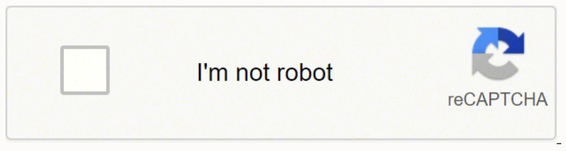

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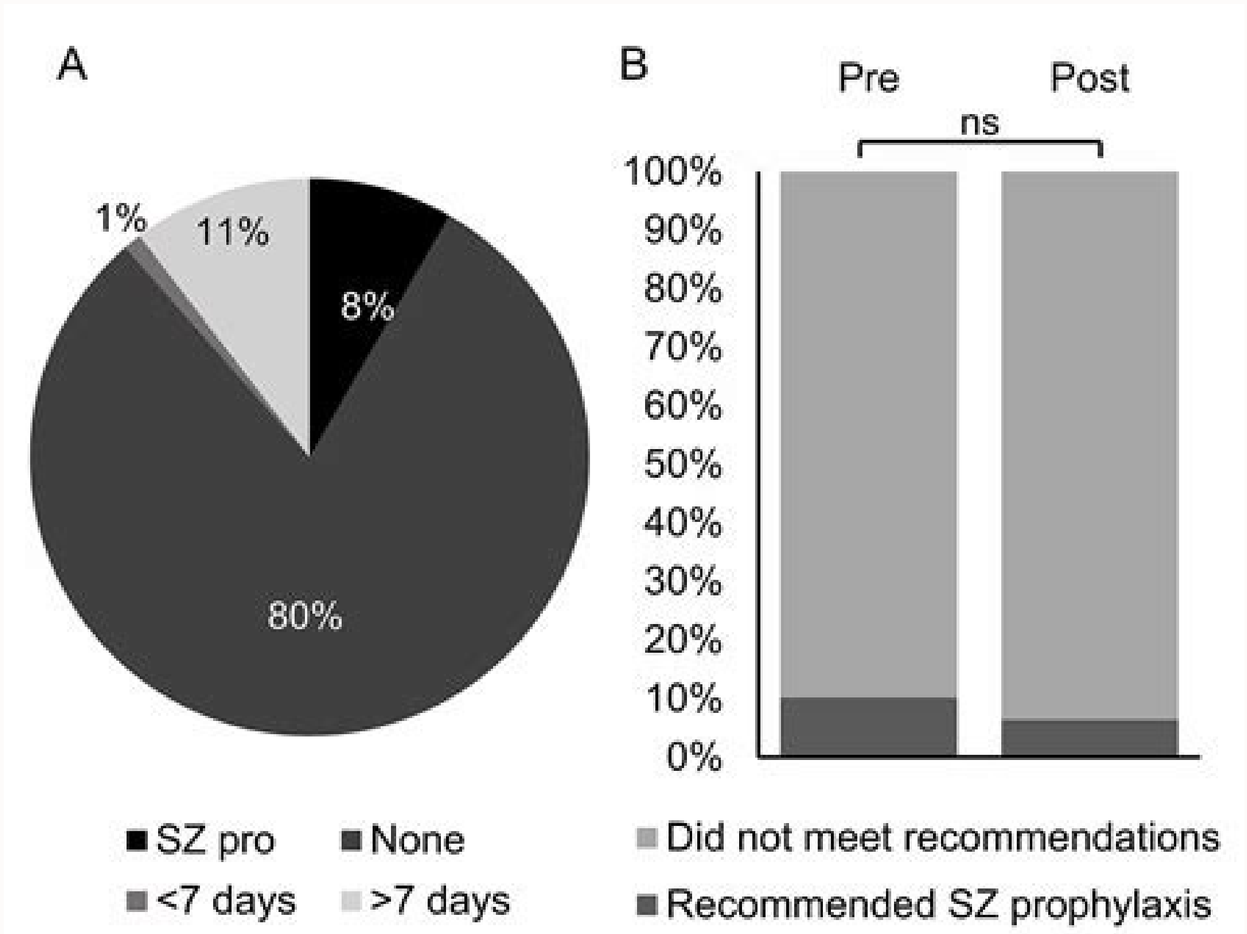

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RESEARCH

JPPT | Clinical Investigation

Early Post-traumatic Seizure Occurrence in Pediatric Patients Receiving Levetiracetam Prophylaxis With Severe Traumatic Brain Injury

Meghan J. Kolf, PharmD; Christopher C. McPherson, PharmD; Kara S. Kniska, PharmD; Caitlyn M. Luecke, PharmD; Michael A. Lahart, PharmD; and Jose A. Pineda, MD

OBJECTIVE Although levetiracetam is used for the prevention of early Post-traumatic seizures (EPTS) after traumatic brain injury (TBI), limited data exist describing the incidence of seizures in pediatric patients receiving levetiracetam prophylaxis. The objective of this research is to evaluate the prevalence of EPTS in children given prophylactic levetiracetam after severe TBI.

METHODS This study was conducted at a Level 1 pediatric trauma center and included pediatric patients with severe TBI who received levetiracetam for EPTS prophylaxis. Demographics and clinical information were retrospectively collected and evaluated. The primary outcome was prevalence of clinical or electrographic seizures within 7 days of initial injury as noted in the EMR.

RESULTS In 4 of 44 patients (9%), seizures developed despite levetiracetam prophylaxis. Concurrent use of other medications with antiepileptic properties was common (91%). There were no differences in demographic or baseline clinical characteristics between the group of patients experiencing seizures and those who did not. However, craniotomy was significantly more common in the seizure group (75% vs. 18%, p = 0.03).

CONCLUSIONS Children receiving prophylaxis with levetiracetam after severe TBI had a lower incidence of seizures (9%) than had previously been reported in the literature (18%). Given the limited literature available supporting the use of levetiracetam for the prevention of EPTS in children experiencing severe TBI, further study is needed to support routine use.

ABBREVIATIONS EEG, electroencephalogram; EMR, electronic medical record; EPTS, early post-traumatic seizures; FDA, US Food and Drug Administration; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IV, intravenous; PICU, pediatric intensive care unit; TBI, traumatic brain injury

KEYWORDS anticonvulsants; head injury; levetiracetam; pediatrics; prophylaxis; seizures; traumatic brain injury

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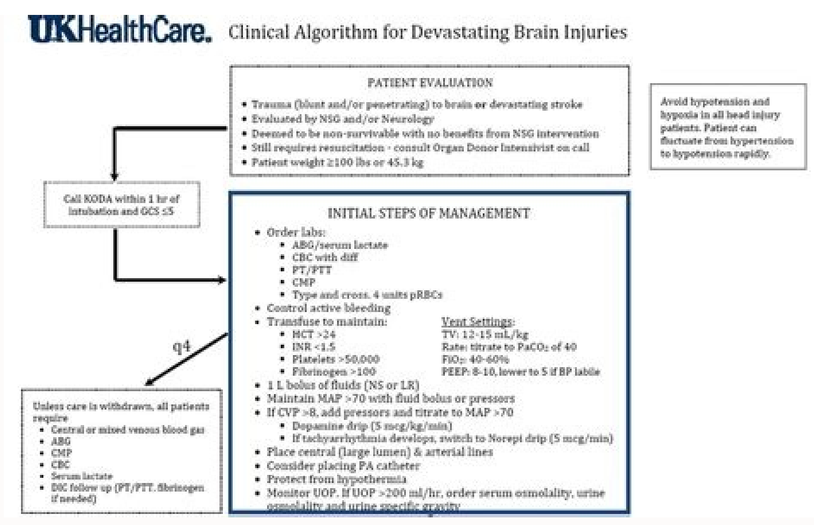
Introduction

The incidence of traumatic brain injury (TBI) has steadily increased in the United States over the last decade and remains a major cause of morbidity and mortality among pediatric patients. Just under half a million children younger than 15 years of age are evaluated annually in the emergency department for TBI.[1] There are a number of mechanisms of injury associated with TBI that can be particularly problematic in the developing pediatric patient. Early post-traumatic seizures (EPTS) occurring after TBI have the ability to perpetuate ongoing neurological damage and affect the long-term quality of life and developmental outcomes of pediatric patients.[2,3]

Due to the potential lasting sequelae from EPTS, some institutions have begun using antiepileptic therapy prophylactically for prevention of EPTS. However, due to lack of data and ambiguous recommendations in the guidelines, practice is highly variable.[4] Historically, prophylactic phenytoin has been used for the prevention of EPTS after TBI. A large randomized controlled trial in adult patients with TBI support its use.[5] The second edition of the pediatric TBI guidelines published in 2012 included a level III recommendation that phenytoin specifically be considered for the prevention of EPTS.[4] In a retrospective study, children with severe TBI who received prophylactic phenytoin had a 15% prevalence of EPTS compared with 53% in children who received no antiepileptic medications.[6] Additionally, a more recent study found antiepileptic drugs, including phenytoin, fosphenytoin, and phenobarbital, protective against EPTS.[7] However, because of many adverse effects, a narrow therapeutic index, and highly variable



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Jones, 2008 Observational prospective (LEV) in comparison with historic control (Phe) 73 (Phe 41, 32 Lev) Severe tbi not declared Phe: Clear Lev: 500mg Q12 Hours in advance Phe ã, â € "0/41 (0%) Lev â €" 1/32 (3%) Achievements anhormal EEG Phe â € "0/32 (0%) Lev ¢ â € ¬ "8/42 (19%) Note: In the above study, EEG was performed as needed Ã â €" 15/32 LEV patients were submitted to 19 EEG and 12/41 Phe patients underwent 19 seµÃsluvnoc seµÃsluvnoc ed o£Ã§Ãneverp an anÃotinef moc o£Ã§Ãarapmoc me matecariteveL od aic¡ÃcifE .sadapicetna sacit¡Ãmuart-s³Ãp seµÃsluvnoc :odatluser o arap sodÃulcni sodutse sªÃrt sod atserolf ad etoL CÃ © Straight patients: a meta-analysis. Epilepsy Pós-Precoce and late in the traumatic brain injury scenario: a meta-analysis and revision of the antiepilan control. Author / Year Type of study Patients, NRITTENING INCLUSION CRITTENING Dosing results Szaflarski, 20103 RCT (2: 1 Light to Phe) 52 (18 Phe, 34 Lev) Severe TBI, SBP > 90 mmhg, age ¥ 17 years no venous access, sci, tbi history, hemodynamic instability, annóxic lesion, hepatic insufficiency Phe: 20mg / kg fos-phe load, then 5mg / kg / day divided Q12 hours (levels followed) Lev: 20mg / kg IV load, then 1G IV Q12 Hours before convulsions PSE PHE Ã, Â € 5/18 (17%) Lev ¢ "7/34 (15%) NOTE: In the above study, all patients were monitored with EEG container for 72 hours or actual and following commands to identify subclean convulsions. 6 Jones Ke, et al. Khan, 20164 RCT (1: 1 Levs for PHE) 154 (77 Phe, 77 Lev) TBI moderate or serious 5-50 years History of previous SZ, delayed presentation> 12h, renal or electronic, PTs submitted to surgery , PTS who died within 7D Phe: 20 mg / kg Flee load, then 5 mg / kg / d divided Q12H (no-rich levels not measured) Lev: 20 mg / kg lev load, after 10-20 mg / kg divided Q12H before psol-traumatic convulsions Phe Ã, Â € 4/77 (5.2%) lev â € "7/77 (7.1%) Note: The above study is in High-tempered risk for prejudices due to absence of monitoring of sést rich Phe, containted EEG absence, lack of blinding and ethical allocation / uncertain allocation Inaba, 20135 prospective observational 813 (407 PHE, 406 Lev) The Age of TBI ¥ 18 years pregnancy, tbi not survivor, use of AED Pr esthospitalar, seizure before PHE inscription: 20mg / kg the IV load followed, 5mg / kg / day divided Q8 hours (levels followed) lev: 1g Q12 earlier hours Ulsions PSHE PHE Ã, Â € 6/407 (1.5%) lev â € "6/406 (1.5%) Note: In the study on on adapurga iof veL setneicap sod airoiam a e)704/693(ortnec mu me adapurga avatse EHP moc setneicap sod airoiam A o ,ortnec siod ed (329/406). PMID: 28712212. Levetiracetam Versus Phenytoin for Seizure Prophylaxis in Severe Traumatic Brain Injury. Apr 2010;12(2):165-72. A Randomized, Double-Blind Study of Phenytoin for the Prevention of Post-Traumatic Seizures. Brain 2016;30(9):1054-61 Thompson K, et Pharmacological Treatments for Preventing Epilepsy Following Traumatic Head Injury. doi: 1016/j.wneu.2017.11.116. Oct 2008;25(4):E3 7 Cotton BA, et al. Medicine (Baltimore). Relevant Literature Search: Despite the increasing use of levetiracetam, there has been no large, prospective, randomized controlled trial comparing the effectiveness of levetiracetam to phenytoin though there have been prospective observational and small randomized clinical trials. BMC Neurol. Jan 2012;72(1):276-81 World Neurosurg. Mar 2013;74(3):766-71. Epub 2017 Dec 2. 5 Inaba K, et al. Aug 1990;323(8):497-502 2 Guidelines for the Management of Severe Traumatic Brain Injury, 4th Edition. (GRADE Level of Quality ¢ÃÂÂ moderate; USPSTF strength of recommendation ¢ÃÂÂ B [intervention is recommended]) Anti-Epileptic Drugs and Doses Phenytoin (DilantinÃ®Â)/Fosphenytoin (CerebyxÃ®Â): Loading dose: Fosphenytoin 15 mg/kg (rounded to nearest 50 mg) Administered over 150 mg/min (e.g. 1g load given over 7 minutes) Maintenance dose: Weight Phenytoin Phenytoin extended release 110 kg Consult pharmacy Consult pharmacy Total phenytoin duration (IV and PO) is 7 days post-injury Enteral tube feeds impair the absorption of phenytoin capsules by up to 70%, so tube feeds should be held for 2 hours before and after Extended release phenytoin should not be crushed and put down an enteral feeding tube as this may affect the extended release Levetiracetam (KeppraÃ®Â): Maintenance dose: 1g PO/IV q12 hours x 7 days post-injury Levetiracetam pills can be crushed and put down enteral feeding tubes without a In the tube bottom delivery in 1990, Temken reported that the phenituary reduced the rate of early ports convulsions from 14.2% to 3.6%. Aug 2016; 30 (8): 677-88 XU JC, et al. Appendice A: Research Strategy As a series of recent systematic revisions on this topic, a more limited survey was performed and the systematic municipal evaluations were used to ensure that no relevant article has been lost. An analysis of minimization of costs of phenyton versus levetiracetam for advance convulsion pharmacoprophylaxis after traumatic brain injury. Below are the results of a search limited by studies comparing phenyton and levetiracetam including: randomized clinical trials, prospective observational studies and prospective observational studies using a historical control group. Neurochromatic care. May 2012; 12: 30 Wilson CD, Burks JD, Rhgers RB, Evans RM, Bakare AA, SafaVi-Abbasi S. A prospective multi-rectural comparison of Levetiracetam versus Phenytãna for early-traumatic prophylaxis. The review of the systematic revisions did not identify a lost randomized clinical trial, a prospective observational study or a prospective observational study using a historical control. 1 Although no study has shown the prevention of posttrumatic convulsions initiated to be associated with the improvement of survival or neurological outcome, they are thought to be the potential benefits to prevent the first crises Traumotics, prevent preventing the development of chronic epilepsy, decreasing the derangement in acute physiology and preventing the hospital.2 The use of Levetiracetam for Pós-traumatic prophylaxis has been increasing, presumably due to the purpose of effect Collateral well described of the Phenyton, including cut-off hypersensitivity reactions, inducement of the P450 hepatic cytochrome system, and drug interactions. 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Search Database Search Term Limits Total Yield: # of Articles # Excluded Articles # Included Articles 1 PubMed phenytoin AND levetiracetam AND traumatic brain injury Clinical Trial 4 1 (LEV not compared to PHE) 1 Prospective observational, 2 RCT 2 PubMed phenytoin AND levetiracetam AND traumatic brain injury Randomized Controlled Trial 3 0 1 Prospective observational, 2 RCT (all duplicates) 3 PubMed phenytoin AND levetiracetam AND traumatic brain injury Systematic Review 9 1 (outcome late post-traumatic seizure); 1 (LEV compared to placebo or no Tx); 7 total 16 3 10 Exclude Multiples 3 Included Papers 10 (2 RCTs, 1 Observational, 7 SRs) Systematic Reviews evaluated: Khan NR, et al. A Systematic Review of the Literature and Meta-analysis. Comparison Of Efficacy Of Phenytoin And Levetiracetam For Prevention Of Early Post Traumatic Seizures. Cost Considerations: Multiple studies have addressed the issue of cost associated with levetiracetam.7,8 However, there has recently been a reduction in the cost of levetiracetam have alleviated. Aug 2015;(8):CD009900 Zafar SN, et Phenytoin versus .niotynehp .niotynehpp vi fo nyad 7 yb dewollof daal niotynehpsof fo mrof eht ni dedivirp era stsoh .0 (82; pes-luj 6102 .SixalyHporp Eruzies citizuart-tsop Rof Niotyvel Fi Sistenu-TsOc .7423100000000000.7423100000000000. "iod â € €" â € ã ¢ yrujni niarb retalyhporp Eruzies rof

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