Original Article

Efficacy of phenytoin for 7 days versus 21 days as prophylactic anticonvulsant in traumatic brain injury patients – A comparative study

Santosh Kumar[1]*, Alok Kumar Bharti[2], Ravi Shankar Prasad[3], Sarita Kumari[4], Anup Singh[5], Ghanshyam Yadav[1]*

Departments of [1]Anaesthesia, [3]Neurosurgery, [4]Trauma Centre (Anaesthesia) and [5]Geriatric Medicine, Institute of Medical Sciences, Banaras Hindu University, Uttar Pradesh, [2]Department of Anaesthesia, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

**Both contributed as First author.*

Abstract

Background: Post traumatic seizures (PTS) are very common after traumatic brain injury and occur more common in severe form of injury. Prophylactic treatment with phenytoin has been found to be effective however till now no uniform internationally agreed guideline is available for the duration of anticonvulsant prophylaxis for traumatic brain injury patients. **Methods:** 100 patients of either sex between age group of 18–65 years who have suffered intracranial injury identified by CT scan, admitted in Trauma ICU were enrolled in this prospective randomized single blinded clinical study. Group 1 (n = 50) received 7 days prophylactic anticonvulsant therapy with phenytoin and Group 2 (n = 50) received for 21 days. The primary end point was the occurrence of seizures, which were classified as early (occurring from time of drug loading to day 7) or late (occurring on day 8 or later after loading of drug). Patients were also assessed for the possible adverse side effects of phenytoin. **Result:** Out of 100 patients, 90 completed the study successfully as 5 patients from each group expired during the duration of the study. On comparing the frequency of seizure from 1st to 7th day after loading dose of phenytoin between two groups, out of 45 patient, 2 (4.4%) developed seizure in group 1 and 3 (6.7%) developed seizure in group 2 and found to be statistically insignificant (P = 0.645). On comparing the frequency of seizure from 1st to 21st day after loading dose of phenytoin between two groups, out of 45 patient, 4 (8.9%) developed seizure in groups 1 and 3 (11.1%) developed seizure in group 2 and found to be statistically insignificant (P = 0.725). **Conclusion:** A 21-day prophylactic anticonvulsant therapy with phenytoin was not more effective than a 7-day prophylactic therapy with phenytoin to reduce the frequency of seizure in a TBI patient in trauma ICU and was also associated with more adverse side effects that were insignificant.

Keywords: Antiepileptic, phenytoin, traumatic brain injury

Introduction

Traumatic brain injury (TBI) affects a large proportion and extensive range of individuals in the population, contributing to increased morbidity and mortality all over the world. Most of the treatments of TBI are aimed at reducing secondary brain insults arising from the injuries. Post-traumatic seizures (PTSs) incidence is high in patients who had experienced traumatic brain injury. PTS can be immediate (occurring in <24 hrs of injury) or early (occurring in <7 days of injury) or late (occurring after 7 days of injury) with incidence of 1-4%, 4-25%, and 9-42%, respectively.[1] Pharmaco-prophylaxis against early onset seizures

Address for correspondence: Dr. Sarita Kumari, Assistant Professor, Trauma Centre (Anaesthesia), Institute of Medical Sciences, Banaras Hindu University, Uttar Pradesh, India.
E-mail: drsarita.anesthesia@gmail.com

Received: 28-02-2022 **Revised:** 15-04-2022
Accepted: 20-04-2022 **Published:** 30-08-2022

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_486_22

How to cite this article: Kumar S, Bharti AK, Prasad RS, Kumari S, Singh A, Yadav G. Efficacy of phenytoin for 7 days versus 21 days as prophylactic anticonvulsant in traumatic brain injury patients - A comparative study. J Family Med Prim Care 2022;11:4805-10.

following TBI is recommended in the Trauma Brain Foundation and recent Trauma Brain Foundation Guidelines-2016 states that anticonvulsants are indicated to decrease the incidence of early PTSs.[2]

The incidence of early onset seizures may be high in certain groups such as those with severe traumatic brain injury. The majority of studies on PTS prophylaxis focuses on patients with severe TBI and tend to exclude those with mild to moderate head trauma. In general, patients with mild TBI have lower rates of PTSs when compared with severe TBI. Effective pharmaco-prophylaxis of early PTS reduces brain metabolic demands, thereby reducing intracranial pressure and neuro-transmitter release, this may turn minimize secondary brain damage.[3] Currently, a limited number of studies report data on PTS prophylaxis in patients with mild TBI, so more studies are required for this group of patients to establish the definitive guidelines.

There are currently no uniform internationally agreed guidelines available for the duration of anticonvulsant prophylaxis for traumatic brain injury patients but prophylactic treatment with phenytoin was effective as evident by a meta-analysis review.[4,5] This study was done to compare duration of prophylactic phenytoin treatment for 7 days and 21 days for TBI. This is immensely beneficial for family healthcare provider and general physicians to know optimum prophylactic duration so as to avoid extended use of phenytoin so as to minimize side effects and maximize cost efficacy.

Material and Methods

The present study was conducted in the intensive care unit, Trauma centre, BHU, Varanasi, between June 2019 and June 2020. After the approval of institutional ethical committee (Letter no.Dean/2018/EC/958) and informed written consent, was taken by patient or his/her relatives, 100 patients of either sex between age group of 18 and 65 years who have suffered intracranial injury identified by CT scan, admitted in Trauma ICU were enrolled in this prospective randomized single blinded clinical study. The exclusion criteria included pregnant patients, history of seizure or use of antiepileptic medication prior to admission, allergy, or contraindication to study drug, any post-injury seizures prior to randomization and pre-existing hepatic/renal disorder.

All patients were randomly assigned into two equal groups (n = 50) using sequentially numbered, opaque, sealed envelope based on computer-generated random numbers. Group 1 received 7 days prophylactic anticonvulsant therapy with phenytoin and Group 2 received 21 days prophylactic anticonvulsant therapy with phenytoin. A total of 100 envelopes with number indicating the sequence of the patients were mentioned on the outside. The group allocation and the study drug were kept inside the envelopes and sealed. These envelopes were given to the drug administrator. The participants involved in collecting data and in the assessment of variables were blinded. The group allocation was revealed only after analysis of data.

Once the patients received in trauma ICU, all the standard ASA monitor were attached in the form of ECG, SpO2, non-invasive blood pressure (NIBP) and temperature to the patients, monitoring continued till the discharge/death of the patients. A loading dose of 20 mg/kg of phenytoin, diluted in 100 ml NS, given intravenous over 30 min within 24 hours of injuries, followed by maintenance dose of 5 mg/kg/day given intravenous for 7 days in group 1 and 21 days in group 2. The primary end point of the study was the occurrence of seizures, which were classified as early (occurring from time of drug loading to day 7) or late (occurring on day 8 or later after loading of drug). Patients were also assessed for the possible adverse side effects of phenytoin. Breakthrough seizure was controlled by giving inj. midazolam 2 mg i.v. and further addition of anticonvulsants which was decided by expert opinion of physician.

Sample size calculation was done based on sealed envelope sample size calculator by taking α = 5%, Power (1-β) = 80%, minimum expected difference between the groups = 15%. A total of 90 patients with 45 in each group. To make provision for dropouts if any, we enrolled 50 patients in each group. Statistical testing was conducted with the Statistical Package for the Social Science system version SPSS 17.0. Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. $P < 0.05$ was considered statistically significant.

Primary outcome measure was to compare the effectiveness of administration of phenytoin for the duration of 7 days to that of 21 days in prevention of seizure activity (in terms of number of patients developing seizure activity) in TBI patients and secondary outcome was to look for any adverse side effects of studied drug.

Results

Out of 100 patients, 90 completed the study successfully because 5 patients from each group were dropped out of the study because they expired during the duration of the study. Both the groups were comparable with respect to age, sex and Glasgow Coma Scale (GCS) and *P* value found to be statistically insignificant (P > 0.05) [Table 1]. On comparison of diagnosis (EDH, SAH, Contusion, SDH, and DAI) between two groups were comparable and found to be statistically insignificant (P = 0.461) [Table 2].

On comparing the frequency of seizure from 1 to 7 day after loading dose of phenytoin between two groups, out of 45 patient, 2 (4.4%) developed seizure in groups 1 and 3 (6.7%)

Table 1: Comparison of mean age, sex, and mean GCS score between two groups

	Group 1 (*n*=45)	Group 2 (*n*=45)	*P*
Age (years)	37.7312.101	37.6012.628	0.959
Sex (M/F)	27 (60%)/18 (40%)	29 (64.4%)/16 (35.6%)	0.664
GCS	10.96 1.858	11.001.907	0.911

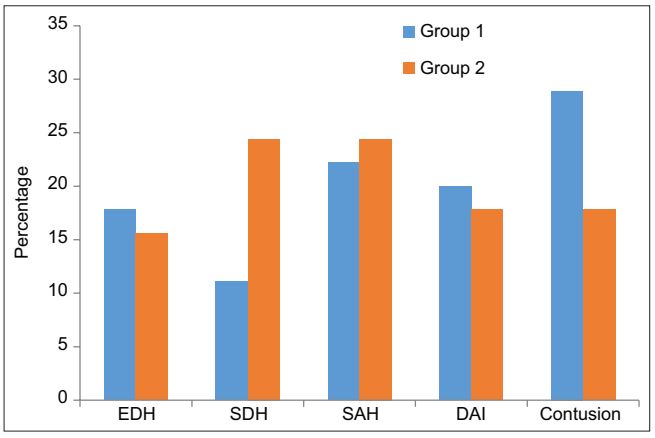
Data presented as mean±SD or number or percentage. *P*<0.05 considered as significant. SD=Standard Deviation GCS - Glasgow Coma Scale

Table 2: Comparison of diagnosis between the two groups

Diagnosis	Group 1		Group 2	
	No.	%	No.	%
EDH	8	17.8	7	15.6
SDH	5	11.1	11	24.4
SAH	10	22.2	11	24.4
DAI	9	20.0	8	17.8
Contusion	13	28.9	8	17.8
Total	45	100	45	100

Data presented as percentage. *P*<0.05 considered as significant. χ^2=3.614; *P*=0.461. EDH – extradural hematoma, SDH – Subdural hematoma SAH – Sub arachnoid hemorrhage DAI – Diffuse axonal injury

Table 2: Comparison of diagnosis between the two groups



developed seizure in group 2 and found to be statistically insignificant (P = 0.645) [Table 3]. On comparing the frequency of seizure from 1 to 21 days after loading dose of phenytoin between two groups, out of 45 patient, 4 (8.9%) developed seizure in groups 1 and 3 (11.1%) developed seizure in group 2 and found to be statistically insignificant (P = 0.725) [Table 4]. On comparing the hemoglobin, urea, sodium, direct bilirubin, albumin, and platelet between two groups at 0, 7, and 21 days there were some derangements noticed in the haemoglobin concentration, total leucocyte count and liver function test of isolated patients on use of phenytoin after 7 days but they were statistically insignificant to arrive at any conclusion for the short period of study. There was no statistically significant side effect or adverse drug reaction was notice during the entire period of study. (P > 0.05) [Table 5].

Discussion

Traditionally prophylactic anticonvulsant therapy is recommended for TBI patients. However, the optimum duration of the prophylactic therapy has been questioned and there were studies to evaluate the efficacy of prophylaxis for short duration (7 days) and relatively longer duration. Recently optimum duration of the prophylactic therapy has generated interest for prevention of convulsion after TBI.

We conducted this prospective randomized double-blinded clinical study on the role of phenytoin in preventing early (<7 days) versus late (>7 days) PTSs in 100 traumatic brain injury patients of either sex between age group of 18–65 years, who had suffered intracranial injury identified by CT scan, admitted in trauma ICU. An antiepileptic drugs have been used for many years in an attempt to prevent the development of PTSs. Early retrospective studies suggested that the prophylactic use of phenytoin was effective.[6-8] However, subsequent prospective, double-blind trials of treatment with phenytoin or a low dose of phenytoin combined with phenobarbital failed to show that such treatment had more benefit than placebo.[9-11] Similarly, Ricky Wat *et al.*[12] in a metanalysis of 3 RCTs and 6 observational studies concluded that though phenytoin is most studied drug, there are modest evidence suggesting effectiveness of anti-epileptic prophylaxis of early PTS. These latter studies have been criticized as inconclusive because the levels of phenytoin that were achieved were generally subtherapeutic and lacked statistical power to detect a clinically important effect and none of clinical trial emphasized on definitive duration of prophylactic use of phenytoin for prevention of PTS in TBI patients.

On comparison of two groups with regard to age, gender, GCS, and diagnosis were comparable and found to be statistically insignificant. (P > 0.461). In our study at the end of 7 days, 4.4% (2) patients in group 1 and 6.7% (3) patients in group 2 developed seizure activity despite phenytoin prophylaxis in both the groups, with *P* value of 0.645 which was statistically insignificant. The cumulative seizure activity at the end of 21 days, was 8.9% (4) and 11.1% (5) patients in group 1 and group 2 respectively with *P* value of 0.725, which was statistically insignificant. Our study was supported by a meta-analysis by Christopher D. Wilson *et al.*[13] Sixteen studies were included. Phenytoin was associated with decreased odds of early seizures relative to placebo (OR = 0.34, 95% confidence interval [CI] 0.19–0.62). There was no difference in early seizure incidence between levetiracetam and phenytoin (OR = 0.83, 95% CI 0.33–2.1). Neither levetiracetam (OR = 0.69, 95% CI 0.24–1.96) nor phenytoin (OR = 0.4, 95% CI 0.1–1.6) was associated with fewer late PTSs than placebo.

Our study was supported by Temkin *et al.*,[14] they did a randomized, double-blind study of phenytoin for the prevention of PTSs and concluded that phenytoin exerts a beneficial effect by reducing seizures only during the first week after severe head injury. However, no significant protective effect was detected between day 8 and the end of the second year of study. For early seizures (drug loading to 7 days), the phenytoin group had a cumulative (±SE) seizure rate of 3.6 ± 1.3 percent at the end of the first week, as compared with 14.2 ± 2.6 percent in the placebo

Table 3: Comparison of patients developing seizure from 1 to 7 day between the two groups

	Group 1		Group 2	
	No.	%	No.	%
Present	2	4.4	3	6.7
Absent	43	95.6	42	93.3
Total	45	100	45	100

Data presented as percentage (%). χ^2=0.211; *P*=0.645

Table 4: Comparison of patients developing seizure between 1 day and 21 day between the two groups

	Group 1		Group 2	
	No.	%	No.	%
Present	4	8.9	5	11.1
Absent	41	91.1	40	88.9
Total	45	100	45	100

Data presented as percentage (%). χ^2=0.123; *P*=0.725

Table 3: Comparison of patients developing seizure from 1 to 7 day between the two groups

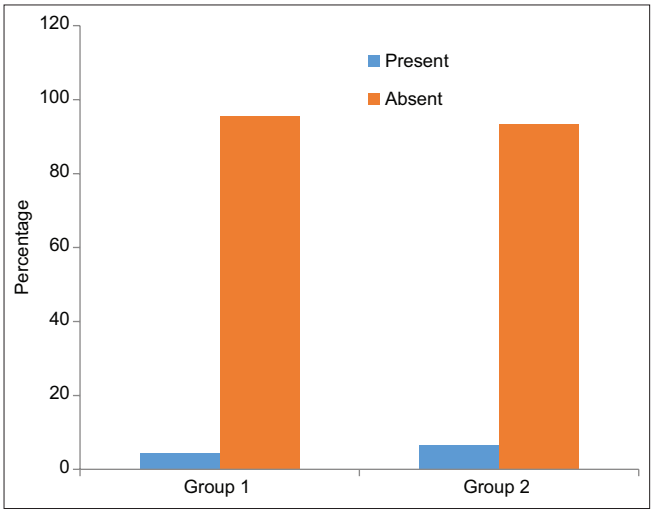
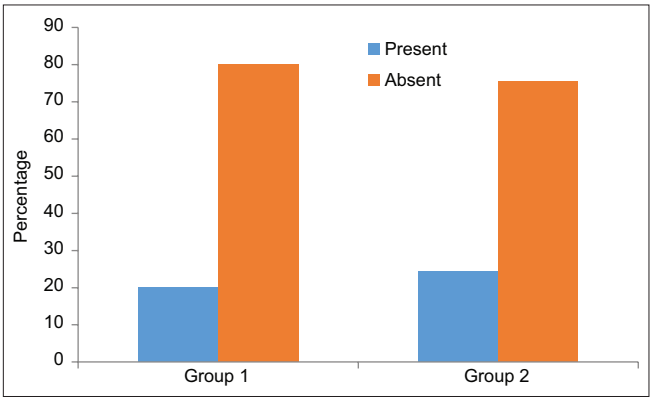


Table 4: Comparison of patients developing seizure between 1 day and 21 day between the two groups



group (P < 0.001). For late seizures (day 8 to 2 years), by year 1, 21.5 ± 3.6 percent of the phenytoin group and 15.7 ± 3.2% of the placebo group had late seizures; by year 2, the differences were similar 7.5 ± 4.0% and 21.1 ± 3.7%, respectively. The differences between the groups were not statistically significant (P > 0.20 for each comparison).

Our study was further supported by North *et al.*,[15] they studied on a blinded randomized study of phenytoin (5-6 mg/kg/day) treatment as prophylaxis against seizures after supratentorial neurosurgery in 281 patients, 36% of whom underwent surgery because of trauma. They concluded that a significant reduction in the frequency of epilepsy was observed in the group receiving the active drug up to the 10th postoperative week.

Another study done by Young *et al.*,[10] as randomized double-blind placebo-controlled study was undertaken in a series of 179 patients to determine whether phenytoin administered soon after head injury, lessens the incidence of late post-traumatic epilepsy and when delayed hypersensitivity to phenytoin developed, the patient was switched to phenobarbital and patients were followed for 18 months to detect the occurrence of seizures and to serially measure plasma phenytoin concentrations. There was no significant difference in the percentage of patients having late seizures in the treated and placebo groups (p = 0.75) and concluded that failure of prophylactically administered phenytoin to prevent late PTSs.

Another study done by Wohns and Wyler's,[7] on retrospective analysis of 62 patients with severe head injury treated with phenytoin, of 50 patient treated with phenytoin, 10% developed epilepsy of late onset seizure and 12 patient not treated with phenytoin, had 50% incidence of epilepsy with injuries of equal magnitude and concluded that "prophylactically administered phenytoin is effective in reducing post-traumatic epilepsy." was well correlated with our study.

In our study, adverse side effects of phenytoin were seen in the both groups and found to be statistically insignificant (P > 0.05). Our study finding was supported by Alan M *et al.*[16] studied on side effects and mortality associated with use of phenytoin for early PTS prophylaxis: a prospective double-blind placebo-controlled study and they concluded that the incidence of early posttraumatic seizure can effectively reduce by prophylactic administration of phenytoin for 1 or 2 weeks without significant increase in drug related side effects.

Best possible mechanism for the role of anticonvulsant to prevent seizure after traumatic brain injury might include TBI induced focal (e.g., contusion or intracranial hematomas) and diffuse (e.g., DAI) insults to the brain that result in cicatrix in the cortex or subcortical regions, and consequences of that, the neighboring neural tissue experiences inflammation, gliosis, and ultimately neuronal sprouting and neurogenesis. These secondary tissue responses in the form of hypoxia and cerebral edema, are

Table 5: Comparison of Hemoglobin (g/dl), Urea (mml/L), Sodium (mm/l), AST (U/L), Direct bilirubin (mg/dl), Albumin (g/dl), and Platelet count (/μL) at 0-day, 7th day, and 21st day between the two groups

	Group 1 MeanSD *n*=45	Group 2 MeanSD *n*=45	*t*	*P*
Hb 0	11.0301.8221	10.9042.0830	0.307	0.760
Hb 7	10.5401.7522	10.4112.0802	0.319	0.751
Hb 21	10.9301.6633	10.6672.0844	0.662	0.509
Urea 0	69.58531.1033	71.30729.6769	0.269	0.789
Urea 7	65.17230.0878	68.61330.5544	0.538	0.592
Urea 21	61.47029.2335	63.59130.7874	0.335	0.738
Na 0	144.6849.2788	148.1088.6776	1.808	0.074
Na 7	146.2289.7052	149.6978.6728	1.788	0.077
Na 21	147.2439.7473	150.6338.7109	1.740	0.085
AST 0	63.62622.8365	59.69624.4560	0.788	0.433
AST 7	73.92022.0545	69.21624.2569	0.963	0.338
AST 21	61.59222.3324	64.70224.4994	0.629	0.531
DB 0	0.5980.2004	0.6250.2526	0.577	0.565
DB 7	0.7460.1986	0.7760.2566	0.610	0.544
DB 21	0.6480.2355	0.6230.2654	0.474	0.637
Alb 0	4.0070.6456	3.8300.6010	1.345	0.182
Alb 7	3.8540.6485	3.6820.6052	1.300	0.197
Alb 21	3.8410.6389	3.6680.5993	1.318	0.191
PLT 0	212816.3155139.541	213496.4954830.066	0.059	0.953
PLT 7	214530.14455106.9555	215180.51354945.9375	0.056	0.955
PLT 21	207010.92954680.0220	207482.40654792.6538	0.041	0.968

Data presented as mean±SD. $P<0.05$ considered as significant. Hb – Haemoglobin AST- Alanine Aspartate Alb – Albumin PLT – Platelet

believed to be the initiating events in a cascade of processes that result in epileptogenesis. Enhanced excitatory neurotransmitter connectivity and decreases in GABAergic inhibition play important role in injury-induced epileptogenesis.

Limitation of our study was that we could not include pediatric age group population and also couldn't measure the therapeutic plasma concentration of drug. Another limitation of our study was small sample size, so studies with large sample size are warranted to externally validate the results and use of bedside EEG would have been of immense importance which could not be done in our study. We could not compare the prophylactic phenytoin in a patient with injuries of same magnitude.

Conclusion

A 21-day prophylactic anticonvulsant therapy with phenytoin was *not* more effective than a 7-day prophylactic therapy with phenytoin to reduce the frequency of seizure in a TBI patient in trauma ICU and was also associated with more adverse side effects that were insignificant.

Key points

1. Trauma to brain may precipitate seizure (immediate, early, late) that may cause secondary brain injury.
2. TBI seizures should and can be prevented with prophylactic use of anti-epileptic agents (e.g., phenytoin - most studied).
3. Prophylactic use of phenytoin to curb seizure episodes in TBI patients is at best of its effectiveness in early seizures (within 7 days).
4. Extended use of phenytoin beyond 7 days (for late seizures) holds no added benefit, rather should be discouraged for its side effect, cost, and patient compliance.

Key take home message

Extended use of phenytoin for more than 7 days as antiseizure prophylaxis in TBI patients holds no added benefit, rather it may burden the patient with side effects, drug interactions, cost, compliance. So, it should be discouraged.

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

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Khan AA, Banerjee A. The role of prophylactic anticonvulsants in moderate to severe head injury. Int J Emerg Med 2010;3:187-91.
2. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, *et al.* Guidelines for the management of severe traumatic brain injury, Fourth Edition. Neurosurgery 2017;80:6-15.
3. Practice parameter: Antiepileptic drug treatment of posttraumatic seizures. Brain Injury Special Interest Group of the American Academy of Physical Medicine and Rehabilitation. Arch Phys Med Rehabil 1998;79:594-7.
4. Temin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: Meta-analysis of controlled trials. Epilepsia 2001;42:515-24.
5. Chen JW, Ruff R L, Eavey R, Wasterlain CG. Post traumatic epilepsy and treatment. J Rehabil Res Dev 2009;46:685-96.
6. Servit Z, Musil F. Prophylactic treatment of posttraumatic epilepsy: Results of a long-term follow-up in Czechoslovakia. Epilepsia 1981;22:315–20.
7. Wohns RN, Wyler AR. Prophylactic phenytoin in severe head injuries. J Neurosurg 1979;51:507–9.
8. Young B, Rapp R, Brooks WH, Madauss W, Norton JA. Posttraumatic epilepsy prophylaxis. Epilepsia 1979;20:671–81.
9. McQueen JK, Blackwood DH, Harris P, Kalbag RM, Johnson AL. Low risk of late post-traumatic seizures following severe head injury: Implications for clinical trials of prophylaxis. J Neurol Neurosurg Psychiatry

1983;46:899-904.

10. Young B, Rapp RP, Norton JA, Haack D, Tibbs PA, Bean JR. Failure of prophylactically administered phenytoin to prevent late posttraumatic seizures. J Neurosurg 1983;58:236-41.
11. Penry JK, White BG, Brackett CE. A controlled prospective study of the pharmacologic prophylaxis of posttraumatic epilepsy. Neurology 1979;29:600–1.
12. Wat R, Mammi M, Paredes J, Haines J, Alasmari M, Liew A, *et al*. The effectiveness of antiepileptic medications as prophylaxis of early seizure in patients with traumatic brain injury compared with placebo or no treatment: A systematic review and meta-analysis. World Neurosurgery 2019;122:433-40.
13. Wilson CD, Burks JD, Rodgers RB, Evans RM, Bakare AA, Safavi-Abbasi S. Early and late posttraumatic epilepsy in the setting of traumatic brain injury: A meta-analysis and review of antiepileptic management. World Neurosurg 2018;110:e901-6.
14. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. N Engl J Med 1990;323:497-502.
15. North JB, Penhall RK, Hanieh A, Frewin DB, Taylor WB. Phenytoin and postoperative epilepsy: A double-blind study. J Neurosurg 1983;58:672–7.
16. Alan M, David W, Temkin R, Sureyya S, Richard S. Side effects and mortality associated with use of phenytoin for early posttraumatic seizure prophylaxis. J Neurosurg 1999;91:588-92.