DOI: https://doi.org/10.53350/pjmhs20221611169

ORIGINAL ARTICLE

Neuropathophysiological Mechanisms and Treatment Strategies for Post-Traumatic Epilepsy

MUHAMMAD MUNWAR ALI[1], MUHAMMAD ASIF KHASKHELI[2], INAYATULLAH AWAN[3], KHAIRUNISA SHAIKH[4], SAFDAR HUSSAIN ARAIN[5], ABRAR SHAIKH[6]

[1]*Assistant Professor of Neurosurgery, Chandka Medical College, S. M. Benazir Bhutto Medical University, Larkana*
[2]*Senior Registrar, Department of Neurology, Khairpur Medical College, Khairpur Mirs*
[3]*Associate Professor of Psychiatry,* [4]*Assistant Professor, Department of Community Medicine, G. M. Mahar Medical College, Sukkur*
[5]*Associate Professor & Head Department of Neurosurgery,* [6]*Dean, Postgraduate & Research, Pir A. Q. Shah Jeelani Institute of Medical Sciences, Gambat*
Correspondence to: Dr. Muhammad Munwar Ali, E-mail: munwardr@yahoo.com Cell: 0334-3309349

ABSTRACT

Aim: To understand and analyze neuropathophysiological mechanisms and treatment strategies for post traumatic epilepsy**.**
Study design: Cohort clinical trial study
Place and duration of study: Department of Neurosurgery, Chandka Medical College Hospital, Larkana 1st January 2021 to 31st March 2022.
Methodology: One hundred and twenty cases of traumatic brain injury were enrolled. In 1st sub group there was 20 cases were given either Sodium valproate (SG1a) while 20 were given its placebo (SG1b). Similarly in subgroup 2nd and 3rd, each had 20 cases who were given Levetiracetam (SG2a) or Phenytoin **(**SG3a) respectively or other given its respective placebo (n=20/SG2b, SG3b). Primary and secondary outcomes were measured.
Results: The mean age was 30.1±3.3 years. There was almost equal number of both genders with slightly higher number of males than females with no significant variance. Around 40.83% of the cases were suffering from traumatic brain injury as a result of fall from a higher/raised building or structure.
Conclusion: The sodium valproate had a highest efficacy in controlling of the post-traumatic brain injury epileptic seizure not only for a short duration but for longer duration as well.
Keywords: Treatment strategies, Post-traumatic epilepsy, Neuropathophysiological mechanisms

INTRODUCTION

The number of traumatic brain injury (TBI) is globally escalated on yearly basis. The incidence of TBI is around 3 million annual cases in United States of America with 10% such cases which are severe[1]. Most of the TBI are related with long term deformities and disabilities with reduced cognition as well as higher risk of psychiatric illness development. Majority of the TBI are resulted from the fall which is followed by cases due to accidents especially from a motor bike. Cases of physical assault are also reported as one of the main causes of TBI especially in female patients[2,3].

The incidence rate has been described in both genders with an equal distribution. The incidence has been recorded in young children as well as teen agers and elderly people. There is a higher risk of disability formation through TBI in patients below 45 years of age with a treatment cost as 60 billion USD[1,4]. The brain traumatic injuries have been documented to result in seizures which can further leads into epilepsy in 4% of the cases[5].

Any new initiated epilepsy may be linked with development disorders as well as other reasons specifically including skull fractures and TBI.[6] Severe TBI has been defined as a state of coma after 24 hours of injury and further requiring the surgical interventions. Those patients who develop seizures after their TBI surgery have been presenting (40%) their epileptic seizures within first 6 months where a 60% of cases have reported epileptic episodes within a year time while 80% reports as later in their life[7-10]

The present study was designed to understand the neuropathological mechanism as well as treatment strategies of post traumatic epilepsy related to brain in various patients. This study was conducted for assessing better health supportive mechanisms for the treatment of patients suffering from TBI.

MATERIALS AND METHODS

This cohort clinical trial study was conducted in the Department of Neurosurgery, Chandka Medical College Hospital, Larkana 1st January 2021 to 31st March 2022 after permission from Institutional Ethical Review Board. The neuropathophysiological mechanism was understood through research of previous literature. There were 120 cases of TBI included in the study. Patient's attendants were contacted for getting written consent of participation from them. There were cases from both genders within the age limit of 18-70 years who were included in the study. Those patients who completely fulfilled the Glasgow Coma-Scale for moderate to severe TBI cases were included in the study. Cases having the Glasgow Coma-Scale within a value of 7-12 at accident scene or those between 3-12 in sedated condition during hospitalization were enrolled. Patients computed tomography scan (CT scan) was conducted and evidence against acute condition of intraparenchymal haemorrhages was collected. Moreover, those patients who were able to take their first dose/placebo within 12 hours of surgery were included as study participants. Patients were divided into 3 main groups. Each main group had two subgroups. In 1st sub group there was 20 cases were given either Sodium valproate (SG1a) while 20 were given its placebo (SG1b). Similarly in subgroup 2nd, and 3rd, each had 20 cases who were given Levetiracetam (SG2a) or Phenytoin **(**SG3a) respectively or other given its respective placebo (n=20/SG2b, SG3b**).** Those patients who were already having epileptic seizures, suffering from neurodegenerative disease or brain tumors were excluded from this research. Each patient was given either actual medication or its placebo which was similar in color, volume as well as packaging in double blinded protocol. Placebo identification was done through random selection computerized numbering allotment. The dosage was given according to standardized protocol (for 7 days). All patients were giving a quality hospital care and medication. Each patient was followed up within their treatment plan. Patients were followed up for 2 years as 1, 3, 6, 9, 12 and 18 up to 24 months post TBI surgery. EEG (frequency 256 Hz) was conducted and data was recorded in accordance with any episode of seizures. Clinical history of each patent was documents with their complete demographic details in a well-structured proforma. Quality of life assessment was conducted through EuroQol three-level version (EQ-5D-3L) (mobility, normal activities, self-care pain or discomfort, and anxiety or depression), as well as EuroQol visual-analogue scale (EQ VAS) (0 as worst imaginable to 100 as best imaginable scale) in a duration of 3, 6, 12 as well as 24 months post TBI. Mechanism of epilepsy if occurred was understood through standard neuropsychologic-tests, which included test-

Received on 17-06-2022
Accepted on 23-10-2022

batteries of the Wechsler-Intelligence Scale III as well as Rey Auditory-Verbal Learning Test in addition to 5 Digit Test at 6 months and then followed at 24 months post TBI. Primary outcomes were generated as unprovoked seizures within duration of day 7 to 24 months post TBI. Secondary outcomes consisted of frequency as well as type of seizures occurred with specification of time point of occurrence within 2 years' time. Data was analyzed using SPSS volume 26.0 through frequency and percentages. Chi square, Mean and standard deviation were also applied for analyses of the result and its interpretations p <0.05 was taken as significant.

RESULTS

It was known that primary and secondary various events occurs within a period of 1 or more years. Reorganization of neural circuits as well as post translational modification occurs. Activation of neuro inflammatory pathways are also observed. Hippocampal-sclerosis in addition to neurodegeneration and neuro-inflammation are observed in the epileptic seizure experiencing TBI patients (Fig. 1).

The mean age was 30.1±3.3 years. The highest percentage of the patients was within the age group of 18-38 years. There was almost equal number of both genders with slightly higher number of males than females with no significant variance. Around 40.83% of the cases were suffering from TBI as a result of fall from a higher/raised building or structure. There were 23.33% such cases who suffered severe TBI as a result of physical assault. Majority of such cases were females (Table 1).

Within the severe cases of TBI related with accident seizure development was noticed in various events as one such was observed in a single case of gunshot. Seizure development was noted at after surgery despite being treated with phenytoin anti-epileptic medication (Fig. 2).

The sodium valproate had a highest efficacy in controlling of the post TBI epileptic seizure not only for a short duration but for longer duration as well. The primary outcomes fir EQ 5D SL presented 0.789±0.28 value for it as well as 68.14±20.7 EuroQol visual-analogue scale (Table 2).

Table 1: Demographic characteristics of the cases of TBI (n=120)

Variable	No.	%
Age in Years		
18-38	62	51.66
39-58	29	24.16
59-70	19	15.83
Genders		
Male	56	46.66
Female	54	45.00
Cause of TBI		
Fall	49	40.83
Accident	33	27.50
Assault	28	23.33

Table 2: Efficacy of epileptic medication post TBI

Anti-Epileptic Medication	Primary outcomes			Secondary outcomes			P value
	No seizures	Early seizures	Late seizures	EQ 5D 3L		EuroQol visual-analogue scale	
				Upto 12 months	Upto 24 months		
Sodium valproate (SG1a) n=20	20	-	-	0.735±0.30	0.789±0.28	68.14±20.7	0.04
Sodium valproate Placebo (SG1b) n=20	17	1	2	0.615±0.30	0.885±0.28	56.21±11.7	
Levetiracetam (SG3a) n=20	18	2	-	0.769±0.29	0.788±0.30	70.14±21.2	0.45
Placebo Levetiracetam (SG3b) n=20	17	2	1	0.622±0.31	0.886±0.27	58.25±12.7	
Phenytoin (SG4a) n=20	14	4	2	0.755±0.25	0.768±0.23	65.14±19.8	0.51
Placebo Phenytoin (SG4b) n=20	16	2	2	0.616±0.31	0.882±0.22	55.24±10.8	

Fig. 1: Neuropathophysiological basis of electrogenesispost TBI[10]

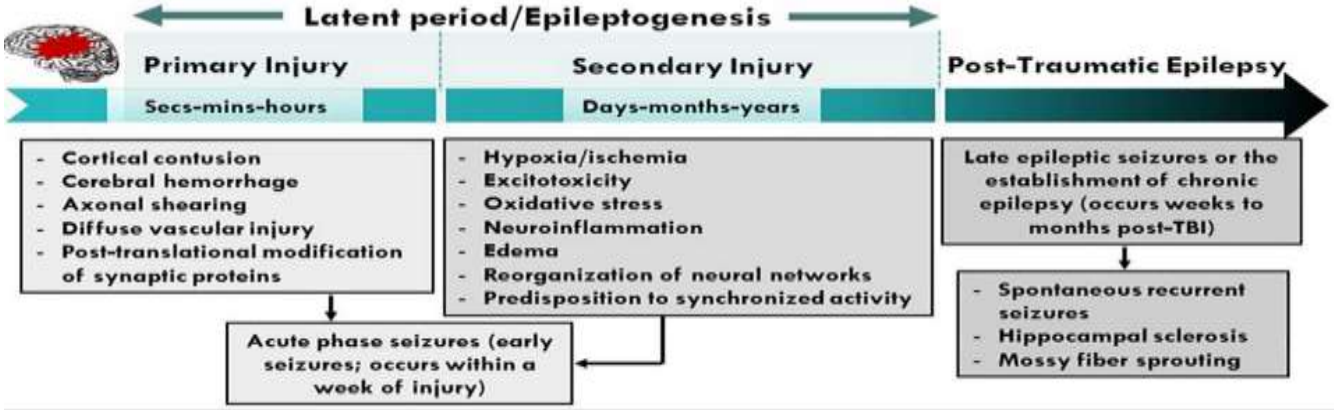
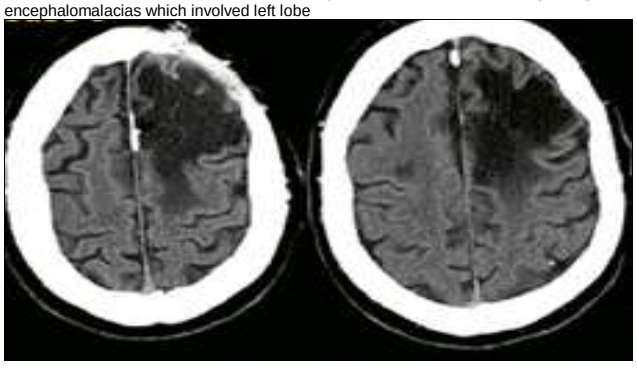


Fig. 2: CT scan illustrated chronic post-operative alterations with larger region of encephalomalacias which involved left lobe



DISCUSSION

Neuroinflammation is triggered in the brain as a result of various functional changes due to infection, trauma or toxic compound formation. Traumatic injuries and malfunctioning can be a major cause for inflammation in neuronal system which can lead into epileptic seizures earlier or later stages of life. In cases whether uncontrolled acute inflammation continues and is not disrupted can result in deleterious responses on the brain[11-13].

The epileptic activities after post traumatic injury have been extensively studies in adults as well as children. The clinically significant TBI hospitalization has been reported in various studies and has been found to be very high in young adults as well as children. The main cause of these injuries is from fall or accidents. Similar has been observed in the present study results[14-16].

A previously reported systematic review has elaborated the incidence of TBI in 15% of the adults with male being more frequently under the risk of brain injury than females. Other factors as intracranial-hemorrhagic as well as fractures of the skull can lead to increase risk for brain injury related post-accident or fall[17-19]. Post-TBI the risk of development of epileptic seizure has been reported with various frequencies depending upon regional and treatment disparities. There have been various treatment plans which has shown high efficacy in treating of the epilepsy long term as well as short term in post TBI cases. Primary and Secondary outcomes are the major source of identifying an assessing the effective of the treatment in controlling post TVI epileptic seizure over a longer time[20].

CONCLUSION

Sodium valproate had a highest efficacy in controlling of the post TBI epileptic seizure not only for a short duration but for longer duration as well. This was followed by the anti-epileptic medication Levetiracetam.

Conflict of interest: Nil

REFERENCES

1. Maas A, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. Lancet Neurol 2017; 16: 987-1048.
2. Ding K, Gupta PK, Diaz-Arrastia R. Epilepsy after traumatic brain injury. In: Laskowitz D., Grant G, eds. Translational Research in Traumatic Brain Injury. Boca Raton, FL: CRC Press, 2016.
3. Centers for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-Related Emergency Department Visits, Hospitalizations, and Deaths - United States, 2019.
4. Faul M., Coronado V. Epidemiology of traumatic brain injury. Clin Neurol 2015; *127: 3*-13.
5. Gupta PK, Sayed N, Ding K, Agostini MA, Van Ness PC, Yablon S, et al. Subtypes of post-traumatic epilepsy: clinical, electrophysiological, and imaging features. *J Neurotrauma 2014;* 31: 1439-43.
6. Mahler B, Carlsson S, Andersson T, Adelöw C, Ahlbom A, Tomson T. Unprovoked seizures after traumatic brain injury: a population-based case-control study. Epilepsia 2015; 6: 438-44.
7. Annegers JF, Hauser WA, Coan SP, Rocca WA. A population-based study of seizures after traumatic brain injuries. New Engl J Med 1998; 338: 20-24.
8. Agrawal A, Timothy J, Pandit L, Manju M. Post-traumatic epilepsy: an overview. Clin Neurol Neurosurg 2006; 108: 433-9.
9. Pohlmann-Eden B., Beghi E., Camfield C., Camfield P. The first seizure and its management in adults and children. BMJ 2006; 332: 339-42.
10. Sharma S, Tiarks G, Haight J, Bassuk AG. Neuropathophysiological mechanisms and treatment strategies for post-traumatic epilepsy. Front Mol Neurosci 2021;14:612073.
11. Herz J, Filiano AJ, Smith A, Yogev N, Kipnis J. Myeloid cells in the central nervous system. Immunity 2017; 46: 943-56.
12. Davies CL, Patir A, McColl BW. Myeloid cell and transcriptome signatures associated with inflammation resolution in a model of self-limiting acute brain inflammation. Front Immunol 2019; 10:1048.
13. Scanlon ST. A myeloid cell atlas of neuroinflammation. Science 2019; 363: 360-62.
14. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg 2018; 130(4): 1080-97.
15. Ahmed S, Venigalla H, Mekala HM, Dar S, Hassan M, Ayub S. Traumatic brain injury and neuropsychiatric complications. Indian J Psychol Med 2017; 39(2): 114-21.
16. Bramlett HM, Dietrich WD. Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. J Neurotrauma 2015; 32(23): 1834-48.
17. Fisher RS. An overview of the 2017 ILAE operational classification of seizure types. Epilepsy Behav 2017; 70: 271-3.
18. Fisher RS, van Emde Boas W, Blume W, Elger C, Genton P, Lee P, et al. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). Epilepsia 2005; 46(4): 470-2.
19. Englander J, Bushnik T, Duong TT, Cifu DX, Zafonte R, Wright J, et al. Analyzing risk factors for late posttraumatic seizures: a prospective, multicenter investigation. Arch Phys Med Rehabil 2003; 84(3): 365-73.
20. Mazzini L, Cossa FM, Angelino E, Campini R, Pastore I, Monaco F. Posttraumatic epilepsy: neuroradiologic and neuropsychological assessment of long-term outcome. Epilepsia 2003; 44(4): 569-74.