Levetiracetam versus phenytoin for seizure prophylaxis in patient with traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is a serious neuro-disorder commonly caused by road traffic accidents (RTAs), sports related events or violence. It is one of the leading causes of disability and death of young adults in industrialized countries presents a major worldwide social, economic, and health problem. TBI are classified according to severity, physical mechanism, pathophysiology and CT findings. Secondary brain injuries are defined as the constellation of cellular and biochemical processes that are set in motion by the primary injury and then evolve over the subsequent hours and days. They include cerebral edema, hematomas, hydrocephalus, intracranial hypertension, vasospasm, metabolic derangement, infection, and seizures. Researches aiming at reducing or preventing the neurological consequences of head trauma are ongoing, but currently the clinical outcome following TBI depends on the circumstances of injury and early clinical management aiming at reducing the occurrence of secondary brain insults. No effective intervention has been found to reverse the pathologic events initiated by the traumatic event. Post-traumatic seizures are seizures that result from traumatic brain injury (TBI and brain damage caused by physical trauma. Post traumatic seizures classified in to immediate post traumatic seizures, early post-traumatic seizures, late post-traumatic seizures and post-traumatic epilepsy. Anticonvulsants may be indicated in the early stages following moderate to severe TBI in order to reduce the incidence of seizures. Seizure medications can be grouped according to their main mechanism of action, although many of them have several actions and others have unknown mechanisms of action. Phenytoin sodium, is a hydantoin-derivative anticonvulsant. The mechanism of action is through limitating of seizure propagation by reduction of post-tetanic potentiation. Side effects including, hypotension if administered too rapidly though the intravenous approach, atrial or ventricular conduction depression, ventricular depression, respiratory depression, toxic hepatitis and liver damage, hematologic effects, local soft-tissue reactions and rash. The objective of our study is to compare the efficacy of Levetiracetam versus phenytoin in the prevention of early post traumatic seizures. The study was conducted on 40 patients with moderate to severe traumatic brain injury admitted to the Critical Care Department of Ain Shams University Hospital. All the forty patients will be divided into two groups A & B: (1) Patients in group (A) will receive PTH within 1st 24 hours after TBI as15mg/kg loading then 7mg/kg/day maintainence for 7 days. (2) Patients in group (B) will receive LEV syrup as 5 cc (500mg) via NGT or OGT / 12 hour. The results of this study show that no significant effect of both treatment of blood picture, electrolytes, kidney function, liver function and vital signs. The value of SGOT & SGPT of studied patients was described. There was no clinical significance in value of SGOT in seven days follow up between two groups. There were no clinical significance in value of SGPT between two groups in first 6 days but there were clinical significance at day seven with (P=0.0.016). The incidence of seizure was 2 patients (10.0%) in LEV group and 1 patient (5.0%) in phenytoin group with no statistically significant difference between the two groups (p=0.925).

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1. Introduction

Traumatic brain injury (TBI) is a common cause of mortality and morbidity with global incidence rates ranging from 91–546 per 100,000 population. TBI are highest in age group of 15–30 years and males are the predominant sufferers. ***(Shukla et al., 2010)***

Neurological damage after TBI is often referred to secondary injuries, including post-traumatic seizures (PTS), which has its own sequelae such as hypoxia, increased intracranial pressure. ***(Vespa et al., 2007)***

PTS can be early (within 7 days of TBI) or late (more than 7 days after TBI) ***(Haddad et al., 2012)***

Post traumatic seizures may lead to worsening clinical outcomes. Moreover, these seizures could be considered as apredictor for future development of epilepsy. ***(So EL et al., 2015)***

The high incidence of PTS after TBI and contribution of seizures to secondary injuries highlight the importance of preventive antiepileptic medication ***(Temkin et al., 2005)***

The Brain Trauma Foundation Guideline recommends the use of Antiepilepticsfor 7 days to prevent early seizures in patients with risk factors associated with PTS ***(Bratton et al., 2007)***

Phenytoin (PHT) has been the drug of choice for PTS prophylaxis, Although it is documented as an effective prophylactic agent in early PTS, it has several rare but high-profile adverse effects such as hepatic toxicity, dermatological events (i.e., Stevens-Johnson Syndrome, epidermal necrolysis), hypersensitivity syndrome, also needs close serum level monitoring, which is affected by decreased protein binding, variable gastrointestinal absorption, and increased drug clearance, to maintain a narrow therapeutic window. Considering this, an alternative prophylactic agent should be considered ***(Gabriel et al., 2014)***

Another good alternative for PTS prophylaxis is levetiracetam (LEV). It could be a good choice because of fewer side-effect profiles, neuroprotective effects, excellent bioavailability, simpler dosing, and no significant pharmacokinetic interactions. ***(Szaflarski et al., 2010).***

Aim of the Work

The objective of the currently designed study is to compare the efficacy of Levetiracetam versus phenytoin in the prevention of early post traumatic seizures.

2. Patients and Methods

Type of Study: This is prospective study.

Study setting: The study will be conducted in Critical Care Department of AinShams University Hospital.

Study Period; from 6 to 12 months.

•Study Population;

Inclusion Criteria:

Patients presented with the diagnosis of traumatic brain injury.
Age more than 18 Years.
Cortical contusion.
Subdural hematoma.
Epidural hematoma.
Depressed skull fracture, penetrating head injury.
Glasgow coma scale (GSC) 12 or less.

Exclusion Criteria:

Patients aged less than 18 Years.
Previous head injury.
History of seizure.
Patient receiving antiseizure medication.
Previous neurosurgery operation.
Renal impairment.
Brain death.
Patient with haemodynamic instability or with GIT dysfunction (can not receive enteral feeding).

•Sampling Method; convenient sampling

•Sample Size; using pass program, setting alpha error at 5%, power at 80%, according to gabriet and rowe 2014, the mean hospital stay for phenytoin was 0.2 _+ 0.22 compared to 0 +_0 for LEV, based on these values the needed sample is 40 patients divided into two groups (20 receiving phenytoin and 20 receiving. LEV)

- **Ethical Considerations;**

All patients must give their informed consent to participate, all participants must choose to participate on their free will and fully informed regarding the procedure of the research and any potential risk, all data are highly confidential.

- **Study Procedures;**

All patients included in the study will be subjected to the followings:

History taking (age, sex)
Physical examination (temperature, blood pressure, heart rate, respiratory rate and chest auscultation).
Glasgow Coma Scale (GCS) on admission.
Standard clinical management.

Enrolled patients will receive the standard treatment for management of severe TBI in the guidelines for the management of severe head injury of the American Association of Neurologic Surgeons.

Patients in group I will receive PTH within 1st 24 hours after TBI as 15mg/kg loading then 7mg/kg/day maintainence for 7 days.

Patients in group II will receive LEV syrup as 5 cc (500mg) via NGT or OGT / 12 hour.

Investigations:

Routine laboratory investigations.

CBC, Na, k, BUN, creatinine, hepatic profile on admission.

Radiological investigation (CT brain) on admission.

Follow-up:

Occurrence of seizures in both groups in the first week will be noticed.

Statistical Analysis;

Data will be presented as Mean and Standard deviation (SD) for quantitative parametric data, and Median and Interquartile range for quantitative non parametric data. Frequency and percentage will be used for presenting qualitative data. Suitable analysis will be done according to the type of data obtained. Student T test or Mann Whitney test will be used to analyze quantitative data while chi square test and fisher exact test will be used to analyze qualitative

data. P-value <0.05 will be considered statistically significant**.**

The Data was col006Cected and entered into the personal computer. Statistical analysis was done using Statistical Package for Social Sciences (SPSS/version 22) software.

The statistical test used as follow:

1. Arithmetic mean ($\overline{X}$):

Was calculated as follows:

$$\bar{x} = \frac{\sum x}{n}$$

Where: $\bar{x}$ = arithmetic mean

Σx = Sum of observations

n = number of observations

2. Standard deviation (SD):

Was calculated as follows:

$$\mathbf{SD} = \sqrt{\frac{\sum x^2 - \frac{(\sum x)^2}{n}}{n-1}}$$

Where:Σx^2 = sum of squared observations.

$(\Sigma x)^2$ = square of the sum of observations.

n = number of observations.

3. Chi-square (X^2):

For comparison between distribution of patients according to different items of study and use this formula for calculation:

$$X^2 = \sum \frac{(O-E)^2}{E}$$

O = Observed results E = Expected results

$(O-E)^2$ = Difference squared

Where E = $\frac{\text{Total row x total column}}{\text{Grand total}}$

4. The probability "p" value:

It was obtained from special table for probability (p) value, where the degree of freedom (n1+ n2 – 2) was used Where;

n1= Number of observations of the first group (the control group)

n2= Number of observations of the second group (the patients group)

A "p" value of less than 0.05 was considered statistically significant.

Statistical Package;

The collected data will be revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001).

3. Results

Demographic Data

The gender of the studied patients were (12) male (60%) in LEV group and (11) male (55%) in phenytoin group, while (8) female (40%) in LEV and (9) female (45%) in phenytoin group. There was predominance of male gender in studied patients in both groups with no statistically significant difference between the two groups (p=0.31).

The age of studied patients ranged from 22 to 81 with a mean of 43.3 ± 17.1 years in LEV group and ranged from 22 to 77 with a mean of 43.7 ± 16.4 years in phenytoin group. There was no statistically significant difference between the two groups (p=0.77).

Table (1): Comparison between the two studied groups according to demographic data.

	LEV (n = 20)		**Phenytoin (n = 20)**		**Test of Sig.**	**p**
	No.	**%**	**No.**	**%**		
Sex						
Male	12	60.00	11	55.00	χ^2= 0.652	0.31
Female	8	40.00	9	45.00		
Age (years)						
Min. – Max.	22 – 81		22 – 77		t-test	0.77
Mean ± SD.	43.3±17.1		43.7 ± 16.4		0.98	

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups

t-test, p: student t-**test** for comparing between the two groups

GCS score

The GCS score of the studied patients ranged from 3 – 12 with a mean of 8.5± 2.3 in LEV group and ranged from 3-12 with a mean of 8.16 ± 3.06 in phenytoin group. There was no statistically significant difference between the two groups (p=0.429).

Table (2): Comparison between the two studied groups according to GCS

	LEV (n = 20)	Phenytoin (n = 20)	t-test	P
GCS				
Min. – Max.	3.0 – 12.0	3.0 – 12.0	1.22	0.429
Mean ± SD.	8.5 ± 2.3	8.6 ± 3.0		

U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Mode of trauma

The MOT was RTA in 13 patients (65%) in the LEV and 15 patients (75%) in the control group. FFH was the etiology in 4 patients (20%) in the LEV group and 4 patients (20%) in the phenytoin group. Alleged Assault was the etiology in 1 patient (5%) in the LEV group and 1 patient (20.0%) in the phenytoin group. Falling down was the etiology in 2 patients (10%) in the LEV group and 0 patients (0.0%) in the control group. There was no statistically significant difference between the two groups (p=0.231).

Table (3): Comparison between the two studied groups according to mode of trauma

	LEV (n = 20)		Phenytoin (n = 20)		χ^2	p
	No.	%	No.	%		
MOT						
RTA	13	65.00	15	75.00	2.01	0.231
Falling down	2	10.00	0	0.00		
FFH	4	20.00	4	20.00		
Alleged Assault	1	5.00	1	5.00		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups
MC: **Monte Carlo** for Chi square test for comparing between the two groups

CT brain finding

EDH was 2 patients (10.0%) in the LEVgroup and 3 patients (15.0)% in phenytoin group. SDH was 3pateints (15.0%) in LEV group and 7 patients (35.0%) in phenytoin group. The IVH was 3 patients (15.0%) in LEV group and 4 patients (20.0%) in phenytoin group. ICH was 1 patient (5%) in LEV group and 1 patient (5.0%) in phenytoin group. SAH was 5 patients (20.0%) in LEV group and 4 patients (20.0%) in Phenytoin group. MHC was 3 patients (15.0%) in LEV group and 1 patients (5.0%) in phenytoin group. Brain edema was5 patients (25.0%) in LEV group and 5 patients (25.0%) in phenytoin group. Depressed farcture was 2 patients (10.0%) in LEV group and no onein Phenytoin group. Fissure fracture was 3 patients (15.0%) in LEV group and 4 patients (20.0%) in phenytoin group. There was no statistically significant difference between the two groups according to CT brain finding.

Table (4): Comparison between the two studied groups according to CT brain finding

	LEV (n = 20)		Phenytoin (n = 20)		FE	P
	No.	%	No.	%		
CT Brain Finding						
EDH	2	10.0	3	15.0	0.89	0.321
SDH	3	15.0	7	35.0	1.526	0.107
IVH	3	15.0	4	20.0	0.921	0.285
ICH	1	5.0	1	5.0	0.00	1.0
SAH	5	25.0	4	20.0	0.92	0.289
MHC	3	15.0	1	5.0	1.44	0.311
Brain edema	5	25.0	5	25.0	0.0	1.00
Depressed Fracture	2	10.0	0	0.0	0.71	0.366
Fissure fracture	3	15.0	4	20.0	0.92	0.287

FE: **Fisher Exact** for comparing between the two groups when the number less than 5.

CBC on admission

Hemoglobin in LEV ranged from 7-14 with mean value 10.9±2.2 and in Phenytoin ranged from 7-14 with mean value 10.5±2.6. WBC in LEV group ranged from 10-20 with mean value 15.5±3.1 and in Phenytoin group ranged from 11-18 with mean value 14.4±1.8 and Plateletin LEV group ranged from 200-366 with mean value 282.3±35.8 and in Phenytoin group ranged from 224-326 with mean value 296.8±28.2. There was no statistical significant difference between the two studied groups according to CBC on admission (p>0.05).

Table (5): Comparison between the two studied groups according to CBC on admission

CBC	LEV (n = 20)	Phenytoin (n = 20)	Test of Sig.	P
Hb (g/dl) Min. – Max. Mean ± SD.	7-14 10.9±2.2	7-14 10.5±2.6	0.925	0.301
WBC (×10³/µl) Min. – Max. Mean ± SD.	10-20 15.5±3.1	11-18 14.4±1.8	0.9852	0.091
Platelet (×10³/µl) Min. – Max. Mean ± SD.	200-366 282.3±35.8	224-326 296.8±28.2	1.65	0.064

t, p: t and p values for **Student t-test** for comparing between the two groups

Electrolytes on admission

Serum sodium in LEV ranged from 130-148 with mean value 139.0± 5.0 and in Phenytoin ranged from 130-148 with mean value 138.6± 4.9. Serum potassium in LEV group ranged from 3-5 with mean value 3.9 ± 0.7 and in Phenytoin group ranged from 3.2-4.7 with mean value 3.9 ± 0.4. There was no statistical significant difference between the two studied groups according to electrolytes on admission (p > 0.05).

Table (6): Comparison between the two studied groups according to electrolytes on admission

Electrolytes	LEV (n = 20)	Phenytoin (n = 20)	Test of Sig.	P
Serum sodium (Na^+) (meq/L) Min. – Max. Mean ± SD.	131 - 148 139.0± 5.0	130 - 147 138.6± 4.9	0.89	0.388
Serum potassium (K^+) (meq/L) Min. – Max. Mean ± SD.	3 - 5 3.9 ± 0.7	3.2 - 4.7 3.9 ± 0.4	0.811	0.437

t, p: t and p values for **Student t-test** for comparing between the two groups

Renal function on admission

Urea in LEV ranged from 20-55 with mean value 33.5 ± 10.2 and in Phenytoin ranged from 20-50 with mean value 33.6 ± 7.6. Creatinine in LEV group ranged from 0.2-1.6 with mean value 0.7 ± 0.3 and in Phenytoin group ranged from 0.1-0.9 with mean value 0.6 ± 0.2. There was no statistical significant difference between the two studied groups according to renal function on admission (p > 0.05).

Table (7): Comparison between the two studied groups according to renal function on admission

Renal function	LEV (n = 20)	Phenytoin (n = 20)	Test of Sig.	p
Urea (mg/dl) Min. – Max. Mean ± SD.	20 - 55 33.5 ± 10.2	20 - 50 33.6 ± 7.6	0.821	0.437
Creatinine (mg/dl) Min. – Max. Mean ± SD.	0.2 - 1.6 0.7 ± 0.3	0.1 - 0.9 0.6 ± 0.2	0.755	0.298

t, p: t and p values for **Student t-test** for comparing between the two groups

Liver function on admission

SGOT, in the LEV group ranges from 15 to 38 with a mean of 25.7± 8.0(u/L) while in the phenytoin group ranges from 15 to 36 with a mean of 25.0± 5.9 (u/L). There was no statistically significant difference between the two groups (p=0.828).

SGPT, in the LEV group ranges from 15 to 37 with a mean of 24.2 ±7.0 (u/L) while in the phenytoin group ranges from 17 to 39 with a mean of 27.7 ±5.6 (u/L). There was no statistically significant difference between the two groups (p=0.109).

Table (8): Comparison between the two studied groups according to liver function on admission

Liver function	LEV (n = 20)	Phenytoin (n = 20)	U	p
SGOT (U/L) Min. – Max. Mean ± SD.	 15 - 38 25.7 ± 8.0	 15 - 36 25.0 ±5.9	0.211	0.828
SPGT (U/L) Min. – Max. Mean ± SD.	 15 - 37 24.2 ±7.0	 17 - 39 27.7 ±5.6	0.968	0.109

U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Vital signs "clinical" on admission

HR in LEV ranged from 70-95 with mean value 82.0 ± 7.0 and in Phenytoin ranged from 70-120 with mean value 87.7 ± 14.0. Mean blood pressure in LEV group ranged from 55-95 with mean value 80.0 ± 12.0 and in Phenytoin group ranged from 55-95 with mean value 78.4 ± 12.7 and temperature in LEV group ranged from 37.3-38.8 with mean value 37.8 ± 0.4 and in Phenytoin group ranged from 37-38.9 with mean value 37.7± 0.5. There was no statistical significant difference between the two studied groups according to vital signs "clinical" on admission (p > 0.05).

Table (9): Comparison between the two studied groups according to vital signs "clinical" on admission

Vital signs "clinical"	LEV (n = 20)	Phenytoin (n = 20)	t-test	p
HR (beat/min) Min. – Max. Mean ± SD.	 70 - 95 82.0 ± 7.0	 70 - 120 87.7 ± 14.0	1.52	0.077
Mean blood pressure (mmHg) Min. – Max. Mean ± SD.	 55 - 95 80.0 ± 12.0	 55 - 95 78.4 ± 12.7	0.911	0.328
Temperature (^{o}C) Min. – Max. Mean ± SD.	 37.3 - 38.8 37.8 ± 0.4	 37 - 38.9 37.7 ± 0.5	0.714	0.304

U, p: U and p values for **Mann Whitney test** for comparing between the two groups

Liver function follow up

The value of SGOT & SGPT of studied patients was described. There was no clinical significance in value of SGOT in seven days follow up between two groups. There were no clinical significance in value of SGPT between two groups in first 6 days but there were clinical significance at day seven with (P=0.0.016).

Table (10): Comparison between the two studied groups according to liver function follow up

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
SGOT	**LEV (n = 20)** Min. Max. Mean Sd.	 18 60 31.6 9.9	 20 87 36.0 16.9	 22 100 37.8 20.6	 19 140 41.4 30.5	 25 163 45.6 38.1	 25 174 47.4 42.8	 20 180 41.6 35.1
	Phenytoin (n = 20) Min.	 22	 24	 25	 25	 24	 24	 24

	Max.	60	87	100	140	163	174	184
	Mean	33.5	39.8	45.2	52.1	57.5	57.6	60.9
	Sd.	10.5	18.9	26.0	37.4	45.9	48.4	57.8
	T	1.02	0.98	1.23	1.27	1.33	0.92	1.87
	P	0.280	0.245	0.145	0.146	0.165	0.220	0.093
SGPT	**LEV (n = 20)**							
	Min.	18	20	22	19	25	24	20
	Max.	65	85	96	104	135	174	160
	Mean	31.7	36.0	36.5	36.5	41.4	46.2	38.8
	Sd.	10.0	16.8	18.5	21.9	30.0	41.0	30.8
	Phenytoin (n = 20)							
	Min.	22	24	24	24	25	24	20
	Max.	66	85	102	124	145	160	187
	Mean	37.3	42.7	48.6	55.1	62.4	68.3	75.5
	Sd.	14.0	22.8	30.0	41.0	50.2	59.6	71.3
	T	1.81	0.626	1.78	2.11	1.96	1.88	2.41
	P	0.067	0.135	0.061	0.036*	0.046*	0.066	0.016*

t, p: t and p values for **Student t-test** for comparing between the two groups
*: Statistically significant at $p \leq 0.05$

SGOT and SGPT was normal in 18 patients (90.0%) and elevated in 2 patients (10.0%) in the LEV group and was normal in 17 patients (85.0%) and elevated in 3 patients (15.0%) in phenytoin group. There was no statistically significant difference between the two groups according to liver function follow up ($p > 0.05$).

Table (11): Comparison between the two studied groups according to liver function follow up

	LEV (n = 20)		**Phenytoin (n = 20)**			**p**
	No.	**%**	**No.**	**%**		
SGOT						
Normal	18	90.0	17	85.0		0.925
Elevated	2	10.0	3	15.0		
SGPT						
Normal	18	90.0	18	90.0		1.00
Elevated	2	10.0	2	10.0		

χ^2, p: χ^2 and p values for **Chi square test** for comparing between the two groups FE: Fisher Exact test

Incidence of seizures

The incidence of seizure was 2 patients (10.0%) in LEV group and 1 patient (5.0%) in phenytoin group with no statistically significant difference between the two groups (p=0.925).

Table (12): Comparison between the two studied groups according to incidence of seizures

	LEV (n = 35)		**Phenytoin (n = 35)**			**p**
	No.	**%**	**No.**	**%**		
Effect						
No Seizure	18	90.0	19	85.0	0.098	0.925
Yes	2	10.0	1	5.0		

FE: **Fisher Exact** for Chi square test for comparing between the two groups.

4. Discussion

Traumatic brain injury (TBI) is a serious neuro-disorder commonly caused by road traffic accidents (RTAs), sports related events or violence. ***(Centers for Disease Control and Prevention2015).*** (TBI) have been defined as "an alteration in brain function, or

other evidence of brain pathology, caused by an external force". ***(Bryan-Hancock et al., 2010)*** WHO forecasts that by 2030, TBI will become a leading cause of disability and death globally. ***(Centers for Disease Control and Prevention 2015)***

TBI are classified according to: severity, physical mechanism, pathoanatomic type, pathophysiology and CT findings. ***(Office of Communications and Public Liaison 2015)***.

Secondary brain injuries are defined as the constellation of cellular and biochemical processes that are set in motion by the primary injury and then evolve over the subsequent hours and days. ***(Black et al., 2015).*** They include cerebral edema, hematomas, hydrocephalus, intracranial hypertension, vasospasm, metabolic derangement, infection, and seizures. ***(Meeker et al., 2005).***

Assessment of head injured patient include primary trauma survey airway, breathing, circulation, disability. Secondary trauma survey includes Obtaining history, head to toe examination and neurological assessment. ***(McHugh et al., 2007).***

Critical care management of severe TBI patients is a dynamic process, starts in the pre-hospital period with the (ABCDE) approach, ***(Wilde et al., 2010)*** then the in- hospital care once the severely head-injured patient has been transferred to the ICU, the management consists of the provision of high quality general care and various strategies aimed at maintaining hemostasis.

Post-traumatic seizures are seizures that result from traumatic brain injury (TBI) and brain damage caused by physical trauma. ***(Haacke et al., 2010)*** Posttraumatic seizures classifed in to immediate post traumatic seizures, earl y post-traumatic seizures, late post-traumatic seizures and post-traumatic epilepsy. ***(*Hicks *et al., 2013).***

Anticonvulsants may be indicated in the early stages following moderate to severe TBI in order to reduce the incidence of seizures. ***(Lingsma et al., 2015)*** Seizure medications can be grouped according to their main mechanism of action, although many of them have several actions and others have unknown mechanisms of action. phenytoin sodium, is a hydantoin-derivative anticonvulsant. The mechanism of action is through limitating of seizure propagation by reduction of post-tetanic potentiation. ***(Maas et al., 2015)*** Side effects including suicidality risk porphyria, ***(*Maas *et al., 2010)*** possible local or generalized lymphadenopathy, hypotension if administered too rapidly though the intravenous approach, atrial or ventricular conduction depression, ventricular depression, respiratory depression ***(*Maas *et al., 2015)***, toxic hepatitis and liver damage, hematologic effects, local soft-tissue reactions and rash ***(Manley et al., 2013).***

Levetiracetamis structurally unrelated to other anticonvulsant drugs (ACDs). The mechanism of action is possibly related to a brain-specific stereo-selective binding site. ***(Marmarouet al., 2007).***

The aim of our study is to compare the efficacy of Levetiracetam versus phenytoin in the prevention of early post traumatic seizures.

This is prospective randomized study conducted in Critical Care Department of AinShams University Hospital.

All the forty patients will be divided into two groups A & B

Patients in group (A) will receive PTH within 1st 24 hours after TBI as15mg/kg loading then 7mg/kg/day maintainence for 7 days. Patients in group (B) will receive LEV syrup as 5 cc (500mg) via NGTor OGT / 12 hour.

Enrolled patients will receive the standard treatment for management of severe TBI in the guidelines for the management of severe head injury of the American Association of Neurologic Surgeons. The study groups will be compared as regard: Demographic data (History taking, age, sex, Physical examination temperature, blood pressure, heart rate, respiratory rate a).

Glasgow Coma Scale (GCS) on admission. (CT brain) on admission and follow up.

The demographic data of this study showed higher percentage of males (60 and 55.0%) in the two groups. This male predominance is a quiet common finding in most of the studies dealing with trauma as males are more vulnerable to injuries due to social and environmental considerations. The same percentage approximately was present in the study carried by ***(Ahmed et al., 2017)*** who found TBI rates were 29% higher in males compared to females. Also like what found in the study done by (***Allard et al 2009)*** who had 55 patients (76%) of them were males, and (24%) were females. Similarily the study done by ***Shebl et al.,*** on 120 patients with traumatic brain injury, they found that male 84 patients (70%) and female 36 patients (30%) These studieswere very close to our study as regard sex distribution. (***Shebl et al., 2017)***

In the current study age ranged between 22-81 in LEV group and 22-77 years in phenytoin group. The mean age in the two groups was 43.3 and 43.7 respectively. This was in agreement with the 10008 patients with TBI who were recruited into the Medical Research Council CRASH trial where the mean age was 37±17.1 years, decreasing significantly to 35.8±16 years in low-middle income countries. ***(Predicting outcome after traumatic brain injury 2008).*** Similarly, in the 8509 patients in the IMPACT database the median age was 30 years ***(Roozenbeek, et al., 2013)***

The GCS score of the studied patients ranged from 3.0 – 12.0 with a mean of 8.5 ± 2.3 in LEV, and ranged from 3.0-12.0 with a mean of 8.6 ± 3.0 in phenytoin group. Of those ranged between 9 – 12 (moderate TBI) and presented with GCS < 8 (severe TBI) There was no statistically significant difference between the two groups (p=0.429).

In agreement with our study, a study compared Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury by Jones KE. et al., found that 48 patients had (62.4%) moderate head injury and 29(37.6%) severe head injury (p=0.113) in PHT, 43(55.8%) moderate head injury and 34(44.2%) severe head injury (P=0.942) in LEV group. There was no statistically significant difference ***(Jones et al., 2008)***

In our study regarding the mode of trauma Road traffic accident was responsible for TBI in 13 (65.0%) of the patients in LEV group, while in phenytoin group 15 cases (75.0%) was RTA, 2 (10%) patients in LEV group falling down while no cases in phenytoin group, 4(20%) falling from height in group in both groups, alleged assault in one case in each group, no difference between the two groups regarding mode of trauma.

A common perception is that the majority of TBI patients are young adult males who are injured in motor vehicle accidents. ***(Roozenbeek, et al., 2013; Post et al., 2013).***

Also This is in harmony with the study of Okasha et al. ***(Okasha, 2014)***., who evaluated prediction of outcome in 60 consecutive adult patients with TBI admitted to the Alexandria Main University Hospital intensive care units (ICU). In their study, motor car accidents constitutes the main mechanism of injury in the studied patients.

EDH was 2 patients (10.0%) in the LEV and 3 patients (15.0)% in phenytoin group with, SDH was 3 patients (15.0%) in LEV group and 7 patients (35.0%) in phenytoin group, IVH was 3 patients (15.0%) in LEV group and 4 patients (20.0%) in phenytoin group, ICH was 1 patient (5.0%) in LEV group and 1 patient (5.0%) in phenytoin group, SAH was 5 patients (25.0%) in LEV group and 1 patient (5.0%) in Phenytoin group, MHC was 3 patients (15.0%) in LEV group and 1 patient (5.0%) in phenytoin group, brain edema was 5 patients (25.0%) in LEV group and 5 patients (25.0%) in phenytoin group, depressed farcture was 2 patients (10.0%) in LEV group and no one in Phenytoin group, fissure fracture was 3 patients (15.0%) in LEV group and 4 patients (20.0%) in phenytoin group. There were no statistically significant difference between the two groups between two groups according to CT brain finding.

In agreement with our study, prospective multicenter comparison of levetiracetam versus phenytoin for early post traumatic seizure prophylaxis by ***Inaba K et al*** showed that CT finding were SAH in 62.4% vs. 57.6% (p=0.165), SDH in53.6% vs. 48.3% (P=0.132) and ICH in 25.6% vs. 30.3% (p=0.132) with no statistically significant difference in between both group. (***Inaba K et al., 2013).***

In this study, the incidence of seizures was 4 patients (11.4%) in LEV group and 3 patients (8.6%) in phenytoin group with no statistically significant difference between the two groups (p=0.1000).

In agreement with our study, ***Inaba K et al*** conducted a prospective multicenter comparison of levetiracetam versus phenytoin for early post traumatic seizure prophylaxis showed that there was no significant difference in seizure rate between PHT group and LEV group (1.5% vs. 1.5%, p=0.997). (***Inaba K et al., 2013).***

Similary a Prospective, Randomized, Single-blinded Comparative Trial of Intravenous Levetiracetam Versus Phenytoin for Seizure Prophylaxis conducted by ***Szaflarski JP et al*** found that there was no significant difference in early seizure occurrence (16.6% vs 14.7%, p=1.0) between PHT and LEV group. (***Szaflarski., et al., 2010).***

In harmony with our study, ***Jones KE et. al.*** studied the effect of Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury, there was no statistically significant difference between both group as regard seizure activity (1% vs 0%, p=0.556) ***(Jones et al., 2008)***

In agreement with our study a ***Meshkini A et al*** conducted a met analysis on the comparison of levetiracetam versus phenytoin for seizure prophylaxis in patients with traumatic brain injury: theyfound no significant difference between LEV and PHT in the effectiveness of seizure prophylaxis in patients with TBI, that was consistent with results of previous studies in this filed. ***(Meshkini., et al., 2015)***

In our study the hemoglobin in LEV ranged from 7-14 with mean value 10.9±2.2 and in Phenytoin ranged from 7-14 with mean value 10.5±2.6. WBC in LEV group ranged from 10-20 with mean value 15.5±3.1 and in Phenytoin group ranged from 11-18 with mean value 14.4±1.8 and Platelet in LEV group ranged from 200-366 with mean value 282.3±35.8 and in Phenytoin group ranged from 224-326 with mean value 296.8±28.2. There was no statistical significant difference between the two studied groups according to CBC on admission (p >0.05).

In agreement with our study, Garg A et al., in their study there was an insignificant increase in Hemoglobin, total leukocyte count and platelet count. ***(Garg et al., 2017)***

Serum sodium in LEV ranged from 130-148 with mean value 139.0± 5.0 and in Phenytoin ranged from 130-148 with mean value 138.6± 4.9. Serum

potassium in LEV group ranged from 3-5 with mean value 3.9 ± 0.7 and in Phenytoin group ranged from 3.2-4.7 with mean value 3.9 ± 0.4. There was no statistical significant difference between the two studied groups according to electrolytes on admission ($p > 0.05$).

Urea in LEV ranged from 20-55 with mean value 33.5 ± 10.2 and in Phenytoin ranged from 20-50 with mean value 33.6 ± 7.6. Creatinine in LEV group ranged from 0.2-1.6 with mean value 0.7 ± 0.3 and in Phenytoin group ranged from 0.1-0.9 with mean value 0.6 ± 0.2. There was no statistical significant difference between the two studied groups according to renal function on admission ($p > 0.05$), there was no significant effect of the two drugs on kidney function.

In agreement with our study, Garg et al., (2017) carried out study on the side effect of both drugs, the results show that there was an insignificant increase in renal parameters blood urea and serum creatinine. ***(Garg et al., 2017).***

Regarding serum calcium levels, present findings are same as studies by ***Koo DL et al***, and colleagues who reported that no differences were observed in serum calcium across LEV treatment. ***(Kood et al., 2013)*** Similarly studies by ***Nissen Meyer et al***, observed that neither high or low dose levetiracetam affected calcium levels in study group as compared to controls. ***(Nissen-Meyer et al., 2007)***

In our study SGOT and SGPT on admission was normal in all patients (100.0%) in the LEVand phenytoin groups and was normal in 30 patients (85.7%) and elevated in 5 patients (14.3%) in phenytoin group. There was no statistically significant difference between the two groups ($p=0.428$).

In our study value of SGPT of studied case were described and there was no clinical significance in first7 days but there was significance difference between LEV and PHT group at day seven.

LEV has no effect on liver enzyme as excretion almost completely through urinary system.

This finding surrogate that PHT may cause liver dysfunction as SGPT is more sensitive to liver injury than SGOT.

Limitations of the study:

1. Lacked of 24 hours EEG monitoring of the patients.
2. Lack of plasma level monitoring.
3. There was an element of inter-observer bias since the patients were monitored by different observers during there hospital stay.

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