Advances in the management of generalised convulsive status epilepticus – what have we learned?

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Abstract

Convulsive status epilepticus (SE) is the most serious manifestation of an epileptic diathesis. In the early stages (5-30 minutes), there exists Class A evidence to support the efficacy of benzodiazepines as first-line treatment. As status epilepticus progresses into the later stages, the evidence for treatment becomes less robust until we are depending upon short case series and case reports for the treatment of refractory status epilepticus. However, the past year saw the publication of three randomised controlled trials in the setting of Benzodiazepine-resistant established CSE; the ELiPSE

and ConSEPT studies, compared Levetiracetam to Phenytoin in children, and the ESETT study compared Fosphenytoin, Levetiracetam and Sodium Valproate in adults and children. In addition, the emergence of data from the SENSE study, a multi-centre multi-national prospective cohort study and the publication of a systematic review and meta-analysis of the mortality of SE over the past 30 years, has brought the treatment of SE into sharp focus. In this update we provide a detailed analysis of these studies and their impact on clinical practice. We review contentious areas of management in SE where a consensus is lacking and advance the case for more research on existing and alternative treatment strategies.

Introduction

Convulsive status epilepticus(CSE) is an medical emergency with a high mortality and morbidity [1]. Yet, it has suffered from a lack of evidence-based medicine other than in the early stages. Over the last 20 years, there have been a growing number of randomised control studies demonstrating that early interventions in prolonged acute seizures with benzodiazepines in the community can successfully stop seizure activity. Moreover, the landmark Veterans Affairs Status Epilepticus study [2] established the primacy of the benzodiazepine lorazepam, over phenytoin alone as first-line treatment of early CSE in hospital. Together, these studies have established the initial treatment of SE (buccal midazolam in the community followed by an intravenous benzodiazepine, usually lorazepam, on hospital admission). The choice of subsequent treatments has been less clear, but phenytoin and its prodrug fosphenytoin were the accepted standard of care [3].

The emergence of data regarding the potential efficacy of valproate and levetiracetam in CSE have recently challenged the status quo. Smaller studies have supported their candidacy as viable alternatives to phenytoin, but none of these has had the statistical power to determine best practice. With a lack of a clear-cut evidence, protocols for the treatment of CSE varied between hospitals and countries with little consensus. Indeed, the ease of use and lack of cardiorespiratory compromise with levetiracetam and valproate had even led to the suggestion of using these agents ahead of benzodiazepines [2]. In this review we have chosen to highlight five studies, out of more than 500 clinical reports/reviews published in 2019, that advance knowledge of the current clinical state and management of CSE.

Systemic review of mortality in CSE

In 2019, a systematic review and meta-analysis of mortality in CSE in high-income countries between 1990 and 2017 [4], placed present circumstances in sharp relief. In total 61 studies were included (five were of refractory SE), of which 30 were adult studies with a pooled mortality of 15.9% (95% Confidence Interval (CI) 12.7-19.2). The pooled mortality in 7 paediatric studies was 3.6% (95% CI 2.0-5.2). There were 6 population studies (all ages) identified, with an overall pooled estimated mortality of 13.1% (95% CI 7.2 -19.0). Importantly, however, comparing three different time periods,

employing both linear regression and meta-regression analysis in the paediatric and adult studies, did not demonstrate any significant change in mortality over time. Despite confining the included studies from high-income countries and sub-dividing studies by age group, there was evidence of very high study heterogeneity (I^2>75%). Further sub-analysis of all studies and by age (paediatric, adult and all-age) using individual meta-regression by region (North America, Europe and Asia/Oceania), definition of SE employed (seizure duration > 5 minutes versus any other time period), study design (retrospective vs prospective), setting (ICU vs non-ICU) and time period (1990-99, 2000-2009 and 2010-17) did not demonstrate any significant difference in estimated pooled mortality. Finally, a multivariate meta-regression analysis combining all variables separately in adult, paediatric and all-age groups, did not result in a significant reduction in the heterogeneity demonstrated (I^2>75%). This study highlights two surprising, but critical findings: first, the evidence indicates that the hospital mortality of CSE has not altered significantly in the last 30 years, and secondly the epidemiological studies of CSE, despite its clinical impact, are poor and inconsistent.

SENSE registry for SE: A prospective observational study

Also in 2019, the SENSE study [2], a prospective cohort study of SE between January 2011 and June 2015, included 1,049 patients with 1,179 SE episodes of whom 457 were diagnosed as having CSE . Treatment was initiated within 30 minutes in less than half of the CSE patients. On multivariate analysis, younger age (HR 0.89; 95% CI 0.82-0.97; p=0.01), lower Rankin Score before SE onset (HR 0.89; 95% CI 0.8-0.99; p=0.05), the use of benzodiazepines as initial treatment (HR 9.62%; 95% CI 1.34 -69.3; p=0.040, a higher cumulative dose of anti-convulsants given within the first 30 minutes of treatment (HR 1.02; 95% CI 1.01-1.03; p=0.002) and shorter latency from SE onset to treatment initiation (HR 0.89; 95% CI 0.82-0.97; p=0.04) independently predicted a shorter time to SE cessation within the first hour of treatment. Overall mortality was 9.4% (43), of whom 93% (40) had SE non-cessation within 60 minutes of treatment initiation (p<0.001). This study highlighted and reaffirmed that CSE needs to be treated early and that benzodiazepines remain the first treatments of choice. Indeed, the large number who were treated late and with non-benzodiazepines may, in part, contribute to the failure to detect a fall in mortality in the last 30 years.

Randomised control trials in CSE: EcLipse, ConSEPT and ESETT

2019 saw the publication of three major randomised trials to address the question of treatment after benzodiazepines. Two, EcLipse [5] and ConSEPT, [6] were paediatric open label multicentre studies in which levetiracetam went head-to-head with phenytoin, for the management of established status CSE (30-60 minutes) and the third, ESETT [7], was a large, long-awaited, multicentre study in which valproate, levetiracetam and fosphenytoin were compared in CSE in children and adults in 57 centres in the US.

In the EcLipSE study [5], 152 children (6 months to 18 years) were randomised to levetiracetam (40mg/kg, maximum dose 2.5g, over 5 mins) and 134 to phenytoin (20mg/kg, maximum dose 2g, with a maximum infusion rate of 1mg/kg per min over at least 20 mins). The primary outcome was time from randomisation to cessation of all visible signs of clinical convulsive activity. Research without prior consent (also known as deferred consent) was used because of the time-crucial management of convulsive SE – the process of research without prior consent was formally assessed and evaluated in a nested consent study. Final outcome was recorded 14 days after enrolment. The primary analysis was based on a modified intention to treat (mITT)

SE was terminated in 106 (70%) in the levetiracetam group and 86 (64%) in the phenytoin group with a median time from randomisation to seizure cessation of 35 minutes in the levetiracetam group and 45 minutes in the phenytoin group (hazard ratio (HR) 1.20; 95% CI 0.91-1.60; p=0.20). Median time from randomisation to start of infusion was 11 mins (IQR 8-15) for levetiracetam and 12 mins (8-17) for phenytoin. Secondary outcomes measures such as need for further anticonvulsants for the presenting SE were comparable (24 (15.8%) in the levetiracetam group, 20 (14.9%) in the phenytoin group; RR 1.06 (0.61-1.83); p=0.84145 (95%) in the levetiracetam group and 130 (97%) in the phenytoin group had been discharged. The time from seizure onset to infusion initiation was not given. The study additionally demonstrated that research without prior consent is acceptable and successful with 95% of those randomised and 92% of those treated providing consent.

In the ConSEPT study [6], carried out in 13 centres in Australia and New Zealand, 234 children aged between 3 months and 16 years with CSE, were enrolled. After failure of appropriate benzodiazepine therapy, patients were randomised to receive phenytoin 20mg/kg over 20 minutes or levetiracetam 40mg/kg over 5 mins. The primary outcome was clinical cessation of seizure activity 5 minutes after the completion of infusion of the first trial drug, assessed at 25 minutes (phenytoin) and 10 minutes (levetiracetam), repeated with levetiracetam and phenytoin infusions at 35 minutes if necessary. If possible, the primary outcome assessment was video-recorded to assess the tone and the presence of jerking, limb, face or eye movements.

The mean age of patients was 3.9 years, with the median length of time of seizure activity before infusion was 73 minutes (IQR 52-99). Primary outcome was achieved 5 minutes after infusion in 68 (60%) in the phenytoin group compared to 60 (50%) in the levetiracetam group, p=0.16. There was no evidence of a differential effect of the study drugs in the pre-specified subgroups. At 2 hours, 62(54%) in the phenytoin group and 61 (51%) in the levetiracetam group-maintained seizure control and did not require further treatment. 42 (37%) in the phenytoin group received levetiracetam and 48 (40%) of the levetiracetam group received phenytoin for seizure control. Seizure control at 2 hours after administration of one or both study drugs was achieved in 89 (78%) in the phenytoin group and 86 (72%) in the levetiracetam group (risk difference -5.8% (95% CI -16.9-5.3; p=0.31). 53 (22%) underwent RSI of anaesthesia, 21 (18%) in the phenytoin group and 31 (26%) in the levetiracetam group (risk difference 7.6% (95% CI -3.0% to 18.3%; p=0.16). Rate and length of ICU admission and hospital duration were comparable in both groups. Seizure duration data was available on 196 (84%) of the 233 participants. The median time to seizure cessation was 22 minutes (IQR 9-49) in the phenytoin group and 17 minutes (5-30) in the levetiracetam group (difference -5.0

min (95% CI -13.5 to 3.5; p=0.25. One participant died in the phenytoin group. At 1-month follow-up, outcome measures were comparable in both groups.

In the ESETT Trial [7], the efficacy and safety of levetiracetam, fosphenytoin and sodium valproate were evaluated in the management of benzodiazepine resistant SE. The trial was conducted under the exception from informed-consent requirements for emergency research (FDA regulation). Eligible patients were aged >2 years, and had been treated with a generally accepted cumulative dose (minimal specified dose given) of benzodiazepines for CSE lasting more than 5 minutes and continued to have persistent or recurrent convulsions in the emergency department (ED) at least 5 minutes after the last dose of benzodiazepine, and no more than 30 minutes after the last dose. Patients were randomised to receive either Levetiracetam 60 mg/kg (max 4500mg), fosphenytoin 20 mgPE/kg (max 1500mgPE) or sodium valproate 40 mg/kg (max 3000mg) – the trial drug was administered by an infusion pump programmed with a determined rate over a period of 10 minutes.

The primary outcome was an absence of clinical apparent seizures and improving responsiveness at 60 minutes after the start of trial-drug infusion, without additional ASMs including medication used for ET intubation. Secondary efficacy outcomes included time to termination of seizures, as determined in the subgroup of patients with audio-recordings that made accurate determination of times possible; admission to the ICU, and the length of ICU and hospital stays. The time to termination of seizures was defined as the interval from the start of infusion of the trial drug to the cessation of clinically apparent seizures.

The study design was a response-adaptive comparative-effectiveness design, with patients randomly assigned to receive one of the three trial drugs, initially in a 1:1:1 ratio. After 300 patients, response-adaptive randomisation was initiated with the goal of maximising the likelihood of identifying the most effective treatment. The study could be stopped early for success or futility after planned interim analyses. The maximal sample was 795 patients, with randomisation stratified by age (2-17, 18-65, >65 years).

Response rates in each of the treatment groups (all initially considered to be the most or least effective) were modelled independently with the use of Bayesian analysis, with the probability that each treatment was the most or least effective treatment was calculated. Intention to treat analysis was employed. 400 enrolments of 384 patients were carried. The enrolment was discontinued after planned interim analysis met the predefined futility criteria. Of those enrolled, 39% were aged between 2-17 years, 48% between 18-65 years and 13% >65 years. Approximately 87% had a final diagnosis of SE (10% dissociative seizures) in all three groups. Approximately 2/3 (66.6%) had a prior history of epilepsy.

In the efficiency analysis, primary outcome was achieved in 68 of 145 (47%) in the levetiracetam group, 53 of 118(45%) in the fosphenytoin group and 56 of 121 (46%) in the valproate group. The median duration of seizure at enrolment was approximately 61.0 minutes (IQR 38.5-94.0). 89

(61.4%) in the levetiracetam group received BZDs prior to arrival in the ED compared to 68 (57.6%) in the fosphenytoin and 62 (51.2%) in the valproate group.

The median time from the start of trial-drug infusion to seizure termination (among patients with an audio-recording) was 10.5 minutes (IQR 5.7 to 15.5) in the levetiracetam group, 11.7 minutes (IQR 7.5 to 20.9) in the fosphenytoin group and 7.0 minutes (IQR 4.6 to 14.9) in the valproate group. 30 patients in the levetiracetam group (20.0%) required intubation within 60 minutes after start of trial-drug infusion compared to 33 (26.4%) in the fosphenytoin group and 21 (16.8%) in the valproate group. Seven people (4.7%) died in the levetiracetam group compared to three people (2.4%) in the fosphenytoin group and two people (1.6%) in the valproate group. In the per-protocol population valproate had the highest probability of being the most effective (0.36) compared to fosphenytoin (0.34) and levetiracetam (0.31), whilst in the adjudicated outcome population, the probabilities of being the most effective being valproate (0.48), fosphenytoin (0.35) and levetiracetam (0.17).

In a further analysis, published in 2020 with an additional 78 cases (total 478 cases (462 patients)), consisting of 225 children (aged <18 years), 186 adults (18-65 years) and 51 older adults (>65 years). The primary outcome was met in 52% (95% CI 41-62) of children, 44% (95% CI 41-62) of adults and 37% (95% CI 19-59) of those receiving levetiracetam compared to 49% (95% CI 38-61) of children, 46% (95% CI 34-59) of adults and 35% (95% CI 17-59) of those receiving fosphenytoin, and 52% (95% CI 41-63) of children, 46% (95% CI 34-58) of adults, and 47% (95% CI 25-70) of older adults receiving valproate, with no evidence of a statistical significant difference in primary outcome between the treatment groups [8].

These studies are a welcome addition to the SE corpus. Three salient findings emerge. First, we now have class A evidence for the effectiveness of levetiracetam, phenytoin and sodium valproate in the management of established SE with seizure cessation in approximately two-thirds of patients. Second, EcLipse, ConSEPT and ESETT have shown that large multicentre RCTs in established SE are possible with the achievement of clear procedural and diagnostic advances. In particular, these have established that the concept of research without prior consent or exception from informed-consent (FDA regulation 21 CFR 50.24) in emergency conditions such as SE is feasible and broadly acceptable to patients and family. In addition, these studies have established the feasibility of audio-visual recordings to ascertain the exact timing of seizure cessation in relation to drug infusions. Lastly, all studies underpinned the absolute need for prospective studies of SE with accurate recording of the timing of SE onset and cessation, an issue that has plagued the SE literature [4, 9].

Where do these studies leave us with treatment recommendations?

1.   These studies demonstrate, where timing of CSE was recorded, that a majority of patients in CSE still face significant time delays before treatment initiation for both early and established CSE,

despite the long-established advocacy of the need for early and aggressive treatment in SE. The additional finding of sub-optimal benzodiazepine dosing is a further concern, albeit one that is remediable. One frequently cited fear is the risk of drug-induced respiratory distress, yet the RAMPART study [10] demonstrated that this is more likely to occur with ongoing seizure activity, and in that context is associated with a poorer prognosis [11], rather than due to the effects of benzodiazepines. The median latency to treatment in established SE was 60 minutes in ESETT and 73 minutes (IQR 52-99) in ConSept. In light of increasing refractoriness with time in SE, these findings underscore the need for ongoing awareness and education for swift intervention following onset, adequate initial benzodiazepine dosing and the timely initiation of second-line treatment in benzodiazepine-resistant cases.

2.   The ConSept study demonstrated that a strategy of successive use of intravenous anti-seizure medications (in this case, phenytoin and levetiracetam) in children, where associated morbidity and mortality is extremely low, should be considered before recourse to anaesthetic agents. The extent to which this approach is feasible in adults, where mortality is higher, merits consideration. This strategy is often used in the setting of non-convulsive and focal SE where cardiorespiratory compromise is less of a concern and the desire to avoid intubation, unless absolutely necessary, is strong. Although phenytoin and levetiracetam were trialled in ConSEPT, valproate, lacosamide and even phenobarbital are additional options.

3.   ESETT, ConSEPT and EcLipSE have demonstrated that levetiracetam is a viable alternative to Phenytoin. Its speed of administration, absence of adverse cardiovascular effects, simpler pharmacokinetics along with its increasing familiarity in emergency settings will, in our view, result in its superseding phenytoin to become the default treatment in benzodiazepine-resistant cases. However, an uncritical move in this direction would be remiss; in head-to-head comparisons, levetiracetam has not shown a clear advantage over phenytoin and it's ascendency in the pharmacological hierarchy, is largely predicated on the perceived unfavourable safety profile of its rival. Nevertheless, the frequency of significant side-effects was not significantly higher in the fosphenytoin group (4 (3.2%) of life-threatening hypotension within 60 minutes of drug infusion; 0 life-threatening cardiac arrhythmia within 60 minutes of drug infusion) compared to the levetiracetam group (1 (0.7%) hypotension; 1 (0.7%) cardiac arrhythmia) in the ESETT study. Moreover it is possible, although speculative, that certain aetiologies may be more responsive to one and not the other. Thus, an open mind and some latitude when designing treatment algorithms is required.

Despite the wide-spread use of phenytoin as the default option in CSE, there is surprisingly little evidence to support the perception of its superiority over valproate. Several studies, including a few randomised/non-randomised clinical trials, have shown valproate to be at least as effective as phenytoin [12]. A meta-analysis of five ASMs in benzodiazepine-resistant SE indicated a trend toward valproate being the most effective. Levetiracetam and phenobarbital were similarly effective but the evidence did not support the first-line use of phenytoin; there was insufficient data to support the routine use of Lacosamide [13]. In the case of the ESETT study, if any ASM was to be favoured, it would be valproate which was associated with the shortest duration to seizure cessation and lowest mortality. Moreover, the Bayesian analysis employed [14] favoured valproate with the highest probability of being the most effective therapy.

A recent study of the use of newer ASMs (principally levetiracetam and lacosamide) in over 800 episodes of SE in approximately 700 patients [15] delivers a sobering conclusion; the use of newer ASMs was associated with a higher degree of refractoriness in SE and increasing morbidity. Much of clinical research into SE in recent years has focused on newer ASMs. However, reappraisal of the role of phenobarbital is justified, once a staple of SE treatment algorithms but recently fallen into disfavour. Its efficacy is arguably superior to that of phenytoin's with the landmark Veteran's Affairs SE study demonstrating a similar efficacy to Lorazepam and a trend favouring it over phenytoin alone. There has been some renewed interest in its use, with positive results [16-18]) and a recent head-to-head comparison with valproate favouring phenobarbital [19] . 'Supra' normal doses of phenobarbital have also been used successfully in the setting of refractory SE [20-22]. Its safety profile, principally cardiorespiratory depression continues to militate against wider use.

4.   In light of the absolute need for timely pharmacological intervention, there is a growing argument to shift the focus even more to the pre-hospital setting whereby both benzodiazepine s and intravenous second-line ASMs could potentially be given prior to arrival in the ED, along the lines of the recent SAMUKeppra study [23] in which one arm of the study involved the addition of intravenous Levetiracetam to Clonazepam for the pre-hospital management of SE. Although the addition of levetiracetam conferred no advantage over Clonazepam alone, the study highlighted the high response rate with early treatment and the feasibility of using non- benzodiazepine intravenous ASMs in a pre-hospital setting. Preclinical studies indicate that there may be more suitable adjunctive therapies that demonstrate synergy with benzodiazepines such as valproate or NMDA receptor antagonists [24].

Conclusions

The crystallisation of robust evidence-based current practice in SE is paramount in informing treatment algorithms. Yet, more needs to be done. Aside from the advent of immunomodulatory treatment in suspected autoimmune cases of SE, there has been little expansion of the effective therapeutic armamentarium. Until we have a better understanding of the biological mechanisms that maintain status epilepticus [25] and more importantly the different biological processes that can lead to SE termination, a cascade which includes, *inter alia*, neurotransmitter depletion, ATP depletion, ionic changes, increased GABAergic drive and release of adenosine and peptides and which of these predominate [26], any treatment regimens employed are likely to be sub-optimal. The intersection of these seminal studies in a single year should lend impetus to refocus efforts on what research should to be prioritised and pursued in order to address some of the most sobering aspects of SE, a lack of a decline in mortality, the significant long-term sequelae and often poor functional outcome.

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Authors	Methodology	Primary outcome/finding	Secondary outcomes/findings
Kellinghaus et al.[2] (SENSE study)	Prospective incident multicentre study of SE over 4.5 years	1049 patients of whom 457 had GCSE with a median age of 65 years (IQR 49–78) and in-hospital mortality of 9%	48% treated within ≤30 min of SE onset. Shorter latency to treatment initiation, use of BDZ within 30 min, were predictive of shorter time to cessation
Lyttle et al.[5] (EcLiPSE study)	Open-label multicentre RCT comparing the use of IV LEV to IV PHY as second-line treatment of paediatric CSE	CSE was terminated in 70% in LEV group and 64% in PHY group	15.8% in LEV group and 14.9% in PHY group need further anticonvulsant. Successful discharge at 14 days follow-up (95% (LEV) and 97% (PHY)
Dalziel et al.[6] (ConSEPT study)	Open-label multicentre RCT comparing the use of IV LEV to IV PHY as second-line treatment of paediatric CSE	Clinical cessation of CSE was achieved 5 minutes after infusion in 50% in LEV group and 60% in PHY group	Seizure control at 2 h after administration of one of both drugs was achieved in 78% in PHY group and 72% in LEV group
Neligan et al.[4]	Systematic review and meta-analysis/meta-regression analysis of CSE in high income countries	Pooled mortality ratio of 15.9% in adults, 13.0% in all-age population studies and 3.6% in paediatric studies	No evidence of a difference in SE mortality following sub-analysis by study time period, region, SE definition employed, study design and study setting (ICU vs non-ICU)
Kapur et al.[7] (ESETT study)	Multicentre randomized blinded comparative-effective of three drugs (IV LEV, IV SVP and IV FOS) in BDZ-resistant CSE in children and adults	Absence of seizures and improvement in responsiveness at 60 min was achieved 47% of LEV group, 45% of FOS group and 46% of SVP group	Seizure termination from start of infusion was 10.5 mins with LEV, 11.7 mins with FOS group and 7.0 mins with SVP group. 20.0% in LEV group required intubation within 60 minutes; 26.4% in FOS group and 16.8% in SVP group

Table 1 Summary of the principal findings of the five key studies

BDZ = benzodiazepines; CSE = convulsive status epilepticus; FOS = fosphenytoin; ICU = intensive care unit.; IV = intravenous; LEV = levetiracetam; PHY = phenytoin; SE = status epilepticus; SVP = sodium valproate.