ORIGINAL ARTICLE

Role of Gabapentin in Traumatic Brain Injury: A Prospective Comparative Study

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Received on: 19 October 2023; *Accepted on:* 19 December 2023; *Published on:* 29 January 2024

Abstract

Background: Traumatic brain injury (TBI) is a major cause of mortality among young individuals, accounting for 65% of deaths in road traffic accidents. Paroxysmal sympathetic hyperactivity (PSH) is a common syndrome associated with TBI. This study represents the first prospective investigation aimed at assessing the impact of gabapentin on TBI patients, focusing on the prevention of secondary brain injury and brain edema while enhancing the Glasgow Coma Scale (GCS).

Materials and methods: The study was conducted from September 2019 to July 2021 after receiving ethical committee approval. It included adult ICU patients (≥18 years) with moderate and severe GCS. Patients below 18 years, death within 48 hours, non-consenting, pregnant females, and individuals allergic to gabapentin were excluded from the study. Patients were randomly allocated in two groups: study group received 300 mg of gabapentin orally twice daily and control group received multivitamin tablets twice daily. The treatment period spanned 2 weeks. Follow-up occurred in the ICU and continued for up to 3 months post-discharge, including telephonic conversations.

Results: About 60 patients were involved for analysis. Significant differences were found in GCS change from admission to discharge, Glasgow Outcome Scale (GOS) at 30 and 90 days, PSH episodes, and sedation bolus per day. Glasgow Coma Scale change was 53% in the study group compared with 25% in the control group ($p = 0.009$). Mortality was significantly lower in the study group. Glasgow Outcome Scale change between 30 and 90 days showed a 25% improvement in cases and no change in controls ($p = 0.001$).

Conclusion: This pioneering study underscores the potential of gabapentin in managing traumatic brain injuries.

Keywords: Gabapentin, Paroxysmal sympathetic hyperactivity, Traumatic brain injury.

Indian Journal of Critical Care Medicine (2024): 10.5005/jp-journals-10071-24634

Highlights

- Prospective study carried out to compare and evaluate the effects of gabapentin in traumatic brain injury (TBI) patients and assess their role in prevention of secondary brain injury.
- Not enough studies have assessed the effects of these drugs in improving consciousness and preventing secondary brain injury in TBI patients.
- A 90-day follow-up helps to give a long-term perspective.

Introduction

Trauma is a major contributor to mortality in younger population, with traumatic brain injury accounting for almost 20–30% of deaths.[1,2] It has surpassed many major illnesses as a cause of mortality. All over the world, each year, over 69 million people endure TBI, with more than 4.7 million deaths annually.[3] Following trauma, the direct impact leads to primary brain injury. Complex pathophysiological mechanisms lead to secondary brain injury, and these include excitotoxicity, oxidative stresses, peri-infarct depolarization, inflammation; all these mechanisms take hours or days to take effect.[3,4] Among many syndromes associated with secondary brain injury, PSH is a syndrome where episodes of increased sympathetic activity are seen.[5] The incidence of PSH among the patients suffering TBI is between 7.7 and 33%.[3] Early identification of PSH is imperative as it increases morbidity and long-term disability after brain injury. The pharmacological management of PSH is problematic, because many questions regarding its pathophysiology remain unanswered. Drugs, such as benzodiazepines, nonselective β-blockers, α2-agonists, morphine, baclofen, and gabapentin may be beneficial.[3] Gabapentin is a gamma-aminobutyric acid (GABA) analog commonly used for treating seizures and neuropathic pains.

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How to cite this article: Singh R, Ambasta S, Bais PS, Azim A, Kumar S, Upreti B, *et al*. Role of Gabapentin in Traumatic Brain Injury: A Prospective Comparative Study. Indian J Crit Care Med 2024;28(2):120–125.

Source of support: Nil

Conflict of interest: None

Patient consent statement: The author(s) have obtained informed consent. All patient information has been de-identified to protect the patient privacy.

It acts on GABA system through N-type Ca^{2+} channels, but much of its mechanism of action is still unclear. It affects reticular activating system and is neuroprotective after TBI in animal models.[6–10] It binds to alpha subunit of calcium channel and prevents the release of excitatory neurotransmitter, and thus reduces secondary brain injury and edema.[11,12]

Hence, by understanding the mechanism of action of gabapentin, we propose to use it to reduce sympathetic hyperactivity, and to reduce secondary brain damage by preventing the release of neurotransmitters.

Objectives

We conducted this prospective study to primarily investigate the impact of gabapentin on TBI. The study focuses on the role of gabapentin to avert secondary brain injury, mitigating brain edema, and improving the Glasgow Coma Scale (GCS). Additionally, our research delves into the effects of gabapentin on preventing dysautonomia/PSH stemming from secondary injury and any associated drug side effects.

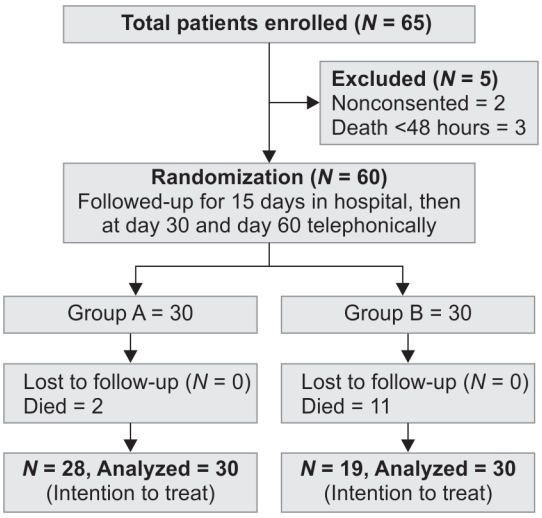

Fig 1: CONSORT diagram showing recruitment and analyses of patients

Materials and Methods

Type and Place of Study

It is a randomized control trial which was conducted from September 2019 to July 2021 in a tertiary care center. After approval by the ethical committee and CTRI registration (CTRI/2020/04/024537), the study was commenced. Patients from three ICUs of a tertiary care hospital in the north of India were recruited. The clinical management of these patients was as per the advice of treating physician and was not affected by our study.

Inclusion/Exclusion Criteria

All adult (≥18 years) ICU patients with TBI with moderately decreased GCS (8–13) and severely decreased GCS (<8) were included in our study. Patients of age <18 years, expected to die within 48 hours, patients who refused consent, those who were pregnant and those allergic to gabapentin were excluded.

Study Protocol

Two groups were created with random allocation of patients under study using computer generated randomized tables as [intervention group (I) and control group (C)]. Gabapentin was administered through oral or enteral route in a dose of 300 mg BD, within 24 hours of admission to ICU, in patients of group I. Multivitamin tablets in BD doses were given to patients in group C. Drugs were administered for a period of 2 weeks, following the protocol of previous studies. The patients were followed up during their ICU stay and up to 30 and 90 days after they were discharged, in follow-up clinics or telephonically. Non-contrast CT Scan (NCCT) brain study was done as per the advice of the treating team and reviewed. As per the discussion with neurosurgical team, brain edema was classified in to grade I as diffuse cerebral, grade 2 as midline shift, and grade 3 as impending herniation. A detailed proforma which included vitals, GCS, and CT scans was filled for each patient. PSH-AM score was calculated and total number of PSH episodes for each patient was recorded (Appendix 1) Glasgow Outcome Scale (GOS) score for each patient was calculated at the time of discharge from ICU and hospital (Appendix 2).

Sample Size Calculation

It was calculated to identify a difference of 1.5 in the GCS between groups, with $p < 0.05$ and 95% confidence interval (Software used for power analysis and sample size (PASS version 8). A minimum of 30 patients were required for the study.

Statistical Analysis

All demographic data was collected and their descriptive analysis was done using mean or median. To analyze the differences in GCS and GOS scores between the two groups, independent-sample *t*-test was used. SPSS16 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 65 patients were enrolled in the study, of which 5 patients were excluded (Fig. 1). The data were analyzed for the rest of the 60 patients who were followed up to 15 days in the hospital and at 30 days and 90 days over the telephone. There were no significant differences between the two groups in age, gender, preoperative GCS, and proportion of patients taken up for surgery.

As per the data, the mean age in group I was 36.53 ± 15.48 years while in group C, it was 40.4 ± 17.66 years. Median GCS score at admission was similar between group I and group C as seen in Table 1 Other variables including GCS (at discharge), GCS change from baseline (admission to discharge), GOS at 30 and 90 days, number of PSH episodes, and sedation boluses per day showed significant change. GCS change (difference in the GCS score between admission and discharge) was 53% among group I and 25% among controls (group C) ($p = 0.009$) (Fig. 2).

About 15 patients in group I needed sedation bolus once during the day, among controls (group C), this need increased up to 4 times per day in 15 patients. Mortality was significantly decreased in group I (6.7%) as compared with group C (36.7%), $p = 0.005$.

Patients were followed up telephonically to record the GOS. Glasgow Outcome Scale change (difference in GOS score between 30 and 90 days of intervention) in group I was 25% and group C was nil, respectively ($p = 0.001$) (Fig. 2).

The number of patients who clinically met the criteria of PSH diagnostic likelihood were comparable in the two groups. Probably, 66.7% in group I, 73.3% in group C ($p = 0.58$). Possible PSH likelihood of 16.7% group I vs 10% in group C ($p = 0.45$). Both the groups had equal number of patients in the Unlikely group (Fig. 3). Mean PSH-AM scoring showed a significant *p*-value when compared for

Table 1: Distribution of the demographic and other variables between cases and controls ($N = 60$)

	Group I (n = 30)	*Group C (n = 30)*	
Variable's	*Median (IQR)/Mean ± SD*	*Median (IQR)/Mean ± SD*	*p-value*
Age (years)	36.53 ± 15.48	40.4 ± 17.66	0.374
GCS (at admission)	8 (5.75, 11)	8 (7, 11)	0.798
GCS (at discharge)	14 (11, 15)	11 (9, 14)	0.028
GCS change (%)	53 (31, 114)	25 (5, 56)	0.009
GOS 30 days	4 (3, 4)	3 (2, 4)	0.043
GOS 90 days	4.5 (4, 5)	3 (3, 4)	0.001
GOS change (%)	25 (0, 33)	0 (–36, 25)	0.001
PSH episodes	2 (0, 3)	5 (1, 5.5)	0.001
Sedation bolus/day	1 (0, 1)	4 (1, 4.5)	0.003
Sex (male)	23 (79.3%)	22 (73.3%)	0.590
Non-survivors	2 (6.7%)	11 (36.7%)	0.005
Surgery (yes)	19 (63.3%)	17 (56.7%)	0.598
PSH diagnostic likelihood			
Probable (≥17)			
No.	20 (66.7%)	22 (73.3%)	0.58
Score	19.26 ± 2.76	22.80 ± 3.20	<0.001
Possible (8–16)			
No.	5 (16.7%)	3 (10%)	0.45
Score	10.77 ± 2.90	11.6 ± 2.40	0.69
Unlikely (<8)			
No.	5 (16.7%)	5 (16.7%)	0.999
Score	3.88 ± 2.73	3.63 ± 2.18	0.877
Type of surgery			
Decompressive craniectomy	5 (16.7%)	5 (16.7%)	0.99
Epidural hematoma clearing	10 (33.3%)	2 (6.7%)	0.011
Subdural hematoma clearing	4 (13.3%)	9 (30%)	0.12
Craniotomy with elevation of depressed fracture	1 (3.3)	3 (10%)	0.30
Front temporoparietal craniotomy	1 (3.3)	1 (3.3)	0.99
Other	9 (30%)	10 (33.3%)	0.79

Presented in median (IQR) compared by Mann–Whitney *U* test. Mean ± SD compared by independent samples *t*-test. Frequency (%), compared by Chi-square test/Fisher exact test. $p < 0.05$ significant

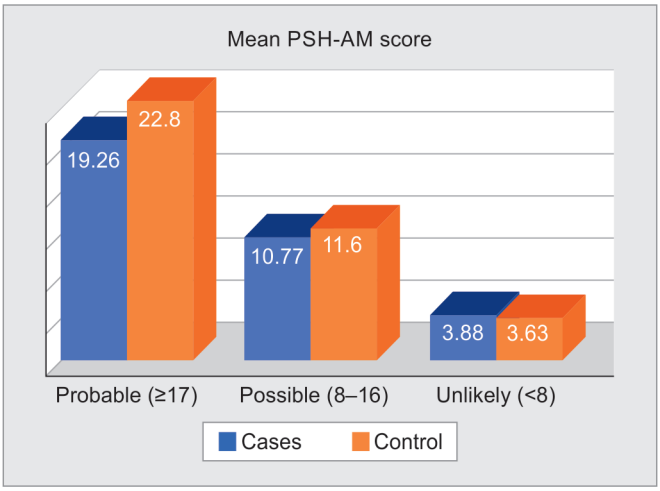

Fig 2: Mean PSH-AM score comparing cases and controls

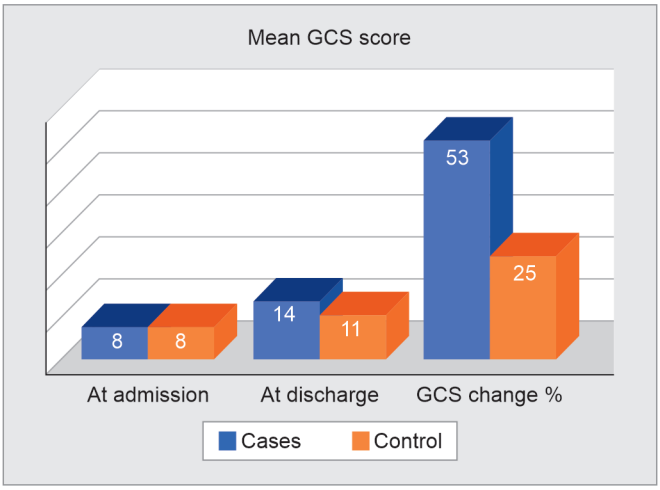

Fig 3: Median GCS score comparing cases and controls

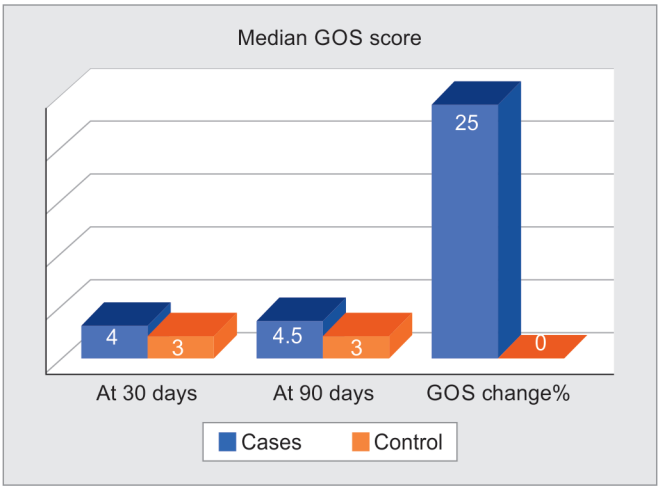

Fig 4: Median GOS score comparing cases and controls

the probable category ($p < 0.001$) while the possible and unlikely categories had similar values (Fig. 4).

Discussion

Paroxysmal sympathetic hyperactivity is a concerning entity affecting morbidity in survivors of TBI. Our study aimed to evaluate the use of gabapentin in reducing morbidity and PSH episodes. In a case series on six subjects with PSH after TBI, they used gabapentin for controlling autonomic changes and posturing. Gabapentin reduced the paroxysms, lead to reduction in medications, without worsening of symptoms.[13] The authors also proposed a theoretical model which can be further verified. They suggested that the neuropathic pain is acting as a driver for dysautonomia and this should be considered as pathophysiological mechanism of PSH and thus treatment for PSH should be based on it. We performed a prospective study, and evaluated the benefits of gabapentin in TBI patients and assessed its role in averting secondary brain injury. It was found in our study that the use of gabapentin reduced the number of PSH episodes significantly as was evident by reduction in the need of sedation boluses. The mean PSH score in cases was 19.26 ± 2.76 and in controls, it was 22.80 ± 3.20 (Fig. 1). Paroxysmal sympathetic hyperactivity is identified as a "syndrome, recognized in a subgroup of survivors of severe acquired brain injury, of simultaneous, paroxysmal transient increases in sympathetic (elevated heart rate, blood pressure, respiratory rate, temperature, and sweating) and motor (posturing) activity."[14] Boluses of sedation needed to control the posturing as well as increase in the heart rate and blood pressure were also less in cases. We also observed that the number of boluses required to control the breakthrough PSH episodes were also significantly reduced in gabapentin group as compared with controls.

Mortality and morbidity in TBI depends on the extent of secondary brain injury and vasogenic edema caused by primary insult.[15] Neurotoxic edema is caused due to sodium–calcium imbalance which occurs as the free radicals are excreted.[16] Gabapentin also has cerebro protective effect in animal models following TBI. To measure the extent of secondary injury following insult, GCS is the most important clinical parameter. Glasgow Coma Scale scores at admission and at discharge showed marked improvement among cases as evident in Figure 2. There was significant reduction in probable PSH episodes also. Patients were followed up during ICU stay, hospital stay and up to 90 days thereafter. A progressive improvement in outcome was observed. A retrospective case-controlled study of 35 patients concluded that delay in identification and treatment of PSH could have an impact on clinical outcomes as measured by GOS, functional independence measure, duration of post-traumatic amnesia, and hospital length of stay (LOS).[1,2,4,6] The longer the stay in ICU and the hospital more is the need for interventions. All these contribute an additional burden on healthcare systems as well an economic burden on the patient.[4] Our patients had a dramatic improvement in GOS and better functionality at 90 days interval (Fig. 3). Glasgow Outcome Scale is a great tool access the efficacy of functional outcome in a patient, but it does not access the disease pathogenesis. EEG and brain biopsy are tools to evaluate the brain cortical function and prognosis determination; however, it was not done on our study.[17,18] Changes in EEG patterns are associated with recovery of consciousness as was seen after treatment with gabapentin in our study. There was also an insignificant improvement in GCS.[3]

Strengths and Limitations

Our study is the first prospective study to analyze the role of gabapentin after TBI in Indian subpopulation. The sample size and 90-day follow-up gives us a fair idea about the outcome parameters in the study. However, major limitations of our study are small sample size, inability to use tests, such as EEG, brain biopsy for objective assessment of brain edema as done in previous studies.[19] Decrease in edema correlated with improvement in GCS and was used as a surrogate marker.[20,21]

Conclusion

Our study has revealed a potential preventive impact of gabapentin on PSH in individuals with TBI. Furthermore, it appears to contribute to improvement in both the GCS and the GOS. It is noteworthy that to date, there is a dearth of research addressing the preventive utility of gabapentin in managing PSH among TBI patients. However, it is imperative that future studies leverage advanced tools such as EEG to further investigate this phenomenon.

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Appendix 1

Clinical Feature Scale (CFS)

	0	*1*	*2*	*3*
Heart rate	<100	100–119	129–139	≥140
Respiratory rate	<18	18–23	24–29	≥30
Systolic pressure	<140	140–159	160–179	≥180
Temperature	<37	37–37.9	38–38.9	≥39
Sweating	Nil	Mild	Moderate	Severe
Posturing during episodes	Nil	Mild	Moderate	Severe

Diagnosis Likelihood Tool (DLT)

1. Clinical features occur simultaneously
2. Episodes are paroxysmal in nature
3. Sympathetic overactivity to normally non-painful stimuli
4. Features persist ≥3 consecutive days
5. Features persist ≥4-week post-injury
6. Features persist despite treatment of alternative differential diagnosis
7. Features ≥ episodes daily
8. Medication administered to decrease sympathetic features
9. Absence of parasympathetic features during episodes
10. Absence of other presumed cause of features
11. Antecedent acquired brain injury

The presence of each item is scored a 1 and their absence as 0 (Range 0–11).

The DLT, which identifies the presence of observed features, thereby estimating the likelihood of those that are due to PSH.

The Summary of PSH-AM

CFS score subtotal—the severity of clinical features:
(nil: 0, mild: 1–6 points, moderate: 7–12 points, severe: ≥13 points)

DLT score subtotal—the presence of observed features likely to PSH
(score subtotal one point for per feature present)

PSH-AM score- the diagnostic likelihood of PSH
(unlikely: <8 points, possible: 8–16 points, probable: ≥17 points)

PSH-AM score = CFS score + DLT score

Clinical application of PSH-AM Tool: the total PSH-AM scores (combined with the CFS and DLT subtotal scores) give an estimate of the probability of a diagnosis of PSH [adapted from Baguley, MarcoPozzi, and their colleagues.[20]

Appendix 2

Glasgow Outcome Score

1. Death
2. Persistent vegetative state: Minimal responsiveness
3. Severe disability: Conscious but disabled; dependent on others for daily support
4. Moderate disability: Disabled but independent; can work in sheltered setting
5. Good recovery: Resumption of normal life despite minor deficits

The GOS categorizes the outcomes of patients after traumatic brain injury.[21]