Hemodynamic Effects and QTc Changes with Intravenous Phenytoin and Fosphenytoin during Propofol and Sevoflurane Anesthesia

Krishna R. Maremanda[1] Singam Geetha[1] Bakkireddy S. Reddy[2] Padmaja Durga[1] Kolli L. Bramarambha[1]

[1] Department of Anesthesiology and Intensive Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India
[2] Department of Anesthesiology, MallaReddy Narayana Super-Speciality Institute, MallaReddy Women's Medical College, Hyderabad, Telangana, India

Address for correspondence Padmaja Durga, MD, DNB, Department of Anesthesiology and Intensive Care, Nizam's Institute of Medical Sciences, Hyderabad, Telangana 500082, India (e-mail: padmajanims@yahoo.com).

J Neuroanaesthesiol Crit Care 2023;10:31–38.

Abstract

Background Phenytoin is a commonly used antiepileptic drug (AED) for postoperative seizure prophylaxis; it is associated with adverse cardiovascular effects. Fosphenytoin is considered a safer alternative but can produce prolongation of QT interval. This hypothesis generating pilot study evaluated the changes in hemodynamics and the heart rate corrected QT interval (QTc) with phenytoin and fosphenytoin during propofol and sevoflurane anesthesia.

Methods Eighty American Society of Anesthesiologists I and II patients aged 20 to 60 years undergoing elective supratentorial craniotomy requiring a loading dose of the intraoperative AED for seizure prophylaxis were randomized into four groups: group PP, receiving propofol (0.2 mg/kg/min) for maintenance and phenytoin (15 mg/kg) for seizure prophylaxis; group SP, receiving sevoflurane (1 minimal alveolar concentration) for maintenance and phenytoin(15mg/kg) for seizure prophylaxis; group PF, receiving propofol for maintenance and fosphenytoin (22.5 mg/kg) for seizure prophylaxis; and group SF, receiving sevoflurane for maintenance and fosphenytoin for seizure prophylaxis. The heart rate, systolic, diastolic, mean arterial pressure, and QTc were measured at baseline before anesthesia, during maintenance of anesthesia, and during various phases of AED infusion and up to 1 hour after completion of AED administration. Appropriate statistical analysis was done and a two-tailed *p*-value of less than 0.05 was considered significant.

Results The incidence of changes in the heart rate and hypotension was not significant among the groups. Administration of fosphenytoin significantly prolonged QTc, which was more remarkable when coadministered with sevoflurane than with phenytoin.

Keywords
- phenytoin
- fosphenytoin
- propofol
- sevoflurane
- cardiovascular effects
- arrhythmias
- QT interval

article published online
May 14, 2023

DOI https://doi.org/10.1055/s-0042-1758483.
ISSN 2348-0548.

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

Conclusion Fosphenytoin did not confer hemodynamic benefits over phenytoin. Fosphenytoin produces prolongation of QTc, and when coadministered with sevoflurane, the prolongation is more significant, suggesting a possible additive effect.

Introduction

Seizure is one of the frequent complications in patients undergoing craniotomy; the reported incidence is approximately 7 to 18%.[1–3] Phenytoin is the most frequently used prophylactic antiepileptic drug (AED).[1] A dose of 15 mg/kg is recommended to prevent seizures.[4] Intravenous phenytoin is reported to be safe at therapeutic levels of 10 to 25 µg/mL when administered slowly at 50 mg/min.[5] The therapeutic safety is altered by intraoperative conditions such as changes in the intravascular volume, hemodilution, and hypothermia.[6] There are several intraoperative serious adverse cardiac events such as hypotension, arrhythmia, and sometimes even cardiac arrest with phenytoin.[6–8] The cardiovascular interactions between anesthetic agents and phenytoin may contribute to the adverse cardiac effects, but it has not been evaluated.

Fosphenytoin, a prodrug of phenytoin, has been introduced as a safer alternative to phenytoin with minimal adverse effects, including cardiovascular adverse effects.[9] However, adverse cardiovascular reactions such as severe hypotension and cardiac arrhythmias like bradycardia, heart block, QT interval prolongation, ventricular tachycardia, ventricular fibrillation, asystole, cardiac arrest, and death[10,11] have been described in elderly, debilitated, children especially infants,[12] critically ill, those with preexisting hypotension and severe myocardial insufficiency. There are no reports of its safety in the intraoperative period. Metabolism of fosphenytoin yields equimolar concentrations of phenytoin and inorganic phosphate. Although many cardiovascular effects of fosphenytoin are directly attributed to the blood phenytoin concentrations, it has been shown to cause less hypotension than phenytoin.[13] The electrocardiogram (ECG) changes, however, are not solely related to phenytoin accumulation. It causes QT prolongation, which is attributed to indirect toxicity from inorganic phosphate and hypocalcemia. Anesthetic agents such as propofol[14] and inhalational agents also influence the QT interval.[15] The interaction of fosphenytoin and anesthetic agents has not been evaluated. We hypothesized that fosphenytoin does not offer a hemodynamic benefit over phenytoin during nonemergent administration of phenytoin and fosphenytoin under anesthesia, and there would be a possible additive effect on the heart rate corrected QT interval (QTc) changes during sevoflurane anesthesia. The trial's primary objective was to compare the changes in hemodynamic parameters and QTc with phenytoin and fosphenytoin in the intraoperative period during propofol and sevoflurane anesthesia. The secondary objectives were to compare the need for cardioactive drugs and the incidence of arrhythmia.

Materials and Methods

After ethical committee approval, informed consent was obtained from 80 American Society of Anesthesiologist grade I and II patients aged between 20 and 60 years, with body mass index between 20 and 30 kg/m^2, belonging to either gender, undergoing elective supratentorial surgery, and requiring intraoperative intravenous loading dose of phenytoin for seizure prophylaxis who were recruited for the study. Patients with baseline QTc more than 420 ms; patients who received AED preoperatively; patients with previous adverse effects to phenytoin, with significant cardiac disease; patients on antihypertensive and other drugs causing QT changes; patients with electrolyte disturbances like hypokalemia, hypocalcemia, patients undergoing surgery for neurovascular conditions; patients with large meningiomas; patients requiring surgery in positions other than supine position; and patients requiring induced hypo or hypertension and induced hypothermia were excluded from the study. Withdrawal criteria were patients with significant blood loss during the study period, patients requiring a change in the anesthetic drug concentration and depth of anesthesia during the study period; patients with significant brain bulge requiring an additional dose of mannitol or frusemide, hyperventilation, or intravenous thiopentone or propofol for control of intracranial hypertension; patients with intraoperative temperature drift to less than 35°C, intraoperative acid-base and electrolyte derangements; patients developing hemodynamic changes due to neurosurgical causes; patients requiring cardioactive drugs such as vasopressors, inotropes, vasodilators, atropine, and β-blockers.

The patients were randomly assigned to one of the four groups using computer-based randomization using the function "Randbetween" on Excel; The group concealment was performed using closed envelopes, and all the investigators were blinded to the group assignment for the AED used. The AED was diluted to 100 mL 0.9% normal saline by a technician not involved in anesthetic management or data entry. Patients in group PP received propofol for the maintenance of anesthesia and intravenous phenytoin as AED; group SP received sevoflurane for the maintenance of anesthesia and intravenous phenytoin as AED, group PF received propofol for the maintenance of anesthesia and intravenous fosphenytoin as AED and group SF received sevoflurane for maintenance of anesthesia and intravenous fosphenytoin as AED. A baseline blood pressure, heart rate, and ECG in the lead II were recorded. To facilitate intubation, patients were induced with propofol 1.5 to 2 mg/kg fentanyl 2 mcg/kg, and muscle relaxant atracurium 0.5 mg/kg, intravenously. Patients were ventilated to maintain an oxygen

saturation of 100% and end-tidal carbon dioxide between 34 and 36 mm Hg. Maintenance of anesthesia was based on randomization to propofol or sevoflurane. In the propofol groups, an infusion of propofol, 2 mg/kg/hr, was administered along with fentanyl, 0.5 mcg/kg/hr, and atracurium, 0.05mcg/kg/hr. In the sevoflurane groups, anesthesia was maintained with end-tidal sevoflurane of 1MAC and fentanyl, 0.5 mcg/kg/hr, and atracurium, 0.05mg/kg/hr, to maintain bispectral Index between 50 and 60. Invasive blood pressure, heart rate, and ECG in the lead II were monitored during the maintenance of anesthesia. Blood gas analysis was performed, and serum electrolytes were measured at the dural opening. Patients were excluded if there was any derangement. Patients with significant brain bulges requiring intervention were excluded from the study. An intravenous loading dose of phenytoin 15 mg per kg or phenytoin equivalent to fosphenytoin (50 mg of phenytoin = 75mg of fosphenytoin) was infused at the rate of 50mg/min after craniotomy and dural opening. Patients were excluded from the study if the core temperature was less than 34°C. Patients with significant blood loss (>500 mL) or hemodynamic disturbance (requiring volume administration of >1,000 mL or use of cardioactive drugs) were excluded from the study. Systolic, diastolic, and mean arterial pressure and heart rate were noted and ECG in the lead II was recorded at the following measurement time points—1. baseline, 2. maintenance of anesthesia after intubation, infusion of phenytoin/fosphenytoin at 25, 50, 75, and 100% completion of infusion (time points 3, 4, 5, 6, respectively) after 5, 15, 30, and 60 minutes after completion of the infusion (time points 7, 8, 9, 10, respectively). Mild dysrhythmia such as bradycardia, defined as heart rate less than 50 beats/min was treated with inj. atropine 0.6 mg. Hypotension, defined as a reduction in systolic blood pressure by 20% of the baseline, was treated initially with a fluid loading of 200 mL; if there was no response, mephentermine 6 mg bolus was given and repeated after 10 minutes if the hypotension persisted. An infusion of dopamine was started for persistent hypotension. Occurrence of arrhythmias and significant hemodynamic changes during and after phenytoin/fosphenytoin infusion were noted. Phenytoin/fosphenytoin was discontinued and administered at a slower rate in patients with significant hemodynamic disturbances, and these patients were excluded from the analysis of hemodynamics and QTc. QTc was calculated using Bazett's Eq.[16]

The hemodynamics and measured QT interval and the heart rate-adjusted QT interval (QTc interval) during infusion of phenytoin and fosphenytoin were compared between the groups.

Statistical Analysis

The sample size was determined using GPower, based on the prior probability of the proportion of patients developing hemodynamic changes. The required sample size was calculated for χ^2 tests—goodness-of-fit tests, with an effect size of 0.45 with df of 5, the α error probability of 0.05, and the power of 0.8 was 64. Eighty patients were recruited for the study.

The categorical data were compared using χ^2 tests—the goodness-of-fit test. The continuous data were compared between the groups using analysis of variance (ANOVA), and posthoc analysis was done using the Bonferroni test. The within-group comparison was made using ANOVA for repeated measures, and posthoc analysis was performed using the Dunnett test with baseline and postanesthesia values as control. A two-tailed p-value of 0.05 was considered significant to reject the null hypothesis that there is no difference between the groups.

Results

Eighty patients were recruited for the study. Twenty-three patients were excluded from the study after initial inclusion (►**Fig. 1**). Eighteen patients were further excluded from the analysis of hemodynamic data and QTc analysis as they developed significant hemodynamic changes requiring slowing of administration of AED causing deviation from protocol. The study included 10 patients in group PP, 9 in group SP, 12 in group PF, and 8 in group SF.

There was no statistically significant difference in the demographic data between the groups. The proportion of patients developing hypotension was higher with phenytoin during propofol (11 [64.7%]) and sevoflurane anesthesia (11 [68%]), but there was no statistically significant difference between phenytoin and ffosphenytoin ($p = 0.09$ i.e., (6 [40%]) in group PF and (4 [44.4%]) in group SF depicted in ►**Table 1**. There was no statistically significant difference in the need for volume or mephentermine to treat hypotension. Fourteen patients responded to volume alone. Seventeen patients required mephentermine to manage hypotension; these patients were excluded from the analysis of QT interval. Ten patients developed bradycardia with hypotension that responded to mephentermine and did not require atropine.

There was no statistically significant difference in the baseline hemodynamic parameters like heart rate, systolic, diastolic, or mean arterial blood pressure. The hemodynamic changes following anesthesia were comparable between the four groups. The heart rate changes during infusion of phenytoin, from baseline, and during anesthesia were not statistically significant. There was a significant reduction in systolic, diastolic, and mean arterial pressure from baseline toward the completion of phenytoin infusion in both PP and SP groups. The fall of blood pressure with propofol was significantly greater than with sevoflurane anesthesia. There was a fall in the systolic and mean arterial pressure compared with baseline at 75% completion of infusion but returned to baseline in group PF and at 25, 50, and 75% completion in the group SF, but these changes were comparable during both propofol and sevoflurane anesthesia (►**Figs. 2–5**).

Prior to the administration of AEDs at measurement point 2, there was no significant change in the QTc from baseline during propofol infusion (in groups PP and PF) and QTc was significantly prolonged during sevoflurane anesthesia compared with the baseline (in SP and SF groups). The infusion of phenytoin during propofol anesthesia did not result in

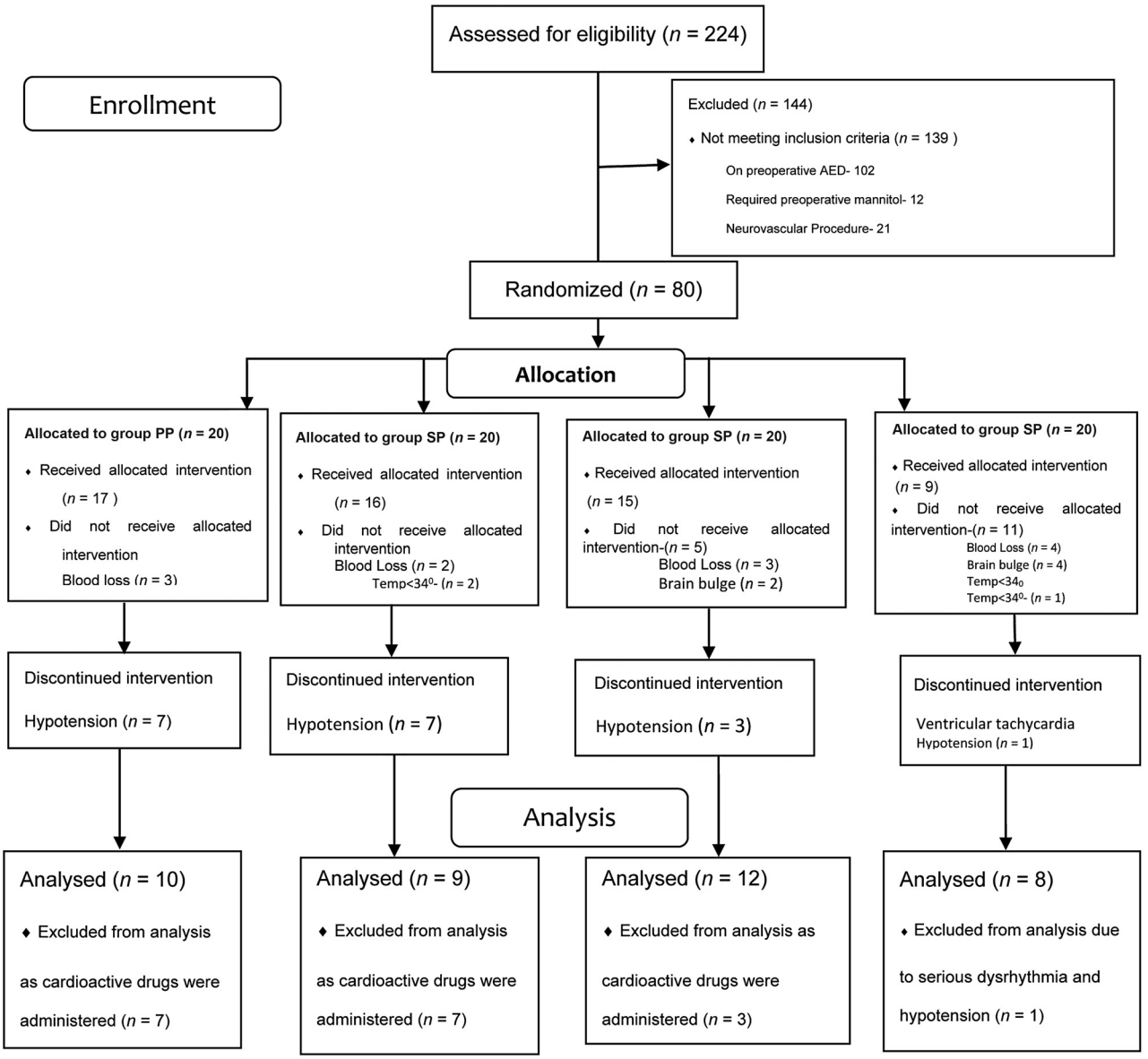

Fig. 1 CONSORT flow diagram. AED, antiepileptic drug.

changes in QTc. There was no further significant change in the QTc with phenytoin infusion during sevoflurane anesthesia. During fosphenytoin infusion in group PF, there was a substantial prolongation of QTc compared with baseline and propofol anesthesia at 50% completion of infusion and remained prolonged even at 30 min after completion of fosphenytoin infusion. There was a significant prolongation of QTc in the group SF compared with the other three groups. The prolongation was significant as compared with baseline and sevoflurane anesthesia (►**Fig. 6**). All patients in groups PF and SF had QTc more than 450 ms; 60% of patients in group SP and 20% in group PP had long QT during the study period. There was one case of significant nodal bradycardia followed by ventricular tachycardia and significant hypotension in the group SF, which was resuscitated with inj. lignocaine, inj. adrenaline, and inj calcium, and administration of AED was discontinued. This case was excluded from analysis due to deviation from protocol, but the ECG showed significant prolongation of PR and QT intervals before developing dysrhythmia.

Discussion

The results of this hypothesis generating pilot study indicate that phenytoin and fosphenytoin produce significant hypotension, which was more pronounced during propofol anesthesia than sevoflurane anesthesia. However, the study failed to show any statistically significant difference in the proportion of patients developing hemodynamic changes and needing volume or mephentermine between phenytoin and fosphenytoin during anesthesia. There was a significantly greater prolongation of QTc in the group SF compared with the other three groups. All patients in groups PF and SF had QTc more than 450ms.

There is no consensus on the efficacy of seizure prophylaxis in patients undergoing craniotomy for nontraumatic

Table 1 Comparison of demographic data and hemodynamic changes between the groups

Group	Group PP ($n=17$)	Group SP ($n=16$)	Group PF ($n=15$)	Group SF ($n=9$)	*p*-Value
Age (y)	43.2 (SD: 14.7)	39.2 (SD: 8.3)	38.9 (SD: 12.1)	35.9 (SD: 12.6)	0.62
Weight (kg)	59.0 (SD: 10.2)	53.3 (SD: 7.7)	61.1 (SD: 6.5)	57.3 (SD: 9.1)	0.30
Gender					0.29
Male	9(52.9%)	6 (37.5%)	8 (53.3%)	7 (77.8%)	
Female	8 (47.1%)	10 (62.5%)	7 (46.7%)	2 (22.2%)	
Bradycardia	2 (11.8%)	1 (6.2%)	3 (20.0%)	4 (44.4%)	0.09
Hypotension	11 (64.7%)	11(68%)	6(40%)	4 (44.4%)	0.34
Mephentermine					
6 mg	5 (29.4%)	7 (43%)	2(13.3%)	1(11.1%)	0.34
12 mg	2(11.8%)				
Volume resuscitation	4 (23.5%)	4(25%)	4(26.7%)	2(22.2%)	0.94
QTc > 450ms[a]	2/10 (20%)	6/9 (60%)	12/12 (100%)	8/8 (100%)	<0.001

Abbreviation: SD, standard deviation.
[a]Analysis of patients after the postinclusion exclusion.

conditions.[2] However, most neurosurgeons prefer to use intraoperative prophylactic AEDs. Even patients taking AEDs preoperatively require additional loading intraoperatively as the plasma levels may fall below the therapeutic levels due to factors such as blood loss.[4,17] The incidence of intraoperative seizures was 2.3%.[3] The incidence of postoperative seizures in patients who did not have seizures preoperatively was 17.7%.[1] Phenytoin, fosphenytoin, and levetiracetam are commonly used intraoperatively for protection against postoperative seizure. It has been shown that phenytoin and fosphenytoin are more protective than levetiracetam.[3]

Phenytoin is an established AED in treating acute repetitive seizures and status epilepticus and is the most commonly used prophylactic anticonvulsant agent for postoperative seizures.[1] However, cardiovascular adverse effects are frequently reported with intravenous use of phenytoin. Phenytoin can cause a lowering in blood pressure as a result of

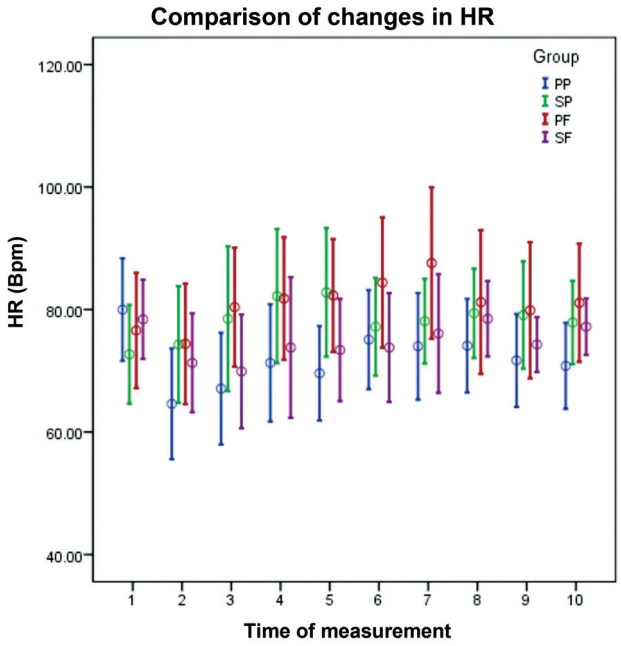

Fig. 2 Comparison of changes in the heart rate (HR). Times of measurement. 1: Baseline; 2: Anesthesia; 3: 25% completion of antiepileptic drug (AED); 4: 50% completion of AED; 5: 75%completion of AED; 6: 100% completion of AED; 7: 5 minutes after completion of AED; 8: 15 minutes after completion of AED; 9: 30 minutes after completion of AED; 10: 1 hour after completion of AED.

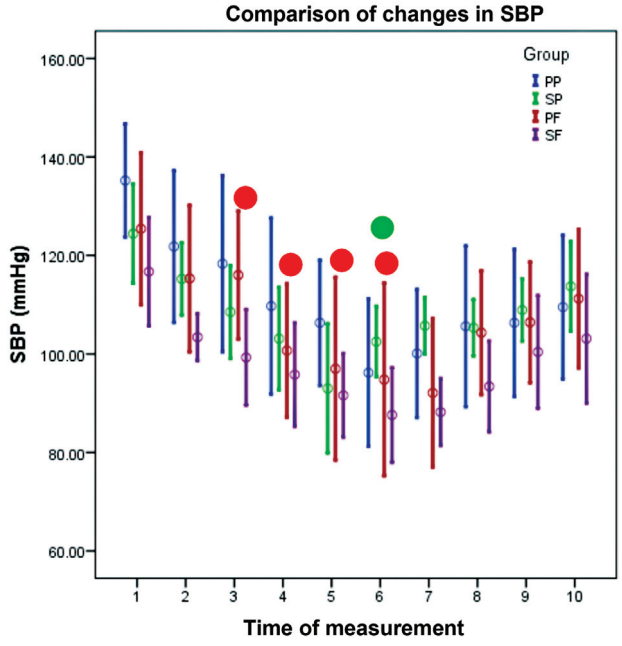

Fig. 3 Comparison of changes in systolic blood pressure (SBP). Times of measurement. 1: Baseline; 2: Anesthesia; 3: 25% completion of antiepileptic drug (AED); 4: 50% completion of AED; 5: 75%completion of AED; 6: 100% completion of AED; 7: 5 minutes after completion of AED; 8: 15 minutes after completion of AED; 9: 30 minutes after completion of AED; 10: 1 hour after completion of AED.

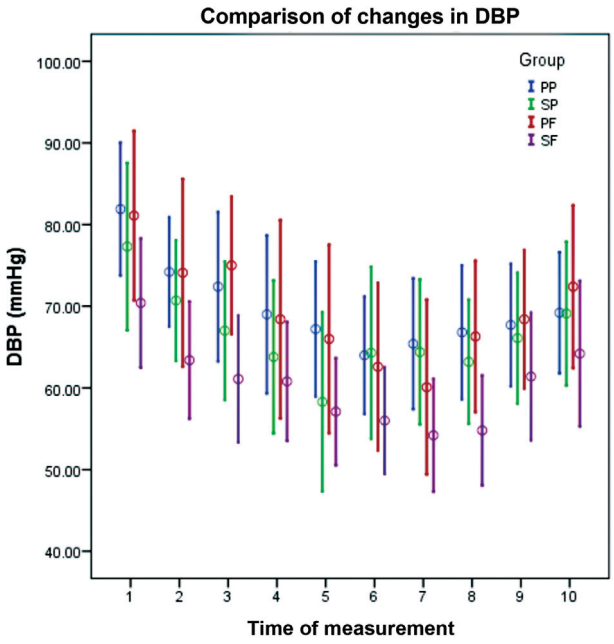

Fig. 4 Comparison of changes in diastolic blood pressure (DBP). Times of measurement. 1: Baseline; 2: Anesthesia; 3: 25% completion of antiepileptic drug (AED); 4: 50% completion of AED; 5: 75%completion of AED; 6: 100% completion of AED; 7: 5 minutes after completion of AED; 8: 15 minutes after completion of AED; 9: 30 minutes after completion of AED; 10: 1 hour after completion of AED.

peripheral vasodilatation and a negative inotropic effect. It is also known that propylene is found in phenytoin preparations to increase water solubility and may cause bradycardia and asystole in toxic dosages. The incidence of hypotension

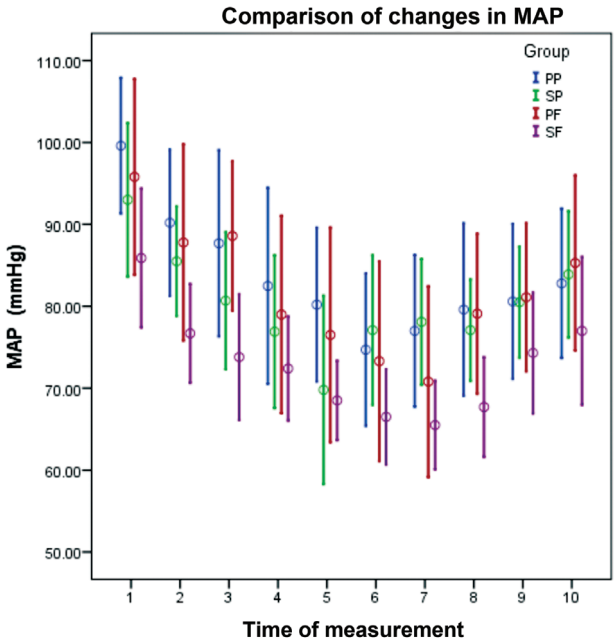

Fig. 5 Comparison of changes in mean arterial blood pressure (MAP). Time of measurement. 1: Baseline; 2: Anesthesia; 3: 25% completion of antiepileptic drug (AED); 4: 50% completion of AED; 5: 75%completion of AED; 6: 100% completion of AED; 7: 5 minutes after completion of AED; 8: 15 minutes after completion of AED; 9: 30 minutes after completion of AED; 10: 1 hour after completion of AED.

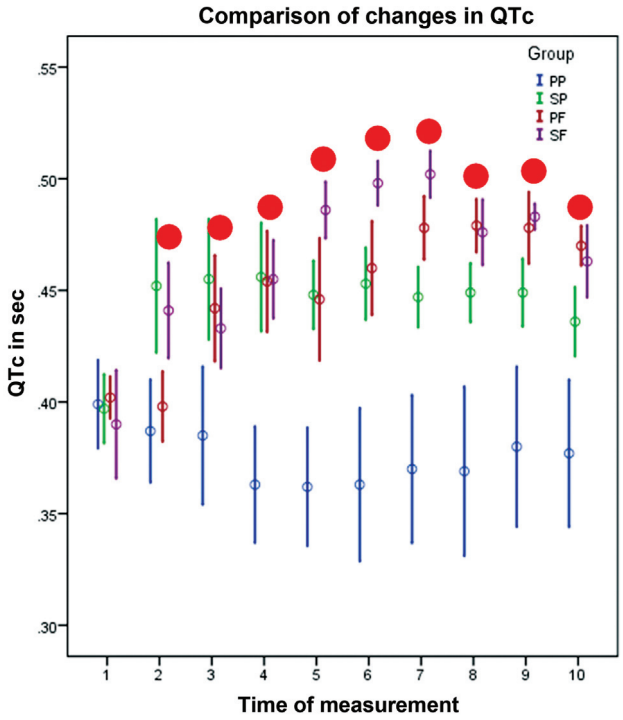

Fig. 6 Comparison of changes in QTc. Times of measurement. 1: Baseline; 2: Anesthesia; 3: 25% completion of antiepileptic drug (AED); 4: 50% completion of AED; 5: 75%completion of AED; 6: 100% completion of AED; 7: 5 minutes after completion of AED; 8: 15 minutes after completion of AED; 9: 30 minutes after completion of AED; 10: 1 hour after completion of AED.

reported with phenytoin administered for seizure prophylaxis is approximately 25%. The infusion rate was the most critical factor in determining the incidence of cardiovascular adverse effects. Most of the reported deaths were in patients who received phenytoin at higher rates (50–100 mg/min) than currently recommended rates.[5] Phenytoin has a narrow therapeutic margin (therapeutic range of [10–20 mg/L]). A rapid infusion may cause temporary high levels of the drug because the distribution of phenytoin in human tissues takes approximately 2 hours. A rate of lower than 50mg per minute resulted in lower cardiovascular changes. The risk factors for adverse cardiac events were age and comorbid cardiac and metabolic disorders.[5] The pre-existent cardiac disease made the patients more vulnerable to the infusion of phenytoin. Metabolic disorders and advanced age may also have changed the elimination and distribution of phenytoin and may have facilitated the adverse effects of hypotension and arrhythmia. The interaction of phenytoin with neuromuscular blocking drugs and its impact on the bispectral index have been studied. There are no reports of cardiovascular changes with intravenous phenytoin administered intraoperatively.

The study population's incidence of hypotension during a 15 mg/kg loading dose of phenytoin administered at 50-mg/min was 65% during propofol anesthesia and 67% during sevoflurane anesthesia. Significant hypotension requiring an inotropic agent was noted in more than 40% of the patients. The intraoperative phenytoin may have resulted in a higher incidence of hypotension due to its interaction with the

anesthetic agents, propofol and sevoflurane, which also influence cardiovascular function. This study was conducted on patients screened for cardiac comorbidities and other concomitant diseases such as hepatic or renal disease, hypoalbuminemia, malnutrition, and metabolic disorders. The inclusion was restricted to selected patients with no risk for phenytoin toxicity undergoing supratentorial craniotomy. Patients with significant intracranial hypertension, blood loss, and electrolyte disturbances, which are not uncommon in neurosurgical patients, were excluded from the study. It is possible that the incidence and magnitude of hypotension would be more significant in these patients.[18] The unfavorable reports on the usage of intravenous phenytoin resulted in the new AEDs with less adverse cardiac effects replacing phenytoin. Still, they are not more effective than phenytoin.[2]

Fosphenytoin is a water-soluble, disodium phosphate ester of phenytoin. It does not contain propylene glycol vehicle, which causes hypotension and cardiac arrhythmias. Hence, it is considered safer to administer parenterally and rapidly with fewer significant adverse cardiovascular effects than phenytoin.[9] The incidence of hypotension with fosphenytoin was 40% during propofol anesthesia and 44% during sevoflurane anesthesia. Though the incidence was lower with fosphenytoin, the study failed to show a statistically significant difference in the incidence of hypotension between phenytoin and fosphenytoin as it was not adequately powered. A similar incidence was seen in other reports too. Intravenous administration of fosphenytoin has shown to be associated with hypotension in 39% and also atrioventricular block in a retrospective case–control study.[19] Studies comparing adverse effects of phenytoin and fosphenytoin in the emergency department did not find a difference between the two.[20] The current study failed to show a significant difference in the incidence of hypotension, but the incidence was higher when phenytoin and fosphenytoin were coadministered with propofol than sevoflurane. Hypotension was associated with bradycardia in ten patients (17.5%), which improved with mephentermine and did not require additional atropine. The incidence of bradycardia was greater in patients who received fosphenytoin, but the difference was not statistically significant. There was no significant change in heart rate during phenytoin or fosphenytoin infusion of a loading dose in patients who did not have significant hypotension.

Prolonged QTc is frequently observed after brain surgery.[21] Hypokalemia, hypocalcemia, and hypothermia can also prolong the QTc. The anesthetic drugs can also influence QT interval. There have been conflicting reports on whether propofol prolongs,[14] shortens,[22] or does not change the QT interval.[23] Sevoflurane has been shown to prolong QTc.[23] Coadministration of drugs that prolong QT has shown to have an additive effect.[24,25] Fosphenytoin can theoretically alter the ECG by two mechanisms: the direct effects of phenytoin on cardiac conduction and phosphate binding of calcium, which could indirectly alter cardiac conduction as a result of hypocalcemia. Its interaction with anesthetic agents has not been studied. Patients receiving sevoflurane 1 MAC for maintenance of anesthesia had significant prolongation of QTc from the baseline, whereas the change in QTc with propofol was not significant. Coadministration of intravenous phenytoin did not result in further changes in QTc. Intravenous fosphenytoin resulted in significant prolongation of QTc. Fosphenytoin coadministered with sevoflurane resulted in a more substantial prolongation of QTc than propofol. However, the sample size was insufficient to demonstrate statistical significance or the nature of interaction with sevoflurane. One patient in group SF had significant bradycardia atrioventricular conduction delay and QT prolongation with subsequent ventricular tachycardia. The remaining patients with long QT had an unremarkable postoperative course. The perioperative period presents several conditions that may prolong QT and increase the patient's risk of developing complications of prolonged QT, such as polymorphic ventricular tachycardia or torsades de pointes. The fosphenytoin-induced QT prolongation may be clinically relevant in the presence of additional risk factors such as electrolyte abnormalities, hypothermia, intracranial hypertension, and massive blood loss, which were excluded from QTc analysis in this study. Even in the low-risk group, long QT (QTc $>$ 450ms) at some point during the study period was seen in all patients who were administered fosphenytoin, in 60% of patients in group SP and the incidence was significantly lower in group PP.

Limitations

The major limitation of this study is the small number of patients included in the analysis. About 225 were screened for possible inclusion to obtain eighty eligible subjects. An interim analysis was performed after 80 cases. The withdrawal was high in this study. The sample size of this study for analysis was small, but the findings were significant and had implications for practice. We did not recruit further after the interim analysis due to the high incidence of serious adverse event. A few changes have been introduced into the practice of prophylactic anticonvulsant administration since. Phenytoin was administered at a rate lower than recommended to reduce the cardiovascular adverse effects. The recommendation by Meek et al for the use of phenytoin in nonemergency situations in patients with a severe concomitant disease such as sepsis, hemodynamic instability, peripheral vascular disease, and hyponatremia was 10 to 20 mg/min[18] that was followed. Subsequently, levetiracetam has become widely accepted as a safer AED for intraoperative use,[26] but its efficacy is not yet established. The other limitation is that the study did not evaluate the serum phenytoin levels or serum ionized calcium levels. The pilot study is hypothesis-generating and needs further studies to validate the results of this proof-of-concept study.

Conclusion

Loading dose of phenytoin and fosphenytoin administered intraoperatively produces significant hemodynamic changes such as hypotension and bradycardia. There was no significant difference in cardiovascular adverse effects between the two drugs. Fosphenytoin, in nonemergent situations, did not offer any hemodynamic advantage. Fosphenytoin, in

addition, produced significant prolongation of QTc, and the prolongation was greater during sevoflurane anesthesia. These agents must be administered cautiously in the intraoperative period with monitoring for hemodynamics and changes in the ECG.

Conflict of Interest
None declared.

References

1 Kale A. Prophylactic anticonvulsants in patients undergoing craniotomy: a single-center experience. Med Sci Monit 2018; 24:2578–2582
2 Greenhalgh J, Weston J, Dundar Y, Nevitt SJ, Marson AG. Antiepileptic drugs as prophylaxis for postcraniotomy seizures. Cochrane Database Syst Rev 2018;5:CD007286
3 Kutteruf R, Yang JT, Hecker JG, Kinney GA, Furman MA, Sharma D. Incidence and risk factors for intraoperative seizures during elective craniotomy. J Neurosurg Anesthesiol 2019;31(02):234–240
4 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
5 Guldiken B, Rémi J, Noachtar S. Cardiovascular adverse effects of phenytoin. J Neurol 2016;263(05):861–870
6 Bhagat H, Bithal PK, Chouhan RS, Arora R. Is phenytoin administration safe in a hypothermic child? J Clin Neurosci 2006;13(09): 953–955
7 Berry JM, Kowalski A, Fletcher SA. Sudden asystole during craniotomy: unrecognized phenytoin toxicity. J Neurosurg Anesthesiol 1999;11(01):42–45
8 DeToledo JC, Lowe MR, Rabinstein A, Villaviza N. Cardiac arrest after fast intravenous infusion of phenytoin mistaken for fosphenytoin. Epilepsia 2001;42(02):288
9 Popławska M, Borowicz KK, Czuczwar SJ. The safety and efficacy of fosphenytoin for the treatment of status epilepticus. Expert Rev Neurother 2015;15(09):983–992
10 Adams BD, Buckley NH, Kim JY, Tipps LB. Fosphenytoin may cause hemodynamically unstable bradydysrhythmias. J Emerg Med 2006;30(01):75–79
11 Keegan MT, Bondy LR, Blackshear JL, Lanier WL. Hypocalcemia-like electrocardiographic changes after administration of intravenous fosphenytoin. Mayo Clin Proc 2002;77(06):584–586
12 Grageda M, Saini AP, Trout LC, Cyran SE, Halstead ES. Severe cardiomyopathy in an infant after iatrogenic fosphenytoin overdose. Clin Pediatr (Phila) 2014;53(08):791–793
13 Boucher BA, Feler CA, Dean JC, et al. The safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular and intravenous administration in neurosurgery patients. Pharmacotherapy 1996;16(04):638–645
14 Scalese MJ, Herring HR, Rathbun RC, Skrepnek GH, Ripley TL. Propofol-associated QTc prolongation. Ther Adv Drug Saf 2016;7 (03):68–78
15 Ege MR, Guray Y. A comparison of the effects of desflurane, sevoflurane and propofol on QT, QTc and P dispersion on ECG. Ann Card Anaesth 2011;14(01):65
16 Kawataki M, Kashima T, Toda H, Tanaka H. Relation between QT interval and heart rate. applications and limitations of Bazett's formula. J Electrocardiol 1984;17(04):371–375
17 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
18 Meek PD, Davis SN, Collins DM, et al; Panel on Nonemergency Use of Parenteral Phenytoin Products. Guidelines for nonemergency use of parenteral phenytoin products: proceedings of an expert panel consensus process. Arch Intern Med 1999;159(22):2639–2644
19 Kim HK, Hwang IG, Koh IS, Kim DW. Incidence and risk factors of hypotension after intravenous fosphenytoin administration. J Clin Pharm Ther 2017;42(05):561–566
20 Coplin WM, Rhoney DH, Rebuck JA, Clements EA, Cochran MS, O'Neil BJ. Randomized evaluation of adverse events and length-of-stay with routine emergency department use of phenytoin or fosphenytoin. Neurol Res 2002;24(08):842–848
21 Capparelli FJ, Abello M, Patricio Maskin L, et al. QTc prolongation after brain surgery. Neurol Res 2013;35(02):159–162
22 Terao Y, Higashijima U, Toyoda T, Ichinomiya T, Fukusaki M, Hara T. The effects of intravenous anesthetics on QT interval during anesthetic induction with sevoflurane. J Anesth 2016;30(06): 929–934
23 Oji M, Terao Y, Toyoda T, et al. Differential effects of propofol and sevoflurane on QT interval during anesthetic induction. J Clin Monit Comput 2013;27(03):243–248
24 Lee JH, Yoo EK, Song IK, Kim JT, Kim HS. Effect of ramosetron on the QT interval during sevoflurane anaesthesia in children: a prospective observational study. Eur J Anaesthesiol 2015;32(05): 330–335
25 Toyoda T, Terao Y, Oji M, Okada M, Araki H, Fukusaki M. [The interaction of low-dose droperidol, propofol, and sevoflurane on QTc prolongation]. Masui 2015;64(06):580–585
26 Kassab MY, Lobeck IN, Majid A, Xie Y, Farooq MU. Blood pressure changes after intravenous fosphenytoin and levetiracetam in patients with acute cerebral symptoms. Epilepsy Res 2009;87 (2-3):268–271