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Preliminary results of the global audit of treatment of refractory status epilepticus

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ABSTRACT

The treatment of refractory and super refractory status epilepticus is a "terra incognita" from the point of view of evidence-based medicine. As randomized or controlled studies that are sufficiently powered are not feasible in relation to the many therapies and treatment approaches available, we carried out an online multinational audit (registry) in which neurologists or intensivists caring for patients with status epilepticus may prospectively enter patients who required general anesthesia to control the status epilepticus (SE). To date, 488 cases from 44 different countries have been collected. Most of the patients had no history of epilepsy and had a cryptogenic etiology. First-line treatment was delayed and not in line with current guidelines. The most widely used anesthetic of first choice was midazolam (59%), followed by propofol and barbiturates. Ketamine was used in most severe cases. Other therapies were administered in 35% of the cases, mainly steroids and immunotherapy. Seizure control was achieved in 74% of the patients. Twenty-two percent of patients died during treatment, and four percent had treatment actively withdrawn because of an anticipated poor outcome. The neurological outcome was good in 36% and poor in 39.3% of cases, while 25% died during hospitalization. Factors that positively influenced outcome were younger age, history of epilepsy, and low number of different anesthetics tried.

This article is part of a Special Issue entitled "Status Epilepticus".

1. Introduction

Status epilepticus affects 5–41/100,000 people annually and has a mortality rate up to 38% [1–4] and over 60% occurring after prolonged seizures duration [1]. Between 31–43% of cases will be refractory to first-line and second-line treatments [5,6], and this subset, termed refractory status epilepticus, has a mortality rate of 30% [7,8]. Common causes of status epilepticus include low antiseizure drug levels (many cases due to drug withdrawal), stroke, and remote central nervous system insults [9], while the etiologies of RSE differ somewhat with encephalitis, and metabolic derangements accounting for a higher percentage of cases in addition to low antiseizure drug levels [7,8]. The management of early status epilepticus is well studied and relies on benzodiazepines [10–12]. Despite a lack of good data from randomized controlled trials for the treatment of established status epilepticus; i.e., after first-line treatments have failed, there is a general consensus to rapidly administer an intravenous antiseizure drug. Preferred agents for this phase include fosphenytoin, valproic acid, phenytoin, phenobarbital, and levetiracetam. A trial comparing fosphenytoin, valproic acid, and levetiracetam for benzodiazepine-refractory SE is planned but is not yet open for recruitment [13]. If seizures continue despite first-line and second-line agents, the patient is said to be in refractory status epilepticus. At this stage, treatment varies according to the type of status epilepticus (i.e., convulsive versus nonconvulsive) and the comorbidities of the individual patient. In most cases and in most published protocols, convulsive RSE is then treated with a continuously infused anesthetic agent, typically, midazolam, propofol, or a barbiturate (thiopental,

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phenobarbital, or pentobarbital). Further, nonanesthetic antiseizure drugs are often used in patients with nonconvulsive SE and in patients who have severe comorbidities which portend a higher risk in the setting of intubation and anesthetic infusion.

Super refractory status epilepticus is defined as SE that continues or recurs despite 24 h of a continuous anesthetic infusion. At this stage, other adjunctive or alternative therapies have also been reported with variable success including ketamine, inhalational anesthetics (isoflurane and desflurane), hypothermia, magnesium, pyridoxine, immunotherapy, ketogenic diet, emergency neurosurgery, electrical stimulation therapies such as deep brain stimulation, and electroconvulsive therapy [14,15].

The evidence-based reporting outcome of therapies in refractory and super refractory status epilepticus consists entirely of single case reports and small retrospective series [7,8,14–16] and at least one multicenter retrospective study designed to examine the safety and efficacy of ketamine [17]. Two randomized controlled trials have been attempted, and both had to be stopped early because of low enrolment [18,19]. A survey of neurologists performed in 2003 [20] and a prospective study examining treatment adherence to guidelines [21] have contributed additional information about treatment practices in the established, refractory, and super refractory stages. Aside from these, there is little published information about the epidemiology and current treatment practices around the world, and none of the widely recommended drugs or procedures have been subjected to an adequate systematic review, despite their adoption worldwide.

There are many reasons for this poverty of high quality data on treatment in the refractory and super refractory stages of status epilepticus. The entity is rare. At one busy urban hospital, 83 episodes of SE were recorded over a 4-year period, of which 26 became refractory [5], and in a second single urban center reporting experience over a 9-year timespan, there were 83 episodes of SE, of which 36 were refractory [6]. Examined on a larger scale, if SE is accepted as affecting 12.5/100,000 persons in a Western population [4], at most, 4.1–5.3/100,000 will experience RSE. Thus, multicenter studies are needed. Recruitment into a study is also difficult because the time window for enrolment is narrow. In some centers, electroencephalography is not available at nights or on weekends. The patient population is also very heterogeneous in terms of etiology and clinical form. Etiologies and outcomes appear to vary by age, although outcomes also vary by etiology. Thus, comparing any treatment requires controlling for these and other important variables which necessitates a larger study population. Multiple therapies are often used in parallel which challenges the interpretation of therapeutic effect. Improvements may be noted days after a therapy has been initiated, further complicating an assessment of treatment effect. It is also doubtful whether double blinding can be maintained in studies of anesthetic drugs as they have unique well-known adverse effects and require different precautions. Finally, there are ethical challenges to randomized interventions in an intensive care setting.

The lack of information to guide treatment in this important entity requires urgent remediation, and because of the difficulties in performing rigorous controlled trials, we carried out a multinational, prospective audit of patients with refractory and super refractory status epilepticus in an intensive care setting. The purpose was to document the demographics, range of treatments used, and patient outcomes in patients with refractory and super refractory status epilepticus around the world [22]. As an audit, with information which is not randomized, it is not possible to draw conclusions about efficacy of treatments of refractory status epilepticus, and we did not attempt this. Nevertheless, as randomized data are so limited on the treatments available, the descriptive results of this registry should assist in the formulation of clinical guidelines and point to areas of future research.

2. Methods

An anonymized online registry was created in which physicians caring for patients with status epilepticus prospectively entered data on patients with refractory or super refractory SE in an intensive care setting. For inclusion, a suitable patient was defined as one who was treated with at least one general anesthetic agent in the intensive care setting.

Intensivists and neurologists were invited from around the world to participate in the audit by engaging a steering committee comprised of neurologists and intensivists from the United Kingdom, United States, Italy, Austria, Finland, France, Israel, Argentina, Kenya, Australia, Iraq, Denmark, Sweden, Serbia, Russia, Taiwan, India, and Moldova. The steering committee was asked to recruit physicians all over the world to participate from their individual regions.

Because it was an audit of physician practice with no protected health information collected and no intervention, most centers did not require ethics approval or patient consent for participation. Individual physicians consulted their institutional review boards prior to participation to determine whether review was required, and approval was formally obtained in those institutions where review was required.

Data were collected by means of an online survey, using an interview mode. Questions were all answerable with drop-down menus, and the whole questionnaire could be completed within a few minutes. We considered this the most efficient method for an international, interative survey. As codes are assigned to the responses automatically, an online questionnaire does not suffer errors from manual coding or nonreadable responses. The online survey was based on simple HTML forms for maximum compatibility. Therefore, limitations of technical equipment (i.e., early version computers and browsers) did not exclude respondents from completing the questionnaires. To implement the online survey, we

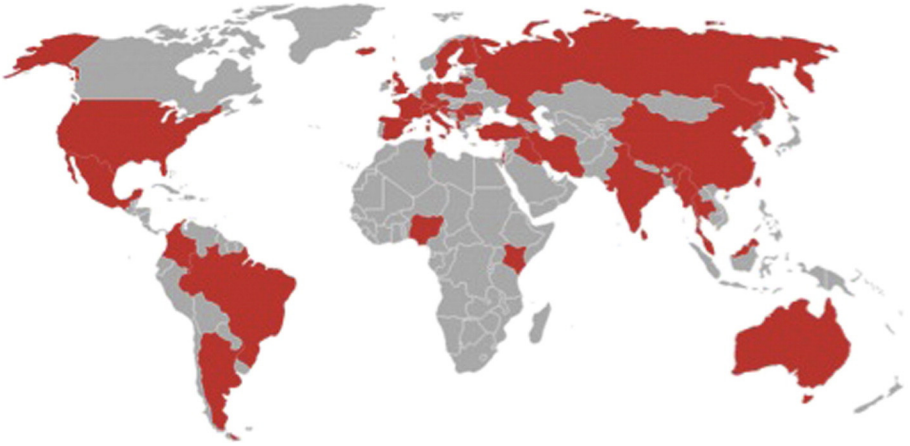

Fig. 1. Map of the countries where the cases have been reported.

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