Risk of seizures in neonates with hypoxic-ischemic encephalopathy receiving hypothermia plus erythropoietin or placebo

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Background:

- Epo has shown to reduce severity of both acute and late seizures in animal models of HIE; FDA label warning as a possible pro-convulsant effect based on older trials in adults with renal disease. Unclear if applicable to neonates; limited , small studies lacking video EEG monitoring for seizure diagnosis.
- High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) Multicenter, randomized trial of Epo vs placebo for neuroprotective in neonates with moderate/severe HIE showed no difference in groups in rate of death or disability at age 2-3 years. Did not assess timing and electrographic seizure burden.

Questions:

- What is the effect of Epo on provoked seizures as compared to placebo?
- Hypothesized that it would have a lower risk and burden

Study Design:

- Ancillary HEAL study
- Eligibility/Exclusion: HEAL study plus cEEG recorded without interruption throughout cooling and rewarming (except for neonates who died during admission) and EEQ quality sufficient for interpretation by a neurophysiologist review
- Assessed timing and dosing of anti-seizure medication (ASM)
- cEEG recordings de-identified and independently reviewed by 2 neurophysiologists
- Seizures were defined as a sudden, abnormal EEG event with a repetitive and evolving pattern with a minimum 2 μV peak-to-peak voltage and duration of at least 10s. Status epilepticus was defined as the summed duration of seizures comprising ≥ 50% of any 1-h epoch of recording. Only electrographic seizures were considered; clinically detected seizures were not considered for this ancillary study.
- Primary outcome: EEG maximal seizure burden (min/h) after Epo administration among neonates with seizures
- Secondary outcomes: Response to initial dose of ASM defined as no further seizures > 30 min after loading dose until the end of recording, overall seizure burden (mins of seizures per minutes of cEEG recording), seizure period (onset to end of last), presence of status epilepticus

Results:

- 235 randomized in HEAL, (~11% cEEG files unavailable) 185 cEEG reviewed to reach pre-specified 150. [83 EPO and 67 Placebo]
- First dose of Epo administered at a median of 18.5 hours
- 20/150 (13%) died; 6 with cEEG removed prior to completing the 72 hour monitoring period
- No significant differences between groups in maternal characteristics, pregnancy and delivery complications, infant characteristics (including severity of encephalopathy), or EEG monitoring
- Electrographic seizures occurred in 46/150 (31%). No diff between groups.
- Timing: 27% before study drug, 27% between first and second dose,11% after second dose. Similar rates in both groups.
- ASM in 36% Epo and 54% placebo
- No meaningful difference in median maximal hourly seizure burden after first dose of study drug between both groups (Epo 18.1 min/h vs placebo 21 min/h)
- 43 (29%) received a ASM loading dose; 13 (30%) had a complete response. Epo treated lower complete response 5/24 (21%) as compared to placebo 8/19 (42%). No significant difference after adjustment for severity and baseline seizure burden prior to first study drug dose
- Seizure burden higher in Epo group 63.8 vs placebo 31.5, but when considering total cEEG recording time, the % of time with seizures not significantly different
- Median period over which a neonate had seizures 16.3 hours not significantly different between groups.
- Status epilepticus was present in 10/46 (22%) and occurred more frequently among neonates treated with Epo 35% vs placebo 5%. Not statistically diff after adjustment for pre-treatment seizure burden and HIE severity

Conclusion:

- Data does not align with animal research. HEAL was Epo plus hypothermia. May act through similar mechanisms. Suboptimal timing (early admin in injury cascade) or dosing?
- Limitations: Lower seizure rate than anticipated and previous published studies (34-65%). Improved OB care/ neuroprotective measures. Seizure ID and treatment at discretion of local care team. ASM+ Epo interactions not assessed. Differences in ASM use between groups unknown could be related to clinically suspected vs electrographic-only. Not all cEEG reviewed and parent study excluded families with unstable social situations.
- Findings consistent with overall trial results that do not support Epo for neonates with HIE undergoing therapeutic hypothermia. No significant increase in seizure risk after Epo admin, however potential for worse seizures (total seizure duration, overall maximal hourly seizure burden, seizure period, and status epilepticus). Possible explanations: chance, less robust ASM, or a true increase in seizure burden related to Epo or its side effects. No apparent pro-convulsant effect

Table 2. Seizures and anti-seizure medications (ASM) of 150 neonates with hypoxic-ischemic encephalopathy (HIE) undergoing therapeutic hypothermia and treated with erythropoietin or placebo who received continuous video-EEG throughout hypothermia and rewarming.

	Total, $N = 150$	Erythropoietin, $N = 83$	Placebo, $N = 67$	aRR (95% CI)*	P value*
Seizures and seizure timing					
N (%) with EEG seizures[a]	46 (31%)	26 (31%)	20 (30%)	1.04 (0.60, 1.80)	0.88
With moderate encephalopathy	29/117 (25%)	16/64 (23%)	13/53 (24%)	0.98 (0.41, 2.34)	
With severe encephalopathy	17/33 (52%)	10/19 (53%)	7/14 (50%)	1.03 (0.62, 1.72)	
After 1st dose of study drug	40 (27%)	22 (27%)	18 (27%)	0.88 (0.44, 1.76)	0.72
Between 1st and 2nd dose of study drug	34 (23%)	19 (23%)	15 (22%)	0.88 (0.45, 1.73)	0.71
After 2nd dose of study drug	16 (11%)	11 (13%)	5 (7.5%)	1.12 (0.41, 3.07)	0.83
ASM administration					
N (%) administered ASM	66 (44%)	30 (36%)	36 (54%)	**0.60 (0.40, 0.89)**	**0.01**
Phenobarbital	64 (43%)	29 (35%)	35 (52%)	**0.62 (0.41, 0.93)**	**0.02**
Levetiracetam	33 (22%)	12 (15%)	11 (16%)	0.73 (0.34, 1.60)	0.44
Phenytoin/fosphenytoin	13 (8.7%)	7 (8.4%)	6 (9.0%)	1.06 (0.39, 2.88)	0.91
Other (midazolam, lorazepam, topiramate)	65 (43%)	34 (41%)	31 (46%)	0.91 (0.61, 1.34)	0.62

aRR adjusted relative risk, *EEG* electroencephalogram, *ASM* anti-seizure medication.
*Adjusted relative risks and *P* values based upon generalized (binary) logistic regression model and adjusts for treatment, HIE severity, and recruitment site.
[a]Logistic regression models additionally adjusted for the maximum seizure min/h observed prior to the first study drug dosing, and a log offset log(T_i) to account for variable lengths of cEEG observation time overall or between study drug doses.
Bold values represent statistical significance $p < 0.05$.