Article published online: 2024-05-03

Research Article

To Study Perioperative Changes in Plasma Phenytoin Levels in Patients with Brain Tumor Undergoing Craniotomy and Its Correlation with Postoperative Seizures

Manjulata Kumawat[1] Amanpreet Singh[2] Prashant Kumar[3] Sanjay Johar[3] Ishwar Singh[4]

[1] Department of Biochemistry, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India
[2] Department Anaesthesiology, MAMC, Agroha, Haryana, India
[3] Department of Anaesthesiology and Critical Care, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India
[4] Department of Neurosurgery, Pt. B.D. Sharma PGIMS, Rohtak, Haryana, India

Address for correspondence Dr. Ishwar Singh, Mch, Department of Neurosurgery, Pt. B.D. Sharma PGIMS, Rohtak 124001, Haryana, India (e-mail: drishwarsingh@yahoo.co.in).

Indian J Neurosurg

Abstract

Introduction Phenytoin, although commonly used for postoperative seizure prophylaxis, exhibits variable results in mitigating seizure frequency following craniotomy. These discrepancies may be linked to a reduction in plasma phenytoin levels subsequent to the surgical intervention.

Aims This prospective study aims to characterize changes in plasma phenytoin levels after craniotomy and their relationship with intraoperative blood loss.

Methods Fifty consecutive patients were enrolled in this study after obtaining written informed consent. These patients had either been on oral phenytoin for at least 7 days or had received an intravenous loading dose before undergoing craniotomy. Serum phenytoin levels were measured 24 hours preoperatively, immediately before craniotomy (prior to skin incision), postcraniotomy (after skin closure), and 24 hours postcraniotomy. Additionally, intraoperative blood loss was calculated using a modified Gross formula.

Results Immediately following craniotomy, there was a statistically significant mean decline of 28.16% in serum phenytoin levels. Furthermore, the analysis revealed a robust positive correlation between the decrease in phenytoin concentration level and several factors, including blood loss during surgery, the duration of the surgical procedure, intravenous fluids administered during surgery, and the occurrence of postoperative seizures.

Conclusion This study underscores the potential utility of routinely measuring perioperative serum phenytoin levels in high-risk patients to prevent postcraniotomy seizures. Moreover, it suggests that patients with substantial intraoperative blood loss may benefit from an additional bolus dose of phenytoin toward the end of the surgical procedure.

Keywords
- phenytoin
- postcraniotomy seizure
- postoperative seizure

DOI https://doi.org/10.1055/s-0044-1785527.
ISSN 2277-954X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

The incidence of postcraniotomy seizures varies significantly, ranging from as low as 3% to as high as 92%.[1–5] These variations are closely linked to the specific site of the surgical procedure and the nature of the underlying pathology. Of particular concern is the observation that the greatest risk of seizures is within the initial 48 hours following a surgery.[3,4]

Depending on the type, extent, and various other factors associated with the surgical procedure, it is estimated that approximately 20 to 50% of patients will experience at least one seizure in the postoperative period.[3–5] This risk is further exacerbated if the patient has a history of preoperative seizures. Intriguingly, a minority (~5–8%) of patients may even develop entirely new seizures in the postoperative period, referred to as de novo seizures.[6]

The consequences of postoperative seizures are a matter of serious concern, as they can lead to complications such as increased edema, neurological deficits, prolonged hospitalization, and, tragically, even death.[4,7] This increased risk of seizures is primarily attributed to the inflammatory and edematous responses generated during the surgical manipulation and any associated bleeding. Notably, edema typically becomes apparent within 24 to 48 hours after surgery, which also coincides with the period of the highest likelihood of seizure occurrences.

These seizures can have grave repercussions. They disrupt the crucial postoperative assessment of the patient's state of consciousness and can potentially progress to a more severe and life-threatening condition known as status epilepticus.[2,8]

Given the potential harm posed by postoperative seizures, the use of antiepileptic drugs (AEDs) for prophylaxis has become a common practice in patients undergoing craniotomy. Among these, phenytoin has traditionally been favored by many neurosurgeons, despite the introduction of newer drugs. However, the literature offers varied results regarding the effectiveness of phenytoin in preventing postoperative seizures.

While some studies have noted the lack of efficacy of phenytoin in reducing the frequency of postoperative seizures,[9–13] others have reported significant success in preventing such seizures.[8,14–16] One hypothesis suggests that the inconsistent results may be attributed to the low plasma phenytoin levels in the immediate postoperative period, but this has not been exhaustively investigated.[3,4,13,17,18]

In light of these complexities, the primary objective of the study at hand is to closely monitor perioperative changes in phenytoin concentration within the bloodstream of patients undergoing craniotomy. This investigation aims to gauge the associations between these perioperative phenytoin level fluctuations and various surgical variables such as the duration of surgery, the extent of blood loss, and the amount of intravenous (IV) fluid administered. Ultimately, the goal is to assess how these changes in phenytoin levels may influence the occurrence of postoperative seizures.

Materials and Methods

The present observational study was conducted in collaboration between the Department of Anaesthesiology and Critical Care and the Department of Neurosurgery at Pt. B.D. Sharma, PGIMS, Rohtak, Haryana, India. The study included 50 patients of both sexes, aged 18 to 45 years, with American Society of Anesthesiologists (ASA) physical status class I to III. These patients were either on oral phenytoin for at least 7 days or had received an IV loading dose before serum phenytoin monitoring, scheduled for craniotomies for brain space-occupying lesions. Patients/patient attendants who refused to participate in the study, patients who had a history of hypersensitivity to phenytoin, intraoperative massive hemorrhage, preoperative Glasgow coma scale (GCS) less than 14, posterior cranial fossa surgery, patients on AED other than phenytoin, and those requiring intraoperative blood transfusion were excluded from the study. Assessments included clinical history, examinations, GCS, and pupillary responses. A blood sample was taken before induction, immediately postoperation, and after 24 hours of surgery for estimation of haematocrit and serum phenytoin levels. Estimation of phenytoin levels was done using the Chromsystems high-performance liquid chromatography (Chromsystems, Germany) based on the principle of reversed-phase adsorption chromatography.[19]

Data on surgery duration, IV fluids, urine output, blood loss, and immediate postoperative seizures were recorded. The intraoperative blood loss was calculated from a modification of the Gross formula given below[20]:

$$ABL = BV\,[Hct\,(i) - Het\,(f)]/Hct(m),$$

where ABL is the actual blood loss, BV is the blood volume calculated from the body weight (blood volume = body weight in kg × 70 ml/kg). Hct(i), Hct(f), and Hct(m) are the initial, final, and mean (of the initial and final) hematocrits, respectively. For statistical analysis, SPSS v15.0 was used, with a p-value less than 0.05 considered significant.

Results

In the study, all the patients older than 18 years were included. The majority fell within the 35- to 45-year age group (68%), ranging from 19 to 70 years. Among the 50 patients studied, 14 were females and 36 were males. The surgical procedures varied, with 24 patients undergoing craniotomy for gliomas, 15 for supratentorial meningiomas, 3 for craniopharyngioma, 3 for epidermoid cysts, 2 for colloid cyst, 2 for trigeminal neurinoma, and 1 for hemangiopericytoma. Serum phenytoin levels were monitored at various points: precraniotomy,

Table 1 Phenytoin levels and hematocrit, blood loss during surgery, duration of surgery, and intravenous (IV) fluids given during surgery and their standard deviation

Phenytoin levels	Minimum	Maximum	Mean	Standard deviation	*p*-value
Preoperative	11.800	20.400	15.048	1.795	
Postoperative	7.400	16.500	10.810	1.722	
24 h	10.400	19,700	14,140	1.635	
Hematocrit (%)					
Preoperative	31.20	39.40	35.59	2.22	0.0001
Postoperative	28.60	36.70	32.70	2.26	
Duration of surgery (min)	180	360	268.8	0.614	
Blood Loss (mL)	215.26	596.52	369.47	85.71	
IV fluid given (mL)	1,600	3,300	2,379	442.86	

postcraniotomy, and 24 hours postoperatively. The mean preoperative level was 15.0481 ± 1.795 µg/mL, which decreased to 10.810 ± 1.722 µg/mL postcraniotomy and then rose to 14.140 ± 1.635 µg/mL 24 hours postoperatively (►**Table 1**). The mean change in phenytoin level during surgery was 4.238 ± 1.107 µg/mL, constituting a 28.16% decrease from the preoperative levels. Before surgery, all 50 patients had serum phenytoin levels within the therapeutic range, but immediately after surgery, only 33 out of 50 patients (66%) maintained the therapeutic levels. The remaining 17 patients had serum phenytoin levels below the therapeutic range, that is, less than 10 µg/mL. Postoperative seizures were observed in six patients, with five of them having postoperative phenytoin levels below 10 µg/mL and one within the therapeutic range (10–20 µg/mL). The details of the site of lesion, histopathology, and type of seizure are described in ►**Table 2**. Each patient was administered an additional IV dosage of phenytoin, and for three of them, a second-line AED was also introduced into their treatment regimen. Postseizure, a computed tomography (CT) scan of the head revealed bleeding at the operative site in two patients, while another exhibited cerebral edema. The patient with an epidermoid cyst displayed symptoms of aseptic meningitis, which was subsequently managed with IV steroids. Preoperative hematocrit levels averaged $35.59 \pm 2.22\%$, which decreased to $32.70 \pm 2.26\%$ postoperatively, with a significant *p*-value of 0.0001. The operative details showed that the mean duration of surgery was 4.480 hours, with mean blood loss of 369.47 ± 85.71 mL and mean IV fluid infusion of $2,379.00 \pm 442.86$ mL. Statistical analysis revealed a strong positive correlation between the decrease in phenytoin levels and blood loss, duration of surgery, IV fluids administered, and postoperative seizures (►**Table 3**). A comparison between the seizure and nonseizure groups showed that the decrease in phenytoin levels, blood loss, and mean phenytoin levels was statistically significant, while the duration of surgery and IV fluids were not (►**Table 4**). Additionally, there was a statistically significant difference in the mean fall in serum phenytoin levels in the postoperative period between patients who had seizures (5.18 ± 1.61 µg/mL) and those who did not (4.11 ± 0.99 µg/mL), with a *p*-value of 0.03.

Discussion

Postoperative seizure is a significant complication that can occur following neurosurgical procedures. These seizures are associated with various negative outcomes, including aspiration pneumonitis, increased mechanical ventilation, prolonged intensive care unit (ICU)/hospital stay, increased edema, and even death.[4,7,21–23] Early postoperative seizures, which occur in approximately 10 to 20% of supratentorial surgeries, are often caused by irritation of the cortex following manipulation during surgery, inflammation, ischemia, or pneumocephalus.[21–23] However, they can also indicate more serious underlying complications such as postoperative hematomas,

Table 2 Showing details of site of lesion, histopathology, and presentation in patients with postoperative seizure

	Site of lesion	Histopathology	Type of seizure
1	L frontal	Gr-II astrocytoma IDH mutated	Focal
2	R frontoparietal parasagittal	Anaplastic meningioma	GTCS
3	R insular	Gr-II astrocytoma IDH mutated	Focal
4	R frontotemporal (sphenoid wing)	Fibroblastic meningioma	GTCS
5	L basifrontal	Epidermoid	GTCS
6	L temporoparietal	GBM	GTCS

Abbreviations: GBM, glioblastoma; GTCS, generalized tonic–clonic seizure; IDH, isocitrate dehydrogenase; L, left; R, right.

Table 3 Showing correlation and significance of changes in phenytoin concentration in blood during surgery with blood loss during surgery, duration of surgery, intravenous (IV) fluid given during surgery and postoperative seizures

Variable	Decrease in phenytoin level concentration	
	r-value	*p*-value
Blood loss during surgery	+0.913**	0.000
Duration of surgery	+0.562**	0.000
IV fluid given	+0.805**	0.000
Postoperative seizures	+0.315*	0.026

Note: *r*-value is the Pearson correlation coefficient; + sign indicates a positive correlation between the two variables and – sign indicates a negative correlation between the two variables.
*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

hydrocephalus, venous edema, or infarction. Factors such as the generation of free radicals due to blood product leakage or disruptions in ion balance caused by ischemia/hypoxia can trigger these seizures. The influx of calcium during ischemic or hypoxic conditions plays a crucial role in the release of excitatory neurotransmitters and the formation of free radicals, further increasing the risk of postoperative seizures.[24,25] Seizures can also be a manifestation of systemic complications such as electrolyte imbalance, infection, or abnormal glucose levels. The standard of care for seizure treatment and secondary prevention is the use of AEDs.[9,26] However, the use of perioperative AEDs solely for prophylaxis has been a topic of controversy. A recent meta-analysis has shown that perioperative AED prophylaxis for brain tumor surgery significantly reduces the risk of early postoperative seizures.[8]

The current cross-sectional study aims to observe changes in phenytoin concentration in the blood of brain tumor patients undergoing craniotomy and assess the association between these perioperative phenytoin level changes, duration of surgery, amount of blood loss, and amount of IV fluid administered. The findings of this prospective study revealed a mean decrease of 28.16% in phenytoin levels following craniotomy, which could potentially be a contributing factor to postoperative seizures. Previous studies have also investigated the changes in perioperative phenytoin levels, and upon comparison, all studies, except for the study conducted by Phunsawat et al,[27] demonstrated a statistically significant decrease in mean phenytoin levels during the immediate postoperative period[3,4,27,28] (►**Table 5**). The decrease in phenytoin levels was found to be positively correlated with the amount of blood loss, operative time, and IV fluid administration in all studies, including the present one. This could be attributed to the loss of phenytoin-rich blood during surgery, which is then replaced by phenytoin-deficient fluids. Hemodilution, resulting in decreased plasma protein concentration, may have also contributed to this phenomenon, as phenytoin is highly protein bound. Furthermore, longer durations of surgery typically involve greater blood loss, increased phenytoin deficit fluid/blood transfusion, increased excretion, and subsequently lower phenytoin levels. It is important to note that a sudden drop in perioperative phenytoin levels could potentially increase the risk of postoperative seizures, similar to the abrupt withdrawal of an anticonvulsant drug in a nonsurgical setting.[3,4,27,28]

Maintaining a therapeutic level of phenytoin is crucial for effective seizure control, as patients with subtherapeutic levels are more susceptible to seizures.[4,13] The occurrence of postoperative seizures is a complex phenomenon, and subtherapeutic level of phenytoin is one of the contributing

Table 4 Comparison of all parameters used in study between two groups, one having seizures and other not having any seizures in their post-operative period

Variable	Seizures		*p*-value
	Present	Absent	
Male:female	4:2	32:12	1.0
Age (y)	42.00 ± 3.41	36.25 ± 9.10	0.13
Weight (kg)	63.67 ± 7.73	62.64 ± 7.27	0.75
Blood loss during surgery (mL)	449.76 ± 124.35	358.52 ± 74.51	0.01*
Intravenous fluid given during surgery (mL)	2,600.00 ± 493.96	2,384.86 ± 432.88	0.19
Duration of surgery (h)	4.83 ± 0.52	4.43 ± 0.61	0.13
Phenytoin levels (µg/mL)			
Preoperative	13.93 ± 1.75	15.20 ± 1.83	0.11
Postoperative	8.75 ± 0.78	11.09 ± 1.64	0.001**
24-h phenytoin	13.15 ± 1.82	14.27 ± 1.58	0.11
Decrease in phenytoin	5.18 ± 1.61	4.11 ± 0.99	0.03*

Note: *p* value is statistically significant when < 0.05.
*Significant.
**Highly significant.

Table 5 Comparison of different studies showing mean perioperative phenytoin (PHT) level, mean blood loss, and mean duration of surgery

Studies	Total patients	Pre-op PHT levels	Immediate post-op PHT levels	24-h post-op PHT levels	Mean fall in PHT level (%)	Mean blood loss (mL)	Mean duration of surgery (min)
Yeh et al[3]	28	13.4 ± 2.6 mg/L	10.0 ± 2.3 mg/L	12.9 ± 2.0 mg/L	26	321	162
Hanish et al[4]	50	46.341 μmol/L	35.383 μmol/L	42.788 μmol/L	23.6	762	267
Radhakrishnan et al[28]	25	13.8 ± 9.4 μg/mL	9.5 ± 7.0 μg/mL	11.8 ± 8.0 μg/mL	NC	681 ± 297	253.48 ± 239.09
Phunsawat et al[27]	20	13.6 ± 4.63 μg/mL	13.26 ± 8.02 μg/mL	18.94 ± 7.6 μg/mL	29.6	935.002	335.25
Present study	50	15.048 ± 1.795 μg/mL	10.810 ± 1.722 μg/mL	14.140 ± 1.722 μg/mL	28.16	369.47	268.8

Abbreviation: NC, not calculated.

Table 6 Different studies showing number of patients with seizure having therapeutic and subtherapeutic level of phenytoin (PHT)

Studies	Total no. of patients	Post-op seizure	Subtherapeutic level of PHT in patients with seizure	Therapeutic level of PHT in patients with seizure
Yeh et al[3]	28	0	0	0
Hanish et al[4]	50	4	4	0
Radhakrishnan et al[28]	25	2	1	1
Phunsawat et al[27]	20	3	1	2
Present study	50	6	5	1

factors, as supported by various studies including the present study (►**Table 6**). However, other factors such as intraoperative brain damage, hematoma, edema, hydrocephalus, infection, inflammation, dyselectrolytemia, and blood glucose levels also play a role. The present study revealed that patients who experienced postoperative seizures had a mean phenytoin serum level of 8.75 ± 0.78 µg/mL, whereas patients without seizures had a mean phenytoin serum level of 11.09 ± 1.64 µg/mL ($p < 0.05$). The decrease in phenytoin levels during craniotomy was more significant in patients with postoperative seizures (5.18 ± 1.61 µg/mL) compared with those without seizures (4.11 ± 0.99 µg/mL; $p = 0.03$). This decrease in phenytoin levels during surgery showed a positive correlation with postoperative seizures (r-value: $+0.315$, $p = 0.026$). Based on this study, it is suggested that a loading dose of 7 to 15 mg/kg may be administered after the closure of dura to prevent a sudden drop in phenytoin levels in the immediate postoperative period, as recommended by other researchers as well.[18,29] Previous studies, along with the present one, have observed that postoperative seizures can occur even when phenytoin levels are within the therapeutic range. Therefore, when a patient experiences an episode of seizure, appropriate investigations should be conducted in addition to measuring serum phenytoin levels. Intraoperative precautions, such as minimizing retraction, meticulous dissection, gentle handling of neural tissue, avoiding excessive coagulation, frequent irrigation, and maintaining proper hemostasis, are of paramount importance in reducing the incidence of seizures.

Conclusion

The occurrence of seizures after surgery varies among patients, and several factors contribute to the development of seizures during the postoperative period. One significant factor is maintaining an adequate level of phenytoin in the bloodstream. This research emphasizes the importance of regularly monitoring plasma phenytoin levels in high-risk patients undergoing craniotomy, as inadequate phenytoin levels significantly increase the risk of postoperative seizures. To mitigate this risk, it is crucial to uphold appropriate perioperative phenytoin levels, and in cases involving substantial blood loss, administering an additional half loading dose of phenytoin (7–10 mg/kg) during surgery is highly advisable. By understanding and managing these factors, neurosurgeons can work to reduce the incidence of postoperative seizures and improve patient outcomes.

Conflict of Interest

None declared.

References

1 Shaw MD, Foy PM. Epilepsy after craniotomy and the place of prophylactic anticonvulsant drugs: discussion paper. J R Soc Med 1991;84(04):221–223
2 De Santis A, Villani R, Sinisi M, Stocchetti N, Perucca E. Add-on phenytoin fails to prevent early seizures after surgery for supratentorial brain tumors: a randomized controlled study. Epilepsia 2002;43(02):175–182
3 Yeh JS, Dhir JS, Green AL, Bodiwala D, Brydon HL. Changes in plasma phenytoin level following craniotomy. Br J Neurosurg 2006;20(06):403–406
4 Hanish B, Gulzar G, Rakesh K, Ashwani CK, Sandeep K, Gupta V. Evaluation of changes in serum phenytoin level after craniotomy and its relation to intraoperative blood loss. Indian J Neurotrauma 2014;11:109–112
5 Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database Syst Rev 2020;4(04):CD007286
6 Horiuchi S, Kanaya K, Horiuchi T. The occurrence and relationship of postoperative seizure and de novo epilepsy after craniotomy surgery: a retrospective single-center cohort study. Front Surg 2022;9:881874
7 Wu AS, Trinh VT, Suki D, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. J Neurosurg 2013;118(04):873–883
8 Joiner EF, Youngerman BE, Hudson TS, et al. Effectiveness of perioperative antiepileptic drug prophylaxis for early and late seizures following oncologic neurosurgery: a meta-analysis. J Neurosurg 2018;130(04):1274–1282
9 Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;54(10):1886–1893
10 Kong X, Guan J, Yang Y, Li Y, Ma W, Wang R. A meta-analysis: do prophylactic antiepileptic drugs in patients with brain tumors decrease the incidence of seizures? Clin Neurol Neurosurg 2015;134:98–103
11 Perry J, Zinman L, Chambers A, Spithoff K, Lloyd N, Laperriere NNeuro-oncology Disease Site Group Cancer Care Ontario's Program in Evidence-Based Care. The use of prophylactic anticonvulsants in patients with brain tumours: a systematic review. Curr Oncol 2006;13(06):222–229
12 Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev 2008;2008(02):CD004424
13 North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy. A double-blind study. J Neurosurg 1983;58(05):672–677
14 Foy PM, Chadwick DW, Rajgopalan N, Johnson AL, Shaw MDM. Do prophylactic anticonvulsant drugs alter the pattern of seizures after craniotomy? J Neurol Neurosurg Psychiatry 1992;55(09):753–757
15 Lee ST, Lui TN, Chang CN, et al. Prophylactic anticonvulsants for prevention of immediate and early postcraniotomy seizures. Surg Neurol 1989;31(05):361–364
16 Franceschetti S, Binelli S, Casazza M, et al. Influence of surgery and antiepileptic drugs on seizures symptomatic of cerebral tumours. Acta Neurochir (Wien) 1990;103(1–2):47–51
17 North JB, Penhall RK, Hanieh A, Hann CS, Challen RG, Frewin DB. Postoperative epilepsy: a double-blind trial of phenytoin after craniotomy. Lancet 1980;1(8165):384–386
18 Tsolaki M, Yannacou-Peftoulidou M, Grammaticos P, Sofianos E, Foroglou G. Phenytoin plasma levels after intraoperative administration, for the prevention of post-craniotomy seizures. Acta Neurochir (Wien) 1987;84(1–2):36–38
19 Hortin GL, Goldberger BA. Chromatography and extraction. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz Textbook of Clinical Chemistry and Molecular Diagnostics. 5th ed. Philadelphia, PA: WB Saunders; 2012:307–328
20 Gross JB. Estimating allowable blood loss: corrected for dilution. Anesthesiology 1983;58(03):277–280
21 Freund B, Probasco JC, Ritzl EK. Seizure incidence in the acute postneurosurgical period diagnosed using continuous electroencephalography. J Neurosurg 2018;130(04):1203–1209
22 Nanda A, Patra DP. Surgical complications in neurosurgery. In: Nanda A, ed. Complications in Neurosurgery. London: Elsevier; 2018:17–22
23 Fugate JE. Complications of neurosurgery. Continuum (Minneap Minn) 2015;21(5, Neurocritical Care):1425–1444

24 Chassoux F, Landre E. Prevention and management of postoperative seizures in neuro-oncology. Neurochirurgie 2017; 63(03):197–203
25 Manaka S, Ishijima B, Mayanagi Y. Postoperative seizures: epidemiology, pathology, and prophylaxis. Neurol Med Chir (Tokyo) 2003;43(12):589–600, discussion 600
26 Pruitt AA. Medical management of patients with brain tumors. Curr Treat Options Neurol 2011;13(04):413–426
27 Phunsawat A, Tuchinda L, Somboonviboon W. Plasma phenytoin levels and incidence of seizure in patients undergoing craniotomy for supratentorial brain tumors. J Anesth Clin Res 2012;3:10
28 Radhakrishnan M, Devaraj ND, Umamaheswara Rao GS, Subhash MN. Additional phenytoin is frequently needed in patients undergoing craniotomy for supratentorial tumour. Eur J Anaesthesiol 2008;25(07):601–603
29 Levati A, Savoia G, Zoppi F, Boselli L, Tommasino C. Peri-operative prophylaxis with phenytoin: dosage and therapeutic plasma levels. Acta Neurochir (Wien) 1996;138(03):274–278, discussion 278–279

