Study Protocol and Statistical Analysis Plan

Title: The prevalence and risk factors of coagulopathy in pediatric patients undergoing surgery for epilepsy: a retrospective cohort study

Date: 2022-11-02

Background:

Epilepsy is a common disease of the nervous system with severe consequences. Epidemiological surveys have shown that the prevalence of epilepsy in China is approximately 0.4–0.7%, comprising 7–10 million patients with epilepsy(1), most of whom are children(2). Although most symptoms of epilepsy can be controlled with the use of anti-seizure medications (ASMs), there are still a few patients who cannot achieve satisfactory seizure control with such medications or cannot tolerate their side effects, thus requiring surgical treatment. Surgical treatment of epilepsy has been recognized as a valuable treatment option for carefully selected patients to achieve better seizure control and quality of life(3). Compared to adults, children with epilepsy with indications for surgery usually have a better prognosis after surgical treatment(4–8). Many children undergoing surgery for epilepsy have a long history of using ASMs. Moreover, ASM therapy usually consists of multiple varieties of drugs, thereby bringing significant attention to the side effects of ASMs, especially those that may be relevant in the perioperative surgical setting.

ASMs have been associated with multiple adverse effects on platelets and the coagulation system(9). Valproic acid (VPA), one of the most commonly used traditional ASM, has been reported to cause multiple hematologic abnormalities, including thrombocytopenia, platelet aggregation dysfunction, fibrinogen (FBG) depletion, bone marrow suppression, decreased factor XIII, and acquired von Willebrand disease(10–17). However, the wide use of novel ASMs in recent decades has led to decreased reports of adverse events. The hematologic consequences of these novel ASMs or combined therapies are rarely reported. Few studies have suggested that levetiracetam (LEV) does not cause clinically significant or relevant hematological disorders(18).

Such reported side effects may be more significant in pediatric patients with epilepsy due to individual differences in age, weight, and pharmacokinetic action of the body on the drugs. The incidence of coagulopathies has been reported to be higher in children than in adults, especially hypofibrinogenemia(19,20). Nevertheless, whether these coagulation dysfunctions increase the risk of perioperative bleeding remains controversial. Most investigators suggest that ASMs, including VPA, are not associated with surgery-related blood loss or transfusion requirements(21–23). However, a few studies have suggested that considering the extra risk of perioperative bleeding, VPA should be discontinued before surgery(14).

Objectives:

This retrospective analysis of 390 children with epilepsy systematically investigated the incidence and risk factors of preoperative coagulation dysfunction in children undergoing surgery for epilepsy and their impact on surgery, with the objective to provide detailed and valuable clinical information.

Design:

This study was a retrospective cohort study.

Methods:

Study population

This retrospective study focused on children who underwent surgery for epilepsy between

January 2015 and December 2021 at the Neurosurgery Department of our hospital. Consecutive patients under 18 years who satisfied the following criteria were enrolled: a discharge diagnosis of “epilepsy” according to the International Classification of Diseases (ICD-10) and surgical treatment during the hospitalization. The following clinical data were collected: sex, age, weight, epilepsy course, and anti-seizure therapy. The initial laboratory data after admission included platelet count (PLT), prothrombin time (PT), activated partial thromboplastin time (APTT), FBG, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The patients' record of intra/post-operative transfusion or no transfusion was obtained from the medical records. The researchers also collected data on non-epileptic children who underwent non-epilepsy neurological surgery and were admitted at the same period from the Hospital Information System (HIS) as a control cohort. A total of 539 patients were initially included in the study. Patients were excluded if the clinical information or laboratory examinations were incomplete, or had concomitant diseases affecting coagulation or liver function. Patients were also excluded if they refuse to be enrolled to the study. Overall, 390 epilepsy cases and 104 non-epilepsy controls were included in the study (figure 1). All the surgeries were performed by the same surgeon.

ASM therapy

All ASM therapies were administered by a specialist at our hospital and recorded once the patient was admitted. Therapy was defined as the ASMs taken at the time of admission, and all ASM therapies were continued till surgery at our center. Based on the frequency of use of ASMs, drugs taken over 10 times in all cases were included in the statistics, including, VPA, LEV, oxcarbazepine (OXC), carbamazepine (CBZ), topiramate (TPM), and lamotrigine (LTG). Simultaneous administration of two or more types of ASMs was defined as “polytherapy.”

Laboratory tests

Following the clinical routine at our center, routine blood tests, coagulation function tests, and liver function tests were performed after admission. The following laboratory data were collected: PLT, PT, APTT, FBG, ALT, and AST levels. Abnormal coagulation function/coagulation dysfunction/coagulopathy was confirmed if the values obtained were more (or less) than the highest (or lowest) normal range values of either PT, APTT, FBG, or PLT (PT>14.5 s, APTT>45 s, FBG< 2 g/L, PLT<150×10^9/L). Abnormal liver function was defined as values higher than the highest range of ALT or AST (ALT>42 U/L, AST>59 U/L).

Statistical analyses

Categorical variables are presented as absolute (n) and relative frequencies (%). Continuous variables are shown as the mean (±standard deviation) or median (interquartile range), where applicable. The χ^2 test was used to evaluate differences among categorical variables. Continuous variables with normal and skewed distributions were compared using the t-test and Wilcoxon rank-sum test, respectively.

Univariate logistic regression analyses were performed to identify possible determinants of coagulation function. Possible relevant variables were included as covariates for multivariate logistic regression analysis to further filter out distractions. The results of the univariate and multivariate logistic regression analyses are presented as OR and 95% CI. The researchers used

R V4.1.2 to conduct statistical analyses.

Reference

1. Ding D, Zhou D, Sander JW, Wang W, Li S, Hong Z. Epilepsy in China: major progress in the past two decades. Lancet Neurol. 2021 Apr 1;20(4):316–26.

2. Ryvlin P, Cross JH, Rheims S. Epilepsy surgery in children and adults. Lancet Neurol. 2014 Nov 1;13(11):1114–26.

3. Malmgren K, Edelvik A. Long-term outcomes of surgical treatment for epilepsy in adults with regard to seizures, antiepileptic drug treatment and employment. Seizure. 2017 Jan 1;44:217–24.

4. Barba C, Cossu M, Guerrini R, Di Gennaro G, Villani F, De Palma L, et al. Temporal lobe epilepsy surgery in children and adults: A multicenter study. Epilepsia. 2021 Jan;62(1):128–42.

5. Engel J, McDermott MP, Wiebe S, Langfitt JT, Stern JM, Dewar S, et al. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. JAMA. 2012 Mar 7;307(9):922–30.

6. Maragkos GA, Geropoulos G, Kechagias K, Ziogas IA, Mylonas KS. Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis. Neurosurgery. 2019 Dec;85(6):741–9.

7. Jenny B, Smoll N, El Hassani Y, Momjian S, Pollo C, Korff CM, et al. Pediatric epilepsy surgery: could age be a predictor of outcomes? J Neurosurg Pediatr. 2016 Aug;18(2):235–41.

8. Spencer S, Huh L. Outcomes of epilepsy surgery in adults and children. Lancet Neurol. 2008 Jun;7(6):525–37.

9. Pacione D, Blei F, Devinsky O, Weiner HL, Roth J. Coagulation abnormalities in children undergoing epilepsy surgery. J Neurosurg Pediatr. 2011 Jun;7(6):654–9.

10. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, et al. Valproate-associated Coagulopathies Are Frequent and Variable in Children. Epilepsia. 2006;47(7):1136–43.

11. Hauser E, Seidl R, Freilinger M, Male C, Herkner K. Hematologic manifestations and impaired liver synthetic function during valproate monotherapy. Brain Dev. 1996 Mar 1;18(2):105–9.

12. Riahi-Zanjani B, Delirrad M, Fazeli-Bakhtiyari R, Sadeghi M, Zare-Zardini H, Jafari A, et al. Hematological Consequences of Valproic Acid in Pediatric Patients: A Systematic Review with a Mechanistic Approach. CNS Neurol Disord - Drug Targets. 21(4):316–25.

13. Kumar R, Vidaurre J, Gedela S. Valproic Acid–Induced Coagulopathy. Pediatr Neurol. 2019

Sep 1;98:25–30.

14. Ranganathan C, Verma NP, Diaz FG. Valproate and epilepsy surgery. J Epilepsy. 1993 Jan 1;6(3):142–4.

15. Loiseau P. Sodium valproate, platelet dysfunction, and bleeding. Epilepsia. 1981 Apr;22(2):141–6.

16. Koenig S, Gerstner T, Keller A, Teich M, Longin E, Dempfle CE. High incidence of vaproate-induced coagulation disorders in children receiving valproic acid: a prospective study. Blood Coagul Fibrinolysis Int J Haemost Thromb. 2008 Jul;19(5):375–82.

17. Kreuz W, Linde R, Funk M, Meyer-Schrod R, Föll E, Nowak-Göttl U, et al. Valproate Therapy Induces von Willebrand Disease Type I. Epilepsia. 1992;33(1):178–84.

18. Boon P, Hulhoven R, Offner F. Levetiracetam and bleeding disorders. Acta Neurol Belg. 2007 Dec 1;107(4):97–102.

19. Post DS, van der Veer A, Schijns OEMG, Klinkenberg S, Rijkers K, Wagner GL, et al. Assessment of need for hemostatic evaluation in patients taking valproic acid: A retrospective cross-sectional study. PloS One. 2022;17(2):e0264351.

20. Zhou W, He Y, Li Q, Li Y, Su Y, Yan L. Clinical Characteristics of Hospitalized Neonates With Hypofibrinogenemia: A Retrospective Cohort Study. Front Pediatr. 2020 Sep 22;8:589.

21. Manohar C, Avitsian R, Lozano S, Gonzalez-Martinez J, Cata JP. The effect of antiepileptic drugs on coagulation and bleeding in the perioperative period of epilepsy surgery: The Cleveland Clinic experience. J Clin Neurosci. 2011 Sep 1;18(9):1180–4.

22. Anderson GD, Lin YX, Berge C, Ojemann GA. Absence of bleeding complications in patients undergoing cortical surgery while receiving valproate treatment. J Neurosurg. 1997 Aug;87(2):252–6.

23. Ward MM, Barbaro NM, Laxer KD, Rampil IJ. Preoperative valproate administration does not increase blood loss during temporal lobectomy. Epilepsia. 1996 Jan;37(1):98–101.