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A meta-analysis: Do prophylactic antiepileptic drugs in patients with brain tumors decrease the incidence of seizures?

Xiangyi Kong, Jian Guan, Yi Yang*, Yongning Li, Wenbin Ma, Renzhi Wang

Department of Neurosurgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, No. 1 Shuaifuyuan Hutong of Dongcheng District, Beijing 100730, PR China

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ABSTRACT

Background: Seizures are a potentially devastating complication of brain tumors. Several studies in the past have attempted to demonstrate that prophylactic antiepileptic drugs (AEDs) in patients with brain tumors can decrease the incidence of seizures. However, it is currently unclear whether AEDs should be routinely administered to patients with brain tumors who have never had a seizure.
Objective: A meta-analysis of randomized trials was conducted to estimate the effectiveness of seizure prophylaxis in people with brain tumors.
Methods: A range of electronic databases were searched (1966–2014): MEDLINE, the Cochrane Library Database, EMBASE, CINAHL, Web of Science and the Chinese Biomedical Database (CBM) without language restrictions. Two independent reviewers assessed trials for eligibility and quality, and meta-analysis was performed using the STATA 12.0 software. Integrated Odd Ratio (OR) with its corresponding 95% confidence interval (95%CI) was calculated.
Results: Six RCTs were included with a total of 547 patients with brain tumors. The meta-analysis results revealed that patients with brain tumors who received prophylactic antiepileptic interventions did not have significantly lower epilepsy incidence than those in controlled groups (OR = 0.939, 95%CI = 0.609–1.448, $z = 0.29$, $P = 0.775$). Sensitivity analysis suggested the statistical results were robust. No publication bias was detected in this meta-analysis ($P > 0.05$).
Conclusion: Although some past studies indicated AEDs can be used in patients with brain tumors to relieve epilepsy, present integrated evidences cannot show in unequivocal terms that brain tumor patients can benefit from seizure prophylaxis.

1. Introduction

Seizures are a potentially devastating complication of resection of brain tumors, often worsening existing neurological deficits, producing new deficits, and prolonging the length of hospitalization after brain tumor surgery [1]. For some people, a seizure might be the first clue that something unusual is happening in the brain. Seizures are particularly common with slow-growing gliomas, meningiomas located in the convexity of the brain, and with metastatic brain tumors. The incidence of seizures is higher with primary tumors than with metastatic lesions, and among patients with primary tumors, seizures are less common with high-grade as opposed to low-grade gliomas.

Up to 60% of people with brain tumors may present with seizures, or may have a seizure for the first time after diagnosis or neurosurgery [2]. (Antiepileptic drugs for preventing seizures in people with brain tumors). Common features of seizures in patients with brain tumors include sudden onset, loss of consciousness and body tone followed by twitching and relaxing muscle contractions, loss of control of bodily functions, at risk for biting tongue, short periods of no breathing (30 s); may turn dusky blue, short duration (2–3 min), etc. After effects include sleepiness, headache, confusion, sore muscles, brief weakness, or numbness.

In people with brain tumors, seizures may be controlled with anticonvulsion or antiepileptic medication [3]. Due to the high rate of seizure activity among people with some types of brain tumors, it is usually a standard part of treatment to include these types of drugs in order to prevent seizures. Prophylactic AEDs' use appears to be widespread, particularly in gliomas, regardless of grade [4,5]. In a recent survey conducted by Glantz et al., 81% of neurosurgeons reported that they prescribed prophylactic AEDs to

* Corresponding author. Tel.: +86 010 69152530.
E-mail addresses: yangyipumch@sina.com, 694130447@qq.com (X. Kong).

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patients without a history of seizures. However, this practice has been put into question. In 2000, the American Academy of Neurology (AAN) published practice guidelines recommending against routine AED use as primary prophylaxis in brain tumor patients. It also suggested AED tapering and discontinuation after the first postoperative week in medically stable patients [6]. In 2006, the neuro-oncology Disease Site Group in Ontario published guidelines, also recommending against primary prophylaxis with AEDs, but considered that there was insufficient evidence to recommend in favor or against prophylactic AED discontinuation [2]. Giving the supporting evidence for the efficacy and safety of perioperative AEDs prophylaxis was little and mixed, we conducted this meta-analysis to assess it further.

2. Materials and methods

2.1. Literature search

The Meta-analysis of Observational Studies in Epidemiology guidelines 7 were followed in performing this meta-analysis. The MEDLINE, EMBASE, CNKI, CBM, WanFang database and the Cochrane library were searched (the latest search date being September 2014). The following key words were used: (1) "Antiepileptic Drugs"; (2) "Brain tumors"; (3) "Seizure". We also manually searched the reference lists of retrieved articles for additional studies. Language restrictions were not used. Two investigators (X.Y.K. and J.G.) independently evaluated the studies for inclusion, before which, the information of these studies which may affect researchers' selecting predispositions was hided. Disagreements were deferred to a third investigator (Y.Y.). Then we did quality evaluation and bias analysis according to the quality evaluation standard put forward in Cochrane Reviewer's Handbook 5.0.

2.2. Inclusion criteria

Studies enrolled in this meta-analysis fulfilled the following inclusion criteria: (1) Study design: All randomized controlled studies published with any sample size whose original data is completely examining the efficacy of AEDs prophylaxis in patients with brain tumors were considered eligible for this meta-analysis. (2) Patients' type: Patients with definite diagnosis of brain tumors who have never had a seizure, not restricted by tumor types, age, gender and race, whether operated or not. (3) Interventions: Experimental group is including, but not limited to, AEDs such as Phenytoin Sodium, Ethosuximide, Levetiracetam, Sodium Valproate, etc. The control group is placebo, or directly blank control. Other treatment should be consistent between the experimental groups and control groups. The follow-up time is required no less than 6 months. (4) The ending index: All randomized controlled studies taking the occurrence of seizure as the judgment index for prophylaxis effect are incorporated into the analysis.

2.3. Exclusion criteria

Studies with any one of the following characteristics were excluded: (1) Not RCTs. (2) Repetition of the published literature. (3) Animal experiment. (4) The interventional measures in the prophylaxis group and control group did not accord with the inclusive criteria, for example, interventions in the control group included AEDs' use. (5) Reviews. (6) The original data are not complete. (7) Purely descriptive research and clinical trials without contrast. (8) Self-control study. (9) The control group is of healthy people or volunteers. (10) No basic information about the subjects or the interventions. (11) Studies with rate of the defaulters higher than 20%.

2.4. Data extraction

Data were extracted with a pre-designed review form. Data to be extracted were as follows: journal name, first author's name, publication year, inclusion and exclusion criteria, and demographic characteristics of the population being studied, dosage schedule of seizure prophylaxis and any adverse drug reactions. We recorded ITT results if available.

2.5. Literature quality assessment

Quality ratings were made according to the modified Jadad scale [7]. The Jadad criteria included four aspects: whether the study was described as randomized; whether allocation concealment was described; whether the study was double blind; and if there was a description of withdrawals and dropouts. The Jadad score ranged from 0 to 7. A score of 1–3 indicates a poor quality and 4–7 means a high quality. We only include the literatures with Jadad score not less than 4. Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion and consensus or by consulting a third independent party.

2.6. Statistical analysis

Statistical analyses were performed with STATA 12.0 (StataCorp LP, College Station, TX, USA). For dichotomous outcomes, the ORs and 95%CIs for determination of preoperative embolization were calculated. Labbe figure, Cochran's Q-test and I^2 test (variation in OR attributable to heterogeneity) were all performed to judge the heterogeneity between included studies [8,9]. In labbe figure, if the points basically present as a linear distribution, it can be taken as an evidence of homogeneity. Heterogeneity was also considered to be significant at $P < 0.10$ for the Q statistic [10]. I^2 values of 25%, 50% and 75% were used as evidence of low, moderate and high heterogeneity, respectively [8]. If there was no evidence of statistical heterogeneity between studies, then a fixed-effects model was used. Otherwise, the random-effects model of DerSimonian and Laird was applied in the presence of significant heterogeneity [10].

To test the robustness of the results of this meta-analysis, a sensitivity analysis was performed by the one-at-a-time method, which meant omitting one study at a time and repeating the meta-analysis. If the omission of one study significantly changed the result, it implied that the result was sensitive to the studies included. Potential publication bias was assessed by visual inspection of the funnel plot, and an asymmetric plot suggested possible publication bias [11]. An Egger linear regression test at the $P < 0.01$ level of significance was also performed to assess the publication bias [12]. Since the included studies are not large enough, meta-regression was not performed.

3. Results

3.1. Literature retrieval results

A flow chart showing the procedure for identifying the studies is presented in Fig. 1. Based on the predefined search strategy, a total of 189 articles relevant to the searched keywords were initially identified without gray literatures applicable. The titles and abstracts of all articles were reviewed and 65 were excluded; full texts and data integrity were then reviewed and another 112 papers were excluded. Finally, seven RCTs were included in this meta-analysis [13–18]. Excluded studies and the rational for exclusion