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Original Article

Incidence and Risk Factors or Early Postoperative Seizure in Patients with Intracranial Tumor Removal: Prasat Neurological Institute Experience

Kullapat Veerasarn, MD
Paveen Tadadontip MD
Prasat Neurological Institute, Bangkok, Thailand

Abstract ***Objectives:*** **To evaluate the incidence and to identify the risk factors of early postoperative seizure (POSz) (within one week after surgery) in patients underwent intracranial tumor removal.**

Methods: **Medical records of patients who had their brain tumor removed during June 2006 - May 2007 were reviewed. Data of demography, clinical presentation, operative records and pathology reports were recorded. The incidence of early POSz was calculated in total number and in subgroup differentiated by location. Univariate chi square and logistic regression analyses were used to analyze association between variables and seizure outcome.**

Results: **The incidence of early POSz for intracranial tumor removal surgery was 9.7 % (21/216) with 13.16 % for convexity lesion, 16.07 % for subcortical location, 2.08 % for posterior fossa location, and 13.89 % for sella and parasellar location. In univariate analysis, male gender, history of pre-operative seizure and location of tumor were found to relate with early POSz. In multivariate analyses male gender and history of preoperative seizure were statistically related with early POSz. Role of antiepileptic drug prophylaxis was also studied and showed a benefit in high risk group with no statistical significance. In patients with early POSz, seizure occurred mostly on the day 0, day 1 and day 2 after surgery and correctable cause could be identified in some cases (evacuation of intracranial hematoma in one case, low antiepileptic drug level in two cases).**

Conclusions: **Early POSz had a high incidence in surgery for tumor located at the locations of convextity, subcortex and sella parasella. History of preoperative seizure and male gender were the risk factors for early POSz. Close observation in these groups of patients during the postoperative period and the prescription of antiepileptic drugs would be necessary.**

Key words: **brain tumor removal, early postoperative seizure**

INTRODUCTION

Postoperative seizure (POSz) is a common complication in neurosurgical practice. It affects the recovery of nervous systems and may cause morbidity and mortality. Incidence of POSz was estimated around 15-20% in supratentorial operation in non- trauma group[1] and varied between 1-5% for infratentorial operation[2,3]. But the incidence of early POSz (within one week after operation) in patients who had craniotomy for brain tumor removal was rarely mentioned in literature[4].

There have been many attempts to reduce the occurrence of postoperative seizure, one common method is anti-epileptic drug prophylaxis. However

Correspondence address : *Kullapat Veerasarn, MD, Prasat Neurological Institute, 312 Ratchavithi Road, Ratchathewi, Bangkok 10400, Thailand; Telehone: +66 2354 7007 Fax: +66 2354 7085; E-mail: kveerasarn@hotmail.com*

the role of antiepileptic prophylaxis is still controversial[4,5]. Recently, the study of seizure prophylaxis in brain tumor patient clearly demonstrated that antiepileptic medication had no benefit in primary prophylaxis[6]. Currently, we do not have a standard guideline for seizure prophylaxis in tumor surgery patients. Neurosurgeons usually prescribe antiepileptic medication in patients considered "high risk" and continue medication around one to three weeks and tapering off if patients have no seizure. This measure is based on the review benefit of anticonvultsant in neurosurgical patients[4].

Many factors were studied and shown a correlation with early POSz such as history of previous seizure, lesion involve motor cortex, degree of cortical injury, postoperative brain edema, hemorrhage and hyponatremia[7]. But some factors such as location and pathology of tumor had rarely been studied. Boarini et al reported incidence of postoperative seizure in glioma patient 39% in non medical prophylaxis group and 21% in prophylaxis group[8]. The objectives of this study were to identify the incidence and the risk factors correlated with early POSz.

Materials and Methods

Operative registration records during June 2006 - May 2007 were retrospectively reviewed. All patients who underwent craniotomy with tumor removal procedure were enrolled in this study. Exclusion criteria were patients with biopsy alone and patients who had more than two procedures within one week. There are nine attending surgeons practicing during that time. Clinical records during admission were reviewed. Histories of preoperative clinical seizure were obtained. Operative records were reviewed. Timings of operation were obtained and classified as less than six hours or more than six hours. Whether the patients underwent corticotomy procedure was recorded. Locations of tumor were classified into seven groups; namely convexity group (extra axial tumor had center or mainly involve cerebral convexity cortex), subcortical lesion group (intra axial tumor had center at subcortical region), sellar & parasellar group, posterior fossa group (including all tumor in posterior fossa - brainstem, cerebellopontine angle, 4th ventricle, cerebellar tumor), pineal region group, intraventricular group (tumor in lateral and 3rd ventricle), and cavernous sinus lesion. Sphenoid meningioma and other extra axial skull base growth were grouped as skull base lesion. Pathology reports were reviewed. Prophylactic antiepileptic prescription were reviewed and recorded in details (drug, dose, timing (relate with operation) and route of administration).

Postoperative course of patients were reviewed. Seizure was declared and recorded if any clinical seizure was noted in physician's progress note or nurse's note. Details of seizure were recorded including postoperative date occurred, investigation performed and clinical course.

Statistical Analysis

Data was reported as descriptive statistics. Correlation between factors and early POSz were tested by Chi square and Mann-Whitney U test for difference of age between two groups. Factors correlated with early POSz in univariate analysis were analyzed by multiple regression analysis models. Data was calculated by SPSS version 15.0.

Results

Two hundred and sixteen consecutive cases of brain tumor surgery were reviewed during June 2006 - May 2007. There were 93 males and 123 females. The youngest patient was 1 yr old while the oldest one was 75 yrs old. The total incidence of POSz was 9.7% (21/216) (Table 1). The incidence of POSz in convexity lesion, subcortical lesion, sellar-parasellar lesion, intraventricular lesion was higher than total incidence (13.16%, 16.07%, 13.89%, 14.29%) whereas posterior fossa group had only 1 of 48 case seizure (2.08%) and no seizure in cavernous sinus and sphenoid wing lesions. Only three pineal tumor operations were performed in that year and no early postoperative seizure found.

Factors including age, gender, tumor histology, location of tumor, corticotomy procedure, duration of operation (< 6 hrs or > 6hrs), history of preoperative clinical seizure and perioperative antiepileptic prophylaxis were analyzed with the occurrence of early POSz (Table 2). Only three factors were found to correlate with early POSz: history of preoperative clinical seizure ($p = 0.001$), male gender ($p = 0.021$) and tumor location ($p = 0.036$). Corticotomy procedure

Table 1 Incidence of early postoperative seizure differentiated by tumor location.

Tumor location	Incidence (%)
Convexity: extra axial mass	5/38 (13.16)
Subcortical lesion: intra axial mass	9/56 (16.07)
Posterior fossa	1/48 (2.08)
Sellar / parasellar lesion	5/36 (13.89)
Pineal location	0/3 (0)
Intraventricular lesion	1/7 (14.29)
Skull base area: cavernous, sphenoid, extra axial mass at skull base	0/28 (0)

showed higher incidence of POSz but not reached statistical significance (p = 0.057). Perioperative antiepileptic prophylaxis showed no correlation with seizure (p = 0.228). Using multivariate regression analysis, male gender and history of preoperative seizure were independently correlated with early POSz while location of tumor failed to show statistical signification correlation (p = 0.284) (Table 4). Peri-operative antiepileptic drugs used in the study were phenytoin or valproic acid in a standard loading and maintenance dose[11]. The timing for prophylaxis was peri-operative

Table 2 The correlation between various factors and early post operative seizure

Factors	Early post operative seizures		P value
	Yes	no	
Pathology			0.101
Glioma group	5 (23.8%)	33 (16.9%)	
Meningioma	5 (23.8%)	79 (40.5%)	
Metastasis	2 (9.5%)	14 (7.2%)	
Schwannoma	1 (4.8%)	21 (10.7%)	
Pituitary adenoma	1 (4.8%)	11 (5.6%)	
Craniopharyngioma	4 (19.0%)	7 (3.6%)	
Other	3 (14.3%)	30 (15.4%)	
Location of tumor			0.036
Cortical surface	5 (23.8%)	33 (16.9%)	
Subcortical lesion	9 (42.9%)	47 (24.1%)	
Posterior fossa	1 (4.8%)	47 (24.1%)	
Sellar, Parasellar region	5 (23.8%)	31 (15.9%)	
Other: pineal, intravent, skull base	1 (4.8%)	37 (19.0%)	
Age	46 (25-59)	44 (34-54)	> 0.05
Male gender	14 (66.7%)	79 (40.5%)	0.021
Corticotomy procedure	10 (47.6%)	54 (27.7%)	0.057
Timing of operation (0-6 hrs / > 6 hrs)	10 (47.6%)	126 (64.6%)	0.125
Preoperative seizure	11 (52.4%)	35 (17.9%)	0.001
No Perioperative seizure prophylaxis	4 (19.0%)	62 (31.8%)	0.228

Table 3 Number of antiepileptic prophylaxis prescribed differentiated by location of tumor and their seizure outcome.

Location	Total case	Prophylaxis		Seizure	
		Yes	No	Prophylaxis	No prophylaxis
Convexity	38	36	2	5 (13.9%)	0
Subcortical lesion	56	52	4	8 (15.4%)	0
Posterior fossa	48	16	32	0	1
Sellar parasellar	35	21	14	2 (9.5%)	3 (21.4%)
Pineal region	3	2	1	0	0
Intraventricular lesion	7	3	4	1 (33.3%)	0
Skull base	29	19	10	0	0

Table 4 Regression analysis to identify correlation between male gender, history of clinical preoperative seizure and location of tumor with early postoperative seizure.

Factors	Odd ratio	P value
Male sex	2.735	0.047
History of clinical preoperative seizure	3.757	0.009
Location of tumor	1.261	0.284

or immediate postoperative depended on each neurosurgeon.

Although there was no correlation between antiepileptic prophylaxis and early POSz, higher percentage of seizure occurred in patients receiving no prophylaxis with tumors in sellar and paresellar location (21.42% and 9.52%). This did not reach statistical significance due to too small sample size

Table 5 Characteristics of patients who had early POSz.

Case	Post op day	Seizure type		Perioperative AE prophylaxis	Drug level	Post op imaging
		Preop	Post op			
1. Atypical meningioma, Occipital convexity	1	-	Generalized	Yes	-	Surgical site hematoma
2. Meningioma, parietal convexity	5	-	Generalized	Yes	Adequate	Surgical site hematoma
3. Meningioma, parietal parasagital	0	-	Motor	Yes	-	Negative study
4. Planum meningioma	5	Generalized	Generalized	Yes	Low level	Negative study
5. Planum meningioma	1	-	Generalized	Yes	Adequate	Negative study
6. DNET, Temporal	0	Generalized	Generalized	Yes	-	Negative study
7. Frontal mixed oligoastrocytoma	4	Generalized	Motor	Yes	Adequate	No imaging
8. Lymphoma, parietal	2	Motor	Generalized	Yes	Adequate	Brain edema
9. Gemistocytic astrocytoma, frontal	0	Generalized	Generalized	Yes	-	Epidural hematoma, need surgical evacuation
10. Metastasis, frontal	3	Motor	Motor	Yes	Adequate	No imaging
11. Frontal mixed oligoastrocytoma	0	Generalized	Generalized	Yes	-	No imaging
12. Metastasis, parietal	0	Motor	Motor	Yes	Adequate	No imaging
13. Frontal GBM	2	Generalized	Motor	Yes	-	Brain edema
14. Frontotemporal astrocytoma	1	Generalized	CPS	Yes	-	No imaging
15. Vestibular schwannoma (with hydrocephalus and intraop ventriculostomy)	1	-	Generalized	No	-	No imaging
16. Craniopharyngioma	6	-	Generalized	Yes	-	Negative study
17. Craniopharyngioma	0	Generalized	Generalized	No	-	Negative study
18. Craniopharyngioma	0	Generalized	Generalized	No	-	Negative study
19. Craniopharyngioma	1	-	Generalized	No	-	Negative study
20. Pituitary adenoma	2	-	Generalized	Yes	Adequate	Surgical site hematoma
21. Pinealoblastoma, intraventricular (lateral ventricle bilateral, 3rd ventricle)	0	-	Generalized	Yes	Low	Negative study

- In CT imaging, negative study means image was normal during postoperative period. No imaging means image was not sent by attending physician.
- For drug level "-" didn't investigate; "adequate" adequate blood level (10-20 mg/ml for phenytoin and 50-100 mg/ml for valproic acid; "low" below therapeutic level.

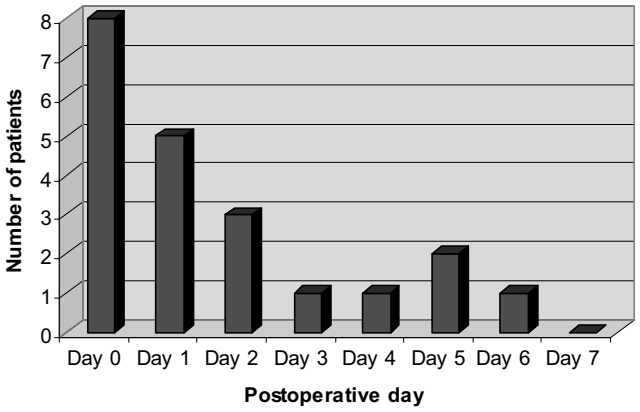

Figure 1 Graph showed the number of patients who developed seizure and post operative day

(Table 3). Most patients in the convexity and subcortical group (88/94) and in the sellar and parasellar group (21/35) received antiepileptic prophylaxis whereas those in the posterior fossa group did not. In the cortical surface and subcortical group, all seizure cases occurred in patients with antiepileptic prophylaxis.

The characteristics of patients who had early POSz were shown in Table 5. Details included date of seizure, seizure characteristic at pre and post operative periods, antiepileptic prophylaxis, drug level when seizure occurred, CT imaging when seizure occurred. Most patients who had early POSz were controlled by adequate intravenous antiepileptic therapy except for one case (Patient No. 2 in Table 5) who developed generalized tonic clonic seizure on the postoperative day 5. After being given adequate intravenous antiepileptic therapy, he regained conscious but still had epilepsia partialis continuae of right upper extremity. He was treated as status epilepticus and seizure was controlled but remained comatose for two weeks. Later on he regained conscious and fully recovered with some right hand weakness.

Most of the early POSz were generalized seizure (14/21; 66.7%). CT brain was positive in 6/15 (40%) cases and one patient needed surgical intervention. In nine cases, blood samplings for anti-epileptic drug level were sent for investigated and two of them (22.2%) were low. Serum sodium was also evaluated and was within normal limit in all cases. Most patients developed seizure as early as the day of surgery and 13/21 (61.9%) had seizure within the first postoperative day. In this study we excluded five patients who expired before the 7th postoperative day; three patients among these had deterioration of consciousness and could not rule out non-convulsive seizure but no EEG record to confirm before they died.

Discussion

The incidence of early POSz was 9.7% in total: 13.16% for convexity group, 16.07% for subcortical group, 13.89% for sellar and parasellar group, and 2.08% for posterior fossa group. For the intraventricular and pineal region and skull base lesion, the numbers of cases were too few. This is the first study that identified the incidence of early POSz in Thai patients who underwent craniotomy for tumor removal. The incidence of POSz in the convexity group, subcortical group and sellar region group were comparable to the non trauma group 1 around 15-20%, and the incidence of POSz in the posterior fossa group (1.8%) was similar to the reported suboccipital craniectomy for all diseases without antiepileptic prophylaxis[2,3].

In this study, we found three factors that correlated with early POSz as follows:

1) Male gender This study showed a correlation between male gender and early POSz in patients with craniotomy for tumor removal. Extensive literature review showed no prior report on the correlation between gender and postoperative seizure[1-3]. Although statistical significance was found on univariate and multivariate analysis, a reasonable explanation could not be made on this finding and most of literatures showed different outcomes. Conclusion of this finding should be awaited for further study. From practical view point this finding may not have an influence on patient care.

2) History of preoperative clinical seizure A strong correlation between this factor and POSz has been shown in many literatures.[7,9] This study showed that correlation was also found in early postoperative period. It might provoke seizure or for most of the cases it improved seizure control in the long term.

3) Location of tumor The present results showed that there was a different incidence in early POSz in various locations of tumors. In univariate analysis, this factor was statistically significant correlated with early POSz but no statistical significance in multivariate analysis. Difference between the incidences of POSz in supratentorial and infratentorial procedures of non-

traumatic patients[1-3] has been well documented. This study investigated a specific tumor surgery group of patients and found the same trend. Furthermore we found that some areas of supratentorial region might have lower incidence of early postoperative seizure (cavernous sinus, sphenoid wing area). However, this study was done in retrospective manner. When patients were categorized into subgroups, the number of patients in some groups was very few leading to an invalid comparison. But this study at least has shown a trend and may guide us in patient's care and suggest for further study.

The following factors showed no correlation with early POSz but should be mentioned:

1) Pathology of tumor This study showed a correlation between early POSz and tumor location rather than tumor pathology. For example, patients with meningioma in convexity location had seizure in 5 of 34 cases (14.7%) whereas no seizure occurred in other areas. This results had the same trend with other study in supratentorial meningioma patients[9]. But in sellar and parasellar groups, almost all cases that had seizure were craniopharyngioma with the risk of POSz was 4/11 (36.4 %) compared with 1/12 (8.3%) for pituitary adenomas. Since the number of cases was small, this result needed confirmation in further study.

2) Corticotomy procedure Many literatures showed that cortical injury might cause POSz[7]. In this study, univariate analysis showed high proportion of patients in the corticotomy group with seizure but value did not reach statistical significance. The extent of cortical dissection was not recorded and therefore was unable to analyze. The POSz in posterior fossa surgery was related to shunt or ventriculostomy procedure[3]. In our posterior fossa group, patients who had seizure underwent intraoperative ventriculostomy procedure.

3) Anti-epileptic (AE) medication prophylaxis Although the use of AE drugs was related with early POSz on univariate analysis, the result could not be interpreted due to selection bias from surgeons. In subgroup analysis, the correlation between seizure and AE medication varied among different locations. In the sellar and parasellar group, the incidence of POSz was reduced to 11.9% in the prophylactic group but did not reach statistical significance.

Issues of perioperative AE medication in term of timing, duration and efficacy have been discussed for a long time[4,5,10]. By now, there was no standard protocol for the use of AE prophylaxis in patients undergoing craniotomy with tumor removal at our institute. AE medication is usually prescribed for high risk patients and tapered off a few weeks postoperatively if the patient has no postoperative seizure. In the present study, the early POSz occurred very early especially on day 0 and 1 implying the inadequate dose of AE medication and the true incidence of POSz. In some cases, the seizure attacked during the ICU stay prior to the first dose of an AE. Therefore, the AE prophylaxis should be given prior to the procedure.

When the seizure occurred it might be from correctable causes, such as low drug level or hematoma. This study showed the importance of imaging and drug level to evaluate postoperative seizure patients. Among our 21 cases of early POSz, 15/21 had a post seizure CT scan and only 9/21 had their blood AE level checked. Forty percent of CTs were abnormal and 22% of blood sample were at low levels of an AE.

The major flaw of this study was in its retrospective nature. Data such as clinical presentation of seizure was difficult to notice and might be missed in clinical record. A prospective study on AE prophylaxis in high risk patients should be carried out in a larger population group.

Conclusion

The incidence of early POSz varied among different locations of tumors. Patients undergoing craniotomy for tumor removal who have preoperative clinical seizure, tumor located in cortical surface, subcortical, or sellar parasellar area should be considered high risk for early POSz. Male gender may have a higher risk for unknown reason. The role and benefit of prophylactic AE drug cannot be concluded but may have benefit in high risk patients.

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