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

Thesis
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LIST OF ABBREVIATIONS

ACDs	Anticonvulsant drugs
AEDs	Antiepileptic drugs
ARDS	Acute respiratory distress syndrome
AV	Atrioventricular node
CBF	Cerebral blood flow
CPP	Cerebral perfusion pressure
CT	Computed Tomography
DAI	Diffuse axonal injury
DVT	Deep vein thrombosis
EEG	Electroencephalogram
EMEA	European Agency for Evaluation of Medicinal Products
FDA	Food and Drug Administration
FFH	Falling from height
GABA	Gamma-aminobutyric acid
GCS	Glasgow coma scale
HR	Heart rate
ICH	Intra crainial haemorhage
ICP	Intra cranial pressure
ICU	Intensive care unit
IJV	Internal jugular vein
IV	Intra venous
IVH	Intraventricular haemorhage
LEV	Levetiracetam
LMWH	Low molecular weight heparin
LOC	Loss of consciousness
LPR	Lactate pyruvate ratio
MAP	Mean arterial blood pressure

MD	Microdialysis
MHC	Multiple haemorrhagic contusions
MOT	Mode of trauma
MRI	Magnetic resonant imaging
PHT	Phenytoin
PN	Parenteral nutrition
PTA	Post traumatic amnesia
PTP	Post-tetanic potentiation
PTS	Post-traumatic seizures
RTAs	Road traffic accidents
SA	Sinoatrial node
SAH	Sub arachnoid haemorhage
SBI	Secondary brain insults
SDH	Sub dural haemorhage
SjvO2	Jugular bulb venous oxygen saturation
TBI	Traumatic brain injury
TCD	Transcranial Doppler
VAP	Ventilator associated pneumonia

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 antiepileptics for 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.

REVIEW OF LITERATURE

Definition of TBI

Traumatic brain injury (TBI) has been defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" (***Menon et al., 2010).*** Alteration in brain function is defined as one of the following clinical signs: any period of loss of consciousness, any loss of memory for events immediately before (retrograde amnesia) or after the injury (post-traumatic amnesia /PTA), neurological deficits, and alteration in mental state at the time of injury e.g. confusion/ disorientation (***Menon et al., 2010).***

Classification of TBI

According to:

- **Mechanism of injury :**Closed; penetrating; crash; blast.
- **Clinical severity: level of consciousness (Glasgow coma scale)**

The GCS score comprises the values from three component tests (eye, motor, and verbal scales). Injuries are classified as severe (GCS 3–8), moderate (GCS 9–13), or mild (GCS 14–15).

Table (1): Glasgow Coma Scale (GCS) (*Thornhill et al., 2000)*

Glasgow Coma Scale		Score
Motor response	None	1
	Extension to pain	2
	Flexion to pain	3
	Withdraws from pain	4
	Localizes to pain	5
	Obeys commands	6
Verbal response	None	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Confused	4
	Orientated	5
Eye opening	None	1
	To pain	2
	To speech	3
	Spontaneously	4
Maximum score	15	

Table (2): Criteria for classifying the severity of traumatic brain injury.

TBI score	GCS	PTA	LOC
Mild	13-15	<1 day	30 minutes
Moderate	9-12	>1 to <7 days	>30 minutes to <24 hours
Severe	3-8	>7 days	>24 hours

GCS: Glasgow Coma Scale.
PTA: post- traumatic amnesia
LOC: Loss of consciousness

- **Classification by Computed Tomography (CT) findings**

Marshall classification ***(Marshall et al., 1991)*** utilizes the status of the mesencephalic cisterns, the degree of midline shift in millimeters, and the presence or absence of one or more surgical masses to grade CT findings as follows:

Table (3): Marshall's classification of CT brain findings in head trauma.

Category	Definition
▪ Diffuse injury I	No visible intracranial pathology
▪ Diffuse injury II	Cisterns present, with midline shift 0 to 5 mm; no high density lesion >25 ml
▪ Diffuse injury III (swelling)	Cisterns compressed or absent, with midline shift 0 to 5 mm; no high density lesion >25 ml
▪ Diffuse injury IV (shift)	Midline shift >5 mm; no high density lesion >25 ml
▪ Evacuated mass lesion	Any lesion surgically evacuated
▪ Non-evacuated mass lesion	High density lesion >25 ml; not surgically evacuated

Types of brain damage

- ***Primary damage***

Results from external forces, as a consequence of direct impact, rapid acceleration or deceleration, or blast waves from an explosion.

The nature and intensity of these forces determine the pattern and extent of damage. On the macroscopic level, damage includes shearing of white-matter tracts, focal contusions, haematomas and diffuse swelling (***Okie, 2005 & Zoroya, 2007).*** The pathological mechanism is much less understood, but injuries are characterized by severe early brain swelling, subarachnoid haemorrhage, and often prominent vasospasm (***Taber et al., 2006 & Armonda et al., 2006).***

- ***Secondary brain injuries***

Secondary, intracranial brain insults include cerebral edema, hematomas, hydrocephalus, intracranial hypertension, vasospasm, metabolic derangement, infection, and seizures (***Dinsmore, 2013 & Unterberg et al., 2004).*** Secondary systemic brain insults are mainly ischemic in nature, ***(Dinsmore, 2013& Unterberg et al., 2004)*** such as: table (4)

Table (4): Causes of Secondary Brain Injury.

Systemic	Neurologic
Hypotension	
Hypoxia	Elevated ICP
Ischemia	Hydrocephalus
Hypercapnia	Intracranial hemorrhage
Hypocapnia	Cerebral edema
Hyperthermia	Vasospasm
Anemia	Seizures
Fluid and electrolyte imbalance	Intracranial infection
Acid-base alteration	
Systemic inflammatory disorder	
Hypoglycemia	
Hyperglycemia	