospital mortality of patients with SRSE was markedly higher than that of patients with RSE. Likewise, mortality at one year was much higher in the patients with SRSE than in the patients with RSE (36% vs. 22%). Compared to earlier studies, the long-term mortality of SRSE in our study was comparable or lower [4,5,13,14]. The exact definitions of RSE and SRSE seem to vary between different studies, making the comparisons difficult. Also in some of the older studies, cases of postanoxic etiologies were included, resulting in higher RSE mortality. In our study, after being treated in the hospital, over 50% of the patients with SRSE were discharged to primary care and only 17% to home. This implies that the short-term neurological outcome was poor.

4.2. Diagnostics and treatment

In Finland, the national current care guidelines for SE were updated in 2009 [8]. According to the protocol, patients receive prehospital treatment with buccal midazolam or rectal diazepam; first-line benzodiazepines such as intravenous diazepam or lorazepam; and second-line medications with chosen AEDs such as fosphenytoin, valproic acid, or levetiracetam. The recommended third-line treatment is suppressive general anesthesia, monitored by continuous EEG. Neurologists and ICU physicians collaborate in the treatment of RSE. In this study, eighty-five percent of the patients had continuous EEG monitoring for evaluation of the depth of coma and burst suppression during anesthesia. Compared to a recent article on this subject in the UK, where only 33% of the trusts had continuous EEG monitoring available [15], patients with SRSE in Finland had greater access to EEG. Ninety-six percent of the patients with SRSE received two or more intravenous anesthetics

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