EFFICACY AND SAFETY OF LEVETIRACETAM VERSUS PHENOBARBITAL FOR NEONATAL SEIZURES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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INTRODUCTION

Seizures are the most common neurologic emergency in the neonatal period. Levetiracetam and phenobarbital remains to be the most commonly used anti-epileptic agents despite conflicting evidence regarding their efficacy, and significant concerns about safety.

OBJECTIVE

To synthesize data from randomized trials evaluating levetiracetam versus phenobarbital as a first-line anti-epileptic drug for seizures in the newborn.

METHODS

A meta-analysis following the PRISMA guidelines was performed. Medline by PubMed, CENTRAL by Cochrane, Embase, Google Scholar, and grey literature for RCTs were searched. Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was used to assess for quality. Quantitative data were pooled and analyzed using Review Manager 5.4

RESULTS

Four studies were included in the analysis. A total of 312 neonates comprised the pooled sample. Efficacy was not significantly different; however, there was a trend towards benefit with phenobarbital. This was consistent after subgroup analysis of clinical seizures and patients with hypoxic-ischemic encephalopathy. Hypotension was more common with phenobarbital. However, neither drug was significantly associated with respiratory abnormalities, requirement for ventilation, or mortality.

	Levetiracetam		Phenobarbital			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year
Perveen 2016	7	30	26	30	23.4%	0.27 [0.14, 0.52]	2016
Pervez 2018	24	34	14	35	25.1%	1.76 [1.11, 2.80]	2018
Gowda 2019	43	50	31	50	26.4%	1.39 [1.09, 1.77]	2019
Sharpe 2020	15	53	24	30	25.1%	0.35 [0.22, 0.56]	2020
Total (95% CI)		**167**		**145**	**100.0%**	**0.71 [0.30, 1.71]**	
Total events	89		95				

Heterogeneity: Tau² = 0.74; Chi² = 50.84, df = 3 (P < 0.00001); I² = 94%
Test for overall effect: Z = 0.76 (P = 0.45)

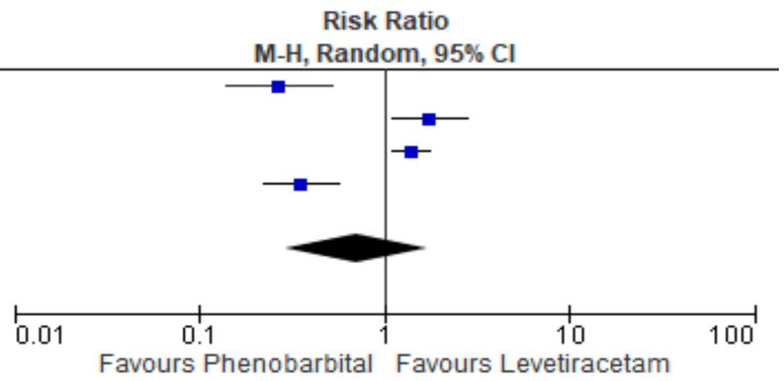

Figure 1. Forest plot of seizure freedom (Phenobarbital versus Levetiracetam)

CONCLUSION AND RECOMMENDATIONS

The statistical analysis did not lend evidence to support the use of one drug over the other. More double-blind RCTs with larger samples are still needed to evaluate the efficacy and safety of levetiracetam and phenobarbital in neonatal seizures.

Keywords: Levetiracetam, phenobarbital, neonatal seizures