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Original Article

Evaluation of changes in serum phenytoin level after craniotomy and its relation to intra operative blood loss

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ABSTRACT

Problems considered: Phenytoin is the drug of choice for post operative seizures while some studies have shown lack of efficacy of phenytoin in reducing seizure frequency after craniotomy, which in turn may be due to fall in plasma phenytoin levels after craniotomy.
Aims: The aim of the study is to describe changes, if any, in plasma phenytoin levels after craniotomy and its relation to intra operative blood loss.
Methods: This was a prospective study in which total of 50 consecutive patients were enrolled after taking written informed consent, who were either on oral phenytoin for at least 7 days or had received intravenous loading dose prior to craniotomy. All patients had serum phenytoin levels monitored 24 h pre operatively, immediately pre craniotomy before skin incision and post craniotomy after skin closure, and 24 h after craniotomy. All patients had intra operative blood loss calculated with help of modification of Gross formula.
Results: There was a mean fall of 23.6% in serum phenytoin level immediately following craniotomy which was statistically significant. Furthermore, analysis indicated that greater the operative duration and blood loss, greater was the fall in serum phenytoin level.
Conclusions: The study concludes that routine measurement of perioperative serum phenytoin levels in high risk patients may be of benefit in preventing post craniotomy seizures and an additional bolus dose should be given towards the end of surgery to patients with significant intra operative blood loss.

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1. Introduction

Phenytoin is the drug of choice of many neurosurgeons for the prevention of postoperative seizures. Many neurosurgeons prefer the use of prophylactic anti epileptic drugs because surgical results can be severely compromised by post-operative epileptic seizures. In the early postoperative period cerebral edema, due to surgical manipulation, may contribute to increased intracranial pressure.

If one assumes that trauma to the brain can predispose to seizure activity, there is perhaps no injury of greater concern to the neurosurgeon that caused by operative manipulation.

Some studies have noted the lack of efficacy of phenytoin in reducing seizure frequency post craniotomy. It has been suggested that the lack of efficacy may be due to low plasma phenytoin levels. There may befall in levels of serum phenytoin after craniotomy which may be due to loss of phenytoin-rich blood during surgery with its replacement by **intra venous fluids**.

2. Subjects and methods

The study was conducted from September 2012 to June 2013 in a tertiary care hospital in which 50 consecutive patients were evaluated for changes in serum phenytoin level if any, following craniotomy. All patients included in study had serum phenytoin levels and blood hematocrit monitoring at various intervals.

Inclusion Criteria
1. Patients with age > 18 years
2. Patients undergoing craniotomy
3. Patients on oral phenytoin for at least 7 days or have received intra venous loading dose prior to serum phenytoin monitoring

Exclusion Criteria
1. Patients not giving consent for study
2. Patients who received intra operative blood transfusion

All patients on oral phenytoin were given phenytoin dose equal to 5 mg/kg body weight while patients who received intra venous loading dose were loaded with phenytoin equal to 17 mg per kg body weight. The serum phenytoin level assays were measured using Cobas Integra 400 plus system using principle of Fluorescence Polarization. Coefficient variation of this method is 2.3% for phenytoin levels <22.2 μmol/L and Coefficient variation is 2.1% for phenytoin levels >64 μmol/L. The therapeutic range of total phenytoin is 10–20 μg/ml or 40–80 μmol/L (1 μg/ml = 3.96× μmol/L).

The intra operative blood loss was calculated from a modification of the Gross formula given below:

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

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^{-1}); Hct (i), Hct (f) and Hct (m) were the initial, final and mean (of the initial and final) Hematocrits respectively. In this study no packed cells/Whole blood was transfused between the preoperative hematocrit and the post operative hematocrit in the study group. **No intra operative bolus doses of phenytoin were given**.

Patients were monitored for signs and symptoms of phenytoin toxicity. Serum phenytoin levels were monitored in all patients included in study. The phenytoin levels were monitored 24 h pre operatively, immediately pre craniotomy before skin incision and post craniotomy after skin closure, and 24 h after craniotomy. Samples were taken just prior to next preceding dose wherever possible. Hematocrit and serum protein were also monitored just before and post craniotomy.

3. Results

All patients above the age of 18 years were included in the study. Majority of the patients belonged to age group 41–50 years (28%) with range of 19–73 years. Out of 50 patients studied, 28 were female and 22 were male.

16 patients underwent craniotomy for gliomas, 15 for supratentorial meningiomas, 15 for intra cranial cerebral aneurysm, one for cerebral abscess, one for Non Hodgkin Lymphoma and two for metastasis.

Mean operative blood loss was 762 ml (ranging from 100 to 1680 ml). 14 patients (28%) had blood loss in the range of 601–800 ml. Mean operative duration was 4 h and 27 min ranging from minimum of 100 min to maximum of 500 min 18 (36%) patients had operative duration between 3 and 4 h.

Mean immediate pre operative serum phenytoin levels were 46.341 μmol/L while mean immediate post operative levels were 35.383 μmol/L. There was a mean fall of 10.958 (23.6%) from pre operative value which was statistically significant ($p = 0.000$) (Fig. 1).

Mean 24 h pre operative serum phenytoin level was 45.866 μmol/L and mean 24 h post operative levels were 42.788 μmol/L. 43 patients (86%) had serum phenytoin levels in therapeutic range before craniotomy. Following craniotomy, only 12 patients (24%) had serum phenytoin levels within therapeutic range with fall in serum phenytoin levels in all patients following craniotomy. There was no statistically significant difference in serum phenytoin levels measured 24 h pre operatively as compared to those at 24 h post operatively (Fig. 2).

Four patients had seizures in immediate post operative period (within 24 h). All these 4 patients had immediate post operative serum phenytoin levels much below therapeutic

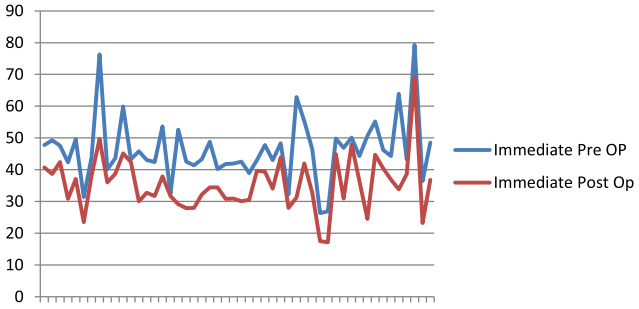

Fig. 1 – Changes in serum phenytoin level after craniotomy.

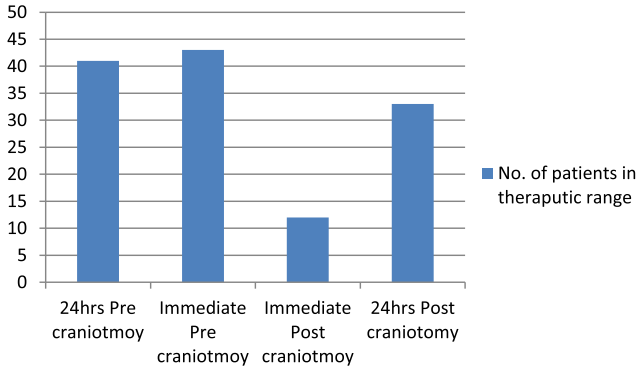

Fig. 2 – Variations in therapeutic range with craniotomy.

range with a mean fall of 36.6% (versus 23.6% fall in the study group) as compared to pre operative levels in the study group. **All of these patients were loaded with additional intra venous dosage of phenytoin and second line antiepileptic was also added in two of these patients**. Also, mean blood loss during surgery in the patients who had seizure was much higher (1312.5 ml) as compared to patients who did not have seizure (715 ml).

4. Discussion

The incidence of post craniotomy seizures varies depending on the site of surgery and nature of underlying pathology, and has conservatively been estimated to be 17% with a wide range from 3 to 92%.[1] The highest incidence of seizures after brain surgery is observed during initial 48 h, and these seizures can have serious adverse consequences.[2] Several groups have evaluated whether prophylactic administration of antiepileptic drugs can reduce this high seizure rate.[3]

Phenytoin, a popular anticonvulsant agent is used both for treatment and prevention of post craniotomy seizures.[4] Several studies have shown a statistically significant reduction in the risk of early postoperative seizures by phenytoin and the patients with sub therapeutic level of plasma phenytoin were at a high risk for immediate and early postoperative seizures. Study by Franceschetti et al also suggests short term preventive treatment with antiepileptic drugs after surgery in patients without preoperative seizures.[5] Seizure control is best when therapeutic levels of phenytoin are maintained.[6]

Seizure in the post operative period adds to morbidity and mortality. During the early post operative course, the major elevations of intra cranial pressure and blood pressure that are associated with a seizure may have catastrophic sequences which makes adequate anticonvulsant prophylaxis in immediate post operative period more important. If one assumes that trauma to the brain can predispose to seizure activity, there is perhaps no "injury" of greater concern to the neurosurgeon than that caused by operative manipulation. In general, where the risk of seizure exceeds 10–15% or where a single seizure may have disastrous consequences, anticonvulsant prophylaxis is recommended.[7]

In this light, a number of recent studies have focused on the incidence of seizures after craniotomy. Freeman et al noted an incidence of seizures of about 25% within 3 years of operation in patients undergoing open prefrontal lobotomy as compared to 1.5% in patients operated upon via the transorbital route.[8]

Several authors have directly addressed the question of the efficacy of a prophylactic anticonvulsant protocol. Mathew and colleagues examined retrospective data collected from four major hospitals on 118 consecutive craniotomies.[9] These authors specifically focused on the incidence of seizures during the 1st postoperative week. These authors conclude that adequate plasma levels of phenytoin should be obtained preoperatively in patients undergoing elective operations maintained through the immediate postoperative period, and gradually tapered if no seizures occur or no epileptiform abnormalities are noted on the EEG.

This prospective study shows that all patients had a fall in serum phenytoin levels post operatively and there was a mean decrease in phenytoin of 23.6% following craniotomy with a gradual return to the preoperative levels within 24 h. Another prospective study by Yeh JS et al showed that in majority (89%) of patients, there is a mean decrease in phenytoin of 26% following craniotomy.[10]

43 patients (86%) had serum phenytoin levels in therapeutic range immediately before craniotomy but following craniotomy, only 12 patients (24%) had serum phenytoin levels within therapeutic range. All patients had a fall in serum phenytoin levels and the mean decrease in phenytoin level was 10.958 μmol/L. 33 patients had serum phenytoin levels within therapeutic range 24 h after craniotomy.

Furthermore, analysis indicated that the greater the operative duration and blood loss, the greater was this fall in serum phenytoin level ($p = 0.005$; $p = 0.000$ respectively). This may be due to the loss of phenytoin-rich blood during surgery with its **replacement by intra venous fluids only**. The amount of blood loss during the operation affects the post operative anti epileptic drug level and should be corrected for.[11]

A simple process of dilution caused by blood and fluid replacement might be responsible for the decrease in phenytoin concentration. Long-duration surgery might have caused increased excretion and lower serum concentration.[12] Hemodilution, with decreased plasma protein concentration, might have also contributed, since phenytoin is highly protein bound. The study has shown that there is an abrupt fall in phenytoin in the immediate postoperative period, and this might be sufficient to provoke seizures in some patients.

Phunsawat et al in a study suggested that routine measurement of perioperative plasma phenytoin levels in the high risk patients may 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.[13]

In this prospective study 4 patients had seizures in immediate post operative period (within 24 h); all of whom had serum phenytoin levels within therapeutic range in the immediate pre operative period. All these 4 patients had immediate post operative serum phenytoin levels much below

therapeutic range with a mean fall of 36.6% (versus 23.6% fall in the study group) as compared to pre operative levels in the study group.

Also, mean blood loss during surgery in the patients who had seizure was much higher (1312.5 ml) as compared to patients who did not have seizure (715 ml) (*p* value 0.002). None of these patients had a preoperative history of seizures. Out of 4 patients who had a seizure in post operative period, 2 had supratentorial meningiomas, 1 had astrocytoma and one had MCA bifurcation aneurysm.

A sudden drop in phenytoin perioperatively might contribute to postoperative seizures, in a similar way to an abrupt withdrawal of anticonvulsants in a non-surgical setting. More the blood loss more was the fall in the level of serum phenytoin level.

Howsoever, other factors that may play a role in incidence of post operative seizures include pathology and location of tumor, operative factors like brain retraction, interruption of cortical vein, arterial damage and extra vascular leakage of blood component during craniotomy and other factors affecting the changes of individual plasma phenytoin levels like protein binding, blood pH, stress, metabolic clearance rate and drug interactions. In clinical practice, the plasma concentration of anti epileptic drugs should be frequently monitored if used in combination with corticosteroid or chemotherapeutic agents.[14]

Given the sub therapeutic phenytoin concentration in a major proportion of our patients, it is advisable to administer an intra operative dose of phenytoin to achieve the therapeutic level after hemostasis has been secured. If anticonvulsant prophylaxis is desired, it might be best to begin the loading of phenytoin at the end of surgery.

5. Conclusion

In this study there was a mean fall of 23.6% in serum phenytoin level immediately following craniotomy. 4 patients had seizure within 24 h in post operative period in study group. The analysis indicated that greater the fall more was the chance of patient getting a seizure. All these 4 patients had immediate post operative serum phenytoin levels much below therapeutic range with a mean fall of 36.6%.

This study concludes that the routine measurement of perioperative plasma phenytoin levels in the high risk patients may be of benefit in preventing post craniotomy seizures as risk of post craniotomy seizures may be attributed to inadequate anticonvulsant prophylaxis. For patients receiving phenytoin who are undergoing prolonged operations or have a significant intra operative hemorrhage, an additional bolus dose should be considered towards the end of surgery, after hemostasis has been secured.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Shaw MD, Foy PM. Epilepsy after craniotomy and the place of prophylactic anticonvulsant drugs: discussion paper. *J R Soc Med*. 1991;84:221–223.
2. Santis AD, Villani R, Sinisi M, Stocchetti N, Perucca E. Add-on phenytoin fails to prevent early seizures for supratentorial brain tumors: a randomized controlled study. *Epilepsia*. 2002 Feb;43(2):175–182.
3. Temkin NR. Prophylactic anticonvulsants after neurosurgery. *Epilepsy Curr*. 2002 July;2(4):105–107.
4. 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;84:36–38.
5. Franceschetti S, Binelli S, Casazza M, et al. Influence of surgery and anti epileptic drugs on seizures symptomatic of brain tumours. *Acta Neurochir*. 1990;103:47–51.
6. North JB, Penha II R, Haneih A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy: a randomized double—blind trial. *J Neurosurg*. 1982;58:272–278.
7. Deutschman CS, Haines SJ. Anticonvulsant prophylaxis in neurological surgery. *Neurosurgery*. 1985;17:510–517.
8. Freeman W. Hazards of lobotomy: study of two thousand operations. *J Am Med Assoc*. 1953;152:487–491.
9. Mathew E, Sherwin AL, WeIner SA, Odusote K, Stratford JG. Seizures following intracranial surgery: incidence in the first post—operative week. *Can J Neurol Sci*. 1980;7:285–290.
10. Yeh JS, Dhir JS, Green AL, Bodiwala D, Brydon HL. Changes in plasma phenytoin level following craniotomy. *Br J Neurosurg*. Dec 2006;20(6):403–406.
11. Kuijlen JM, Teernnstra OP, Kessels AG, Herpers MJ, Beuls EA. Effectiveness of antiepileptic prophylaxis used with supratentorial craniotomies: a meta analysis. *Seizure*. 1996;5:291–298.
12. Radhakrishnan M, Devaraj ND, Umamaheswara Rao GS, Subhash MN. Additional phenytoin is frequently needed in patients undergoing craniotomy for supratentorial tumor. *Eur J Anaesthesiol*. Aug 2008;25(7):601–603.
13. 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. http://dx.doi.org/10.4172/2155-6148.1000255.
14. Yang SH, Lee KS, Lee TK, Jeun SS, Park CK, Hong YK. Seizures in patients with brain tumors. *J Korean Neurosurg Soc*. 2007;41:387–390.