The SAMUKeppra study in prehospital status epilepticus: lessons for future study

Andrew C. Schomer[1], Jaideep Kapur[2]

[1]Department of Neurology, [2]Departments of Neuroscience Neurology, University of Virginia, Charlottesville, Virginia, USA

Correspondence to: Andrew C. Schomer, MD. Assistant Professor, Department of Neurology, University of Virginia, Charlottesville, Virginia, PO Box 800394, Charlottesville, VA 22908, USA. Email: acs8bd@virginia.edu.

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Comment on: Navarro V, Dagron C, Elie C, *et al*. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15:47-55.

Abstract: In the *Lancet Neurology* article "Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial" the authors conducted a prehospital, randomized controlled study to determine which treatment is more effective for status epilepticus (SE): benzodiazepine alone, or in combination with levetiracetam (LEV). Although the study had negative results, several aspects of the trial design likely masked any added effect that LEV may have had in controlling SE, including: higher doses of benzodiazepines, lower thresholds for determining cessation of SE, and a smaller sample size. Regardless, the study reaffirms the effectiveness and importance of early and adequate benzodiazepine dosing and helps guide us in designing future studies for treatment of SE.

Keywords: Status epilepticus (SE); levetiracetam (LEV); clonazepam; SAMUKeppra; prehospital

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In the *Lancet Neurology* article "Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial" the authors conduct a prehospital, randomized controlled study to determine which treatment is more effective for status epilepticus (SE): benzodiazepine alone, or in combination with levetiracetam (LEV) (1). Convulsive SE is a medical emergency, with an overall mortality around 20% (2). The International League Against Epilepsy (ILAE) defines SE as "*a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after 5 minutes). It is a condition, which can have long-term consequences (after 30 minutes), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures*" (3). Significant research has focused on early termination of status in an attempt to prevent secondary injury. Much of the current clinical evidence shows the efficacy of benzodiazepines in terminating seizures (4-6). In the discussed trial, the authors compare clonazepam against clonazepam with the addition of LEV (typically used as second-line therapy) at the onset of SE. Unfortunately the trial had negative results, but it is important to put those results in context with the previous trials to better understand these data.

Early treatment of seizures with benzodiazepines is far more effective than delayed treatment in achieving seizure cessation (7). The effect is thought to be related to the internalization of $GABA_A$ receptors on the cell surface which leads to a progressive reduction in GABA inhibitory potential (8). Lorazepam, midazolam and clonazepam all have high affinity for $GABA_A$ receptors (9).

In the 1998 Veterans Affairs (VA) cooperative study, four drug treatments for SE were examined; diazepam (0.15 mg/kg) and phenytoin (PHT), lorazepam (0.1 mg/kg),

PHT (18 mg/kg) and phenobarbital (PHB) (15 mg/kg). Lorazepam was found to be most effective in stopping SE, with a rate of 64.9% of patients having cessation of seizures. As the authors noted, this efficacy rate was lower than previously reported data, likely due to a more stringent definition of cessation of status which included: cessation of all clinical and electrographic seizure activity within 20 minutes and no recurrence for 40 minutes (4). In the SAMUKeppra study, cessation was defined as 15 minutes with no seizures following administration of a first dose of clonazepam. This shortened time period may have weighted more favorably towards a treatment effect.

In a 2001 study examining the safety and efficacy of out-of-hospital treatment of SE with either lorazepam (2 mg) or diazepam (5 mg), or placebo, 59.1% of patients receiving lorazepam had cessation of seizures as compared to 42.6% receiving diazepam and 21.1% who received a placebo. Cessation was defined as no seizure activity (clinical or electrographic) on arrival to the ED and if the patient regained consciousness (5). The slightly lower efficacy rates in this trial may be attributable to a lower standardized dosing as opposed to a weight-based dose as used in the VA study. The dosing of clonazepam in the SAMUKeppra study was based on an effective initial dose (10) and was then repeated if seizures continued for an additional 5 minutes. Although equivalent dosing of benzodiazepines is unclear without controlled trials, the underdosing of lorazepam and diazepam (done for safety purposes) in the out-of-hospital study could also contribute to the lower rate of seizure cessation, when compared to repeated and appropriate dosing with clonazepam.

In a 2012 Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART), the authors compared intramuscular (IM) midazolam (10 mg for >40 kg; 5 mg for 13–40 kg) and intravenous lorazepam (4 mg for >40 kg; 2 mg for 13–40 kg), and found that IM midazolam had a higher rate of seizure cessation (73.4%) as compared to IV lorazepam (63.4%). Again, seizure termination was defined as cessation at the time of arrival to an emergency room (6). When comparing these three studies, the rate of seizure cessation with lorazepam remains similar (59–65%).

Although most countries use lorazepam and midazolam for initial therapy in SE, there is practice variability related to dosing these drugs, and many countries use clonazepam as the first-line agent. The recommended dose of clonazepam for treatment of SE is 0.015 mg/kg (11). There are not as many controlled trials demonstrating the comparative efficacy of clonazepam to other benzodiazepines, but a recent observational study showed that clonazepam is likely an effective alternative to other benzos and was associated with less refractory SE. It is difficult to generalize based on those findings however, given that loading doses across all hospitals were frequently insufficient and not standardized (9).

Second line therapy in the treatment of SE is not as well-established. Several agents are frequently used as second-line therapy, including: fosphenytoin (FOS)/PHT, valproate sodium (VPA), PHB, LEV, and lacosamide (LAC). There is clinical and scientific equipoise in this setting (12-16). Historically PHT or FOS was the most commonly used for the treatment of Established Status Epilepticus (ESE) because few other anti-epileptic drugs (AEDs) were available in the intravenous formulation. However rapid intravenous administration of FOS (or PHT) can lead to hypotension, cardiac arrhythmias and purple glove syndrome if extravasation of PHT occurs. The effectiveness of FOS in terminating ESE has not been established (12). Intravenous formulations of VPA and LEV, which became available in the last decade, can be safely administered rapidly intravenously (17-21). Multiple publications reporting the treatment of ESE with LEV or VPA have emerged (12,14,22). An analysis of publications until 2009 reported that 707 patients with various forms of SE had been safely treated with LEV, with a success rate was about 70% (3). In ESE, the efficacy of LEV was reported as 51.7% in one study (23) and 73.2% in another study (21). VPA has been used for the treatment of SE in prospective or retrospective series and two randomized open trials (12). An analysis of these trials reported that 693 adults or children in SE had been safely treated with VPA and with a response rate ranging from 60–83%. A pilot prospective randomized open study reported a trend towards superiority of VPA to PHT in treatment of SE (24). Another study reported that VPA controlled SE refractory to PHT (18). Among neurologists surveyed by the Neurocritical Care Society (U.S.), FOS is the most commonly used drug for the treatment of ESE (16). In a retrospective analysis of charts of patients in SE admitted to neurocritical care units, FOS (or PHT) was the most commonly used drug for the treatment of ESE (15).

In a larger-scale, retrospective analysis of protocol-driven treatment of ESE, 187 episodes were identified in which PHT, LEV or VPA were given after benzodiazepines failed. SE did not respond to 25.4% of cases treated with VPA, 41.4% treated with FOS, and 48.3% treated with LEV (23). Importantly, this was an open, nonrandomized trial, and the severity of SE in VPA treated patients may have

been less than the other two groups, which may explain part of the apparent superiority of VPA in the study (23). Two ESE treatment studies were open, randomized, prospective studies. In the first study, 82 patients were randomized to IV LEV or IV VPA after they had failed diazepam treatment of SE (21). SE was terminated by IV LEV in 30 (37%) patients and VPA in 28 (34%) patients, a difference that was again not significant (21). In the second study, 100 patients aged two or older who had failed IV diazepam were randomized to either 20 mg/kg of VPA or 20 mg/kg PHT (18). SE was controlled in 44 (88%) patients treated with VPA and 42 (81%) patients treated with PHT a difference that was not significant (18). In summary, one large head-to-head comparison of these three agents raised the possibility that VPA is superior to LEV for the treatment of ESE, and two other studies showed no significant differences.

Expert evaluation of the published data suggest that VPA (class IIa level A) may be superior to FOS (class IIa level B), which may be superior to (LEV class IIb level C) (13). Current guidelines recommend use of IV FOS, LEV or VPA (13). In summary, equipoise exists between these three agents and there are no high quality clinical trials to guide the treatment of ESE (25).

In an effort to better delineate which second-line therapy is most effective in cessation of SE, the Established Status Epilepticus Treatment Trial (ESETT) began enrollment in October of 2015, with the goal of the recruiting 750 patients (adults and children) over 5 years at 50 sites around the United States. The trial aims to determine which of the three second-line therapies Valproic Acid (30 mg/kg), LEV (60 mg/kg), or FOS (20 mg/kg) is most effective at stopping convulsive SE after benzodiazepines have failed (26). Treatment with a second-line therapy in addition to benzodiazepines, as was done in the SAMUKeppra study, from the onset of status is a novel approach.

The results of the SAMUKeppra study are somewhat difficult to interpret in the context of previous treatment trials for SE. Convulsions stopped after 15 minutes in 84% of patients receiving clonazepam and placebo, a significantly higher percentage than previous trials in which lorazepam was given (59–65%). 43% of those patients in the benzo only group received a second dose of clonazepam at 5 minutes and many of those went on to have seizure cessation. This second dose effect alone could be enough explanation for the higher treatment effect. The duration of observation was shorter than in the VA cooperative study which may have also contributed. Additionally, the sample size was small compared to previous trials. Although the percentage of patients whose convulsions stopped in the clonazepam/LEV group was smaller (74%) than the placebo group, it is important to note that this is still a relatively high success rate in stopping SE when compared to previous trials. Finally, although there is still no clear evidence which agent is most effective in stopping SE, LEV has had some early indication that it may be inferior to FOS and VPA.

One of the important findings from this study is a reiteration of the importance of early and adequate benzodiazepine treatment. As was seen in RAMPART and again in SAMUKeppra, higher doses of benzodiazepine can be effective in early treatment of SE. It is unlikely that the added benefit of LEV was adequately assessed in this trial, as any effect was likely overshadowed by the high success rate of clonazepam. It will be important to see the results of the ESETT trial as to which second-line therapy provides the most benefit, and then potentially apply that knowledge to design future studies aimed at early seizure cessation.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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