

# An observational case-control study comparing the recovery profile in patients receiving additional dose of anticonvulsant vs. regular dose during supratentorial craniotomy

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**Submitted:** 18-Sep-2019

**Revised:** 19-Jan-2020

**Accepted:** 17-Feb-2020

**Published:** 11-Mar-2020

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## ABSTRACT

**Background and Aims:** Anticonvulsants are used routinely for seizure prophylaxis in patients with supratentorial tumour who present with/without seizures. Excessive use of prophylactic anticonvulsant may delay the recovery from anaesthesia. We have studied the recovery profiles of patients who received an additional dose of anticonvulsant in comparison with those who received only the regular dose. **Methods:** In this prospective observational study, patients were anaesthetised using standard anaesthesia protocol. An additional dose of anticonvulsant was administered in one group, while the other group received only the regular dose. Time taken for extubation, eye opening, obeying commands and orientation were compared between the two groups. Haemodynamics, depth of anaesthesia, the plasma anticonvulsant levels and the incidence of seizures were compared between the two groups. **Results:** A total of 36 patients were studied, of which 19 received regular dose and 17 received an additional dose. There was no significant difference in recovery time between the two groups. Subgroup analysis was performed for phenytoin and sodium valproate. There was a clinically significant delay in recovery in patients who received an additional phenytoin compared to those who received regular dose (time to obey commands >15 min and orientation time >1hour) but, it was not statistically significant. Administration of an additional dose of valproate did not prolong the recovery time. **Conclusion:** An additional dose of sodium valproate did not cause a delay in recovery both, clinically and statistically. However, the administration of an additional dose of phenytoin caused a clinically significant delay in recovery but was not statistically significant.

**Key words:** Anticonvulsants, craniotomy, phenytoin, sodium valproate, supratentorial tumour

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Website: [www.ijaweb.org](http://www.ijaweb.org)

DOI: 10.4103/ija.IJA\_625\_19

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## INTRODUCTION

Patients with supratentorial tumour often present with seizure. The prevalence rate of seizure is about 20-40% in this population.<sup>[1]</sup> Seizures, in the perioperative period, can result in complications like aspiration of gastric contents, worsening of brain oedema or permanent neurological damage. Hence anticonvulsants are routinely used for seizure prophylaxis in patients planned for excision of supratentorial tumours. However, the use of anticonvulsants in patients with brain tumours with no previous history of seizures is still debated. American Academy of Neurology

(AAN 2002) guidelines on anticonvulsant use state that the prophylactic use of antiepileptic drugs for craniotomy should be avoided.<sup>[2]</sup>

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**How to cite this article:** Mathew RR, Raju K, Nair BR, Mariappan R. An observational case-control study comparing the recovery profile in patients receiving additional dose of anticonvulsant vs. regular dose during supratentorial craniotomy. *Indian J Anaesth* 2020;64:222-9.

Rampant use of prophylactic anticonvulsant has its downside. It inhibits/induces the hepatic cytochrome P<sub>450</sub> enzyme system, thereby decreases or increases the metabolism of certain drugs which are metabolised by these enzyme systems. It alters the blood levels of other drugs such as dexamethasone, neuromuscular blocking drugs, and opioids. Anticonvulsant can interfere with cognition and prolong the recovery from anaesthesia because of its enhanced effect on GABA transmission and its sodium channel blockade effect.<sup>[2]</sup> Since the blood levels of anticonvulsants are not routinely measured during the perioperative period, deficits in cognition and recovery after surgery are always attributed to tumour resection, brain retraction, and cerebral oedema and hence misdiagnosed and mismanaged. When there is cognitive dysfunction or delayed recovery after the tumour resection, the possibility of high levels of anticonvulsants also needs to be considered as one of the differentials.

Our study was a prospective observational study designed with the hypothesis that the administration of an additional dose of anticonvulsant increases the depth of anaesthesia, thereby prolongs the postoperative recovery. In our institution, one group of surgeons administer an additional dose of anticonvulsant at the start of surgery apart from the routine regular dose. The rationale for administration of the additional dose, is the possibility of declining plasma levels of anticonvulsants due to administration of intravenous fluid and blood/blood products during surgery. The other group of surgeons administer only the regular dose of anticonvulsant and do not administer an additional dose during surgery as per the AAN recommendation. The primary outcome of this research was to study the effect of administration of an additional dose of anticonvulsant on postoperative recovery. The secondary outcomes were the effects of an additional dose of anticonvulsants on the depth of anaesthesia, haemodynamics, plasma anticonvulsant level, and the occurrence of postoperative seizures.

## METHODS

This study was a prospective observational study, conducted after obtaining the Institutional Review Board (IRB) and ethics committee approval (IRB Number-9268). All ASA 1-3 patients who underwent supratentorial craniotomy for tumour resection, aged between 18-60 years, who were receiving single anticonvulsant medication for more than one-week

duration were included in the study. Patients with liver disease, renal dysfunction (creatinine >1.3 mg/dl), severe left ventricular dysfunction, seizures within one week prior to surgery despite the use of antiepileptic drug, patients who were on two anticonvulsants, patients with GCS <15, those with deep-seated tumours, tumour size >4 cm associated with midline shift of >5 mm, surgery lasting longer than 5 hours with >30% blood volume loss, were excluded.

The day before surgery, all patients who met the inclusion criteria were explained about the study in detail, and informed consent was obtained. No sedative premedication was given. Anticonvulsant, dexamethasone and ranitidine were continued as per schedule. On the day of surgery, after establishing the standard monitors, [electrocardiogram (ECG), pulse oximeter (SpO<sub>2</sub>), non invasive blood pressure (NIBP)], an 18 or 16 G peripheral line and 20 G arterial line were inserted under local anaesthesia. The first blood sample was then taken for measuring the serum anticonvulsant level. After adequate pre-oxygenation, anaesthesia was induced with 2 µg/kg of Fentanyl, 2 mg/kg of Propofol and neuromuscular blockade achieved with 0.1 mg/kg of Vecuronium. The lungs were ventilated for 3-5 minutes, after achieving 1 MAC concentration of Isoflurane, patient's trachea was intubated. After securing the airway, anaesthesia was maintained with air, oxygen and 0.8-1 MAC Isoflurane. A peripherally inserted central venous catheter (PICC line) was inserted for the administration of mannitol or vasopressors, if needed. Temperature, Bispectral Index (BIS), and neuromuscular monitors were connected. Muscle relaxation was maintained with an infusion of vecuronium, which was titrated to keep one twitch on the Train of Four (TOF). An additional dose of Fentanyl (0.5 µg/kg) and Propofol (0.5 mg/kg), and local anaesthetic infiltration was given for head pin application. Scalp block was given using 20 ml of 0.25% Bupivacaine. In patients who received an additional dose of anticonvulsant, it was administered over a period of 20 mins at the start of the first burr hole. We chose to administer anticonvulsant at this time because it was considered as least surgical stimulus period, during which the haemodynamic changes caused by the anticonvulsant administration can be well appreciated. During the anticonvulsant administration, the MAC was kept constant at 0.8. Propofol or fentanyl was not administered during this period. Changes in haemodynamics (heart rate and blood pressure) and BIS were recorded for every 5 min till one hour of anticonvulsant administration.

Intraoperative pain and hypertensive response (>15% from the baseline) were treated with 0.5 µg/kg Fentanyl and Propofol 0.5 mg/kg. Intraoperative fluids were titrated to keep the pulse pressure variation <13%. Intraoperative ABG was done at the end of tumour resection to ensure the electrolytes, sugar, oxygenation, carbon-di-oxide level and haemoglobin were within normal limits. During the dural closure, 0.5 µg/kg of Fentanyl and 15 mg/kg of Paracetamol was given, followed by Ondansetron (0.1 mg/kg). Vecuronium infusion was stopped after the bone flap was replaced. The concentration of Isoflurane was reduced at the time of skin closure to keep MAC at 0.6. Isoflurane was turned off while applying skin dressing, and lignocaine 1.5 mg/kg was given for smooth extubation. FGF was increased to 6-8 L/min after the removal of the pin. Residual neuromuscular blockade was reversed using Neostigmine (50 µg/kg) and Glycopyrrolate (10 µg/kg). Patients were not stimulated (call name, or suction) till they met adequate tidal volume and respiratory rate while breathing spontaneously. Once the swallowing reflex returned, patients were called by name, and oral suction was given. Once they started to open their eyes or move purposefully while calling their names, the patient's trachea was extubated as per the institutional protocol. Time taken from stopping the Isoflurane to extubation, eye-opening, to obey command and to get oriented was taken as extubation time, eye-opening time, time to obey the command, time to orientation, respectively. After extubation, a second blood sample was taken for measuring the serum anticonvulsant level.

To study the primary outcome, the difference in the recovery time of 10 min between the 2 groups was considered clinically significant. Assuming the mean difference of 10 min between the groups with 90% power and 1% alpha error, the number needed to study was around 9 in each group. (There were 4 groups: Regular/Additional Phenytoin/Regular/Additional Sodium valproate). A total of 36 patients were needed to study the significance in each group.

The data were analysed using SPSS 16.0 statistical package (SPSS for Windows, Version 16.0. Chicago, SPSS Inc.). The frequencies, percentages and descriptives were calculated for the measurements. The 2 groups were compared using Mann Whitney U test, and pre-post analysis was done with the Wilcoxon signed-rank test. The graphical representation was done with a boxplot. *P* value < 0.05 was considered as statistically significant.

## RESULTS

In this study 36 patients were included, of which 19 patients received the regular dose, and 17 received an additional dose of anticonvulsant. Patients who received the regular dose are marked as Regular group and those that received additional dose are marked as Additional group. Preoperatively all patients received either Phenytoin or Sodium Valproate for at least a week; 19 patients received Phenytoin, and 17 patients received Sodium Valproate. Out of 19 patients who received phenytoin, 12 patients received the regular dose, and 7 received additional dose during craniotomy. Out of 17 patients who received Sodium Valproate, 7 patients received the regular dose, and 10 received additional dose. In the additional Phenytoin group, all patients received an additional 300 mg of Phenytoin, which is equivalent to a total daily dose. In the additional Valproate group, 2/3<sup>rd</sup> or 1/2 of the total daily dose was given over the regular dose. The regular group received the usual dose of anticonvulsants as per the preoperative schedule. The demographic details of the participants are shown in Table 1.

Since the recovery time was in the extreme ranges for five patients, the results were interpreted using Median with the interquartile range (IQR 25-75). The time taken for extubation, eye opening, to obey commands, to get orientated to time, place, person is expressed in Table 2. The results were analysed as an additional vs. regular group and found that there was no significant difference between the two groups in all parameters.

A subgroup analysis of the recovery parameters was performed separately for patients who received

**Table 1: Demographic details of study between the regular and the additional group**

Parameter/Group	Regular group	Additional group
Number of patients	19	17
Age <45/>45 years	10/9	9/8
Body weight in Kg	59	62
Sex (male/female)	12/7	7/10
Duration of Anaesthesia (min)	285	279
Tumour location		
Frontal/Temporal/Occipital/Parietal	9/2/1/7	12/2/0/3
Tumour pathology		
Meningioma/Glioma/Astrocytoma/Epidermoid/others**	10/3/2/1/3	7/2/1/1/6
Co-morbidities None/Diabetes/Hypertension/IHD*	11/2/6/0	10/1/5/1
Preoperative seizures - yes	10	7

\*IHD - Ischaemic Heart Disease. Others\*\* - Tuberculoma, Metastasis, Cavernoma, Cysts

phenytoin and valproate to see whether the individual drugs have an impact on recovery. This revealed patients who received additional phenytoin had a significant delay in recovery parameters compared to a regular group [Table 3]. The time taken to obey commands and for orientation between the two groups were 33 vs. 48 min and 42 vs. 120 min, respectively. Though this time difference is clinically very significant, it was not statistically significant. A similar analysis was performed between the two groups for the valproate group. We did not find any significant difference both, clinically or statistically between the regular vs. additional valproate group [Table 3].

The depth of anaesthesia was monitored using BIS while keeping the anaesthetic level constant (MAC 0.8). The BIS values were lower in the additional group compared to regular group both for phenytoin and sodium valproate groups, but, it was not statistically significant. (*P* value for Phenytoin group and Valproate group was 0.30 and 0.597, respectively).

The haemodynamic effects of anticonvulsants (Heart rate and Blood pressure) were studied for phenytoin and valproate separately because of its variable effects on haemodynamics. With regards to change in heart rate (HR), patients in the additional phenytoin group had drop in HR after 20 min of drug administration and it continued till the end of the monitoring period. This change was not noted in the regular phenytoin group. Though the drop was clinically significant, it was not statistically significant (*P* = 0.302). In the Valproate group, the HR was noted to be in the higher

range in the additional group compared to a regular group, however, the difference is not statistically significant (*P* = 0.602).

Since the depth of anaesthesia and the haemodynamics can be confounded by the total dose of Propofol and Fentanyl used intraoperatively, the requirement of Propofol and Fentanyl were compared between the two groups, and it was lower in the additional group. The mean dose of Fentanyl used was 260 ± 62.2 µg and 251 ± 76 µg in the regular and additional group, respectively. The mean dose of Propofol used was 296 ± 73 mg and 251 ± 65 mg in the regular group and additional group respectively. But, it was not statistically significant.

With regards to BP change, patients in the phenytoin group, the trends of systolic, diastolic and the mean BP were lower in an additional group compared to a regular group. However, it looked clinically significant; it was not statistically significant. (*P* = 0.559, 0.556, 0.88 respectively). In the valproate group, the trends in systolic and mean BP were marginally lower in the additional group compared to the regular group, which was not statistically significant. (*P* = 0.521, 0.653). Phenytoin administration caused a greater decrease in BP compared to Valproate clinically despite receiving a lesser dose of propofol. The requirement of Phenylephrine, and Noradrenaline were compared between the regular and the additional groups for phenytoin (*p*- value 0.459, 0.949) and sodium valproate (*p*-0.238, 0.5610), but this was not statistically significant.

Serum anticonvulsant levels were measured before and after craniotomy was correlated with the amount of intravenous fluid (IVF) administered. The normal serum therapeutic level of phenytoin is 10-20 µg/ml. In the regular Phenytoin group, the mean pre-induction serum value was 10.03 µg/ml, and the post craniotomy value was 9.755 µg/ml. The mean drop was 0.27 µg/ml. In the additional Phenytoin group, the mean pre-induction serum level was 10.87 µg/ml and post craniotomy level of 10.824 µg/ml,

**Table 2: The recovery time between the Regular and the Additional group**

Time/Group	Regular group median (IQR 25-75)	Additional group median (IQR 25-75)	<i>P</i>
Time to ETT removal (min)	15 (13-20)	14 (13-19)	0.75
Time to open eyes (min)	23 (15-31)	24 (16-27)	0.824
Time to obey commands (min)	33 (25-45)	33 (24-67)	0.824
Time to orientation (min)	42 (35-53)	57 (37-128)	0.208

ETT - Endotracheal tube; IQR - Interquartile range

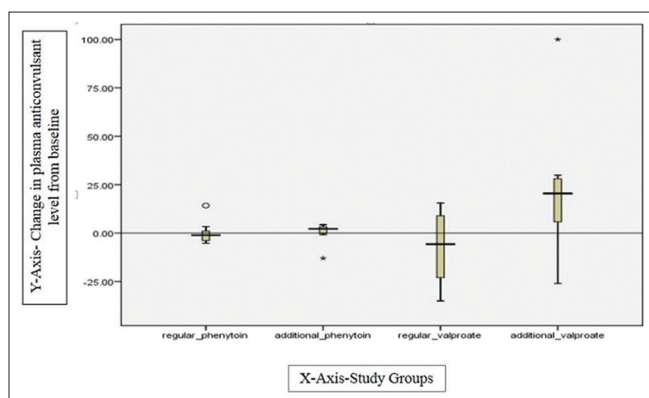
**Table 3: The subgroup analysis of recovery parameters between the Phenytoin and Sodium valproate group**

Recovery parameters/Group	Phenytoin Median (IQR 25-75)		<i>P</i>	Sodium Valproate Median (IQR 25-75)		<i>P</i>
	Regular	Additional		Regular	Additional	
Time to ETT removal (min)	16 (13-19)	14 (13-15)	0.308	14 (12-21)	17 (12-21)	0.475
Time to open eye on call (min)	22 (15-29)	26 (18-38)	0.291	30 (13-48)	21 (14-26)	0.313
Time to obey commands (min)	33 (25-44)	48 (30-20)	0.247	37 (21-53)	31 (20-48)	0.364
Time to orientation (min)	42 (35-52)	120 (39-210)	0.159	42 (35-53)	51 (31-102)	0.757

ETT - Endotracheal tube; IQR - interquartile range

showing a drop of only 0.05 µg/ml. The normal serum therapeutic level of valproate is 50-100 µg/ml. In the regular Valproate group, the mean pre-induction serum level was 78.47 µg/ml and post craniotomy mean levels were 70.87 µg/ml, with the mean drop of 7 µg/ml. In the additional Valproate group, the mean pre-induction level was 60.79 µg/ml, and post craniotomy was 80 µg/ml, an increase by 20 µg/ml. But it was well within the therapeutic range. [Figure 1]

In the Phenytoin group, most patients were on Phenytoin more than 14 days before surgery, despite this, only 32% had a therapeutic range in contrast

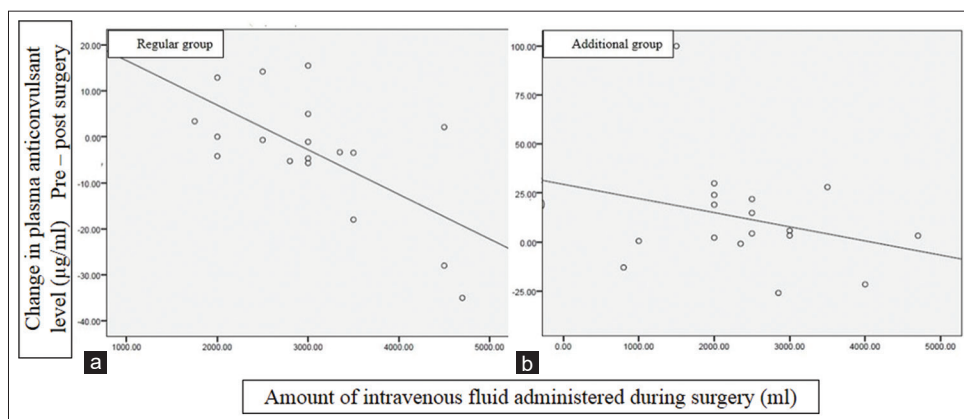


**Figure 1:** Box plot showing the change in plasma anticonvulsant level from the baseline for both groups

to valproate group which had 52% of patients who were in the therapeutic range. Table 4 shows a comparison of the number of patients who had sub, therapeutic and supratherapeutic serum levels pre and post-surgery.

The total amount of crystalloid and colloid administered in the regular group was 2618 ± 678 and 331 ± 236 ml respectively, and it was 2215 ± 935 and 235 ± 257 ml for the additional group. In this study, we have found that there was a definite correlation between the amount of IVF administered and the drop in plasma anticonvulsant level, both in the regular as well as in the additional group. The drop was very significant in the regular group (correlation co-efficient 0.59, *P* = 0.006) compared to additional group (correlation co-efficient 0.05, *P* = 0.835). Figure 2a and 2b shows the scatter plot diagrams showing the correlation between the amount of IVF administered and the change in plasma anticonvulsant level in regular and the additional group.

The total volume of blood loss was 392 ± 236 ml in the regular group, while it was 420 ± 235 ml in the additional group. There was a significant correlation between the amount of blood loss and the drop in plasma anticonvulsant level. The additional group showed more statistical significance (Correlation co-efficient



**Figure 2:** (a and b) Scatter Plot showing the correlation between the amount of intravenous fluid administered and the drop in plasma anticonvulsant level (µg/ml) in regular and the additional group

Table 4: Comparing the plasma concentration of anticonvulsant before and after surgery in both, regular and the additional group				
Groups/Time period	Blood concentration	Pre surgery No of patients (Incidence)	Post-surgery No of patients (Incidence)	
Phenytoin (µg/L)	<10 (Sub therapeutic)	11 (58%)	10 (56%)	
	10-20 (Therapeutic)	6 (32%)	7 (39%)	
	>20 (Supra therapeutic)	2 (10%)	1 (5%)	
Sodium valproate (µg/L)	<50 (Sub therapeutic)	5 (30%)	2 (13%)	
	50-100 (Therapeutic)	9 (52%)	12 (70%)	
	>100 (Supra therapeutic)	3 (17%)	3 (17%)	

0.51, *P* value 0.03) than the regular group, as the blood loss is slightly higher in the additional group.

Five out of 36 patients developed postoperative seizures despite being on anticonvulsants. Out of 2 patients who had post-operative seizures in a regular group, one had a sub-therapeutic level, and one had a normal therapeutic level. Out of 3 patients in the additional group, one had sub-therapeutic, one had normal therapeutic and the other one had supratherapeutic level. Results show that there is no correlation between the postoperative serum level and the occurrence of seizure. All patients who had seizures were females. 4 of the 5 patients who had post-op seizure had presented with preoperative seizure, and 3/5 had frontal tumours. So, we had studied the correlation between age, sex, tumour site, presence of preoperative seizure, post-surgery plasma anticonvulsant level with the occurrence of a postoperative seizure, none of them achieved statistical significance except female gender. A significant correlation was found between female patients and the occurrence of postoperative seizures. (*P* = 0.016) None of the patients who had postoperative seizure had poor outcome or mortality.

## DISCUSSION

This study was undertaken to assess whether an additional dose of anticonvulsant administered during surgery has an impact on recovery from anaesthesia, intraoperative haemodynamics, depth of anaesthesia, and the incidence of postoperative seizures. The administration of an additional dose of Phenytoin delayed the time taken for obeying commands and for orientation compared to patients who received the regular dose. Though the differences are clinically significant, it was not statistically significant because of the smaller sample size. However, administration of an additional dose of Valproate did not prolong the time taken for obeying commands or orientation when compared to patients who received the regular dose.

There are various factors which can alter the recovery from anaesthesia in the neurosurgical population. Surgical factors such as age, tumour location, tumour size, presence of cerebral edema, mass effect, surgical technique, brain retraction/manipulation during surgery, and duration of surgery. To reduce the influence of the above mentioned factors on recovery, patients were selected carefully. Only surface tumours of <4 cm in size which were not vascular and had less peritumoral edema and no mass effect were selected.

Surgical duration more than 5 hours and blood loss more than 30% of blood volume were excluded from the study. There are various anaesthetic factors which can cause a delay in recovery such as hypoxia, hypercarbia, hypo or hyperglycaemia, hypothermia, acute hyponatraemia, these were avoided and ruled out in every patient. Since the confounders of surgical and anaesthetic factors for delayed recovery were minimised and there were no differences in demographic parameters, duration of anaesthesia between the two groups, we are attributing this delay in recovery to the administration of an additional dose of anticonvulsant.

Five patients whose recovery time (Time to orientation) was >2 hours, they all were on Phenytoin, and those patients' plasma levels were within the therapeutic range. This can be explained by the sedative and hypnotic effects of phenytoin even in therapeutic range, causing delayed recovery. There are reports of acute administration of phenytoin, causing delayed awakening.<sup>[3]</sup> The study by Bithal PK has shown that preoperative administration of phenytoin increases the anaesthetic depth which was monitored by BIS and also reported that it reduces the haemodynamic response to laryngoscopy and intubation because of its blood pressure reducing properties.<sup>[4]</sup> In our study similar findings were noted while administering the additional dose of Phenytoin. There was no significant delay in recovery in the additional valproate group; this may be due to the fact that sodium valproate has less sedative and hypnotic effect compared to phenytoin.<sup>[5]</sup> This can also be attributed to the lesser additional dose given for the additional valproate group (2/3<sup>rd</sup> or 1/2 of the daily dose) compared to phenytoin (full daily dose).

Phenytoin is a class I b anti-arrhythmic, it blocks the sodium channels in the cardiac tissue and causes junctional bradycardia and sinus arrest. There are case reports of oral Phenytoin causing sinus bradycardia and asystole in the literature.<sup>[6]</sup> In our study also, we have found that administration of additional dose of Phenytoin slowed down the heart rate, this could be attributed to its anti-arrhythmic effect. We could not explain the mechanism for the increase in heart rate in the additional valproate group. The blood pressure drop was more apparent in the additional Phenytoin group and is proven by the amount of vasopressors used to maintain stable haemodynamics which was larger in this group despite less Propofol consumption. Ishii *et al.* in their study, have shown that there is decrease in the amount of Propofol needed to reach a

BIS value of 60 in patients who were pre-treated with Valproate for bipolar affective disorder (BPAD) during electro convulsive therapy.<sup>[7]</sup> Our study also has shown the similar result and proven that the additional anticonvulsant group patients received less Propofol compared to the regular group. It has been reported that compared to Phenytoin, Sodium Valproate causes less haemodynamic instability such as hypotension and bradycardia.<sup>[8]</sup> Our study results also has shown the similar effects.

The American Academy of Neurology guidelines (2002) has suggested that prophylactic anticonvulsants for craniotomy is not effective in preventing the post-craniotomy seizures. In our study, 5 out of 36 patients (14%) had seizures in the immediate post-operative period (within 48 hours) despite being on anticonvulsant for two weeks. Because of the smaller sample size, we could not identify the risk factors for developing postoperative seizure except the female gender.

In our study, we found that despite starting the anticonvulsant more than two weeks prior to surgery, 58% of patients had sub-therapeutic level. Our study results were almost similar to the study done by Umamaheswara Rao *et al.*, in which they have shown that despite starting preoperative Phenytoin 7 days prior to surgery, 50% of their patients had sub-therapeutic levels.<sup>[9]</sup> Compared to Phenytoin, only 30% of patients on valproate had a sub-therapeutic level. There was a correlation between the amount of IVF administered, the blood loss with a drop in anticonvulsant level, which was similar to other study results.<sup>[9]</sup> It signifies that patients who are resuscitated with the large amount of IVF and who had large blood volume loss may need an additional dose of anticonvulsant, especially in patients who are at high risk for postoperative seizure. Among all the perioperative risk factors, only the female gender has been identified as a significant risk factor for developing postoperative seizure. Future studies with larger sample size are required in order to study the risk factors for developing postoperative seizure.

This study has following strengths and limitations. Firstly, this study is the first to compare the recovery profile of patients who received the regular dose with those who received an additional dose of anticonvulsant in patients undergoing supratentorial craniotomy. Secondly, to the best of our ability, all the screened patients were carefully recruited after ruling

out the surgical and non-surgical confounders, so that delay in recovery could be attributed only to an additional anticonvulsant drug.

The major limitation of this study was the smaller sample size. So, our study results have to be interpreted with caution. We were not able to continue the study as both Phenytoin and Valproate are being replaced with Levetiracetam, as it has less systemic toxicity. The second limitation is we did not do an immediate post-op CT brain to rule out the non-operative surgical causes for delayed recoveries such as cerebral oedema and pneumocephalus before attributing this delay to Phenytoin.

## CONCLUSION

The administration of an additional dose of sodium valproate did not cause significant delay in recovery. However, the administration of an additional dose of phenytoin caused a clinically significant delay in recovery, but it was not statistically significant. To draw a definite conclusion, future studies are needed with a larger sample size.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

### Financial support and sponsorship

Internal Fluid research grant was obtained to conduct the study. (IRB minute number - 9268).

### Conflicts of interest

There are no conflicts of interest.

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### ISA NATIONAL ACADEMIC PROGRAMS 2020 CALENDAR

Sr. No.	Title	Date	Venue
1	ISA Sponsored Research Methodology Workshop and CME	22/12/2019	Nadiad, Gujarat
2	ISA Sponsored National CME	05/01/2020	Pimpri- Chinchwad, Maharashtra
3	ISA Sponsored West Zone PG Assembly	17/01 – 19/01/2020	Kolhapur, Maharashtra
4	ISA Sponsored East Zone PG Assembly	31/01 – 02/02/2020	Patna, Bihar
5	ISA Sponsored National CME	16/02/2020	Bareilly, Uttar Pradesh
6	ISA Sponsored South Zone PG Assembly	22/02 – 23/02/2020	Coimbatore, Tamil Nadu
7	ISA Sponsored National CME	29/02/2020	Delhi
8	ISA Sponsored National CME	01/03/2020	Calicut, Kerala
9	ISA Sponsored National CME	08/03/2020	Madurai, Tamil Nadu
10	ISA Sponsored Central Zone PG Assembly	13/03 – 15/03/2020	Lucknow, Uttar Pradesh
11	ISA Sponsored National CME	15/03/2020	Karad, Maharashtra
12	ISA Sponsored Central Zone PG Assembly	03/04 – 05/04/2020	Raipur, Chhattisgarh
13	ISA Sponsored National CME	05/04/2020	Rishikesh, Uttarakhand
14	ISA Sponsored National CME	12/04/2020	Aurangabad, Maharashtra