A systematic review of peri-operative seizure prophylaxis during brain tumor resection: the case for a multi -center randomized clinical trial

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Introduction

The majority of neurosurgeons administer anti-epileptic drugs (AED) prophylactically for supratentorial tumor resection. There is not clear evidence in the literature to support this practice. The putative prophylactic benefit of perioperative seizure prophylaxis must be weighed against the risks of adverse effects and drug interactions in patients without a history of seizures. Consequently, the authors conducted a systematic review of prospective randomized controlled trials (RCT) that have evaluated the efficacy of perioperative seizure prophylaxis during brain tumor resection among patients without a history of seizures.

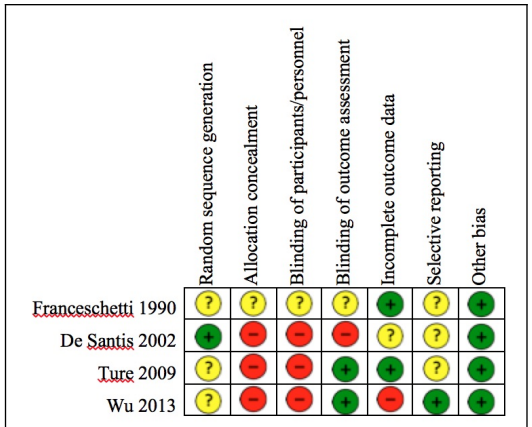

Figure 1. Risk of bias summary for each included study. Green plus sign = low risk; red minus sign = high risk; yellow question mark = not reported.

Methods

Five databases (Pubmed/MEDLINE, the Cochrane Central Register of Controlled Trials, CINAHL/Academic Search Complete, Web of Science, and ScienceDirect) were searched for RCTs investigating perioperative seizure prophylaxis in brain tumor resection published before May 2017. Of the 496 unique research articles identified, there were four studies selected for inclusion in this review.

Table 1. Systematic Review

	Franceschetti 1990	De Santis 2002	Ture 2009[c]	Wu 2013[d]
Location	Italy	Italy	Turkey	USA
Study design	RCT	Open-label RCT	RCT	RCT
Sample size	63[a]	200	80	123
Sample characteristics	Mean age: 55 34 M; 29 F	103 M; 97 F Preoperative seizures: 67 Preexisting AED therapy: 185	36 M; 39 F	67 M; 56 F
Tumor type	Supratentorial neoplasms Tumor location Frontal: 12 Temporal: 18 Central: 2 Parietal: 16 Occipital: 15 Meningiomas: 27 Malignant glial: 23 Metastases: 13	Supratentorial brain tumors Tumor location Frontal: 70 Temporal: 47 Parietal: 41 Sellar: 17 Occipital: 7 Deep structures: 6 Intraventricular: 6 Tentorial: 6 Glioma: 95 Meningioma: 81 Metastases: 10 Other: 14	Supratentorial brain tumors Surgical route Frontal: 17 Parietal: 6 Temporal: 4 Parietal: 48 Meningioma: 32 Glioma: 42 Metastases: 1	Intraparenchymal supratentorial tumors Tumor location Frontal: 48 Temporal: 34 Parietal: 17 Occipital: 18 Other: 6 Metastases: 77 Glioma: 46
Anti-epileptic drugs (AED) type	Phenobarbital (PB) or Phenytoin (PHT)	PHT in addition to current AED therapy	Gabapentin	PHT
Control group	No medication	Current AED therapy	PHT	No medication
Timing of intervention	Not specified	Intraoperatively	7 d before surgery	Intraoperatively
Duration of intervention	Not specified	7 d	6-12 months for meningiomas or indefinitely for glial tumors	Tapered on POD 8
Follow-up interval	Minimum of 6 mo	7 d	1 mo	12 mo
Outcome definition	Early (≤7 d) and late postoperative seizures	Early postoperative seizures (≤7 d)	Seizure activity at 0, 15, 30 min, 1, 2, 4, 6, 12, 24, 48 hrs, and 1 mo postoperatively	Early seizure (≤30 d) or clinically significant seizure with neurological deficits assessed daily for 3 d after surgery, on POD 8, and every 2-3 mo for up to 12 mo
Seizure incidence	Early seizures in 18% of untreated and 7% of PB or PHT treated Late seizures in 21% of untreated and 12% of PB or PHT treated	Early seizures in 13 PHT treated and 11 controls	One patient in the PHT group had a partial seizure on POD 3 All patients were seizure-free at 1-month follow-up	Seizures in 18% of control and 24% of prophylaxis groups (p=0.51) Early seizures (≤30 days) in 8% of control and 10% of prophylaxis groups (p=1.00) Late seizures (>30 days) in 10% of control and 14% of prophylaxis groups (p=1.00) Clinically significant seizures in 2% of control and 3% of prophylaxis groups (p=0.62)
Risk estimate	Not specified	Not specified	Not specified	Odds of early seizure in prophylaxis relative to control was 1.4 (95% CI: 0.425-4.763)
Statistical significance	No	No	No	No
Authors support prophylactic AED use	Yes	No[b]	No	No

[a] After removal of population of patients with preoperative seizures
[b] Conclusions only extend to short-term PHT prophylaxis in addition to current AED therapy
[c] Study designed to assess postoperative analgesic efficacy of gabapentin compared to phenytoin
[d] Trial closed early due to limited power to observe significant differences between groups

Results

This systematic review identified four RCTs that met inclusion criteria. The weighted average seizure incidence was 10.65% within the untreated groups. No significant difference was observed in the seizure rates among patients who received seizure prophylaxis when compared to those who did not. Using the observed seizure incidence, it was estimated that a total of 1,236 patients would be required for a RCT to demonstrate non -inferiority based on a Farrington-Manning non-inferiority test performed at the 0.05 level using a non-inferiority difference of 0.05%. None of the current RCTs to date have met this sample size, which highlights the need for a multi-center RCT.

Conclusions

Based on our systematic review of major RCTs, there is not a significant reduction in the incidence of seizures among those who receive prophylactic AEDs following brain tumor resection when compared to controls. A large multi-center RCT is required to assess whether perioperative seizure prophylaxis provides benefit for patients undergoing brain tumor resection.

Table 2

Seizure Rate (%)			
AED group	**Untreated group**	**N (total)**	**# sites[a]**
10%	14%	26,092	131
10%	13%	6,322	32
10%	12%	2,720	14
10%	11%	1,480	8
10%	10%	914	5
10%	9%	612	4
10%	8%	434	3

Table 2: Expected sample size required for a non-inferiority study aimed to demonstrate similar seizure rates for treatment and control groups. This information is based on a Type-I error=0.05, Power=80%, Diff=0.05. a Number of sites calculated from an accrual rate of 50 per site each year for 4 years.