10 years old, vegetarian child weighing 30 kg who was normal earlier brought with history of unprovoked tonic-clonic generalized seizure activity for the last 30 minutes. There was no history of fever, trauma, drug intake, animal bite and previous episode of similar complain. Vitals were HR 120/min, RR 34/min, jerky respiration, saturation 91%, BP 130/84 mmHg and GCS 8/15. Pupils were B/L equal and reacting to light. Tendon reflexes were silent. There was family history of similar complaint in father and older sister. Blood sugar was 184 mg/dL, serum sodium 132 mEq/L, potassium 5.6 mEq/L, serum creatinine 0.8 mg/dL, serum calcium (ionized) 1.2 mmol/L, CPK 123, troponin I was positive. CT brain revealed diffuse cerebral edema. Airway was secured using endotracheal intubation and 100% was started using AC mode of ventilation and intravenous fluid crystalloid was also started. Child received midazolam and phenytoin as per protocol. Seizure activity still continued using benzodiazepine and loading dose of phenytoin.

Q. Who will you define seizure and status epilepticus?

Answer: Seizure is a transient event as a result of brain dysfunction (cortical genesis of seizure and involving reticular activating system in synchronization of cortical neuron) manifested by involuntary motor, sensory, automatic or psychic phenomenon alone or in combination of all and epilepsy is two episode of unprovoked seizures 24 hours apart or diagnosis of epileptic syndrome. Seizure activity lasting for 5 minutes or two or more seizures without return to base line is termed as status epilepticus (SE) and ongoing clinical or electrographic seizures despite adequate initial benzodiazepine doses followed by second acceptable anti-epileptic drugs is called as refractory status epilepticus (RSE). Super-refractory status epilepticus is SE which has failed to resolve or reoccur within 24 hrs despite therapy that includes infusion of midazolam and /pentobarbital. New onset refractory status epilepticus can occur in patient due to many reasons without prior epilepsy. Any child who presents in emergency department should be treated as status epilepticus for clinical/operational purpose.

Q. What are the stages of status epilepticus?

Answer: Seizure activity which is continuous or two or more episodes for more than thirty minutes without regaining consciousness is termed as SE (stages of SE are; incipient stage 0-5 min, early stage 5-30 min, transitional stage, late stage 30-60 min, refractory stage >60 min, and postictal stage). Prodromal SE is characterized by increasing frequency of seizures with recovery of consciousness. Impending SE is defined as seizure activity lasting more than five minutes or intermittent clinical or EEG seizure activity lasting for more than fifteen minutes without regaining consciousness.

Seizures are difficult to recognize in intensive care unless EEG monitoring is done. Various form of status epilepsies has been described in literature (generalized tonic, clonic, focal motor, myoclonic, absence, complex partial seizure, classical form and SE in coma). Different stages of SE have been defined on the basis of clinical and EEG findings.
Q. What are the diagnostic criteria of non-convulsive status epilepticus?

Answer:
- A period of behavior changes from baseline
- EEG evidence of epileptic activity lasting for at least 10 seconds
- Clinical response to AED

Q. What is basis of clinical symptomatology?

Answer: Clinical symptoms depend on area of cortex and synaptic connections involved. Underlying cause is imbalance of excitatory and inhibitory currents with predominance of excitatory neurotransmitters such as glutamate and aspartate or diminished activity of gamma-aminobutyric acid. One of the five mechanisms responsible for seizure activity is intrinsic electrical instability, toxic or metabolic, central nervous system infections, structural defects, and abnormal brain perfusion. Most seizures have average duration of 62 seconds and stop spontaneously in 4 minutes. Seizure that lasts for less than 5 minutes without full recovery of consciousness is called as incipient SE.

Q. What are common etiological factors for SE in ICU?

Answer:
Most common factors are:
- Prolonged febrile seizure
- Idiopathic status epilepticus
- Acute brain insult
- CNS Infections
- Autoimmune encephalitis
- Hypoxic-ischemic encephalopathy
- Non-compliance of drug
- Known case of epilepsy
- Sepsis
- Uremia
- Electrolytes abnormalities (hyponatremia, hypernatremia, hypocalcemia, hypoglycemia)
- Metabolic: Acute liver and renal insufficiency, mitochondrial diseases
- Traumatic brain injury
- Drugs (carbapenems, metronidazole, fluoroquinolones, theophylline)
- Toxin exposure
- Sub-therapeutic anti-epileptic drug
- Nutritional deficiencies
- Neurocutaneous syndromes
- Genetic: Inborn error of metabolism, Wilson disease
- Vascular stroke
- Hypertensive encephalopathy

Q. Discuss some pathophysiological changes associated with SE.

Answer: It is beyond doubt that seizures belong to most commonly encountered neurological disorder in children. Increased cell membrane excitation, and abnormal neurotransmitters release and postsynaptic receptors are major pathophysiological changes occur at cell level. As the duration of activity increases seizures become difficult to control. Majority of seizures respond to antiepileptic drugs (AED’s) and most of the AED’s possess more than one mechanism of action i.e. blockade of voltage dependent sodium and or calcium channels, enhancing GABA activity through different mechanism, T-blocking of T-type calcium channel and drugs which reduces event mediated excitatory amino acids.

Initially at cellular level the activity begins and propagate leading to cell injury and death. Brain dynamics limit the cell injury if continued result into systemic effects. Due to adrenergic and non-adrenergic surge and muscular activity in early phase of status epilepticus child will have tachycardia, hypertension, hyperthermia, acidosis, hyperglycemia, increased cerebral blood flow. In later stage (beyond 30 minutes also known as transition phase) adaptive mechanism fails leading to normalization of blood pressure and glucose. Respiratory compromise and neuronal injury are also feature of this phase. Finally, SE results in to respiratory acidosis, hypoxemia, hypo/hyperglycemia, hyperpyrexia, hypotension, cardiac arrhythmia, peripheral leukocytosis, cerebrospinal fluid pleocytosis, rhabdomyolysis, myoglobinuria, and acute kidney injury.
Q. How will you manage a child with SE?

Answer:

General management
- Emergency supportive care
- Termination of seizure activity
- Prevention of recurrence
- Searching underlying etiology
- Prevention and treatment of complication

Pre hospital treatment
- Avoid physical injury
- Prehospital management include midazolam (buccal 0.15-0.3mg/kg or nasal 0.15-0.3mg/kg or intramuscular 0.2mg/kg) or rectal diazepam 0.5mg/kg or lorazepam 0.1mg/kg intranasally. Alternatively, clonazepam may be massaged to buccal mucosa.
- Place the child in recovery position to avoid aspiration

In hospital management

Three phases of management:
- Emergent initial therapy (identify seizure, maintain vitals, treat seizure if >5minutes), identify underlying etiology and treat, plan AED therapy)
- Urgent initial therapy
- Refractory initial therapy

Emergent initial management of SE follows the principle of basic life support which includes maintaining adequate airway (may require airway adjuncts for proper ventilation) and providing supplementary oxygenation using high flow devices such as non-rebreathing mask (NRM) to prevent hypoxemia. Decision to intubate is based on clinician judgement or when ventilatory failure is suspected. If patient requires intubation, one should use rapid sequence induction. Short acting non-depolarizing neuromuscular blocking agents, rocuronium or vecuronium may be used during intubation. Avoid use of depolarizing neuromuscular blocking agents such as succinylcholine because of increased risk of hyperkalemia & raised intracranial hypertension. It is also preferred to suppress cough reflex by giving injectable lidocaine or local spray to prevent increase in intracranial pressure. Cardiovascular system should be assessed and adequate vascular access must be achieved for administration of fluids/vasopressors and other drugs. Age appropriate mean arterial pressure (MAP) should be maintained using fluid bolus and vasoactive agents as the need may be. General support also includes management of fever and other metabolic abnormality. Child with SE should have minimum continuous cardiac monitoring to prevent risk of hypoxemia & cardiac arrhythmias. Continuous electroencephalography monitoring may be required in some cases.

Routine investigations which includes complete blood count, blood sugar, lactate, ABG, ammonia, calcium, electrolytes, liver function tests, serum creatine kinase, anti-epileptic drug levels (if no treatment), troponin I, urine for toxic screening, EEG within 24 hrs, and neuroimaging (CT/MRI) should be carried out. Lumbar puncture should be avoided at initial stage of SE.

Treatment of Status and Refractory Epilepticus

a. Follow principles of basic life support (BLS). Maintain airway (positioning, triple airway maneuver to keep airway patent, and suctioning if needed), adequate breathing by provide 100% oxygen using non-rebreathing mask (NRM) or bag/mask ventilation. If required go for early endotracheal intubation [avoid use of neuroparalytic agents, use thiopental 3-5mg/kg intravenously) and mechanical ventilation (Indications are; hypoxemia, hypoventilation, Glasgow Coma Scale <8 consider rapid sequence induction) and achieve immediate vascular access. Use etomidate, propofol, xylocaine, and thiopentone depending on the availability and circumstances to blunt raised intracranial pressure during intubation. Attach multipara monitor to record vital and ongoing activity. Attach EEG monitor if available. Assessment of respiratory and cardiovascular system must be ongoing process since various drugs used are also going to compromise both. If hypotensive use isotonic fluid boluses to augment perfusion and reassess after each bolus.

b. Obtain appropriate samples for lab studies (blood sugar, electrolytes, calcium, CBC, arterial blood
gas, LFT, RFT, CPK, troponin, toxins and drugs level, urine analysis, EEG)
c. Administer dextrose (5mL/kg of 10% or 2mL/kg of 25% dextrose) if hypoglycemia is detected. Thiamine (50-100mg) may be given in children at risk of nutritional deficiencies. Electrolyte abnormality if detected should be corrected. Antibiotics are also administered in a child with suspected infection. Fever should be controlled.
d. In hospital administer lorazepam 0.1 mg/kg intravenous at a rate of 0.04mg/kg/min (dilute 1:1 with normal saline) or diazepam 0.15mg/kg IV (anti-convulsant effect of lorazepam are longer compared to diazepam which also have higher elimination half-life due to high lipid solubility & causes more respiratory depression). One can use midazolam 0.2mg/kg intravenously or same dose as intramuscular, intranasal and buccal 0.5mg/kg if intravenous route is not available. May repeat the dose after 5 min. There is no role of benzodiazepines if 10 minutes are already over.
e. Seizures continuing after 10 min, start phenytoin 20mg/kg intravenously [dissolved in normal saline in concentration of 10mg/mL to be given over 20 min (therapeutic level 10-20ug/mL)] OR fosphenytoin 20mg/kg i.v. (intramuscular if no vascular access is available) no faster than 150mg/min., if no response phenobarbital may be used. Alternately valproic acid (20-40mg/kg intravenously over 15 minutes) or levetiracetam (30-60mg/kg loading) may be used. Monitor respiratory and cardiovascular functions. Valproic acid has been considered superior to phenytoin. Successful treatment requires both clinical and EEG termination of seizure activity within 20 minutes and no seizure recurrence in next 60 minutes. If seizure still persist dose of phenobarbital may be given.
f. Seizures still continuing, manage as refractory status epilepticus (clinical or EEG seizure activity that lasts for more than 60 min despite using one first line AED and one second line AED)
g. Transfer to intensive care unit
h. If seizure still persist mini bolus of phenytoin 10mg/kg may be given
i. Start midazolam bolus 0.2mg/kg & begin infusion (0.2-0.6mg/kg/hr) 1μg/kg/min increase till seizures are aborted. If seizures are controlled for 24 hours, taper drug 1μg/kg/min every 15min. Monitor EEG & blood pressure. Dose is titrated under EEG seizure suppression and after 12hours of suppression dose is reduced. Tachyphylaxis often develops in 24 hrs and dose to be modified accordingly.
j. If seizure still persist, administer pentobarbital 5-15mg/kg i.v. up to maximum of 50mg/min (hypotension, myocardial depression, immune suppression, pulmonary secretion clearance, loss of gastrointestinal motility). Give infusion 1-10 mg/kg/hr. Monitor CVP, blood pressures and EEG OR Propofol 2-5 mg/kg loading IV followed by infusion 1-4 mg/kg/hr not more than 12 hrs. Monitor for complications Propofol Infusion Syndrome (PIR) e.g. cardiac and renal failure, metabolic acidosis, rhabdomyolysis, and enlarged or fatty liver. Propofol should not be infused >48hrs and dose should not exceed than 4mg/kg/hr.
k. Other drugs used are lidocaine (2-3mg/kg bolus over 5 minutes followed by infusion of 1mg/kg/ hour and should not be used more than 12 hours), levetiracetam (15-70mg/kg i.v.), ketamine (1.5mg/kg), paraldehyde and inhalational anesthetic agents and Isoflurane/desflurane may be used in refractory status epilepticus if above measures fail.
l. Optimize anticonvulsant medications & continue to treat underlying etiology and complications
m. Consider alternative therapy based on clinical situation: Immunotherapy (corticosteroids, ACTH, plasmapheresis, IV immunoglobulin). Hypothermia, electrical stimulation therapy, vagal nerve stimulation, magnesium, inhaled anesthetic agents, transcranial magnetic stimulation and ketogenic diet
n. In children below 2 years intravenous pyridoxine 100mg may be tried.
o. Ketamine, ketogenic diet, hypothermia and enteral topiramate may also be used in some cases.
Figure 1: Flow Diagram of SE Management: Adapted from Textbook of Neuroanaesthesia & Neurocritical Care 2019
p. No more than three AED’s should be used. Anesthetic agents may be used for 5-7 days.

q. Midazolam and propofol should be tapered slowly while thiopental can be stopped abruptly.

r. Rarely electroconvulsive therapy and surgery (focal cortical resection, hemispherectomy, multiple subpial transections and corpus callosotomy)

s. Treat complications: Rhabdomyolysis, hyperthermia, cerebral edema, cardiac arrhythmias

t. Continue IV therapy for 24-48 hrs after seizure control before gradually withdrawing the drugs and continue maintenance AED.

For withdrawal seizure use another AED and taper after 24hrs of seizure control or start continuous infusion of same AED in the dose prior to tapering.

Points to remember

- Diazepam: Maximum dose 20mg, close monitoring for 3-8hours
- Lorazepam: Contains benzyl alcohol which is toxic to neonates, to be diluted in normal saline, dextrose-normal saline in equal amount
- Successful treatment is defined as control of seizure within 20minutes

Neonatal Status Epilepticus:

Newborn usually have primary pathology responsible for SE and definition of SE is still not clear.

Special situation and management of seizure in ICU

- Hyponatremia: Use IV 3% sodium chloride
- Hypocalcemia: Use IV calcium gluconate or calcium chloride
- Isoniazid overdose: Pyridoxine 70mg/kg
- Salicylate toxicity
- Lithium toxicity: Hemodialysis
- Eclampsia in adolescent girls

Flow Diagram of SE Management: Adapted from Textbook of Neuroanaesthesia & Neurocritical Care 2019

Q. What are complications of SE?

Answer:

Respiratory: Apnea, airway obstruction, aspiration, pulmonary edema, acute respiratory distress syndrome

Cardiovascular: Shock, hypertension, cardiac arrest

Neurological: Hypoxia, ischemia, stroke, brain damage, hemorrhage, cerebral edema

Metabolic: Hypoglycemia, hyponatremia, hypokalemia, metabolic acidosis, hyperthermia, rhabdomyolysis

Renal: Acute kidney injury

Q. Differentials of child with SE.

Answer:

- Hypoglycemia
- CNS vascular event
- CNS infection
- Drug toxicity
- Psychiatric illness
- Metabolic encephalopathy

Q. Name few drugs which can lower seizure threshold in ICU.

Answer:

- Cefepime
- Fluoroquinolones
- Cisplatin
- Cyclosporine

Q. Enlist the effect of ICU medications on antiepileptic drugs.

Answer:

- Rifampicin: ↓ Phenytoin
- Isoniazid: ↑ Phenytoin
- Omeprazole: ↑ Phenytoin
- Folic acid: ↓ Phenytoin
- Fluconazole: ↑ Phenytoin
- Glucocorticoids: ↓ Phenytoin
- Salicylates: ↑Valproate

Q. Principle mechanism of action of AED’s

Answer:

- Phenytoin: Sodium channel inhibitor
- Phenobarbital: GABA potentiation
- Valproic Acid: GABA potentiation, NMDA inhibition, Sodium channel inhibitor, T-type calcium channel inhibition
Carbamazepine: Sodium channel inhibitor
Oxcarbazepine: Sodium channel inhibitor
Levetiracetam: SV2 A modulation
Diazepam: GABA potentiation
Lorazepam: GABA potentiation
Clobazam: GABA potentiation
Gabapentin: Calcium channel inhibition
Propofol: GABA potentiation and NMDA inhibition

Q. Describe pharmacological aspects drug monitoring of the following: Phenytoin, phenobarbital, benzodiazepines, levetiracetam, valproate.

Answer:
Phenytoin:
- Therapeutic range: 10-20mg/dL
- Toxic range: >30mg/dL
- Oral bioavailability ≥80%, volume of distribution 0.5-0.8L/kg
- Protein binding 90%
- Time to steady state 6-21 days
- Serum level 20μg/mL (far-lateral nystagmus, Serum level 30μg/mL (ataxia), Serum level 40μg/mL (change in mental status), Serum level 50μg/mL (coma), Serum level 95μg/mL (death)
- Valproate increases free fraction of phenytoin
- Phenytoin can decrease plasma level of aceterminophen and albendazole and diuretic effect of furosemide
- Monitor: CBC, LFT, and phenytoin level
- Contraindication: Absence seizure and myoclonic jerks

Phenobarbital:
- Therapeutic range: 15-45mg/dL
- Toxic range: >50mg/dL
- Oral bioavailability ≥90%
- Time to steady state 15-29 days
- Volume of distribution 0.54L/kg
- Monitor: CBC, LFT, serum phenobarbital level

Valproate:
- Therapeutic range: 50-100mg/dL
- Toxic range: >200mg/dL
- Monitor: CBC, LFT, serum ammonia, and valproate level
- Management: Decontamination, supportive measures, hemodialysis, carnitine

Levetiracetam:
- Therapeutic range: 12-46μg/mL
- Toxic range: >30mg/dL
- Oral bioavailability 100%, volume of distribution 0.6-0.7L/kg
- Protein binding <10%

Seizure control and dose-related neurotoxicity should be the primary end points. Generally, treatment with one drug at higher doses is preferable over two drugs at lower doses because of the reduced risk of adverse events.

Phenytoin and valproic acid are highly protein bound and in a child with hypoalbuminemia and renal failure serum level of drugs become less predictable leading to more toxicity. Also, valproate displaces protein binding phenytoin rendering higher fraction of drug in active form. Phenytoin has nonlinear pharmacokinetic profile.

Q. Enumerate complications of status epilepticus.

Answer:
Respiratory: Apnea, airway obstruction, aspiration, neurogenic pulmonary edema, acute respiratory distress syndrome, hypoxemic respiratory failure
Cardiovascular: Shock, hypertension, cardiac arrhythmia, stress induced cardiomyopathy, cardiac arrest
Neurological: Hypoxia, ischemia, stroke, brain damage, hemorrhage, cerebral edema, temporal sclerosis, epilepsy
Metabolic: Hypoglycemia, hyponatremia,
hypokalemia, metabolic acidosis, hyperthermia, rhabdomyolysis

**Renal:** Acute kidney injury, hyperkalemia

**Musculoskeletal:** Fractures, joint dislocation

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