

EFNS guideline on the management of status epilepticus in adults

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The objective of the current article was to review the literature and discuss the degree of evidence for various treatment strategies for status epilepticus (SE) in adults. We searched MEDLINE and EMBASE for relevant literature from 1966 to January 2005 and in the current updated version all pertinent publications from January 2005 to January 2009. Furthermore, the Cochrane Central Register of Controlled Trials (CENTRAL) was sought. Recommendations are based on this literature and on our judgement of the relevance of the references to the subject. Recommendations were reached by informative consensus approach. Where there was a lack of evidence but consensus was clear, we have stated our opinion as good practice points. The preferred treatment pathway for generalised convulsive status epilepticus (GCSE) is intravenous (i.v.) administration of 4–8 mg lorazepam or 10 mg diazepam directly followed by 18 mg/kg phenytoin. If seizures continue more than 10 min after first injection, another 4 mg lorazepam or 10 mg diazepam is recommended. Refractory GCSE is treated by anaesthetic doses of barbiturates, midazolam or propofol; the anaesthetics are titrated against an electroencephalogram burst suppression pattern for at least 24 h. The initial therapy of non-convulsive SE depends on type and cause. Complex partial SE is initially treated in the same manner as GCSE. However, if it turns out to be refractory, further non-anaesthetising i.v. substances such as levetiracetam, phenobarbital or valproic acid should be given instead of anaesthetics. In subtle SE, in most patients, i.v. anaesthesia is required.

Background

Incidence, mortality and morbidity

Generalised convulsive (GCSE) and non-convulsive status epilepticus (NCSE) are important neurological conditions potentially associated with significant mortality and morbidity rates. In Europe, annual incidence rates of GCSE range from 3.6 to 6.6 per 100 000 and of NCSE from 2.6 to 7.8 per 100 000 [1–3]. A prospective study from the US demonstrated an incidence rate including all forms of SE of 41 per 100 000 [4]. This

exceptionally high incidence is probably because of the predominance of non-white individuals in the study population that are at a significantly higher risk to develop SE. Mortality and morbidity rates of SE are heavily influenced by the underlying aetiology, patients' age and clinical seizure form. Therefore, patient fatality in different studies is quite heterogeneous ranging from 3% to 33% [1–7]. In a recent large US sample including more than 11 000 patients, predictors of in-hospital mortality were old age, mechanical ventilation, cerebrovascular disease, female sex and a higher comorbidity index [7]. In particular, mortality rates of NCSE after profound brain damage are high and usually because of the injury itself [6].

There is general agreement that immediate and effective treatment is required. Prospective data indicate that first-line anticonvulsants like benzodiazepines and phenytoin fail to terminate SE in 35–45% of patients [8]. SE continuing after such failure is termed refractory status epilepticus (RSE) and represents an even more

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difficult clinical problem. Drug treatment approaches in this situation are based on prospective observational studies, retrospective series, case reports and expert opinions. The goal of this article is to summarise published treatment options for GCSE and NCSE. Post-anoxic myoclonus is not considered in this guideline because there is no agreement regarding its epileptic nature. The focus of this article is on initial and critical care management of SE in adults, and children are not considered.

Mechanisms

The basic processes generating SE may be seen as a failure of the normal mechanisms that terminate seizures. Reduced inhibition and persistent excessive excitation create interactions that produce and sustain ongoing seizure activity. During prolonged seizure activity, dynamic changes in gamma-aminobutyric acid (GABA)_A and N-methyl-D-aspartate (NMDA) receptor function are seen that have been termed 'receptor trafficking' [9]. Ongoing seizure activity results in gradual reduction of GABA_A receptors at the synaptic membrane following receptor internalisation into endocytotic vesicles and subsequent degradation [10]. This process results in erosion of endogenous GABAergic inhibition giving rise to sustained epileptic activity. Loss of post-synaptic GABA_A receptors is a relevant pathophysiological factor on the way to progressive pharmacoresistance of drugs such as benzodiazepines, barbiturates and propofol. In contrast, during ongoing epileptic activity, NMDA receptors are progressively transported to the synaptic membrane, resulting in increasing numbers of excitatory NMDA receptors per synapse [11]. This process facilitates neuronal excitability and consecutively sustained SE. On the other hand, the enhanced expression of glutamate receptors may present a useful target in the pharmacological management of advanced stages of SE. Absence SE with 3-Hz spike-wave discharges is induced by excessive inhibition [12]. This form of SE does not lead to the neuronal injury seen with excessive excitation [13].

Search strategy

One member of the Task Force Panel (HM) searched available published reports from 1966 to 2005 and for the purpose of the current updated version from 2005 to 2009 using the database MEDLINE and EMBASE (last search in January 2009). The search was limited to papers published in English. The subject term 'status epilepticus' was combined with the terms 'controlled clinical trial', 'randomised controlled trial', 'multicentre study', 'meta analysis' and 'cross over study'. Further-

more, the Cochrane Central Register of Controlled Trials (CENTRAL) was sought. Finally, the websites of the World Health Organisation (WHO), the International League against Epilepsy (ILAE) and the American Academy of Neurology (AAN) were explored to look for additional information.

Evaluation of published literature

The evidence for therapeutic interventions (Class I–IV) and the rating of recommendations (Level A–C) were classified by using the definitions previously reported [14].

Methods for reaching consensus

A proposed guideline with specific recommendations was drafted for circulation to all panel members. Each panellist studied and commented in writing on each successive guideline draft, revised to progressively accommodate the panel consensus. Where there was a lack of evidence but consensus was clear, we have stated our opinion as good practice points (GPP). In a further step, the draft of the guideline was circulated to all members of the EFNS scientific committee for their comments. These have been incorporated into the current version of the guideline.

Definitions

The time that has to evolve to define ongoing epileptic activity as 'status epilepticus' is as yet not generally agreed upon. The Commission on Classification and Terminology of the ILAE defines SE as 'a seizure [that] persists for a sufficient length of time or is repeated frequently enough that recovery between attacks does not occur' [15]. Experimental studies have shown irreversible neuronal damage after about 30 min of continuing epileptic activity [16]. Therefore, this time window has been adopted by the majority of authors [1,2,17]. On the other hand, some clinical data indicate that spontaneous cessation of generalised convulsive seizures is unlikely after 5 min [18,19] and therefore acute treatment with anticonvulsants is required. Consequently, Lowenstein *et al.* [20] have proposed an operational definition of SE that is based on a duration of 5 min. Currently, clinical studies are based on 5 min [21], 10 min [8,22] or 30 min [2,23] of ongoing epileptic activity to define SE. The diagnosis of NCSE is based on changes in behaviour and/or mental processes from baseline associated with continuous epileptiform discharges in the electroencephalogram (EEG) [24]. There is currently no generally accepted duration of electroclinical alterations incorporated in the diagnostic criteria of NCSE.

NCSE includes the subtypes of absence status, complex partial and subtle SE. Absence SE with 3-Hz spike-wave discharges is a benign type of NCSE, in most cases of which a small intravenous (i.v.) dose of lorazepam or diazepam will terminate the event. Therefore, absence SE is not further considered in this article. Complex partial status epilepticus (CPSE) represents the most frequent type and accounts for almost every second case of all forms of SE [2]. Subtle SE evolves from previously overt GCSE and is characterised by coma and ongoing electrographic seizure activity without any or with only subtle convulsive movements [8]. Therefore, subtle SE is a form of NCSE that develops from GCSE if the latter has been treated insufficiently or has not been treated at all.

An appropriate definition of refractory SE also is still missing. The failure of two [22,25] or three [26,27] anticonvulsants has been suggested in combination with a minimal duration of the condition of 1 h [22,28,29] or 2 h [25,30] or regardless of the time that has elapsed since onset [23,26].

Results

Literature and data on treatment

Initial treatment of GCSE

High level evidence for the initial pharmacological treatment of GCSE has been given in some randomised controlled trials (RCTs) that are indicated below. In 384 patients with GCSE, i.v. administration of 0.1 mg/kg lorazepam was successful in 64.9% of patients, 15 mg/kg phenobarbital in 58.2% of patients and 0.15 mg/kg diazepam directly followed by 18 mg/kg phenytoin in 55.8% of patients, the efficacy of these anticonvulsants was not significantly different [8] (Class I). The same trial has shown that in pairwise comparison, initial monotherapy with 18 mg/kg phenytoin is significantly less effective than administration of lorazepam. Another RCT has focussed on the pre-hospital treatment of GCSE performed by paramedics [21] (Class I). A total of 205 patients were administered either 2 mg of i.v. lorazepam, 5 mg of i.v. diazepam or placebo, the injection of identical doses of benzodiazepines was repeated when seizures continued for more than 4 min. Lorazepam terminated SE in 59.1% of patients and was as effective as diazepam (42.6%). Both drugs were significantly superior to the administration of placebo (21.1%). An earlier RCT on 81 episodes of all clinical forms of SE compared i.v. administration of 4 mg lorazepam versus 10 mg diazepam which were repeated when seizures continued or recurred after 10 min [31] (Class II). In episodes of GCSE with or without focal onset ($n = 39$), 13 episodes responded to

lorazepam after the first administration and three after the second whilst three episodes did not respond. With diazepam, 14 episodes responded to the first administration and two to the second whilst four episodes did not respond. In a recent randomised open study, first-line anticonvulsant treatment of GCSE with 30 mg/kg valproic acid in 35 patients has been compared to 18 mg/kg phenytoin in another 33 patients [32] (Class III). Valproic acid terminated SE in 66% of patients, whilst phenytoin was successful in 42% ($p = 0.046$). Unfortunately, this study was underpowered giving rise to cautious interpretation of the results. Also, the study was not limited to adults, but also included a significant number of children and adolescents in whom SE usually is less difficult to terminate. Another randomised open study on first-line treatment of SE compared valproic acid in 18 patients to phenytoin in nine patients using the same doses as in the latter earlier mentioned study [33] (Class III). Valproic acid (72%) was found to be as successful as phenytoin (78%). Unfortunately, this study too did not yield data of major relevance for the treatment with first-line substances, because it also was underpowered and included patients with GCSE and CPSE, each of which is known to be associated with a different prognosis.

Initial treatment of CPSE

Currently, there are no studies available focussing exclusively on the initial anticonvulsant treatment of CPSE. Some trials included patients with CPSE but did not specify the success rate of anticonvulsant drugs in this form of SE [33,34].

Initial treatment of subtle SE

The pharmacological treatment of subtle SE has been addressed in a RCT with 134 patients [8] (Class I). The i.v. administration of lorazepam (0.1 mg/kg), diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), phenobarbital (18 mg/kg) and phenytoin (18 mg/kg) terminated SE in 8–24% of patients, only. Success rates were not significantly different between the drugs or drug combinations tested. However, key criterion for study entry was the evidence of subtle SE at the time of evaluation, regardless of prior treatment. Though not further specified, it can be assumed that in some of the patients, anticonvulsants have been administered before.

Side effects of initial treatment of SE

Safety issues of the common initial anticonvulsants have been compared in patients with overt GCSE as well as in patients with subtle SE [8] (Class I). In overt GCSE, hypoventilation was observed in 10–17% of patients, hypotension in 26–34% and cardiac arrhythm-

mias in 2–7%. These side effects were more frequent in subtle SE and ranged between 3% and 59% of patients. Distribution of side effects was not significantly different in patients treated with lorazepam, diazepam followed by phenytoin, phenobarbital and phenytoin in overt and subtle SE. Out-of-hospital administration of benzodiazepines compared to placebo did not result in more complications such as arterial hypotension, cardiac arrhythmias or respiratory depression requiring intervention [21] (Class I). These side effects occurred in 10.6% of patients treated with lorazepam, 10.3% treated with diazepam and 22.5% given placebo.

Refractory GCSE and NCSE

The rationale for treating refractory SE with anaesthetising anticonvulsants is to prevent both severe acute systemic and long-term neuronal consequences. Acute systemic complications such as pulmonary oedema and – potentially fatal – cardiac arrhythmias may occur early in the course of GCSE [35] but are rarely seen in CPSE. In humans, the correlation of duration of SE with neuronal damage is not known. In contrast, in experimental animal models, prolonged electrographic seizure activity results in brain damage [36,37]. It is unclear to what extent these findings can be translated to the human situation. But it is for this reason that most authorities recommend prompt and aggressive treatment using general anaesthesia if initial therapy has not controlled SE within 1–2 h. However, there are no studies comparing anaesthetic therapy with continuing non-anaesthetising anticonvulsants. The therapeutic decision is based on the type of SE, age, comorbidity and prognostic issues. This is of special relevance in patients with CPSE because the risks of anaesthesia (e.g. arterial hypotension, gastroparesis and immunosuppression) may be greater than the risks of ongoing non-convulsive epileptic activity [38]. In view of the lack of controlled studies, the decision on further treatment is based on a few retrospective studies and expert opinions. Retrospective studies have analysed the further treatment options after failure of initial anticonvulsants [22]. It should be noted that treatment pathways were naturally influenced by multiple variables such as aetiology, age and comorbidity. In 26 episodes of RSE, after failure of first- and second-line drugs, 23 episodes were treated with a third-line drug that was non-anaesthetising in all but one case. In twelve of these episodes, seizures were controlled, but eleven patients needed further more aggressive treatment [22] (Class IV). In another study, RSE was terminated by further non-anaesthetising anticonvulsants in 18 of 35 episodes [39] (Class IV). However, data in both studies did not differentiate between GCSE and CPSE.

In view of the very few clinical studies, further available evidence has to be based on experts' opinions.

Two surveys amongst critical care neurologists and epileptologists from Europe and the United States have been performed. In the American study, there was no agreement as to how to proceed in pharmacological treatment of GCSE after failure of benzodiazepines and phenytoin or fosphenytoin: more than 80% would not directly proceed to an anaesthetic (43% administer phenobarbital and 16% valproic acid), whilst 19% would directly administer anaesthetic [40] (Class IV). However, this survey did not include the management of refractory CPSE. The European survey revealed that after failure of benzodiazepines and phenytoin, two-thirds of the participants would administer in both GCSE and CPSE another non-anaesthetising anticonvulsant, the majority preferred phenobarbital. Immediate administration of an anaesthetic was preferred by 35% in GCSE and by 16% in CPSE [41] (Class IV). Three-fourths of the experts did not administer anaesthetics in refractory CPSE at all, whilst all did at some time point in GCSE. Administration of anaesthetics was withheld in CPSE: more than 60% of the participants administer anaesthetics not earlier than 60 min after onset of status compared to only 21% of participants waiting that long in GCSE.

Further non-anaesthetising anticonvulsants

Though phenobarbital has been assessed in the initial anticonvulsant treatment [8] of SE, sufficient data on the efficacy of this substance after failure of benzodiazepines and phenytoin/fosphenytoin are missing. Doses of 20 mg/kg infused at a rate of 30–50 mg/min are used.

The role of i.v. valproic acid in the treatment of RSE is yet to be defined. Valproic acid is a non-sedating substance that has not caused hypotension or respiratory suppression and has been reported to be effective in generalised convulsive and complex partial RSE [42] (Class IV). In a randomised open study, SE refractory to diazepam administered in adequate doses was treated with valproic acid (20 mg/kg) or phenytoin (20 mg/kg) in 50 patients each [43] (Class III). Treatment success was 88% and 84%, respectively. The clinical forms of SE that were included into the study are not reported, and approximately 30% of patients were younger than 18 years. In a retrospective study that included 63 patients with previously untreated or refractory GCSE, overall efficacy rates of 63% were reported, valproic acid was even more successful in RSE [44] (Class IV). Loading doses of 25–45 mg/kg at infusion rates of up to 6 mg/kg/min have been suggested [45] (Class IV), and favourable tolerance of rapid administration ranging from 200 to 500 mg/min was reported [44] (Class IV).

Levetiracetam is a second-generation antiepileptic drug with proven oral efficacy in epilepsies with generalised and/or partial seizures. The substance is

non-sedating and has almost no interactions with other drugs. In 2006, its i.v. formulation has been introduced into the market. Retrospective data describe treatment success in at least benzodiazepine-refractory SE in 16 of 18 episodes with loading doses of i.v. levetiracetam between 250 and 1500 mg [46] (Class IV). A recent prospective observational study reported termination of 10 of 11 episodes of various clinical forms of SE with i.v. levetiracetam administered in a dose of 2500 mg in 5 min [47] (Class IV). In both studies, adverse effects of i.v. levetiracetam were negligible.

Lacosamide has been licensed in Europe and the United States in autumn 2008 as oral and i.v. formulation for the adjunctive treatment of partial epilepsies. The pharmacokinetic profile is interesting for the treatment of SE as well, however, so far there has been only one report on its efficacy in a patient with non-convulsive predominantly aphasic SE [48].

Both levetiracetam and lacosamide are not licensed for the treatment of SE.

Anaesthetising anticonvulsants

Most authorities recommend administration of anaesthetic agents to a depth of anaesthesia which produces a burst suppression pattern in the EEG [41] (Class IV) or an isoelectric EEG [49]. Studies are needed in this area, as these issues give rise to ethically highly problematic decisions.

Barbiturates, propofol and midazolam are commonly used in refractory SE [41] but it is extremely difficult to achieve burst suppressions with midazolam (Class IV). There have been no RCT comparing these treatment options. These substances have been assessed in prospective observational studies. Thiopental anaesthesia was induced in 10 patients with an initial bolus of 5 mg/kg and additional boluses of 1–2 mg/kg to achieve burst suppressions [50]. Thereafter, the infusion rate was started at 5 mg/kg/h and had to be increased to a median of 7 mg/kg/h to maintain burst suppression. In no patient, epileptic seizure activity re-occurred following tapering of thiopental. Mean arterial pressure decreased in all patients and required catecholamines in four. Nine patients were treated with antibiotics because of infection indicating that high-dose thiopental anaesthesia may be immunosuppressive. Midazolam anaesthesia was induced in 19 patients with a bolus of 0.2 mg/kg followed by continuous infusion at a starting rate of 1 µg/kg/min [51] (Class IV). Infusion rate was increased to a median of 8 µg/kg/min to control clinical seizures. Seizure activity was terminated in all but one patient, and no patient developed haemodynamically relevant arterial hypotension or other important medical side effects. Propofol anaesthesia was induced in 10 consecutive patients with a bolus of 2–3 mg/kg, and

further boluses of 1–2 mg/kg were given until a burst suppression EEG pattern was achieved [52] (Class IV). Thereafter, an infusion of 4 mg/kg/h was initiated, however, the maintenance of a continuing burst suppression pattern was difficult to achieve and required incremental doses of propofol with a median maximum infusion rate of 9.5 mg/kg/h. The anaesthetic was tapered after 12 h of satisfactory burst suppression, and epileptic seizures re-occurred in three patients. Arterial hypotension was treated with fluid resuscitation in all patients, and seven patients received norepinephrine.

A systematic review of drug therapy for RSE including barbiturates, midazolam and propofol assessed and compared data on 193 patients from 28 retrospective trials [53] (Class IV). Pentobarbital was more effective than either propofol or midazolam in preventing breakthrough seizures (12% vs. 42%). However, in most studies, barbiturates were titrated against an EEG burst suppression pattern whilst midazolam and propofol were administered to obtain EEG seizure cessation. Accordingly, side effects such as arterial hypotension were significantly more frequently seen with pentobarbital compared to midazolam and propofol (77% vs. 34%). Overall mortality was 48% but there was no association between drug selection and the risk of death. A retrospective study assessed treatment aggressiveness on prognosis revealing that outcome was independent of the specific coma-inducing agent used [54] (Class IV).

The earlier mentioned progressive loss of GABA_A receptors with ongoing seizure activity limits the efficacy of anticonvulsants with predominantly GABAergic mechanisms of action. In advanced stages of SE when NMDA receptors are increasingly expressed, specific antagonists may be good candidates to be administered. Ketamine has been described in some case reports and patient series to terminate SE after failure of GABAergic anticonvulsants [55–57] (Class IV).

Recommendations

The use of an in-house protocol for the general management and specific pharmacological treatment of SE is highly recommended (GPP) to provide the highest quality of care.

General initial management

General management approaches in generalised convulsive, complex partial, and subtle SE should include: assessment and control of the airways and of ventilation, arterial blood gas monitoring to see if there is metabolic acidosis and hypoxia requiring immediate treatment through airway management and supplemental oxygen, ECG and blood pressure monitoring.

Other measures include i.v. glucose and thiamine as required, emergency measurement of antiepileptic drug levels, electrolytes and magnesium, a full haematological screen and measures of hepatic and renal function. The cause of the status should be identified urgently and may require treatment in its own right (GPP).

Initial pharmacological treatment for GCSE and NCSE

In GCSE, the preferred treatment pathway is i.v. administration of 0.1 mg/kg lorazepam (Level A rating). Depending on the patient's general medical condition, the clinician may decide to start treatment at a lower dose of 4 mg and repeat this dose if SE is not terminated within 10 min (Level B rating). A single shot of 4 mg lorazepam has proven to be sufficient in more than 80% of patients with successfully treated SE. If i.v. lorazepam is not available (e.g. in France), 10 mg diazepam directly followed by 18 mg/kg phenytoin or equivalent fosphenytoin may be given instead (Level A rating). Phenytoin should be loaded rapidly with an infusion rate at 50 mg/min, this regimen is as safe as anticonvulsant treatment using other drugs (Level A rating). However, it should be kept in mind that length of infusion time for diazepam followed by phenytoin is about 40 min compared to the 5 min for administration of lorazepam. If possible, pre-hospital treatment is recommended, and in GCSE, i.v. administration of 2 mg lorazepam is as effective as 5 mg diazepam (Level A rating). Out-of-hospital, i.v. administration of benzodiazepines in GCSE is as safe as placebo treatment (Level A rating). So far, available studies have not convincingly demonstrated a good-enough efficacy of valproic acid to be included in the group of first-line substances for the treatment of generalised convulsive or other clinical forms of SE. CPSE should be treated initially in the same way as GCSE (GPP). Subtle SE evolving from previously overt GCSE in most patients will already have been treated with anticonvulsants. In the rare patients with previously untreated subtle SE, the initial anticonvulsant treatment should be identical to that of overt GCSE (GPP).

General management of RSE

GCSE that does not respond to initial anticonvulsant substances needs to be treated on an intensive care unit (GPP).

Pharmacological treatment for refractory generalised convulsive and subtle SE

In generalised convulsive and subtle SE, we suggest to proceed immediately to the infusion of anaesthetic

doses of midazolam, propofol or barbiturates because of the progressive risk of brain and systemic damage. Because of poor evidence, we can not recommend which of the anaesthetic substances should be the drug of choice.

Depending on the anaesthetic used in the individual in-house protocol, we recommend titration against an EEG burst suppression pattern with propofol and barbiturates. If midazolam is given, seizure suppression is recommended. This goal should be maintained for at least 24 h. Simultaneously, initiation of the chronic medication, the patient will be treated with in future should be initiated (GPP).

Barbiturates

Thiopental is started with a bolus of 3–5 mg/kg, then further boluses of 1–2 mg/kg every 2–3 min until seizures are controlled, thereafter continuous infusion at a rate of 3–7 mg/kg/h (GPP). Pentobarbital (the first metabolite of thiopental) is marketed in the United States as the alternative to thiopental and is given as a bolus dose of 5–15 mg/kg over 1 h followed by an infusion of 0.5–1 mg/kg/h, increasing if necessary to 1–3 mg/kg/h (GPP).

Midazolam

Effective initial i.v. doses of midazolam are a 0.2 mg/kg bolus, followed by continuous infusion at rates of 0.05–0.4 mg/kg/h (GPP).

Propofol

Initial i.v. bolus of 2–3 mg/kg should be administered followed by further boluses at 1–2 mg/kg until seizure control, then continuous infusion at 4–10 mg/kg/h (GPP).

In cases of elderly patients in whom intubation and artificial ventilation would not be justified, further non-anaesthetising anticonvulsants may be tried (see below) (GPP).

Pharmacological treatment for refractory complex partial SE

In complex partial SE, the time that has elapsed until termination of status is less critical compared to GCSE. Thus, general anaesthesia because of its possible severe complications should be postponed and further non-anaesthetising anticonvulsants may be tried before. Because of poor evidence and lack of any head-to-head comparison studies, we can not recommend which of the non-anaesthetising anticonvulsants should be the drug of choice (GPP).

Phenobarbital

Initial i.v. bolus of 20 mg/kg i.v. at an infusion rate of 50 mg/min, administration of additional boluses requires intensive care conditions (GPP).

Valproic acid

Intravenous bolus of 25–45 mg/kg infused at rates of up to 6 mg/kg/min (GPP).

Levetiracetam

Intravenous bolus of 1000–3000 mg administered over a period of 15 min (GPP).

If the treatment regimen includes the administration of anaesthetics, the same protocol applies as described for refractory GCSE.

Conflicts of interest

HM has declared no conflict of interest. PB has received Editorial/Advisory board fees from Cyberonics, Elsevier, Medtronic, Pfizer, Sanofi and UCB and Speaker's fees from Cyberonics, Medtronic and UCB. BE has declared no conflict of interest. KG has declared no conflict of interest. SS has received Editorial/Advisory board fees from UCB and Speaker's fees from UCB. PT has declared no conflict of interest. MH has received Speaker's fees from UCB.

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