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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 Twenty-two percent of patients died during treatment, and four percent had treatment actively withdrawn because of an anticipated poor outcome.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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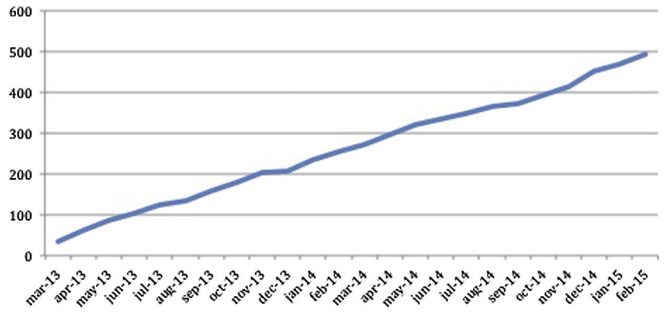

Fig. 2. Recruitment rate over the study period.

chose the platform SoSci Survey® that provided the necessary features to automate the majority of processes including survey registration and data collection. A website was created to allow participants to register to the audit (https://www.status-epilepticus.net). By submitting the registration form, the physician's email address was enlisted, and a unique key for further reference to the physician was assigned. Once a month, each email address registered to the audit received an email that asked to report new cases of status epilepticus. This "active surveillance" method was utilized to help ensure that participating physicians reported all their cases. The email included a personalized hyperlink leading the participant to a blank questionnaire form. As soon as the participant followed the personalized hyperlink and completed the first questionnaire, a new data case was initialized, and follow-up emails for subsequent questionnaires were automatically scheduled. These emails contained case-specific hyperlinks, leading to the second questionnaire (sent every two weeks). As soon as the respondent indicated the end of intensive care unit therapy, the outcome questionnaires were automatically scheduled for 3 and 6 months. Using a case-specific hyperlink allowed the software to auto-assign the data from the different questionnaires to one specific case without the requirement of identifying the patient in each questionnaire. For reasons of data security, SSL-encryption was used whenever doctors reported data via the Internet. All entered information was de-identified including the physician name and institution. To this end, participants were instructed to assign a specific code to each case and not to use patient names. This way, our questionnaires could clearly refer to different patients while ensuring that they remained completely anonymous.

Recorded information included basic demographic information, prior history of epilepsy, seizure type, etiology, duration of status epilepticus, antiseizure drug selection, anesthetic selection and duration of therapy, use of nonpharmacologic therapies, duration of ICU stay, and outcome on discontinuation of anesthesia and at 6 months as measured by modified Rankin Scale.

There were three possible final outcomes of the SE cases: recovery from SE, with seizures improved or stopped and anesthetic discontinued (irrespectively from the neurological status at the end of anesthesia); withdrawal of therapy by physicians because of poor outcome; and death of the patient during the treatment.

Continuous variables are presented as mean ± standard deviation (SD), and categorical variables are presented as whole number and percentages. When comparing continuous variables, Student's *t*-test and Mann–Whitney test were used. The analysis of categorical variables was performed using the Pearson chi-square or Fisher exact test. Statistical analyses were conducted using statistical software (IBM SPSS Statistics, version 20).

Table 1
Clinical characteristics of the 488 patients.
When data are missing, percentages are calculated based on the known cases.

Age	36.8 years (mean) SD 25.9	0–92 years (range)
Gender	M: 263 (54%) F: 225 (46%)	
Prior history of epilepsy[a]	Yes: 181 (38%) No: 296 (62%)	
Type of status epilepticus	Convulsive (including tonic–clonic SE)	273 (56%)
	Nonconvulsive	93 (19%)
	Convulsive evolving to nonconvulsive	102 (21%)
	Other[b]	16 (3%)
Etiologies (can be multiple per patient)	N	% (out of 478)
Unknown (cryptogenic)	95	20%
Vascular (including stroke)	64	13%
Acute encephalitis	61	13%
Anoxic (including cardiac arrest)	55	11%
Antiepileptic drug reduction/withdrawal	40	8%
Other infection	36	7%
Cerebral tumor	24	5%
Metabolic	23	5%
Alcohol	19	4%
Trauma	18	4%
Immunological: other	18	4%
Acute meningitis	13	3%
Genetic/chromosomal	7	2%
Mitochondrial disease	7	2%
Immunological: NMDA receptor antibodies	5	1%
Toxins	4	1%
Immunological: lupus (seropositive)	3	1%
Immunological: VGKA antibodies	2	0.4%
Other	52	11%
Total number of causes reported	547	
Total number of patients with reported etiology	478	100%
Number of different causes per patient	1 cause: 415	87%
	2 causes: 57	12%
	3 causes: 6	1%

[a] Data missing.
[b] Myoclonic status epilepticus, epilepsia partialis continua.

Table 2
Duration of status epilepticus before any treatment.

	N (%)
1 h or less	171 (37.6)
1–6 h	137 (30.1)
6–12 h	30 (6.6)
12–24 h	49 (10.8)
1–7 days	49 (10.8)
>7 days	17 (3.7)
Total	453 (100)

3. Results

Between the 1st of March 2013 and the 1st of March 2015, 145 different physicians completed 553 "new case" questionnaires in the online platform. A map of the 44 countries of origin of the reported cases is shown in Fig. 1.

Ten cases were erased because they were duplicated. Fifty-five cases were excluded because they did not satisfy the inclusion criteria for the audit (patient was not receiving at least one anesthetic agent in an ICU setting). A total of 488 reported cases were considered for this preliminary analysis, while a more comprehensive analysis will be performed once 1000 cases have been collected. The recruitment rate is shown in Fig. 2.

Table 3
Duration of status epilepticus before the first anesthetic was administered.

	No.	%
<1 h	73	15.6
<1 day	234	50.2
>1 day	158	33.9
Total	466	100.0

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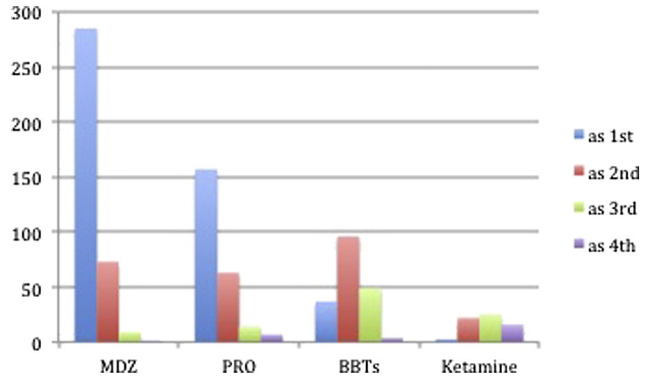

Fig. 3. Choices of anesthetic drugs. MDZ, midazolam; PRO, prof=pofol; BBTs, thiopental or pentobarbital.

The clinical characteristics of patients are summarized in Table 1. Most of the patients had no history of epilepsy and a cryptogenic etiology for the status epilepticus. In 63 patients, multiple etiologies were reported (2 etiologies for 57 patients; 3 etiologies for 6 patients).

The timing of the treatment of cases of status epilepticus is shown in Tables 2 and 3. Only 38% of the cases received first-line treatment in 1 h or less, and in 32% of the cases, treatment was delayed for more than 6 h from the beginning of the episode. There was a significant difference ($p < 0.001$) in the timing of the treatment in different types of SE: while 49% (125/254) of the cases of convulsive SE received a treatment in less than 1 h, only 24% (19/61) of the cases of nonconvulsive SE did.

Most of the patients received the first anesthetic in less than 1 day, while only 16% of the total number of cases received anesthesia in less than 1 h.

3.1. Treatment

Surprisingly, only 33% of cases received benzodiazepines as first-line treatment. Phenytoin was used as first choice in 30% of the cases, followed by levetiracetam (18%), valproate (8%), and phenobarbital (5%).

The number of different anesthetics used in sequence was just one in only 214 cases (44%), while for the rest of the cases, at least two different anesthetic agents were used in sequence to control the status epilepticus: two anesthetics in 161 cases (33%), three in 81 cases (17%), four in 29 cases (6%), and five in 2 cases.

The most widely used anesthetic as first choice was midazolam, given in 285 cases (59%). Propofol was the first choice in 157 cases (32%), and barbiturates (thiopentone or pentobarbital, considered together from this point) only in 37 cases (8%). Conversely, as shown in Fig. 3, barbiturates become the most widely used anesthetics when more than one different anesthesia trial is needed. Similarly, ketamine was used as first choice in 3 patients only but became relevant in the latest stage of treatment.

Other anesthetics used in the reported cases include lidocaine, sufentanil, and remifentanil.

Duration of the first single anesthetic agent was 24 h or less for 141 cases (35%), from 1 to 7 days for 225 cases (55%), from 8 to 14 days for 21 cases (5%), and more than 14 days for 20 cases (5%, 407 total cases with data reported). Similar percentage was reported for the subsequent anesthetic drugs added, so in most of the cases, the duration of use of the single anesthetic agent ranged from 1 to 7 days.

All the other therapies used in those cases are reported in Table 4. One or more other therapies were used at least in 173 cases out of the total 488 cases (35%). The most frequently reported therapy was steroids (39%), followed by intravenous immunoglobulin (20%), ketogenic diet (13%), hypothermia (8%), and plasma exchange (8%). A handful of cases have been treated with neurosurgery, vagal nerve stimulation, electroconvulsive therapy, and transcranial magnetic stimulation.

Table 4
Other reported therapies.

	As first	As second	As third	As fourth	Timing not specified	Total	% out of 347
Hypothermia	22	3	2	0	2	29	8.4
Neurosurgery	6	1	0	0	0	7	2.0
Steroids	95	22	0	0	19	136	39.2
IVIg	19	29	5	0	17	70	20.2
Plasma exchange	2	14	3	0	6	25	7.2
Ketogenic diet	16	5	10	3	11	45	13.0
Vagal nerve stimulation (VNS)	2	0	0	1	0	3	0.9
Other[a]	11	8	6	3	0	28	8.1
Electroconvulsive therapy (ECT)					1	1	0.3
Transcranial magnetic stimulation (TMS)					1	1	0.3
Allopregnanolone					2	2	0.6
Total	173	82	26	7	59	347	100.0

[a] Includes the following: magnesium, acetazolamide, osmotic therapy, verapamil, biotin, and pyridoxine.

Table 5
Neurological outcome of patients at the end of anesthesia.

mRS	N (%)
0 — No symptoms.	37 (9.4)
1 — No significant disability. Able to carry out all usual activities despite some symptoms.	43 (10.9)
2 — Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities.	25 (6.3)
3 — Moderate disability. Requires some help but able to walk unassisted.	37 (9.4)
4 — Moderately severe disability. Unable to attend to own bodily needs without assistance and unable to walk unassisted.	60 (15.2)
5 — Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	95 (24.1%)
6 — Dead.	97 (24.6)
Total	394 (100.0)

3.2. The outcome of the status epilepticus

We were able to classify 413 patients into these three categories, while for 75 patients, the final outcome of the status epilepticus was considered missing because of the lack of sufficient data: 304 patients recovered from status epilepticus (74%), 93 patients died (22%), and 16 patients had the therapy actively withdrawn (4%). It is important to note that the status epilepticus outcome is referring just to the seizure control, while the neurological status of the patients is considered separately and shown in Table 5.

According to the modified Rankin Scale [23], 36% of the patients had a good outcome at the end of anesthesia, defined as mRS classes ranging from 0 (no significant disability) to 3 (moderate disability), 39.3% had a poor outcome, defined as mRS classes of 4 (moderate severe disability)

Table 6
Six months outcomes.

mRS	N (%)
0 — No symptoms.	14 (13.0)
1 — No significant disability. Able to carry out all usual activities despite some symptoms.	20 (18.5)
2 — Slight disability. Able to look after own affairs without assistance but unable to carry out all previous activities.	12 (11.1)
3 — Moderate disability. Requires some help but able to walk unassisted.	23 (21.3)
4 — Moderately severe disability. Unable to attend to own bodily needs without assistance and unable to walk unassisted.	13 (12.0)
5 — Severe disability. Requires constant nursing care and attention, bedridden, incontinent.	18 (16.7)
6 — Dead.	8 (7.4)
Total	108 (100.0)

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Table 7
Duration of ICU stay.

Total ICU stay	N	% out of 353
<7 days	108	31
7–14 days	99	28
15–29 days	79	22
30–59 days	51	14
60–210 days	16	5
	353	100

or 5 (severe disability), and 24.6% of the patients died. A long term outcome at six months of follow-up was available for 108 of the survived patients (Table 6): the neurological outcome is quite good, with an obvious selection bias.

The total ICU stay duration was reported for 353 cases: the mean duration of stay was 18 days (SD of 22.7). As shown in Table 7, only 31% of the patients had an ICU stay duration of less than 7 days, and for 19% of the cases, the duration of ICU stay was for more than 1 month.

3.3. Factors affecting outcome

We divided the final outcome of status epilepticus into two categories: "recovered" and "not recovered" (the latter category being the patients who died during the treatment and patients who had the therapy withdrawn because of poor outcome). The results are shown in Tables 8 and 9. No differences were found in the outcome regarding gender, type of SE, or time of any treatment. Prior history of epilepsy and younger age were positively associated with recovery from status epilepticus.

Surprisingly, patients who received the first anesthetic agent later (more than 1 day after the beginning of the status epilepticus) seemed to have a better outcome than patients who were treated earlier. This relationship, however, may not be causal but simply reflect a bias in that less severe or acute cases are treated later. The numbers currently are too low to draw comprehensive conclusions regarding the influence of etiology on outcome, but it is shown in Table 9 that patients with postanoxic status epilepticus have a worse outcome than all the other causes, while those whose status epilepticus is due to antiepileptic drug withdrawal have a better outcome.

The total number of different anesthetic agents used was lower in patients who recovered than in patients who did not recover (mean: 1.72 (SD: 0.83) and mean: 2.2 (SD: 1.01), respectively; $p < 0.001$). The anesthetic used as first choice did not appear to influence outcome, although again, the nonrandomized nature of the data precludes definitive analysis. The choice of the last anesthetic used was correlated with differences in outcome. Patients receiving midazolam as the last anesthetic agent showed a higher percentage of seizure control than all the others (Fig. 4). Nevertheless, patients who recovered and who were receiving midazolam as the last anesthetic were also more frequently those cases that had the status epilepticus controlled just by a single anesthetic agent, so these might have been less severe cases. On the contrary, in cases where barbiturates or ketamine were used as the last anesthetic agent, there was usually a need for multiple trials of anesthesia (Fig. 5).

No correlation was found between neurological outcome and the last anesthetic agent used except for the use of ketamine ($p < 0.01$) which was associated with a worse neurological status at the end of the treatment (Fig. 6). Again, this correlation is likely not to be causal but simply to reflect the usual practice of reserving ketamine as the "last resort" therapy for very severe cases.

Table 8
Factors affecting outcome of the status epilepticus: clinical characteristics.

	Recovered	Died/therapy withdrawn	p
Prior history of epilepsy	Yes: 130 (86%) No: 169 (67%)	Yes: 22 (14%) No: 84 (33%)	0.003
Age	Mean: 34.5 years (SD: 25.1)	Mean: 45.7 years (SD: 28.0)	<0.001
Time to any treatment			n.s.
Type of SE			n.s.
Gender			n.s.
Time to first anesthetic	<1 day: 182 (70%) >1 day: 111 (81%)	<1 day: 76 (30%) >1 day: 26 (19%)	0.02

Table 9
Causes of status epilepticus and outcome.

Cause	Recovered	Died/therapy withdrawn
Antiepileptic drug reduction/withdrawal	28 (90%)	3 (10%)
Genetic/chromosomal	6 (86%)	1 (14%)
Cerebral tumor	18 (82%)	4 (18%)
Unknown (cryptogenic)	63 (80%)	16 (20%)
Trauma	12 (80%)	3 (20%)
Mitochondrial disease	3 (75%)	1 (25%)
Vascular (including stroke)	42 (74%)	15 (26%)
Acute meningitis	8 (73%)	3 (27%)
Other infection	23 (72%)	9 (28%)
Alcohol	12 (67%)	6 (33%)
Other toxins	2 (67%)	1 (33%)
Immunological, all	17 (65%)	9 (35%)
Acute encephalitis	32 (65%)	17 (35%)
Metabolic	13 (62%)	8 (38%)
Anoxic (including cardiac arrest)	22 (49%)	23 (51%)

4. Discussion

In recent years, there has been a marked increase in the number of medical registries and in publications using registry data. The reasons for this interest rely on some general limitations of randomized trials, their duration to completion, expense, patient populations, and 'nonreal world' nature. Registries can provide useful information but should be performed according to high methodological standards to ensure completeness and minimize bias. The validity of a registry depends on the range of participation and the quality of its data.

A primary concern is whether the data are accurate and complete. Over the first year of data collection, we modified the format of the questionnaires several times, as we were not satisfied with the data accuracy, so the percentage of "missing information" for every reported case sensibly dropped over time. Nevertheless, for 18% (75/488) of the cases reported, the more important information about the outcome of the SE was still missing. Increasing complexity reduces the number of cases reported, and so we settled for a compromise collecting, for instance, no data about dose and instructing data to be entered without needing patients' notes.

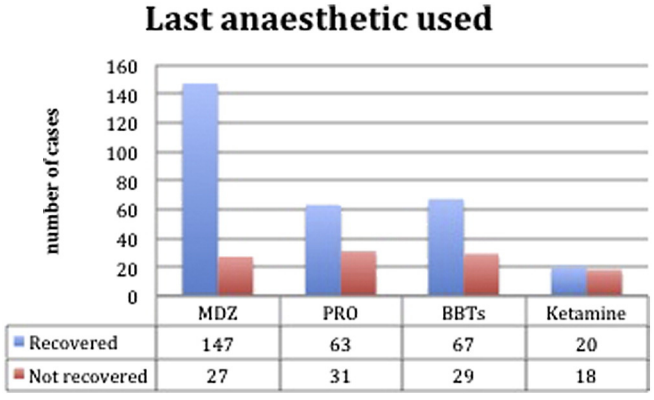

Fig. 4. Outcome of SE depending on the last anesthetic agent used. MDZ, midazolam; PRO, prof=pofol; BBTs, thiopental or pentobarbital.

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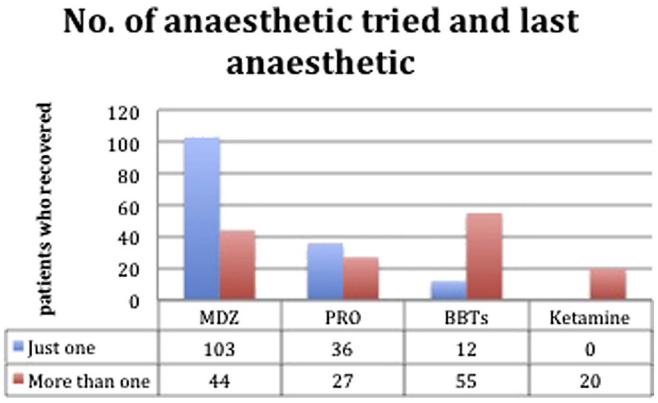

Fig. 5. Number of anesthetics tried and the last anesthetic used in patients who recovered from status epilepticus. MDZ, midazolam; PRO, prof=pofol; BBTs, thiopental or pentobarbital.

Registries are typically more generalizable to real-world practice because of their observational design. However, the selection bias (as allocation of patients to the treatment is not random) and the lack of monitoring for data entry weaken the "generalizability" of findings obtained from registry data [24]. For these reasons, registries can provide useful information, but care must be taken when they go beyond their original purpose and attempt to answer effectiveness questions [25].

The 488 cases, collected from 44 different countries, provide a better understanding of the range of treatments and the percentage of usage in status epilepticus around the world, together with important information about demographics and etiologies of refractory and super refractory status epilepticus. The survey revealed some notable results.

First, regarding etiology, the greatest number of cases in this survey was recorded as cryptogenic. There has been an increasing interest in the last decades for new-onset refractory SE of unknown origin, and several different acronyms have been applied, although we feel that these are relatively meaningless as they probably are heterogeneous and certainly do not comprise a 'syndrome' (for instance NORSE (new-onset refractory status epilepticus [26]) or DESC (devastating epileptic encephalopathy in school-aged children [27]) and FIRES in children (febrile infection-related epilepsy syndrome [28])). The advancement in the knowledge of immunological causes of SE and seizures will help to better define these cases, and our results confirm that more efforts are needed in this direction, as the condition seems to be common.

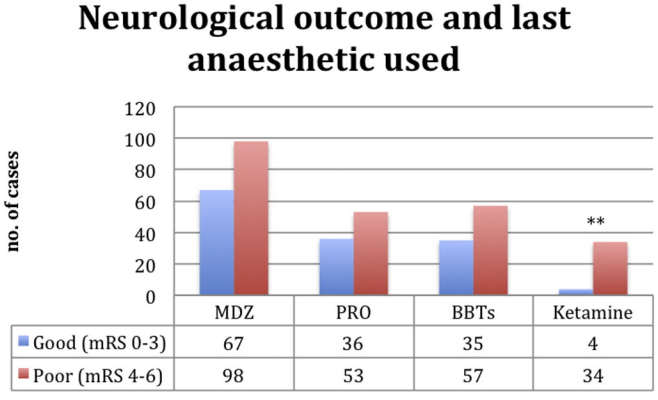

Fig. 6. Neurological outcome according to the modified Rankin Scale depending on which anesthetic agent was used as last. Good outcome is defined as mRS classes ranging from 0 (no significant disability) to 3 (moderate disability). Poor outcome is defined as mRS classes ranging from 4 (moderate severe disability) to 6 (dead). MDZ, midazolam; PRO, prof=pofol; BBTs, thiopental or pentobarbital.

The population selected by our inclusion criteria mainly included very severe cases of refractory status epilepticus: 66% of the cases required more than one anesthetic agent in sequence, and the total ICU stay duration was very long.

The first treatment for the cases of SE was often delayed, even more in the cases of nonconvulsive status epilepticus. As previously shown, a quick intervention to stop the seizure is important to prevent the maladaptive cascade leading to receptor trafficking, reduction in GABAergic activity, and activation of the glutaminergic system [29]. Moreover, it is well known that early treatment of status epilepticus reduces the number of patients with persistent seizures [11], and the RAMPART study suggested that patients treated with IM midazolam were more likely to have stopped seizing at emergency department arrival than those treated with intravenous lorazepam because of rapidity of administration [12]. Our data suggest that in a population of very refractory status epilepticus, the delay of treatment certainly plays a role.

The choice of the first-line treatment is quite surprising. Only 33% (156/474) of cases received benzodiazepines, and only 12% (55/474) lorazepam, while the most common benzodiazepine was diazepam (71/474, 15%). The most frequently used first-line treatment was phenytoin (145/474). It is possible that respondents were referring to in-hospital treatment only (we have no way of testing this) or that the failure to use first-line treatments in a timely fashion is more likely to result in refractory cases, and quality of treatment can affect the mortality in status epilepticus [30]. On this basis, we cannot exclude that the frequent departure from common guidelines in the first stage of the treatment of these cases has some effect in causing drug resistance. Furthermore, in an in-hospital setting, there are also many reasons for erratic therapy (patients in severe general condition, nonadherence to protocol for personal preference of the on call doctor). Less surprising was the choice of anesthetics. Midazolam was the most widely used anesthetic as first choice because of its safety and efficacy in most of the cases. Among 304 patients who recovered from refractory status epilepticus, a single anesthetic agent controlled SE for 151 (50%) of them, and midazolam 103 (34%). Barbiturates were rarely used as first choice (8%), but they became relevant in the later stages of treatment. As this is a registry, it cannot draw conclusions about their relative effectiveness.

Of special interest is the wide use of different therapies, steroids and immunotherapy mainly. As most of the patients had a cryptogenic SE, probably an immune-mediated mechanism had to be postulated in several of these cases.

In a high percentage of cases (74%) in this survey, the seizures were controlled. This percentage include postanoxic SE, but it referred just to seizure cessation and include then patients with very severe neurological condition at the end of the status epilepticus, as only 36% of the cases had a good neurological outcome at the termination of anesthesia. Among factors affecting outcome, the delayed treatment with general anesthesia was associated with a better outcome. It has been recently suggested [31] that there is an association between treatment with anesthesia for SE and a worse outcome. In our opinion, this conclusion confuses correlation with causality. Our data and Sutter's are more likely to simply underline how an early treatment with general anesthesia is usually reserved for the most gravely ill patients, who are likely to have a worse outcome [32]. As previously suggested [33], the most important factor affecting outcome was etiology, with antiepileptic drug withdrawal showing the best outcome while anoxia the worse, and younger age and positive history of epilepsy were positively associated with recovery from SE.

We are currently at about half of the planned recruitment for this study, and stratification for etiology (with exclusion of postanoxic case) has to be made. However, the registry shows a high accuracy of the data and very interesting, sometimes surprising, information. As a registry, it would not be possible to reach any definitive conclusion about efficacy of treatments of refractory status epilepticus from these data. Nevertheless, as the treatment of refractory and super refractory status epilepticus is a "terra incognita" from the point of view of

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evidence-based medicine, and randomized or controlled studies that are sufficiently powered are basically not feasible, we hope that the final results of this registry will progress the knowledge of this difficult field, help the formulation of clinical guidelines, and point to areas of future research.

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Conflict of interest statement

None of the authors have any conflict of interest to disclose.

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