DEM Journal Club

Article Appraisal

Article: Levetiracetam versus Phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT). The Lancet, 2019

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Background and Study Objective(s):

Management guidelines for pediatric status epileptics unanimously recommend benzodiazepines as the first-line pharmacologic intervention, and phenytoin (or fosphenytoin) as the second-line agent of choice. The use of benzodiazepines is well supported by high-level evidence from RCTs and meta-analyses, while the use of phenytoin is based solely on observational studies and expert opinion. There are significant side effects associated with phenytoin (hepatotoxicity, SJS, hypotension, extravasation injury) and it needs to be given over 20 minutes to avoid cardiac arrhythmia. An alternative to phenytoin with a more favorable side effect profile and more rapid administration is levetiracetam. There is no high-level evidence to support the use of levetiracetam over phenytoin as a second-line agent for convulsive status epilepticus; the ConSEPT trial sought to determine which agent is superior in the management of convulsive status epilepticus in children by directly comparing phenytoin vs. levatiracetam. The primary outcome of the study was clinical cessation of seizure activitiy 5 minutes after the completion of infusion of the first trial drug.

Study Design:

The investigators conducted an open-label multi-centre randomized control trial across 13 emergency departments in Australia and New Zealand. The study included 234 children aged 3 months – 16 years with persistent convulsive status epilepticus despite receiving two doses of benzodiazepines. Convulsive status epilepticus was defined as per the International League Against Epilepsy statement. Patients were randomly assigned to receive levetiracetam 40 mg/kg IV/IO over 5 minutes or phenytoin 20mg/kg IV/IO over 20 minutes. Treating physicians and the research team were not blinded to the treatment received. Patients were assessed by the most senior treating physician 5 minutes after the trial drug infusion finished. Patients were assessed for increased tone, jerking movements, and level of consciousness as per the AVPU scale. If seizure activity was present, the alternative trial drug was administered. If seizure activity still persisted after both trial drugs had been administered, patients were managed as per local protocol (RSI and intubation). Patient demographics, time of seizure cessation and adverse events (before and after drug administration) were recorded. Exclusion criteria included children previously enrolled and randomly assigned in the study, children already taking regular phenytoin or levetiracetam, patients who had received phenytoin, levetiracetam, phenobarbital, or paraldehyde in the past 24 hours, patients who had a management plan stating

they were refractory to phentoyin, those with a contraindication/allergy to phenytoin or levetiracetam, and those in status epilepticus due to an obvious head injury or due to eclampsia in late pregnancy. Of note, the primary outcome assessment was video recorded in as many cases as possible to explore possible observer bias related to the unblinded nature of the study as well as the relatively subjective primary outcome. The videos were reviewed by two Emergency Physicians and one neurologist who were masked to treatment allocation. Analysis of the primary outcome was by intention to treat as well as per protocol. Categorical data was compared using □2 tests. Differences between continuous data was analyzed using unpaired t tests. Subgroup analyses were proposed using logistic regression, but no evidence of interaction between groups was detected, so subgroup analyses were not conducted.

Results:

Clinical cessation of seizure activity 5 minutes after the completion of infusion of the first study drug occurred in 60% of patients in the phenytoin group, and 50% of patients in the levetiracetam group. This difference did not reach statistical significance. Median time to termination of seizure activity from initiation of trial drug was 22 minutes in the phenytoin group and 17 minutes in the levetiracetam group. In the group that received phenytoin and then levetiracetam, seizure cessation was achieved in 78% of patients; in the group that received levetiracetam, seizure cessation was achieved in 72% of patients. With regards to the recorded data to confirm seizure cessation, reviewers disagreed with treating clinician assessment in 4 patients in the phenytoin group, and 3 patients in levetiracetam group. No difference between trial drugs was detected across prespecified subgroups (based on age, focal versus generalized onset, febrile versus afebrile, or use of midazolam versus other benzodiazepines). At 2 hours, 54% of patients that had received phenytoin, and 51% of patients that had received levetiracetam maintained seizure control and did not require further anti-convulsant treatment. Rate and length of ICU admission and hospital length of stay were similar between groups. Rates of adverse events were similar between the two treatment groups. Both treatment groups required similar volume of fluid to remain blood pressure and had similar rates of requiring airway intervention and tracheal intubation. Neither drug precipitated cardiac arrhythmia. There was only one recorded purple glove syndrome (in the phenytoin + levetiracetam group). At 1 month after hospital discharge, seizure frequency, recurrent episodes of convulsive status epilepticus and proportion of patients receiving anticonvulsants were similar in both groups as well.

Validity of Results:

The consensus of Journal club attendees that the study methodology and statistical analysis undertaken in this study were reasonably sound. There were two main concerns discussed. Firstly, as stated above in the methods, the unblinded nature of the study and relatively subjective outcome resulted in risk of observer bias. Investigators attempted to mitigate this bias by videotaping as many of the primary outcome assessments as possible (67%) for later, blinded review. Reassuringly, video review largely correlated with clinician assessment and discordance was similar between groups. Secondly, the variation in the time to primary outcome assessment (a difference of 15 minutes) between groups resulted in a potential bias toward phenytoin being the more effective drug since the seizure had an additional 15 minutes to “naturally decay”. Unfortunately it is hard to mitigate this bias as the two trial drugs have different infusion times and it would be impossible to assess the primary outcome at identical times for this reason. Both of these concerns were addressed in the published study discussion.

Generalizability of Results:

This was a multicentre trial across 13 emergency departments in Australia and New Zealand. Journal club attendees agreed that the results of this study were largely generalizable to our population seen here in Canada (age, race, past medical history, type of seizures). Pediatric status epilepticus was defined as per international guidelines that are also followed here in Canada. The only variation that was discussed was the “median length of seizure before first study drug.” In this study, the median time to trial drug was 74 minutes in the phenytoin group and 72 minutes in the levetiracetam group – in Canada, unless in a rural community with long transport times, we suspect that the time to a second line agent would be significantly less than these times.

The Bottom Line:

Overall, this study is the first robustly powered RCT comparing these two drugs in pediatric status epilepticus. The consensus of Journal club attendees was that this was a very well done multicentre randomized control superiority trial. Three main conclusions were drawn from the study. Firstly, this study did not find that levetiracetam is more effective than phenytoin. Importantly, we cannot conclude that levetiracetam is non-inferior, as the study was not designed to determine this. Secondly, there was no significant difference between levetiracetam and phenytoin with regards to safety outcomes; however, the risks of phenytoin are well documented and need to be considered. Finally, both drugs were associated with considerable failure rates, but both drugs together reduced the failure rate by 50%, suggesting that perhaps utilizing the two drugs sequentially could improve outcomes and negate the need for RSI/intubation in some cases if the clinical situation permitted. While sequential use of the study drugs cannot be endorsed based on this study, these results indicate that there may be potential for more effective seizure algorithms, illuminating an area for further research.