Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/ijnt

Original Article

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

*Bansal Hanish* [a,*], *Gupta Gulzar* [b], *Kaushal Rakesh* [c], *Chaudhary K. Ashwani* [d], *Kundra Sandeep* [e], *Vishnu Gupta* [f]

[a] *Assistant Professor, Department of Neurosurgery, DMC&H, Ludhiana, Punjab, India*
[b] *Associate Professor, Department of Neurosurgery, DMC&H, Ludhiana, Punjab, India*
[c] *Professor & Head, Department of Neurosurgery, DMC&H, Ludhiana, Punjab, India*
[d] *Professor, Department of Neurosurgery, DMC&H, Ludhiana, Punjab, India*
[e] *Associate Professor, Department of Anesthesia, DMC&H, Ludhiana, Punjab, India*
[f] *Consultant, Department of Neurosurgery, Fortis Hospital, Ludhiana, Punjab, India*

ARTICLE INFO

*Article history:*
Received 20 September 2014
Accepted 2 December 2014
Available online 16 December 2014

*Keywords:*
Phenytoin
Craniotomy
Seizure

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.



* *Corresponding author*. 10-B Udham Singh Nagar, Ludhiana, Punjab 141001, India. Tel.: +91 9915024500.
E-mail address: y2khanish@rediffmail.com (B. Hanish).
http://dx.doi.org/10.1016/j.ijnt.2014.12.001

## 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

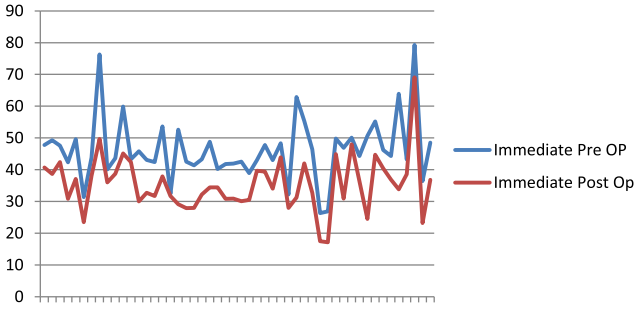


**Fig. 1 – Changes in serum phenytoin level after craniotomy.**