

Levetiracetam vs. Phenytoin for Seizure Prophylaxis

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ORIGINAL ARTICLE

Prospective, Randomized, Single-Blinded Comparative Trial of Intravenous Levetiracetam Versus Phenytoin for Seizure Prophylaxis

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Background

- Seizures after acute brain injury are common
 - Incidence of seizures (covert & overt) after TBI or SAH have been reported at $\geq 20\%$
- Seizures are associated with secondary injuries
 - Aneurysmal rupture/re-rupture, increased ICP, hypoxia, physical injury, death.
 - These complications may adversely affect neurological status and worsen clinical outcome
- Early seizures may predict subsequent epilepsy
- These issues result in frequent use of prophylactic AEDs in the Neuro-ICU
 - PHT is the most commonly used AED

Background

- PHT is associated with significant side effects & medication interactions, thus better treatment options are needed
- LEV has been studied in the acute care setting
 - Retrospective chart reviews or open-label design
 - Majority have shown that LEV is associated with lower complication rates and shorter ICU stays
- LEV may be a desirable alternative to PHT, but a comparative trial was needed
- We designed a prospective trial comparing IV PHT and LEV

Study Goals

- Primary objective
 - Compare safety of LEV and PHT in critically ill NSICU patients
- Secondary objectives
 - Compare rate of clinically evident and sub-clinical seizures
 - Compare long-term outcomes between groups

Methods: General Design

- Investigator initiated trial
 - Original design: enroll 104 patients (52 SAH; 52 sTBI)
 - Recruitment and funding issues prompted a change: focus on sTBI; stop enrollment at 52.
- Prospective, randomized, single-blinded trial comparing IV LEV to PHT
 - 2:1 ratio; NCT00618436
 - Enrollment within 24 hours after admission
- Blinding
 - Electrophysiologist was blinded to group assignment & diagnosis; reported EEG results to PI daily
 - Managing physicians were partially blinded
 - Research coordinators were blinded to treatment group

Inclusion / Exclusion

■ Inclusion

- TBI (or SAH)
- GCS score 3-8 (inclusive), or GCS motor score ≤ 5
- Abnormal admission CT
- Hemodynamically stable
- At least 1 reactive pupil
- ≥ 17 years of age
- Signed informed consent / HIPAA authorization

■ Exclusion

- Spinal cord injury
- Previous brain injury
- Hemodynamically unstable
- Suspected anoxic events
- Peripheral trauma causing liver failure
- Hypersensitivity to AEDs
- Anything that contraindicated treatment with LEV or PHT
- No informed consent / HIPAA authorization

Methods

- Standard of Care Protocols
 - TBI management: based on the Guidelines for Management of Severe TBI
 - SAH management: based on TUH DNS CV Service treatment algorithms
- Endpoints
 - Adverse events
 - Seizure frequency
 - Outcome: GOSE & DRS were assessed by blinded research coordinators at discharge, 3 & 6 months

Adverse Events

- Seizures
- Fever
- Neurological
 - General worsening
 - New stroke / bleed
 - ICP elevations
- Hematologic
 - Anemia
 - Thrombocytopenia
 - Coagulopathy
- Cardiovascular
 - Hypotension
 - Arrhythmias
- Dermatological
- Gastrointestinal
 - Liver failure
 - Nausea / vomiting
 - Ileus
- Renal failure
- Death

Glasgow Outcome Score

Unfavorable Outcome			Favorable Outcome	
1	2	3	4	5
Dead	Vegetative state	Severe disability	Moderate disability	Good recovery
Loss of life	Unresponsive +sleep cycles +eye opening	Conscious but dependent for daily care	Disabled but able to assist in self care	Minor (?) residual deficits

Disability Rating Scale

- 4 categories of assessment
 - 1 – 3 items scored in each category
 - Scores totaled, range from 0 – 30.

Favorable Outcomes				Unfavorable Outcomes					
0	1	2-3	4-6	7-11	12-16	17-21	22-24	25-29	30
None	Mild	Partial	Mod	Mod Severe	Severe	Ext Severe	VS	Ext VS	Death

AED Management

- IV LEV or PHT
 - PHT: loaded with fos-PHT 20 mg/kg PE IV; maintenance with 5 mg/kg/day every 12 hours
 - LEV: loaded with 20 mg/kg IV; maintenance of 1000 mg IV every 12 hours
- Doses adjusted to maintain therapeutic serum PHT concentrations or for seizures.
 - PHT levels were checked on days 2 and 6
 - LEV dose was adjusted based on therapeutic effect
- Maintained on IV study medications for 7 days
 - If no seizures at that time, medication was discontinued

cEEG / Seizure Management

- cEEG monitoring
 - Performed for 72 hours or until following commands
 - cEEG was continued if seizures occurred
- If seizures occurred, study medication was escalated to maximum recommended dose
 - PHT: measured therapeutic level of 20 $\mu\text{g}/\text{dL}$ for PHT
 - LEV: 1500mg IV BID
- Continued failure to suppress seizure activity
 - Addition of PHT or LEV to the current medication
 - If this regimen did not provide benefit, treatment with other AEDs was initiated

Statistical Analysis

- Groups characterized using descriptive statistics
- Analysis
 - Medians and ranges for continuous variables
 - Frequencies and percentages for categorical variables
- Comparisons between groups were based on:
 - Mann-Whitney U-test for continuous variables
 - Fisher's Exact tests for categorical variables
 - Generalized linear models used to test for differences between groups adjusted for confounding factors
- Analyses conducted using SPSS version 17.0

Results

- 52 patients randomized (LEV=34; PHT=18)
 - 89 % with TBI
 - Median duration of AED use = 7 days
 - Hospital LOS: PHT = 15 days; LEV = 14 days
 - No difference in neurosurgical interventions

Demographics (All patients)	PHT (n = 18)	LEV (n = 34)	p-value
Age	35 (18-80)	44 (17-75)	0.805
Male	13 (72%)	26 (77%)	0.747
Female	5 (28%)	8 (23%)	
TBI	16 (89%)	30 (88%)	1.000
SAH	2 (11%)	4 (12%)	
GCS in ED	4	5	0.419
ISS	27	28	0.953

Results

- Mortality
 - Overall = 35%: PHT 4/18 vs. LEV 14/34 ($p = 0.227$)
 - Early death = 12%: PHT 2/18 vs. LEV 4/34 ($p = 0.150$)
 - Early withdrawal of care (≤ 30 days after injury):
PHT 0/18 vs. LEV 5/34 ($p = 1.00$)
 - Late withdrawal of care (> 30 days after injury):
PHT 2/18 vs. LEV 5/34 ($p = 1.00$)
 - Withdrawal of care was based on quality of life issues
- Seizure occurrence: no difference
 - Overall seizure incidence = 8/52 (15%)
 - During cEEG: PHT 3/18 vs. LEV 5/34 ($p = 1.0$); all NCS
 - 6 months: PHT 0/14 vs. LEV 1/20 ($p = 1.0$)

Adverse Events	PHT (n = 18)	LEV (n = 34)	P-value
Fever	10 (56%)	18 (53%)	1.000
Increased ICP	8 (44%)	13 (38%)	0.769
Stroke / expanding bleed	3 (17%)	7 (21%)	1.000
Gen Neuro worsening	9 (50%)	6 (18%)	0.024
Hypotension	2 (11%)	7 (21%)	0.470
Arrhythmia	6 (33%)	14 (41%)	0.766
Anemia	4 (22%)	17 (50%)	0.076
Thrombocytopenia	3 (17%)	5 (15%)	1.000
Liver test abnormalities	0 (0%)	2 (6%)	0.538
Renal failure	1 (6%)	2 (6%)	1.000
GI issues	4 (22%)	1 (3%)	0.043
Early death	2 (11%)	4 (12%)	1.000
Care withdrawn early (< 1 mo)	0 (0%)	5 (15%)	0.150
Care withdrawn late (> 1 mo)	2 (11%)	5 (15%)	1.000

Adverse Events Survivors Only

- Significance of generalized neurological worsening increased
 - PHT = 6 (43%); LEV = 1 (5%) ($p = 0.012$)
- Significance of GI symptoms was lost
- All other categories were unchanged

Results: Outcomes

- All patients: no differences between groups
- Survivors: LEV group had better outcomes
 - Persisted when controlled for admission GCS

Survivors	PHT (n = 14)	LEV (n = 20)	p-value
GCS, discharge	10 (3-15)	11 (6-15)	0.396
GOSE, discharge	3 (2-3)	3 (2-4)	0.545
DRS, discharge	22 (7-29)	22 (7-26)	0.436
GOSE, 3 mos	3 (2-5)	4 (2-7)	0.107
DRS, 3 mos	11 (5-23)	5 (0-23)	0.006
GOSE, 6 mos	3 (3-7)	5 (3-8)	0.016
DRS, 6 mos	6 (0-20)	3 (0-17)	0.037

Conclusion

- LEV group had fewer episodes of
 - General worsening of neurological status
 - GI events
- Efficacy of seizure prevention was similar
- Outcome measures favored use of LEV
 - significantly improved GOSE and DRS at 3 & 6 months
- LEV appears to be an alternative to PHT for seizure prophylaxis in the ICU setting

Limitations

- Only partial blinding
- Small study size
- Powered for assessing incidence of adverse effects related to AEDs
 - Not powered for efficacy or outcomes
 - Initial enrollment goal was decreased
- Statistical analyses have not been adjusted for multiple comparisons
- Mortality data is concerning
 - Family expectations?

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Questions?



Interventions

All Patients	PHT (n = 18)	LEV (n = 34)	P-value
ICP Monitor	15 (83%)	29 (85%)	1.000
Licox	14 (78%)	22 (65%)	0.529
Craniotomy	6 (33%)	14 (41%)	0.766
Hematoma Evacuation	4 (22%)	9 (27%)	1.000
Decompression	3 (17%)	9 (27%)	0.0507

- Survivors only: no significant variations

Results: Outcomes

- All patients: no differences between groups
- Survivors: LEV group had better outcomes
 - Persisted when controlled for admission GCS

All Patients	PHT (n = 18)	LEV (n = 34)	p-value
GCS, discharge	10 (3-15)	10 (5-15)	0.617
GOSE, discharge	2 (1-3)	2 (1-4)	0.334
DRS, discharge	23 (7-30)	24 (7-30)	0.547
GOSE, 3 mos	3 (1-5)	3 (1-7)	0.612
DRS, 3 mos	13 (5-30)	15 (0-30)	0.959
GOSE, 6 mos	3 (1-7)	3 (1-8)	0.892
DRS, 6 mos	9 (0-30)	17 (0-30)	0.787