Randomized Trial of Lacosamide versus Fosphenytoin for Nonconvulsive Seizures

Background:

- Seizures are associated with increased mortality, decreased cognition, and the development of epilepsy.
- The management of convulsive seizures is well documented, however, non-convulsive seizure management is still lacking sufficient data.

Objective:

- Determine if lacosamide is non-inferior to fosphenytoin at stopping a non-convulsive seizure

Methods:

- **Study design:** prospective, parallel, multi-center, and randomized trial containing data from 74 participants.
- **Study duration:** The duration of the study lasted for 28 hours for each participant, and enrollment lasted from August 2012 to December 2013.
- **Inclusion criteria:** ≥ 18 years old, undergoing continuous EEG for non-convulsive seizure lasting between 10 seconds and 30 minutes, and seizure requiring IV medications.
- **Exclusion criteria:** Previously receiving lacosamide, fosphenytoin, or phenytoin, hypersensitivity or contraindication to study drugs, hypothermia, or convulsive seizures.
- **Drug regimen:** Participants could have been selected to receive 400mg lacosamide IV over 30 minutes or 20 phenytoin eq./kg of fosphenytoin IV over 30 minutes. If participants experienced another non-convulsive seizure during the 24 hours watch period, they were treated with the medication from the other group.
- **Primary outcome:** Number of participants in each group that stopped seizing after receiving the first treatment drug.
- **Secondary outcome:** Number of participants that received a rebolus of the initial drug, number of participants receiving the crossover drug and rebolus of crossover drug, and reduction in seizure burden
- Power was not mentioned
- **Data handling:** Intent to treat, modified intent to treat (received continuous EEG readings for at least 16 hours), and safety population.

Results:

- 74 patients completed the study
- **Primary outcome:** 19/30 (63.3%) participants in the lacosamide group and 16/32 (50%) participants taking fosphenytoin met the primary outcome RR = 1.27 (90% CI 0.88 – 1.81)(p=0.02).
- **Secondary outcome:** Of the secondary outcomes, none of the findings were

statistically or clinically significant. However, the crossover medication was administered in 15/35 (42.9%) participants in the initial lacosamide group and 10/37 (27%) participants in the initial fosphenytoin group (p = 0.18). This could insinuate that lacosamide is actually less effective than fosphenytoin, as almost 14% more of the lacosamide group had to receive the crossover drug.

- The study reported no statistically significant differences between adverse events.

Author's conclusion: This study demonstrates that lacosamide is non-inferior to fosphenytoin in controlling non-convulsive seizures with no significant differences in adverse effects.

Strengths:

- Study rationale

Limitations

- Small sample size due to lack of funding
- Unclear methods
- Poor treatment standardization protocol for participants in the study.
- Use of non-standard dosing

Conclusions

- The authors of the study did demonstrate that lacosamide was non-inferior to fosphenytoin in stopping non-convulsive seizures, however, the manner in which they did so was inappropriate. Overall, the results of this study should not be extrapolated into clinical practice, as the limitations that exist are too important to ignore.
- **Further studies:** Further studies must be done and should involve the following:
    - Standardized protocol for treating patients in the study beginning at admission
    - Appropriate dosing of medications
    - Parallel design with no chance of crossover during the study
    - Large sample size with appropriate power

Husain AM., Lee JW., Kolls BJ., *et al.* Randomized Trial of Lacosamide versus Fosphenytoin for Non-convulsive Seizures. Ann Neurol 2018;83:1174–1185.

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