



CLONIC Proposal

Can Levetiracetam Oppress seizures iN IntraCerebral hemorrhage?



Background

- ICH is the most fatal form of stroke
- Clinically apparent seizure activity occurs in 7-17% of all patients
- The incidence of any seizure activity (clinical and EEG is 30-40% among those with lobar ICH.
- Many providers are using prophylactic AEDs!



Are seizures associated with worse outcome?

?Is there confounding by indication?

Table 1. Observational studies of seizures and outcome.

Study	n	Incidence	Association with outcome
Vespa et al ³	63	28%	Increased midline shift Worse neurologic outcome
Claasen et al ²¹	102	31%	Hematoma expansion Worse neurologic outcome
Claasen et al ²⁶	247	7%	Worse neurologic outcome
Szaflarski et al ²⁷	715	8%	Increased mortality
Taylor et al ²⁸	85	8%	Improved neurologic outcome in those receiving LEV
Naidech et al ²	98	7%	Worse outcome after phenytoin No change after LEV
Messe et al ¹	295	2%	No association with outcome Worse outcome after phenytoin

Vespa PM, O'Phelan K, Shah M, Mirabelli J, Starkman S, Kidwell C, Saver J, Nuwer MR, Frazee JG, McArthur DA, Martin NA. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology*. 2003;60:1441-1446 ; Messe SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care*. 2009;11:38-44; Naidech AM, Garg RK, Liebling S, Lavoisier K, Macken MP, Schuele SU, Batjer HH. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke*. 2009;40:3810-3815; Claassen J, Jette N, Chum F, Green R, Schmidt M, Choi H, Jirsch J, Frontera JA, Connolly ES, Emerson RG, Mayer SA, Hirsch LJ. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology*. 2007;69:1356-1365 ; Szaflarski JP, Rackley AY, Kleindorfer DO, Khoury J, Woo D, Miller R, Alwell K, Broderick JP, Kissela BM. Incidence of seizures in the acute phase of stroke: a population-based study. *Epilepsia*. 2008;49:974-981 ; Taylor S, Heinrichs RJ, Janzen JM, Ehtisham A. Levetiracetam is associated with improved cognitive outcome for patients with intracranial hemorrhage. *Neurocrit Care*. 2011;15:80-84

Current guidelines

FP2 - C4

➤ American Heart Association: “the utility of prophylactic anticonvulsant medication remains uncertain”

C4 - O2

Fp2 - T4

➤ “Prophylactic anticonvulsant medication should not be used (Class III)” but highlights the need for further study.

T4 - O2

Fp1 - C3

➤ Neurocritical Care Society: No AED prophylaxis (but maybe a short course for lobar ICH and those undergoing surgical evacuation).

C3 - O1

Fp1 - T3

T3 - O1

How might AEDs help?

FP2 - C4

➔ Electrographic seizures may be neurotoxic, leading to worse outcome.

C4 - O2

Fp2 - T4

➔ Clinical seizure activity can prolong ICU LOS and hospital LOS

T4 - O2

Fp1 - C3

➔ AEDs may both reduce the risk of adverse events and iatrogenesis, and provide neuroprotection and improve outcome.

G3 - O1

Fp1 - T3

T3 - O1

CLONIC Proposal

FP2 - C4

C4 - O2

Fp2 - T4

T4 - O2

Fp1 - C3

C3 - O1

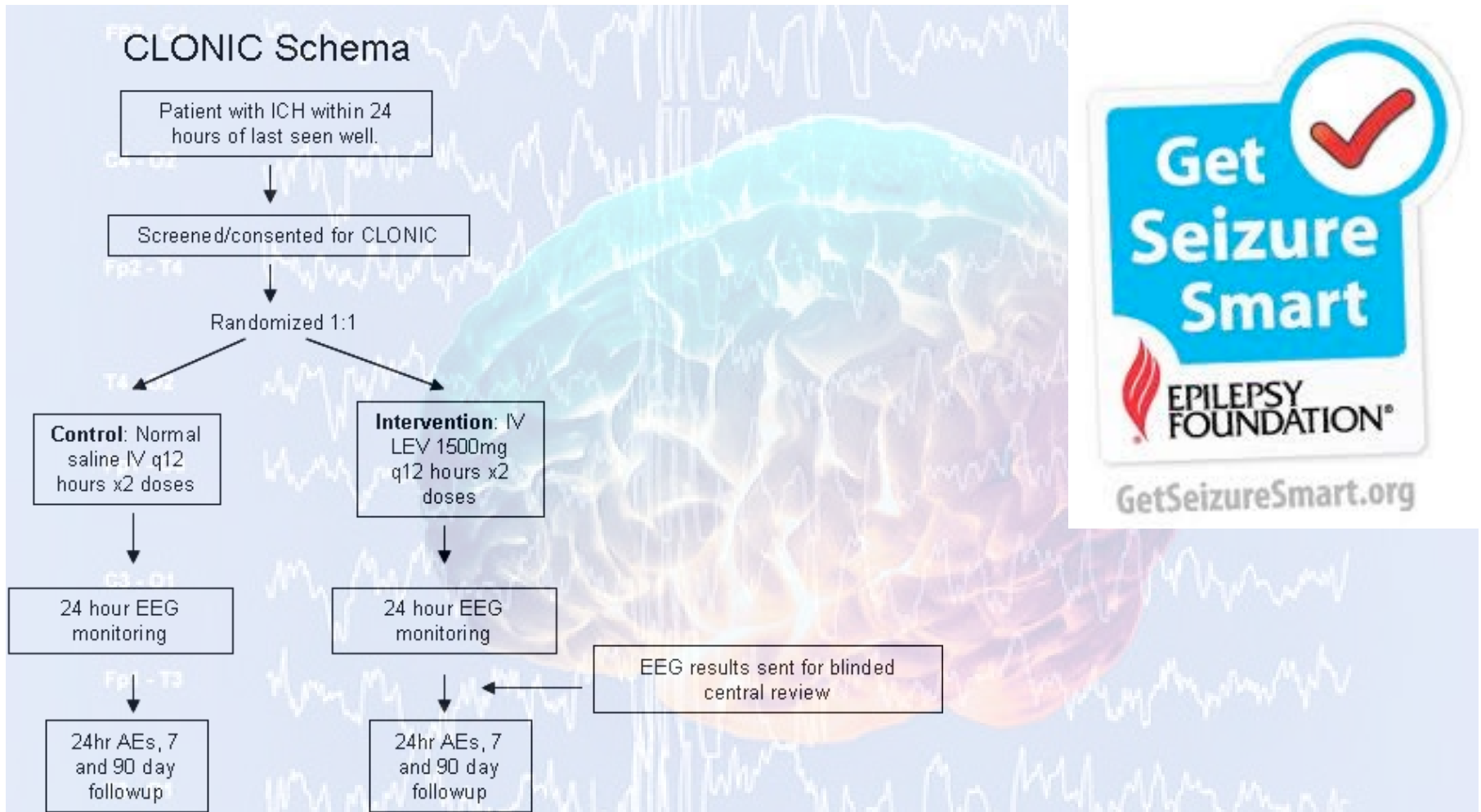
Fp1 - T3

T3 - O1

➤ Inclusion:

- Primary ICH within 24 hours of onset
 - Age > 18
 - Lobar location
 - No clinical seizure activity prior to randomization
 - Written informed consent
- Randomized controlled trial

Schema



CLONIC Proposal

FP2 - C4

➤ Phase II/III Randomized controlled trial

C4 - O2

➤ Phase II Primary endpoint: Reduction in risk of “any clinical or electrographic seizure activity”

Fp2 - T4

➤ Futility analysis:

T4 - O2

➤ 90day mRS to determine whether to move forward with phase III.

Fp1 - C3

➤ Phase III Primary endpoint: Improved 90 day mRS

G3 - O1

Fp1 - T3

T3 - O1