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Plasma Phenytoin Levels and Incidence of Seizure in Patients Undergoing Craniotomy for Supratentorial Brain Tumors

Aitsaraporn Phunsawat*, Lawan Tuchinda and Wanna Somboonviboon

Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Chulalongkorn Hospital, Thailand

Abstract

Phenytoin is often used to prevent seizures especially postoperative seizures after craniotomy for supratentorial brain tumors but the effectiveness is controversy. To investigate perioperative changes in plasma phenytoin levels and incidence of immediate postoperative seizure in patients undergoing craniotomy for supratentorial brain tumors. The study is prospective observational descriptive study. Twenty patients who received phenytoin and undergoing craniotomy for supratentorial brain tumors were enrolled in this study. The measurement of plasma phenytoin levels were done at preoperative, intraoperatively and postoperative period after the second dose of phenytoin. Demographic data of the patients were recorded include age, sex, weight, preoperative seizure, pathology, size and location of brain tumors, operative duration, amount of fluid replacement and blood loss. If postoperative seizure occurred, plasma phenytoin level was measured again. Intraoperative plasma phenytoin level was decreased from preoperative period by 29.6% in fourteen patients. Intraoperative plasma phenytoin level was increased from preoperative period by 52% in six patients. Three from 20 patients had immediate postoperative seizure and plasma phenytoin levels were 8.18, 16.43, 18.7 mcg/ml. In these three patients, bleeding at operative site was found in two patients while one more patient had cerebral edema with acute hydrocephalus. Intraoperative plasma phenytoin levels can be either increase or decrease from preoperative period. This study suggested that the routine measurement of perioperative plasma phenytoin levels in the high risk patients may be benefit for adding intraoperative dose of phenytoin to achieve the postoperative therapeutic level. However, seizures can occur from others complications after craniotomy such as bleeding, cerebral edema and acute hydrocephalus even in patients who had therapeutic range of phenytoin level.

Keywords: Plasma phenytoin levels; Seizure; Supratentorial brain tumors; Craniotomy

Introduction

Phenytoin is generally prescribed in patients with supratentorial tumors to decrease the risk of seizures during craniotomy [1,2]. An additional intraoperative of phenytoin is generally used to prevent postoperative seizures but the effectiveness is controversy. Earlier studies showed that plasma phenytoin concentration may not be in the therapeutic range despite continued therapy [3,4]. In our institution, it has been common practice to administer phenytoin intraoperatively, but the postoperative seizures remain to occur and plasma phenytoin level is not routinely measured. The objective of this research is to study perioperative changes of plasma phenytoin levels in normal practice and incidence of immediate postoperative seizure in patients undergoing craniotomy for supratentorial brain tumors.

Materials and Methods

This study was approved by the Institutional Review Board of the hospital and informed consent was obtained from all patients. Patients who had ASA physical status class I-II, age 18-65 years, underwent elective craniotomy for supratentorial brain tumors and had history of taking phenytoin until the day before surgery were enrolled in this study. Patients who had history of phenytoin allergy, history of serious cardiovascular disease, liver or kidney disease and pregnancy were excluded from the study.

All patients received dexamethasone 5 mg IV every 6 hours and did not receive premedication. Blood samples for plasma phenytoin level were done 24 hours before surgery. Demographic data of the patients include age, sex, weight, previous seizure; duration and dosage of preoperative phenytoin, pathology, size and location of brain tumors were recorded. In the operating room, standard monitors were used including arterial line. Anesthesia was induced with thiopental 3-5 mg/kg and fentanyl 1-2 mcg/kg. Tracheal intubation was done with pancuronium 0.1 mg/kg. Anesthesia was maintained with 1%–2% end-tidal isoflurane, 50% N_2O in O_2. Fentanyl was added according to pain stimuli. Ventilation was controlled to maintain end-tidal CO_2 between 30 and 35 mm Hg. Temperature was maintained above 35.5°C. Arterial blood gas and blood sugar were examined 30 minutes after incision. Blood sugar was controlled to be less than 200 mg/dl. Mannitol 20% 0.25–1 g/kg was administered for brain relaxation. Intraoperative fluid and blood components were adjusted by anesthesiologists to keep normovulemia. After the brain tumors were removed. Blood samples for plasma phenytoin level were collected and phenytoin dose by neurosurgeon order was administered as an IV infusion rate of 25–50 mg/min to prevent cardiovascular side effects. Neostigmine 0.05 mg/kg and atropine 0.02 mg/kg were given IV to reverse the effect of muscle relaxant. Tracheal extubation was done if the patients met extubation criteria's. Intraoperative data were recorded include vital sign, operative time, volume of fluid replacement and blood loss, dosage of intraoperaive phenytoin, side effects and toxicity of phenytoin if occurred.

At neurosurgical ICU, all patients were received phenytoin 100 mg IV every 8 hours after last phenytoin dose in operating room. Thirty minute after second dose of phenytoin, blood sample for plasma

***Corresponding author:** Phunsawat A, Department of Anesthesiology, Faculty of Medicine, Naresaun University, Phitsanulok 65000, Thailand, Tel: 055-965541; E-mail: Polla_0241@hotmail.com

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phenytoin level was obtained. Clinical seizure was observed immediate postoperatively until 24 hours. If postoperative seizure occurred, blood sample for plasma phenytoin level was repeated and standard treatment of seizure was done immediately including head CT scan. Plasma phenytoin concentrations were determined using a fluorescence polarization immunoassay (FPIA) and optimum therapeutic range was 10–20 mcg/ml [5]. The authors classified patients in to three groups according to plasma phenytoin concentration. Plasma phenytoin concentration less than 10, 10-20 and more than 20 mcg/ml were low, normal and high plasma levels respectively which are illustrated in figure 1.

Statistical analysis

The sample size was calculated to detect a significant difference in plasma phenytoin levels in preoperative, intraoperative and postoperative periods. A pilot study was done to compare plasma phenytoin levels in perioperative periods (9.56 ± 3.6, 7.58 ± 3.06, 8.64 ± 3.94 mcg/ml). Sample size was determined using a 95% power at an alpha value of 0.05 and acceptable error of 0.2 based on the previous studies and our pilot study. The analysis showed 20 patients would be enough for this study. Data was expressed in mean ± SD and percentile. Nonparametric variables were analyzed using the Fisher's exact test or Mann-Whitney U-test, as appropriate. Parametric variables were analyzed using the unpaired *t*-test. A *P* value ≤ 0.05 was considered statistical significant.

Results

A total of 20 patients were included in this study. The mean ± SD age of the patients was 46.5 ± 13.04 years (range 19-66 years). Thirteen patients were females. The average weight was 59.85 ± 11.15 kg. Demographic data of patients and preoperative data included medical history, previous seizures and brain tumors characteristic were shown in table 1.

Preoperative plasma phenytoin level

Average preoperative plasma phenytoin level was 13.6 ± 4.63 mcg/ml. Sixteen patients (80%), 3 patients (15%) and 1 pateint (5%) had normal, low and high plasma therapeutic level respectively as in table 2. Fifteen patients were received preoperative phenytoin less than 7 days had preoperative plasma phenytoin level of 13.5 ± 4.78 mcg/ml. Five patients were received preoperative phenytoin more than 7 days had preoperative plasma phenytoin level of 12.06 ± 4.45 mcg/ml. There was no significant difference of preoperative plasma phenytoin levels between the two groups (P=0.554). There were two pattern of preoperative phenytoin administered. Seven patients who received 800 mg of phenytoin loading entirely followed by daily phenytoin 300 mg orally had preoperative plasma phenytoin level of 15.69 ± 5.9 mcg/ml and 13 patients who received daily phenytoin 300 mg orally without loading dose had preoperative plasma phenytoin level of 11.79 ± 3.29 mcg/ml. The preoperative plasma phenytoin levels were not statistical significant difference between these two groups (p=0.071). One patient who received loading dose had the plasma phenytoin level lower than therapeutic range.

Intraoperative plasma phenytoin level

Mean plasma phenytoin level before intraoperative additional phenytoin dose was 13.26 ± 8.02 mcg/ml. Ten patients (50%), 8 patients (40%) and 2 patients (10%) had normal, low and high plasma phenytoin therapeutic levels respectively as in table 2. Fourteen patients (70%) had the intraoperative plasma phenytoin level decreased from preoperative period by 29.6% (14.68 vs10.34 mcg/ml). Six patients (30%) had the intraoperative plasma phenytoin level increased from preoperative period by 52% (9.26 vs 20.06 mcg/ml). One patient had the intraoperative plasma phenytoin level 40mcg/ml without serious complications. However, the changes of perioperative plasma phenytoin (PHT) levels in 20 patients were shown in figure 2. Factors affecting the intraoperative plasma phenytoin level were shown in table 3. There was no statistic significant in age, sex, weight,

Patient	Sex	Age (y)	Weight (kg)	Medical history	Prior seizure	Brain tumours characteristic		
						Location	Size (ml)	Pathology
1	female	33	60	none	yes	Lt parasagital	126	Meningioma gr 1
2*	female	61	48	HT,DLD, DM	no	Rt insular	215.04	Oligodendroglioma gr 2
3	female	50	77	none	yes	Rt sphenoid ridge	41.44	Meningioma gr 2
4	female	63	63	HT,DLD, DM	no	Lt clinoid process	89.544	Meningioma gr 1
5	male	19	51	none	no	Olfactory groove	133.65	Meningioma gr 2
6	male	38	49	none	no	Lt parasagital	273.5	Meningioma gr 3
7	female	38	53	none	no	Lt sphenoid ridge	42	Meningioma gr 1
8	female	54	55	none	no	Lt thalamus	45.08	GBM gr 4
9	female	66	45	HT,DLD, DM	yes	Lt parietal	29.4	Meningioma gr 1
10	female	41	52	none	yes	Lt parietal	10.125	Lymphoma
11	female	42	57	none	no	Rt frontal	35.2	Astrocytoma gr 2
12	female	45	48	none	yes	Lt parasagital	38.4	Meningioma gr 1
13*	male	43	65	none	no	Rt frontal	80	GBM gr 4
14	male	53	73	none	yes	Corpus callosum	9	GBM gr 4
15	female	48	88	none	no	Rt sphenoid ridge	6.048	Meningioma gr 1
16*	male	58	70	none	yes	Suprasella	106.08	Craniopharyng gr 1
17	female	60	54	none	no	Tuberculum sella	11.6	Meningioma gr 1
18	male	29	68	none	no	Pineal	10	Germinoma
19	male	60	64	none	no	Rt sphenoid ridge	181.44	Lymphoma
20	female	29	57	none	yes	Lt sphenoid ridge	50	Meningioma gr 2

HT: hypertension,DLD: dyslipidemia, DM: diabetes mellitus, GBM: glioblastoma maltiforme, Rt: right side, Lt: left side
* Patients had postoperative seizure in 24 hours.

Table 1: Patient characteristics and data from preoperative period.

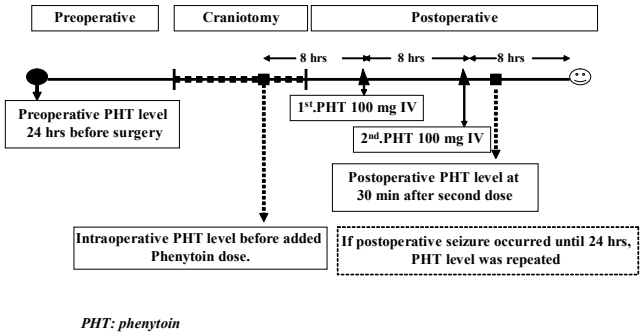

Figure 1: Diagram of methodology.

Periods	Plasma level of PHT	Values (mcg/ml)	n (%)
Preoperative	Therapeutic range	13.93 ± 3.02	16 (80%)
(13.6 ± 4.63 mcg/ml)	Low	5.76 ± 0.06	3 (15%)
	High	23	1 (5%)
Intraoperative	Therapeutic range	14.3 ± 3.16	10 (50%)
(13.26 ± 8.02 mcg/ml)	Low	7.29 ± 1.69	8 (40%)
	High	31.9 ± 11.46	2 (10%)
Postoperative	Therapeutic range	15.76 ± 2.66	7 (35%)
(18.94 ± 7.6 mcg/ml)	Low	8.63 ± 1.85	3 (15%)
	High	25.43 ± 4.17	10 (50%)

Table 2: Perioperative plasma phenytoin (PHT) levels.

Variables	Intraoperative PHT blood level		*P* value
	Increase (n=6)	Decrease(n=14)	
Female:male (n)	4:2	9:5	1
Age (yrs)	50.83	44.64	0.34
Weight (kg)	65.3	57.5	0.16
Size of tumor (ml)	63.38	82.37	0.66
Duration of preoperative phenytoin (d)	9.67	15.37	0.13
Blood loss (ml)	791.67	996.43	0.49
Operative time (min)	329.17	337.86	0.89
Crystalloid (ml)	2608.33	2921.42	0.6
Colloid (ml)	250	357.14	0.72
PRC (unit)	0.5	1.35	0.44
FFP(unit)	0	0.28	0.66

Table 3: Factors affecting the level of increased or decreased intraoperative plasma phenytoin (PHT).

size of tumor, duration of preoperative phenytoin usage, amount of blood loss, volume of fluid replacement and operative time between the patients who had increased or decreased intraoperative plasma phenytoin levels from preoperative plasma phenytoin levels.

Intraoperative phenytoin administration and postoperative plasma phenytoin level

Mean dose of intraoperative phenytoin administration was 9.46 ± 2.4 mg/kg with the range of 5.68-16.67 mg/kg. Mean postoperative plasma phenytoin level was 18.94 ± 7.6 mcg/ml (range 6.5-35.31 mcg/ml). Seven patients who had high postoperative plasma phenytoin received 8.96 ± 1.94 mg/kg of intraoperative phenytoin. Three patients who had normal the postoperative plasma phenytoin levels received 10.89 ± 2.63 mg/kg kg of intraoperative phenytoin. Ten patients who had low postoperative plasma phenytoin levels received intraoperative phenytoin 7.74+2.03 mg/kg of intraoperative phenytoin (Table 4).

High: PHT level > 20 mcg/l, Normal: PHT level 10-20 mcg/l, Low: PHT level < 10 mcg/l.

Incidence of seizures

Postoperative seizure was occurred in 3 patients (15%) and plasma phenytoin levels during seizure were 8.18, 16.43, 18.7 mcg/ml. Brain tumor characeristics were craniopharyngioma 106.08 ml at suprasella region, glioblastoma maltiforme 80 ml at right frontal region and oligodendroglioma 215.04 ml at right insula lobe. Head CT scan were performed after seizure, it revealed bleeding at operative site in two patients while the other patient had cerebral oedema with acute hydrocephalus. There was no statistic significant difference in age, sex, weight, previous seizure, size of tumor, duration of preoperative phenytoin usage, plasma phenytoin level, intraoperative phenytoin administration, amount of blood loss, volume of fluid replacement and operative time between the patients who had or had no seizure postoperatively (Table 5).

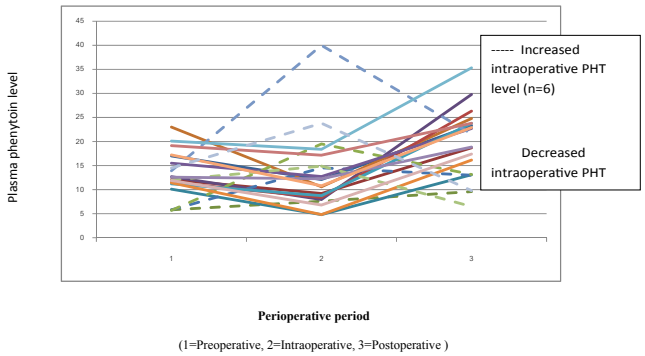

Figure 2: The changes in perioperative plasma phenytoin (PHT) levels.

n	Postoperative PHT level (mcg/ml)	Intraoperative Dose of PHT (mg/kg)	Preoperative PHT level (mcg/ml)	Intraoperative PHT level (mcg/ml)
7	High (25.43 ± 4.17)	8.97 ± 1.95	16.13 ± 3.9	14.69 ± 9.56
3	Normal (15.76 ± 2.66)	10.89 ± 2.63	9.95 ± 2.97	10.28 ± 5.48
10	Low (8.63 ± 1.85)	7.74 ± 2.031	10.76 ± 4.48	15.43 ± 8.11

Table 4: Correlation between perioperative plasma phenytoin (PHT) and intraoperative dose of phenytoin (PHT).

variable	seizure		P value
	Yes(n=3)	No (n=17)	
Female:male (n)	1:2	12:5	0.27
Age (yrs)	54	45.18	0.29
Weight (kg)	61	59.64	0.86
Previous seizure (n)	1	7	1
Size of tumor (ml)	133.67	66.61	0.12
Duration of preoperative Phenytoin (d)	3	15.32	0.48
Intraoperative PHT dose (mg/kg)	9.6	9.42	0.91
Blood loss (ml)	683.33	979.42	1
Operative time (min)	290	343.23	0.48
Crystalloid	2366.67	2908.83	0.36
Colloid	500	294.12	0.39
PHT level (mcg/ml)			
Preoperative	12.88 ± 0.94	13.21 ± 5.03	0.91
Intraoperative	20.49 ± 16.97	11.97 ± 5.43	0.42
Postoperative	19.71 ± 1.62	19.49 ± 7.92	0.92

Table 5: Variables in patients with or without postoperative seizures.

Discussion

This study found that level of intraoperative plasma phenytoin was changed to both increase and decrease from preoperative period. Intraoperative plasma phenytoin level was decreased from preoperative period by 29.6% in 14 patients (14.68 vs 10.34 mcg/ml) and increased from preoperative period by 52% in 6 patients (9.62 vs 20.06 mcg/ml). Previous study showed that the plasma phenytoin level was decreased by 26% after craniotomy in most patients (13.4 vs 10.0 mcg/ml) [6]. Another study showed plasma phenytoin level was significantly lower in the immediate postoperative sample compared with the preoperative sample (9.567 vs 13.869 mcg/ml) and serum phenytoin concentration was a sub therapeutic range in 15 out of the 25 study patients [7]. Preoperative plasma phenytoin level, operative time and amount of blood loss were found to significantly correlate with the decrease in plasma phenytoin level [6,7]. Our study had not found statistic significant correlation of these factors with the change in plasma phenytoin level but we found that patients with intraoperative subtherapeutic plasma phenytoin group trend to have size of tumors, operative duration, volume of fluid replacement and amount of blood loss more than patients with intraoperative therapeutic plasma phenytoin group. Other factors affecting the changes of individual plasma phenytoin levels included protein binding, blood pH, stress, metabolic clearance rate, drug interaction and genetic had been reported in earlier studies (1,2). Drug interaction especially the interaction between dexamethasone that administered to all patients and phenytoin had been reviewed. Phenytoin uniformly decreases the plasma levels of dexamethasone, accelerating its metabolism through induction of hepatic microsomal enzymes. On the other hand, both increased and decreased plasma levels of phenytoin were observed under co medication with dexamethasone. The exact mechanisms for these conflicting phenomena remain to be elucidated, but increased levels are attributed to competition on protein binding, whereas decreased levels may be caused upon induction of hepatic metabolism [7].

The presented and the previous studies found that in majority of the patients had subtherapeutic intraoperative phenytoin level [8,9]. Therefore, it was reasonable to add an intraoperative dose of phenytoin to achieve the therapeutic level of 10-20 mcg/ml but the actual dose of intraoperative phenytoin remained questionable. The presented showed that mean additional intraoperative dose of phenytoin was 10.89 ± 2.63 mg/kg in the group of patients who had prior preoperative and intraoperative plasma phenytoin levels in therapeutic range in order to maintain the therapeutic level at postoperative period. Tsolaki et al. gave the intraoperative dose of 7 mg/kg of phenytoin and measured plasma phenytoin levels up to 12 hours. The postoperative plasma phenytoin levels decreased in first 8 hours but remained in the therapeutic range [10].The lower postoperative plasma phenytoin level was seen in our patients who received the intraoperative dose of phenytoin 7.74 ± 2.03 mg/kg.

The incidence of seizures in patients who underwent surgery for supratentorial brain tumors has been estimated to be 15–20% [11]. The value of prophylactic administration of antiepileptic drugs in patients with brain tumors remains controversial. Some studies showed a statistically significant reduction in the risk of early postoperative seizures by phenytoin and the patients with subtherapeutic level of plasma phenytoin was also at a high risk for immediate and early postoperative seizure [12-14]. In another study, phenytoin was administered to maintain therapeutic phenytoin concentrations did not decrease the incidence of postoperative seizures [15]. This study showed that 3 patients (15%) had immediate postoperative seizure at 1,4,18 hours after surgery. Plasma phenytoin levels were examined, two patients had normal plasma therapeutic level (16.43, 18.7 mcg/ml) and another patient had low plasma therapeutic level of pheytoin (8.18 mcg/ml). Head CT scans were performed after seizure. The imaging showed the bleeding at operative site in two patients while one more patient had cerebral oedema with acute hydrocephalus.

Due to a small number of patients, we cannot find significant difference in age, sex, weight, previous seizure, size of tumors, preoperative, intraoperative and postoperative plasma phenytoin level, intraoperative phenytoin administration, amount of blood loss, and operative time between the patients who had and had no seizure. Furthermore, the risk of early seizure was greatest in the first 24 hours postoperative. Location of tumors, especially frontal and temporal lobe, low grade glioma which large size of tumor, tumors with dissection through the cortex and history of previous seizure were the risk factors for developing postoperative seizure [16-21]. Manaka et al. found that the operation itself such as brain retraction, interruption of cortical vein, arterial damage and extra vascular leakage of blood component during craniotomy mediated free radical generation which induced epileptogenic foci. Brain tissue ischemia and hypoxia during procedure was leading to ion imbalance across cell membrane and induced postoperative seizure as well [22].

The presented showed that seizures can be occurred from others complications after craniotomy such as bleeding, cerebral edema and acute hydrocephalus despite therapeutic plasma phenytoin level.

Conclusion

Intraoperative plasma phenytoin levels can be either increase or decrease from preoperative period. This study suggested that the routine measurement of perioperative plasma phenytoin levels in the high risk patients may be benefit for adding intraoperative dose of phenytoin to achieve the postoperative therapeutic level. However, seizures can occur from others complications after craniotomy such as bleeding, cerebral edema and acute hydrocephalus even in patients who had therapeutic range of phenytoin level.

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