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The anesthetic drug treatment of refractory and super-refractory status epilepticus around the world: Results from a global audit

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ABSTRACT

Multinational and multicenter registries collecting cases of refractory and super-refractory status epilepticus help to understand what the current practice in the treatment of such conditions is and can improve the rational therapy. We prospectively collected 776 cases of refractory status epilepticus requiring continuous intravenous anesthetic drugs in an intensive care unit setting, through online questionnaires compiled by the treating physicians in 50 countries. Initiation of an intravenous anaesthetic drug was relatively delayed in middle-income compared with high-income countries. There were marked regional differences in the choice of initial intravenous anaesthetic drug. Generally, midazolam was the most commonly used initial anesthetic drug (56%), followed by propofol (35%), in Europe, propofol was preferred over midazolam. In addition to anesthesia, 26% of cases received some form of immunosuppression (with corticosteroids and/or intravenous immunoglobulin). In this observational study, outcome was not affected by choice or sequence of anesthetic drugs, and nor was the use of barbiturate anesthetics associated with poorer outcome. The proportion of patients responding to cycles of different anaesthetic drugs was high even after failure of the earlier anesthetics, but the neurological outcome progressively worsened the longer anaesthetic drugs were needed and the longer the status epilepticus continued. However, even in the 158 patients who required three or more different anaesthetic trials, 49% had seizure control on tapering the third anesthetic, and 20% had a good neurological outcome anywhere. For these reasons we believe that it is important to persist with therapy in patients who are intractable initially, especially as etiology, not the number of duration of anesthesia, is the primary determinant of prognosis.

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1. Introduction

The treatment of early stage of tonic–clonic status epilepticus (SE) has been well studied and extensively discussed in recent years. There are various out-of-hospital and in-hospital randomized controlled trials in adults and in children. All support the use of benzodiazepines to limit the duration of ongoing seizures and to prevent progression to refractory SE and as a result all contemporary protocols take a staged approach to treatment using benzodiazepines in the first stage (the stage of early status) [1–3]. In benzodiazepine-resistant SE, IV antiepileptic drugs are then generally given (this is the stage of established SE). A gold standard comparative trial (the Established Status Epilepticus Treatment Trial) is underway to determine if there are major differences between available IV antiepileptic therapies.

However, in about 15% of patients, the seizures continue despite the use of benzodiazepines and IV antiepileptic drugs [4]. Such patients are deemed to be in refractory SE, and since the 1970s, the standard treatment has been the use of continuous intravenous anesthetic agents with mechanical ventilation and Intensive Care (ITU) support [5]. Super-refractory status epilepticus (SRSE) is the final stage and is

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defined as patients whose seizures continue or recur after 24 h despite anesthetic treatment. A variety of different anesthetic agents can be used, but, despite their widespread usage for decades, there is no robust data to guide choice of agent, dose, or duration of treatment. It is universal practice to cycle through anesthesia, and if seizures are not controlled on withdrawal of one anesthetic agent to either return to this agent, to substitute a second agent, or in select cases to consider further therapy to be futile. However, there is no evidence at all to support the order in which anesthetic agents should be tried. Nor it is known to what extent these treatments differ in different regions of the world. Furthermore, the effect of different therapies on outcome is also largely unstudied, except for recent work suggesting, on the basis of retrospective and uncontrolled data that barbiturates may contribute to a worse outcome [6]. The evidence-base supporting the use of any specific drug or order of drugs is extremely sparse, consisting entirely of single case reports or small series [7].

Comparative trials in refractory and SRSE are difficult to undertake because of their relative infrequency, emergency nature, heterogeneous etiologies, and treatment variability. In view of this, interest has grown in multinational (or multicenter) registries, in order to understand what current practice is and how it varies in different settings. Only with this knowledge, can rational therapy in this stage of treatment be improved [8,9]. This paper summarizes the results of a very large scale global prospective descriptive audit of physician practice, with the aim of describing the differences in the therapies used in the stages of refractory and SRSE around the world and analyse their impact on outcome.

2. Methods

The audit procedures have been described previously [10]. In summary, this was an anonymized online registry, collecting information from treating physicians in an ITU setting about cases of refractory and super refractory SE, through a web platform. The treating physicians were invited regularly (monthly through an active surveillance method) to report new cases via online questionnaires. We collected adult and pediatric cases inclusive of all etiologies.

Refractory SE in this study is operationally defined as SE treated with continuous IV anesthetic drugs in an ITU setting. Super-refractory SE is defined as a condition in which seizures continue despite maximal treatment with IV anesthetic drugs for more than 24 h in an intensive care unit. If seizures are not controlled on withdrawal of one anesthetic agent, it is universal practice either to reintroduce the same anesthetic or to substitute a different agent, or to decide that therapy is futile. So in this study, we have ascertained the effect of the anesthetic drug treatment on weaning (tapering) success and have grouped the response into one of three categories: seizures controlled on withdrawal of anesthetic drug (after any number of cycles with the same anesthetic drug) and no further anesthetic drug needed; seizures recurred and anesthetic drug changed; and seizures recurred and the patient died or care was withdrawn. Neurological outcome data were collected via the modified Rankin scale (mRS) at discharge. A score of 0–3 was considered a good outcome. All countries were divided by income level according to the new country classification of World Bank (2017–2018, http://www.worldbank.org/). The study was linked to the biennial London-Innsbruck colloquia on SE and acute seizures, and the participants came from the delegates and their networks.

All data were analysed using statistical software (IBM SPSS Statistics, version 20).

3. Results

Data were collected from the 1st of March 2013 to the 1st of March 2017. A total of 776 cases were included from 50 countries of origin. Patients were from Europe (56%), Asia (23%), the Americas (18%), Australia and New Zealand (2%), and Africa (1%). According to the new country classification of World Bank, 526 cases were collected from high-income countries (72%), 118 cases from upper-middle income (16%), and 90 from lower-middle (12%), making a total of 208 (28%) of cases from middle-income countries.

Mean age was 39.8 years (±25.9 Standard Deviation (SD)), with 423 male (55%) and 353 (45%) female. Most frequent etiologies were: cryptogenic (26.1%), infectious (19.6%), and vascular (14.5%). Details of the etiologies and clinical characteristics of patients have been previously reported [11]. As an audit, ethical approvals were not required in most centers. In other centers, ethical approvals were obtained by the reporting clinicians.

3.1. Treatment

The timing of onset to treatment with anesthetic drugs is shown in Table 1 stratified by region. Drugs used in different regions are shown in Table 2. In 36% of patients, the duration of anesthetic infusion was 24 h or less, while more frequently (53%), duration of anesthetic infusion was between 1 and 7 days. This was significantly more pronounced for the subsequent anesthetic trials, indicating a tendency to prolong anesthesia cycles in resistant cases ($p < 0.01$).

Among other therapies reported, the most widely used were steroids (24%), intravenous immunoglobulin (11%), and plasma exchange (5%). A total of 202 patients (26%) received some form of immunotherapy. Ketogenic diet was tried in 57 patients (7.3%) and hypothermia in 42 patients (5.4%). A few patients were treated with neurosurgery, electrical stimulation therapies, magnesium, verapamil, pyridoxine, or allopregnanolone.

There were some notable differences in the treatment among countries of different income levels. Patients from middle-income countries were significantly younger than those from high-income countries (mean age 24.7 ± 20.3 versus 46.4 ± 25.5 years). Initiation of an intravenous anesthetic drug was relatively delayed in middle-income countries, with 42% of patients treated more than 1 day after the start of SE, compared with 28% in high-income countries (Table 1). The choice of the anesthetic agents also significantly differed by location. Propofol was much more commonly chosen as initial therapy in high-income countries and midazolam in middle-income countries (Table 2). Propofol was the initial choice in 273 patients (35.4%). In high-income countries in Europe, propofol was however preferred over midazolam (51% versus 40%) but this was not in the case in the USA (where midazolam was used as initial choice in 65% and propofol in 26%). The use of barbiturates at any time (predominantly in later stages) was approximately similar in middle-income and high-income countries (39% versus 31%). There was no difference in the use of ketamine between groups. Also, the number of different anesthetic agents tried was similar in both groups, perhaps reflecting a similarity in the severity of the cases among countries.

Among all the other therapies in SRSE, steroids and immunotherapies were used more frequently in middle-income than in high-income countries (41% versus 20%).

3.2. The response to treatment and outcomes

General information about etiology and outcomes has been previously reported [11]. Here, we report the impact on seizures of specific anesthetic drugs in the 686 patients, and the order in which further drugs were tried and the responses to sequential administrations (Fig.

Table 1
Duration of SE prior to the use of anesthetic agents.

Time to first CIVAD	No (and % of known cases)	Middle-income countries	High-income countries
Less than 1 h	113 (15.3%)	19 (9.4%)	90 (18.2%)
Less than 1 day	378 (51.4%)	96 (47.7%)	264 (53.4%)
More than 1 day	243 (33.1%)	86 (42.7%)	140 (28.3%)

Table 2
Anesthetic drugs used in different regions.

	Total[a] n (%)	Middle-income countries n (%)	High-income countries n (%)
First anesthetic			
Midazolam	434 (56%)	164 (80%)	242 (46%)
Propofol	273 (35%)	19 (9%)	245 (47%)
Barbiturates	57 (7%)	21 (10%)	32 (6%)
Ketamine	6 (1%)	2 (1%)	4 (1%)
Others	1 (0%)	0 (0%)	1 (0%)
Second anesthetic			
Midazolam	128 (29%)	13 (12%)	109 (36%)
Propofol	121 (28%)	29 (27%)	83 (27%)
Barbiturates	136 (31%)	49 (46%)	79 (26%)
Ketamine	32 (7%)	12 (11%)	19 (6%)
Others	19 (4%)	3 (3%)	16 (5%)
Third anesthetic			
Midazolam	21 (13%)	9 (18%)	12 (11%)
Propofol	16 (10%)	10 (20%)	5 (5%)
Barbiturates	71 (43%)	14 (28%)	49 (46%)
Ketamine	44 (26%)	14 (28%)	30 (28%)
Others	15 (9%)	3 (6%)	10 (9%)
Fourth anesthetic			
Midazolam	1 (2%)	1 (6%)	0
Propofol	7 (16%)	2 (12%)	2 (9%)
Barbiturates	7 (16%)	1 (6%)	6 (27%)
Ketamine	21 (49%)	10 (62%)	9 (41%)
Others	7 (16%)	2 (12%)	5 (23%)

Others: include inhalational anesthetics and others not specified.
[a] Contains cases with unknown origin.

1). Of the 686 patients, 394 were cycled onto a second anesthetic upon withdrawal of the first, and 162 onto a third anesthetic upon withdrawal of the 2nd. Thirty nine patients required a 4th anesthetic, and 2 patients required a fifth anesthetic. In some patients, it is a possibility that one anesthetic agent was added to another and both used together, but we were not able to confirm how often this occurred from our database. We also report the outcome related to the different anesthetic drug treatments in the 649 patients in whom outcome data were available. Among these patients, 274 (42%) were treated with a single intravenous anesthetic drug, 217 (33%) received 2 different agents, 119 (18%) received 3, 36 (5%) received 4, and 3 patients (0.4%) received 5 different intravenous anesthetic drugs (Fig. 2). The choice of initial drug related to outcome is shown in Table 3, and the outcome where only one drug was used in Table 4. The relationship between the order of the first and second anesthetic agents, in the 195 patients requiring a sequence of two of the most commonly used 4 anesthetic drugs, and outcome is shown in Table 5.

The percentage of patients with a good neurological outcome at discharge decreased consistently with each subsequent intravenous anesthetic drug trial, but nevertheless there was significant portion of patients in whom outcome was good even after the third or fourth different trials of anesthesia (Fig. 2). In this descriptive database, the anesthetic used as first choice did not appear to influence outcome, although the nonrandomized nature of the data and the limitations inherit in a registry precludes meaningful analysis.

The choice of third-line drugs varied significantly between high- and middle-income countries, with barbiturates more commonly used in middle-income countries (Table 2). The use of ketamine was associated

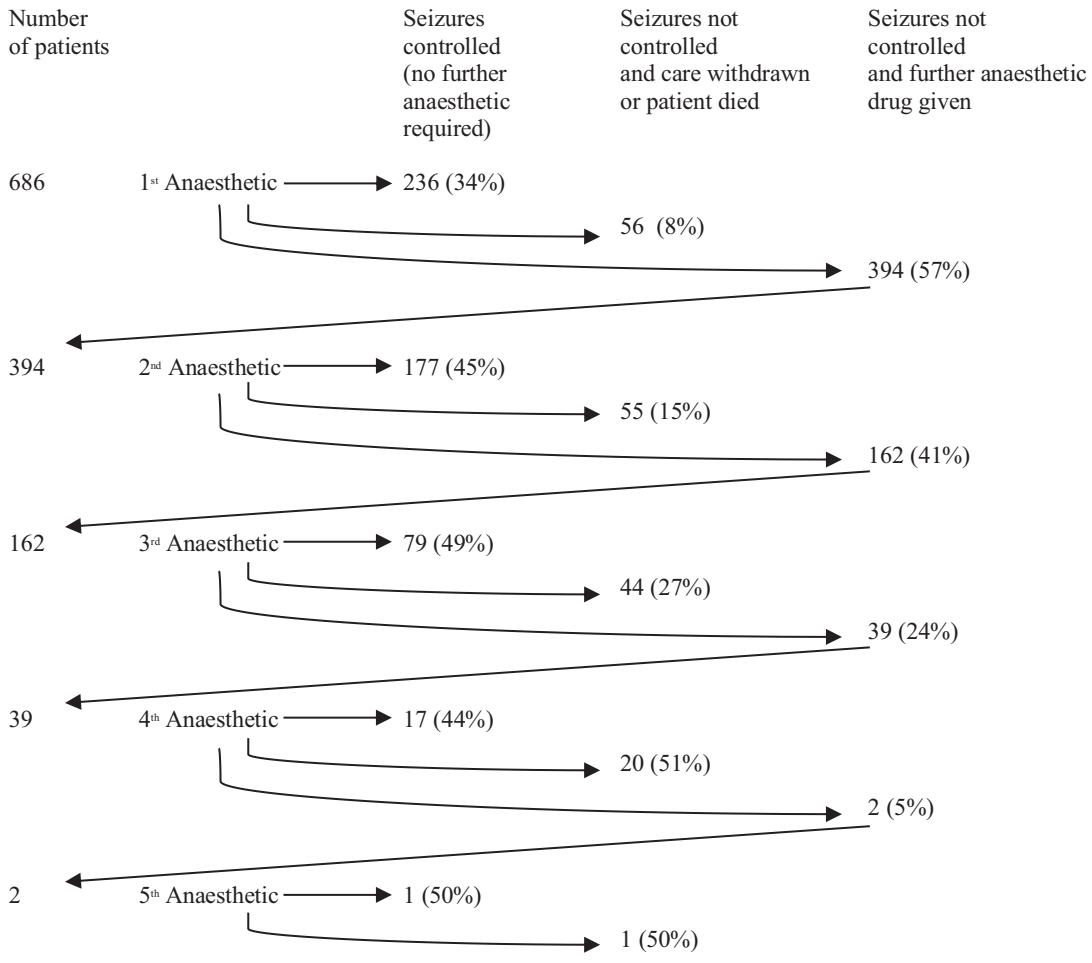

Fig. 1. Flow chart showing response to treatment after anesthetic treatments (1st to 5th anesthetics).

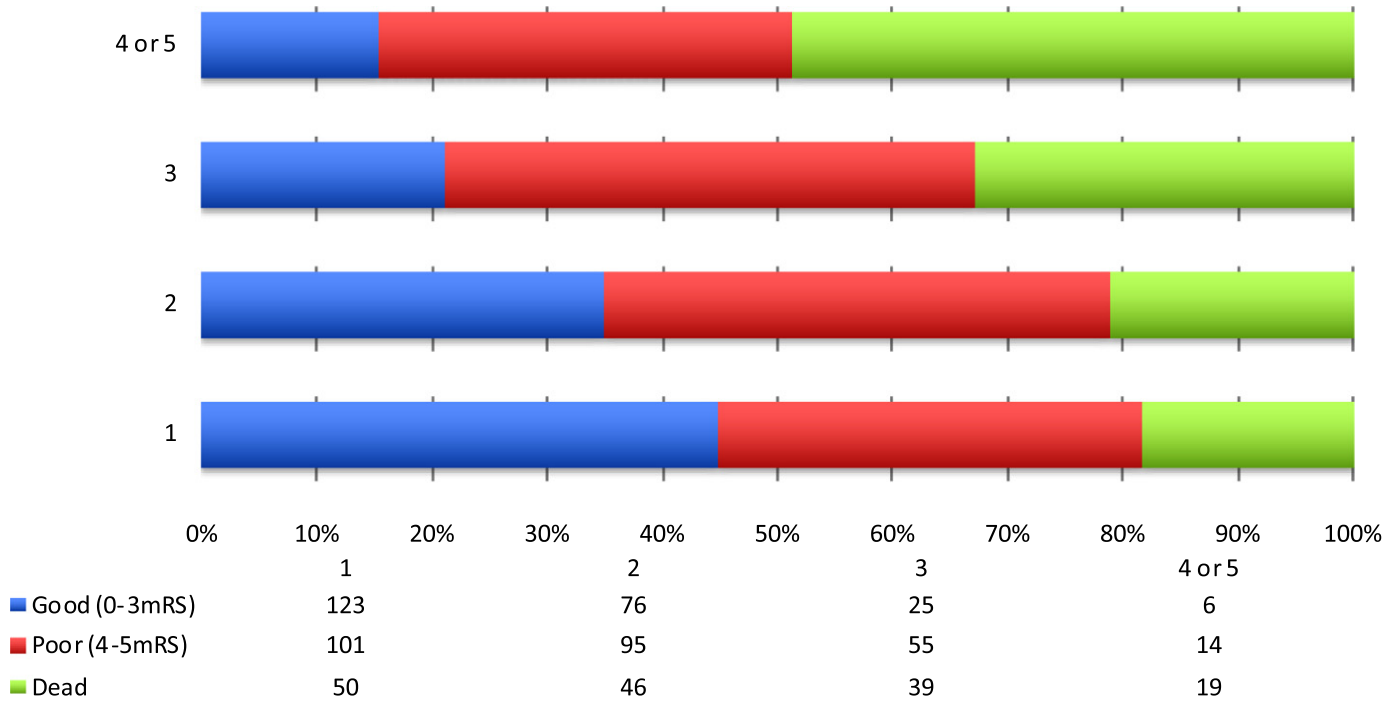

Fig. 2. No. of anesthetics required and neurological outcome (mRS) at discharge.

with a worse neurological status at the end of the treatment and may well reflect the tendency to use ketamine as a "last resort" therapy for very severe cases.

The outcome of individual drugs as initial therapy, or when only one drug was needed, differed with initial midazolam or propofol associated with better outcomes than barbiturates (Tables 3 and 4). However, when the outcomes of these drugs used as first and second line are combined, the proportion of good outcomes for each drug is similar (43% of 84 cases with barbiturate; 42% of 226 cases with midazolam; 39% of 131 cases with propofol) (Table 5).

The percentage of patients where the status was controlled did not differ between middle-income and high-income countries (76.5% versus 74.4%, respectively). Moreover, neurological outcome of patients did not differ between these two groups.

4. Discussion

This study used an audit methodology to recruit large numbers of patients in what is a relatively uncommon condition. In most comprehensive study to date, the incidence of refractory SE was found to be only 3.5/1000,000/year and SRSE 0.7/100,00/year [12]. In previous papers [8,10], we have described the active prospective surveillance methodology, the automated nature of the questionnaires, the efforts made to simplify data collection and to encourage active participation from all reporting physicians. These underpinned the ability of the audit to achieve large numbers and to provide, in our view, as unselected a study cohort as possible. Of course, as the collection was nonrandomized and uncontrolled, and despite the fact that case ascertainment was prospective and participating physicians (all of whom had expressed an interest in SE) were asked to include all cases under their care, there is a possibility of bias in case ascertainment and for that reason no comparative statistics are included in our analysis. The fact that most reporting physicians were the physicians in the ITU where case ascertainment was likely to be optimised also reduces the risk of selection bias. Similar considerations are a conundrum for all big data collections, but it has been shown in studies of large datasets that in general the larger the collection the more representative it becomes [13]. We consider therefore that the results are reasonably representative of those providing the standard of care in various countries and regions, and for these reasons that this audit can provide useful and unique data.

In this paper, we have studied the use of continuous intravenous anesthetic therapy and related this to region and outcome. The timing and initial anesthetic given are shown in Tables 1 and 2 by region. The type and number of drugs and their order are shown in Tables 3–5 related to initial success in controlling seizures (Fig. 1) and also to the neurological outcome of the patients at discharge from hospital (Fig. 2). The type and number of drugs and their order are shown in Tables 3–5 related to initial success in controlling seizures (Fig. 1) and also to the neurological outcome of the patients at discharge from hospital (Fig. 2). One limitation of the outcome data is that mRS level of the patients prior to the episode of SE was not recorded, and so the number of patients with poor outcomes is likely to be an overestimate as some individuals might have been at this level prior to the status episode.

There were marked regional differences in the choice of initial intravenous anesthetic drug. Midazolam was the most commonly used

Table 3
Relationship between outcomes to the initial anesthetic drug used.

Initial anesthetic agent	N	Good n (%)	Poor n (%)	Mortality n (%)
Midazolam	368	146 (40%)	136 (37%)	86 (23%)
Propofol	222	70 (31%)	96 (43%)	56 (25%)
Barbiturate	48	12 (25%)	25 (52%)	11 (23%)
Ketamine	5	1 (20%)	3 (60%)	1 (20%)

Table 4
Relationship between outcome in patients treated with only one anesthetic agent and choice of anesthetic drug used.

	N	Good n (%)	Poor n (%)	Mortality n (%)
Midazolam	167	77 (46%)	62 (37%)	28 (17%)
Propofol	87	41 (47%)	26 (30%)	20 (23%)
Barbiturate	16	5 (31%)	10 (62%)	1 (6%)
Ketamine	1	0	0	1 (100%)

Table 5
Relationship between outcome in patients treated with two anesthetic agents and choice of anesthetic drug used.

Order of anesthetics (First and second)	N	Good n (%)	Poor n (%)	Mortality n (%)
Midazolam, propofol	49	16 (33%)	21 (43%)	12 (24%)
Midazolam, barbiturate	50	29 (58%)	11 (22%)	10 (20%)
Midazolam, ketamine	8	4 (50%)	1 (12%)	3 (37%)
Propofol, midazolam	47	13 (28%)	28 (59%)	6 (13%)
Propofol, barbiturate	18	2 (11%)	9 (50%)	7 (39%)
Propofol, ketamine	3	1 (33%)	2 (67%)	0
Barbiturate, midazolam	12	4 (33%)	6 (50%)	2 (17%)
Barbiturate, propofol	3	2 (67%)	1 (33%)	0
Barbiturate, ketamine	1	0	1 (100%)	0
Ketamine, midazolam	0	0	0	0
Ketamine, propofol	3	1	2	0
Ketamine, barbiturate	1	0	1	0

initial anesthetic drug and propofol followed however in high-income countries in Europe, propofol was preferred over midazolam. This differed from the United States of America, where midazolam was more commonly used than propofol as a first line anesthetic drug. There is no comparative study or even anecdotal information supporting the use of one agent over the other, but results probably reflect the familiarity with propofol by anesthetists in Europe who were often in charge of the intensive care units, and the lesser importance of cost as a factor in middle-income countries. A barbiturate (thiopentone or pentobarbital) was the initial choice in only 57 (7.4%) patients. Conversely, barbiturates and ketamine were more frequently chosen when the first intravenous anesthetic drug had failed, and ketamine in particular seems to have been used as an anesthetic of last resort. In the past, barbiturates were more commonly given, but the trend away from barbiturate anesthesia may reflect the suggestion that they carry extra risk (notably cardiorespiratory depression, immunosuppression, ileus, etc.) despite their undeniably strong antiepileptic effect [14]. This shift in practice is not evidence-based, and whether it has improved or even worsened, outcome is unclear.

Ketamine is the only anesthetic that does not suppress cardiorespiratory function or cause hypotension and furthermore uniquely is an N-methyl-D-aspartate (NMDA)-receptor antagonist as opposed to a GABAergic drug. For these reasons, it may theoretically have significant advantages as an early anesthetic in refractory SE, but this audit shows it is rarely used as such. In the future, prospective studies of early ketamine would, in our view, be of great interest and importance.

The proportion of patients responding to repeated cycles of anesthetic treatment did not change greatly (Fig. 1) but the neurological outcome progressively worsened the longer anesthetic drugs were needed and the longer the SE continued (Fig. 2). This, in our view, is more likely to reflect the inherent severity of the SE (the easy cases responding quicker than the more difficult cases) rather than being attributable to differences in treatment. It is worth noting that even in the 158 patients who required three or more different anesthetic trials, 49% had seizure control on tapering the third anesthetic, and 20% had a good neurological outcome, emphasising the point that it is important to persist with therapy in those who are intractable to treatment initially.

There was wide variability in the duration of anesthesia, which again is unsurprising, and this reflects the lack of evidence about the optimal duration of an anesthetic cycle, how fast to wean, or how aggressively to treat patterns on the ictal–interictal continuum that arise during weaning. We observed that the longer the SE continued, the greater was the length of cycle.

Because treatment was not randomised, the drugs cannot be directly compared. The apparently worse response to barbiturate and ketamine, compared to midazolam or propofol used as an initial drug (Table 3) is more likely to reflect a selection bias – with the latter drugs used in easier cases and but barbiturate or ketamine more commonly used in severe cases or those with more dangerous etiologies. It is noticeable that the proportion of good outcomes for each drug, when the first or second usage is combined, is similar (43% of 84 cases using barbiturate; 42% of 226 cases using midazolam; 39% of 131 cases using propofol), and this is despite the fact that barbiturate was probably used in the more difficult cases (Tables 4 and 5). Equally, we found no evidence that barbiturate was associated with higher mortality when used as a first and second drug (i.e., 21% of 84 cases using barbiturate; 16% of 224 cases using midazolam; 24% using propofol) despite the fact that barbiturate will be used in patients with etiologies associated with higher mortalities. Randomization will be needed to provide gold-standard data about the relative value of different drugs. Nevertheless, contrary to other reports, the limited evidence from this audit provides no signal at all that barbiturates worsen outcome.

In SRSE, other therapies were also employed on an entirely empirical basis. Twenty-six percent received some form of immunosuppression (with corticosteroids and/or intravenous immunoglobulin). Hypothermia and the use of a ketogenic diet were also used on an occasional basis, and other therapies only rarely. Hypothermia and allopregnanolone have both been the subject of negative randomised controlled trials [15,16] but, in both instances, the negative result could have been due to methodological considerations rather than ineffectiveness of the therapy. None of the other therapies has been subjected to any robust study, an unsatisfactory state of affairs especially as each seems widely employed.

The more anesthetic agents that were required, and hence the longer the duration of the SE was, the worse was the outcome. Nevertheless, in a not insignificant portion of patients, a good outcome sometimes occurred even after a long duration of status and trials of multiple anesthetic drugs (Fig. 2). Thus, although prognosis does decline the longer the status remains refractory, it is important to stress that the ultimate outcome need not necessarily be bad [17,18]. As emphasized repeatedly in all studies of outcome, the underlying etiology is a major determining factor and often more important than control of seizures [19]. It should not be forgotten also that the role of the anesthetic agents in SE is essentially to control seizures to allow vital functions and to provide life-saving protection against the deleterious effects of status [20]. The anesthetics do not alleviate or cure the underlying etiologies. They are essentially buying time while the underlying cause of the status runs its course or is reversed. Thus, it should be recognized that when the underlying cause is the primary determinant of prognosis, the choice or effectiveness of anesthesia may well have only a small influence on outcome.

Ethical publication statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Declaration of Competing Interest

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

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