**Anesthetic Considerations in Epilepsy**

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**Abstract**

**Background:** A brain disease defined by any of the following conditions: At least two unprovoked (or reflex) seizures occurring > 24 hours apart; One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; Diagnosis of an epilepsy syndrome. It is extremely difficult to confirm the exact cause of epilepsy and only in 25 35% of the patients, one can possibly be sure of the exact aetiology. Following are few of the known causes of epilepsy Genetic, Trauma, Tumor, Infection Cerebral degeneration, Cerebrovascular disease, Multiple sclerosis,. Alcohol, Metabolic disorders.Review of Anesthetic management of epileptic patients as well as Anaesthesia for epilepsy surgery.

**Keywords**: AED, brain disease , Epilepsy and reflex.

1. **Introduction**

Epilepsy is a disorder of the brain characterized by a predisposition to generate abnormal synchronous neuronal activity that results in recurrent and unpredictable interruptions of normal brain function, observed clinically as epileptic seizures ***(1)***.

Epilepsy affects around 70 million people worldwide and causes more than 17 million disability‐adjusted life‐years annually. Head trauma, central nervous system infection, brain tumours and cerebrovascular disease are common risk factors ***(2)***.

The standard treatment for adults with epilepsy is antiepileptic drug (AED) therapy, but resective surgery may be considered in those patients in whom seizure control is not achieved ***(1).***

Management of an epileptic patient is a huge challenge for the attending anesthesiologist during the perioperative period. Various drug interactions of anesthetics with antiepileptics, intraoperative and postoperative seizures management and management of status epilepticus are few considerations which an anesthesiologist can confront both during emergency or elective surgery ***(3***).

Perioperative care of patients with epilepsy should focus on minimization of interference in normal AED regimes and avoiding physiological or pharmacological disturbances that may lower the seizure threshold ***(1).***

**2. Epilepsy**

**Epilepsy syndrome** refers to a group of clinical characteristics that consistently occur together, with similar seizure type(s), age of onset, EEG findings, triggering factors, genetics, natural history, prognosis, and response to antiepileptic drugs (AEDs). The nonspecific term “seizure disorder” should be avoided (**4**).

**2.1 History of epilepsy**

The entomology of “epilepsy” is from the Greek word *epilambanein*, meaning “to seize” or “to attack”. It is described, by many cultures, in ways that suggest mystical or supernatural origins. In ancient times, epilepsy was believed to be a sacred disease resulting from invasion of the body by a god; it was thought that only a god could deprive a healthy person of their senses, throw them to the ground, convulse them, and then rapidly restore them to consciousness *(****5****)*.

**2.2 Incidence and prevalence**

Epilepsy is a chronic non communicable disease (NCD), affecting all ages and sex, with a worldwide distribution. Epilepsy affects an estimated 50 million people (***6***), making it one of the most common neurological diseases globally (***7***).

Nearly 80% of those with epilepsy reside in low and middle-income countries (LMIC), where rates of epilepsy prevalence and incidence are higher than in high-income countries (HIC) (***8***).

Epilepsy accounts for a significant proportion of the world’s disease burden. Epilepsy accounts for over 13 million disability-adjusted life years (DALYs) and is responsible for more than 0.5% of the global burden of disease (GBD) (***9***).

**2.3 Classification of epileptic seizures**

Epileptic seizures can be classified as partial, generalized, pseudoseizures, nonepileptic seizures and status epilepticus (***3)***

**Table (1):** Showing the classification pattern of various seizure disorders (**3)**

**2.4 Pathophysiology**

Excessive and synchronous neuronal discharges that characterize epileptic phenomenon may originate from one point of the cerebral hemisphere (focal seizures) or a more extensive area involving the two hemispheres (generalized seizures). The focal seizures may become secondarily generalized seizures with the spread of the discharge (***10***).

These excessive and synchronous neuronal discharges are provoked by excitatory stimuli, mediated mainly by glutamate (the major excitatory neurotransmitter) or the lack of inhibition mediated by GABA (gamma aminobutyric acid), an inhibitory neurotransmitter (***10***).

**2.5 Causes of epilepsy**

It is extremely difficult to ascertain the exact cause of epilepsy and only in 25‑35% of the patients, one can possibly be sure of the exact aetiology. Following are few of the known causes of epilepsy (***3***):

**2.6 Diagnosis of epilepsy**

Epilepsy is conventionally diagnosed after two unprovoked seizures occurring at least 24 h apart. This reflects the fact that After two non-febrile seizures, more than 70% of people will have another seizure within 4 yrs ***(1)*** whereas only 40–50% of people will go on to develop epilepsy after a single unprovoked seizure (***11***).

The diagnosis of epilepsy is based on clinical history, description of seizure activity by those who witnessed, physical examination (looking for focal findings) and encephalographic findings ***(12).***

Physical examination between seizures in idiopathic epilepsy shows no abnormalities, but in the immediate posictal period, extensor plantar response can be observed ***(13)***.

A CT scan or MRI is indicated for patients with focal neurological signs and symptoms, focal seizures or EEG findings of a focal seizure; some neurologists routinely indicate imaging for all patients in the initial evaluation of a seizure ***(13)***.

Other tests used in diagnosis of epilepsy include video EEG, functional magnetic resonance imaging, positron emission tomography (PET) and single photon emission computed tomography (SPECT) ***(5).***

More than 60% of patients with epilepsy may have normal investigations (idiopathic epilepsy) and diagnosis is often difficult. As a result, it is believed that 5–30% of people diagnosed with epilepsy in the UK may have an incorrect diagnosis (***14***)

**2.7 Differential diagnosis**

It is extremely essential to diagnose a case of epilepsy for an appropriate and timely therapeutic management. The diseases which are important for differential diagnosis of epilepsy includes syncope, transient ischemic attack, migraine, hyperventilation, narcolepsy, cataplexy, and nonepileptic seizures (***15***).

**2.8 Prevention of epilepsy**

**Table (1):** Summary of preventable causes of epilepsy and interventions. **(16**)

|  |  |  |
| --- | --- | --- |
| Primary preventive measures | Estimated attributable fractioh | Cause |
| Maternal and child health care systems with universally available: screening for pregnancy complications; trained birth attendants and hygienic birthing environments; referral to obstetrical and neonatal care as needed; and standardized protocols for care during the pre-, peri- and postnatal periods | 5% (HIC)11% (LMIC} | Pre- and perinatal insults E.g. prematurity, fetal exposures to infections, toxins, cerebral haemorrhage or infarction, hypoxic - ischaemic ericephalopathy |
| Communicable disease control programmes making universally available: immunizations for *H. influenzae* **b,** N. *meningitidis* and *S. pneumonlae:* malaria control programmes in endemic areas; and hygienic pig husbandry programmes and humansanitary waste management | 2% (HIC)5% (LMIC) | Central nervous system infections E.g. bacterial meningitis, viral encephalitis, parasitosis |
| Multiple road traffic safety measures and programmes; fall prevention measures for children, older adults and high-risk occupations: violence prevention programmes | 5% (HIC)4% (LMIC) | Traumatic brain injury E.g. attributable to road traffic collision, falls and violence |
| Individual interventions and community programmes to reduce cardiovascular risk factors: e.g. hypertension, diabetes mellitus, hyperlipidaemia, obesity and tobacco use | 12% (HIC) 3c70 (LMIC) | StrokeCerebral infarction and haemorrhage |
| See above | 253 (HIC)24% (LMIC) | TotalCombined pre- and perinatal insults, CNS infection,traumatic brain injury and stroke |

**2.9 Management of epilepsy**

Patients with poor seizure control despite AED polytherapy should be referred to a specialist multidisciplinary epilepsy clinic. Epilepsy surgery is a treatment option in these cases and may be curative or palliative ***(1***).

Surgical options include implantation of a vagal nerve stimulator to reduce seizure frequency, curative respective surgery such as an anterior temporal lobectomy, or disconnective procedures that interrupt the propagation of seizures such as a corpus callosotomy or a multiple pial transection (***1***).

**2.10 Prognosis for patients with epilepsy**

In those patients with adefined epilepsy aetiology, their prognosis will depend on the underlying cause. Patients with idiopathic epilepsy have a normal lifespan if their seizures are well controlled, but this falls if seizure control is not achieved. This reflects the higher incidence of accidents and suicides in this group and also the risk of sudden unexpected death in epilepsy (SUDEP) (***1)***.

SUDEP is the sudden death of a seemingly healthy individual with epilepsy, usually occurring during, or immediately after, a tonic–clonic seizure. The mechanisms are incompletely understood, but seizure-related respiratory depression, cardiac arrhythmias, cerebral depression, and autonomic dysfunction are all implicated (***17***).

Risk factors for SUDEP include male sex, long duration of epilepsy, frequent occurrence of tonic–clonic seizures, and AED polytherapy. Patients should be counselled and given advice regarding treatment and lifestyle choices to avoid poor seizure control and minimize the risk of SUDEP (***1***).

**3. Pharmacology of Antiepileptic drugs**

**3.1 Antiepileptic drugs (AEDs)**

Epilepsy is one of the most common neurological diseases; its first-line treatment is the administration of antiepileptic drugs (AEDs) ***(18***). AED therapy should only be started once the diagnosis of epilepsy is confirmed. The decision to initiate AED therapy should be taken between the child, young person or adult, their family and/or carers (as appropriate) and the specialist after a full discussion of the risks and benefits of treatment. The AED treatment strategy should be individualised according to the seizure type, epilepsy syndrome, co-medication and co-morbidity, the child, young person or adult's lifestyle, and the preferences of the person and their family and/or carers as appropriate (***1***).

The AEDs are divided into first, second, and third generation AEDs. first-generation include AEDs [carbamazepine (CBZ), clobazam (CLB), clonazepam (CZP), ethosuximide (ETS), phenobarbital (PB), phenytoin (PHT), sulthiame (STM), valproic acid (VPA)] and second-generation AEDs [felbamate (FBM), gabapentin (GPT), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), pregabalin (PGB), tiagabine (TGB), topiramate (TPM), vigabatrin (GVG), zonisamide (ZNS) (***19).***

The most recently approved drugs, referred to as third-generation or newer AEDs, include eslicarbazepine acetate (ESL), lacosamide (LCS), perampanel (PER), retigabine (RTG), rufinamide (RUF), and stiripentol (STP). Most of the second- and third-generation AEDs are licensed as an adjunctive treatment of epilepsy (***20)***

**3.2 Anesthetic drugs and epileptic patient**

 Numerous drugs used in anesthesia have potential drug interactions with anti-epileptic agents which can be highly detrimental during surgical procedures (***3***). Also Many of the Anesthetic agents used possess both pro-convulsant and anticonvulsant properties, which could impact on the choice of anaesthetic agents (***21).***

**3.3 anaesthetic agents**

The effects of i.v. anaesthetic agents on the EEG are complex, but they are generally proconvulsant at low levels and anticonvulsant at doses used for general anaesthesia **(*1)***

**3.4 Local Anesthetics:**

local anesthetics have pro-convulsant and anticonvulsant properties due to the stabilizing effect of the membrane. In small doses, local anesthetics reduce cerebral blood flow and metabolism, as well as brain electrical activity, and act as anticonvulsants, sedatives and analgesics, while at high doses it act as pro-convulsant drug, lowering the seizure threshold in the cerebral cortex, amygdala and hippocampus, leading to generalized convulsions (***22***).

The systemic toxicity associated with regional anesthesia is a cause of seizures in approximately 5/10.000 patients, which can be found even with local anesthetics for use later. It is more frequent with bupivacaine and those regional anesthesia techniques in which large doses of local anesthetics such as epidural and caudal are employed ***(10***).

**4. Perioperative management for patient with epilepsy**

 Perioperative care of the patients with neurological diseases can be challenging. Most important consideration is the management and understanding of pathophysiology of these disorders and evaluation of new neurological changes that occur perioperatively. Perioperative generally refers to 3 phases of surgery: preoperative, intraoperative, and postoperative (***23***).

The risk of perioperative seizures is dependent on baseline control of patients with seizures and epilepsy (***24***). Anesthesia, metabolic derangements, drug and alcohol withdrawal, intracranial surgery, and baseline control of seizures are the factors causing seizures in perioperative patients. Seizures puckering intraoperatively may be anesthetic related, but postoperative seizures are generally not related to the effects of anesthesia, which warrants investigation in patients without unknown underlying epilepsy (***23)***.

**4.1 Preoperative assessment and premedication:**

In the preoperative management of epileptic patients, it is important, whenever possible, an adequate control of the disease, being essential a careful review of medical history, Antiepileptic drugs (AEDs), including dosages and adherence, Seizure type, frequency, and date of most recent seizure (***25***), especially in regard to the evolution of the disease, factors triggering the seizures (fasting, stress, sleep deprivation, alcohol and drugs), and comorbidities and their treatment. The presence of mental retardation, hypotonia, and risk factors for aspiration and airway obstruction should be examined (***12***).

A preoperative evaluation of the neurologist responsible for the patient is recommended, especially in the case of recent changes in disease evolution (***26***)

The premedication is usually carried out with the use of a benzodiazepine, midazolam being the most widely used due to its potent anticonvulsant and anxiolytic effects. It is important to emphasize that some anticonvulsants, and the ketogenic diet can cause sedation and interact with benzodiazepines (***10)***

**4.2 Anesthetic considerations in epilepsy surgery**

Patients with poor seizure control despite AED polytherapy should be referred to a specialist multidisciplinary epilepsy clinic. Epilepsy surgery is a treatment option in these cases (***1***).

**Table (2)**: Proconvulsant and anticonvulsant effects of anesthetic agents in epileptic patients (***27)***

|  |  |  |
| --- | --- | --- |
| **Agent** | **Praconvulsant** | **Anticormulsant** |
| **Intravenous agents** |  |  |
| 'Thiopental | — | + |
| Iviethohexital | + | + |
| Et omi da tie | + | + |
| ketanaine | + | + |
| Propofol |  | + |
| Ben zod iaze pin es |  | + |
| In Ka lational agents |  |  |
| Nitrous Oxide |  | — |
| Halo( ha ii e | + | + |
| Enfl u ran e |  | + |
| Isoflurane | + | + |
| Sevoriurane | — | ? |
| Desilurane | — | + |
| (+) — present, {•—) — it bs en t . (?) — Information nut available. |
| Proconvulsant .— Provoke seizures. Anticonvulsant-suppress status epilepticus. |

**4.2.1 Preoperative Localization of Epileptogenic Focus**

Success of the epilepsy surgery depends on the precise localization of epileptogenic foci. A multidisciplinary approach with both noninvasive and invasive investigations is performed to identify the location of the seizure foci as well to determine the feasibility to resect the epileptogenic foci safely without major neurological or cognitive deficits ***(28).***

**5. Status epilepticus**

Status epilepticus is one of the most dreaded medical emergencies which an anesthesiologist can encounter during emergency or elective surgery in a case of known epileptic patient ***(3).*** Status epilepticus was defined by the International League Against Epilepsy (ILAE) more than 20 years ago as a single epileptic seizure of >30 minutes duration or a series of epileptic seizures during which function is not regained between ictal events in a 30 minute period (***29***).

The new proposed operational definition for status epilepticus by (ILAE) is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures” (table 11) ***(30)***.

**5.1 Etiology:**

The main causes of status epilepticus are low blood concentrations of antiepileptic drugs in patients with chronic epilepsy (34%), metabolic causes (including hypoxia, electrolyte imbalance and alcohol and drug withdrawal) (30%) remote symptomatic causes (24%), cerebrovascular accidents (22%). Additionally in studies from India central nervous system infections contribute to 28–67% of the etiologies. No clear aetiology can be identified in 20% of cases (***31***).

**5.2 Physiological changes seen in status epilepticus:**

During the first stage of convulsive status epilepticus (CSE), there is an increase in cerebral metabolism, increased blood flow, and increased glucose and lactate concentration. This is associated with massive catecholamine release, raised cardiac output, hypertension, tachycardia, and increased central venous pressure. These compensatory mechanisms prevent cerebral damage in the first 30–60 min ***(32).***

**Table (3):** Drug administration details for CSE***.*** Doses are i.v. unless stated otherwise ***(33)***

|  |  |  |
| --- | --- | --- |
| **Other information** | **Dose** | **Drug** |
| **Premonitory stage of status** |
| Dose can be repeated if necessary | 10 mg nasal or buccal | Midazalam |
| Dose con be repeated if necessary | 10-20 mg pl. or0.2-0.3 mg kg-1 | Diazepam |
| **Early status epilepticus** |
| Dose con be repeated if necessary | 0.1 mg kg-1: or 4-8 mg i.v. bolus | Lora zepam |
|  | I.V.—same dose as above | Diazepam |
| **Established CSE** |
| Administer slowly through a large-bore cannulo via a 0.2 grn filter, immediately after reconstitution | **15-18** mg kg-1 loading dose given **at 50** mg min-1 | Pherytoin |
| Risk of respiratory depression | 10-15 mg kg-1 given at 100 mg min-1 | Phenobarbital |
|  | **25** mg kg-1 over 30 min-1 then 100 mg h-1 for 24 h | Sodium |
| **Vaproate107** |
|  | **20D0 -** 3000 mg day-1 | Levetiracetam |
| **Refractory CSE** |
| Adjust dose to maintain burst suppression. All will require intensive care and ventilatory support Titrate infusion doses to EEG burst suppression Corticosteroid replacement required if etomidate infusion is used | 100-250 mg i.v. bolus (then SO mg increments until seizures controlled) then 3-5 mg kg-i h-1 | Thiopental |
| Consider as on alternative to barbiturates | 0.1-0.3 mg kg-1 bolus then **0.05** -0.4 mg kg-1 h-1 infusion | Midazotam |
|  | 2 mg kg-1 i.v. bolus, then 5-10 mg kg-1 h-1 | Propofal |
| Dose from case reports up to **7.5** mg kg-1 h-1 109 | 0.4 mg kg-111-1 then titrate up to response | Ketamine |

**5.3 Refractory status (30–60 min):**

Refractory status epilepticus is defined as the failure of adequate doses of two intravenous drugs to stop seizures (**31**), is associated with a high risk of complications. These include tachyarrhythmias, pulmonary oedema, hyperthermia, rhabdomyolysis, and aspiration pneumonia. RSE has a high mortality rate and less than one-third of patients recover to their pre-morbid level of functioning ***(34).***

In patients not responding to other measures, general anaesthesia should be induced and maintained with midazolam, propofol, or barbiturates (thiopental or pentobarbital) ***(32).***

**Maintenance Therapy:** Along with emergency treatment, attention must be given to maintenance AED therapy to prevent recurrence of seizures. In patients with known epilepsy, their usual AEDs must be continued and dose adjustments made by monitoring AED levels. In patients presenting with new onset of status epilepticus, the AEDs, phenytoin or valproic acid, which are given as an initial IV loading must be continued as oral maintenance therapy (***35)***

**5.4 Non-convulsive status epilepticus:**

NCSE is the term applied to the finding of electrographic seizure patterns on EEG without clinically detectable seizure phenomena. In the intensive care setting, such patients are usually unconscious ***(36).***Such cases may represent advanced CSE, where the motor activity has become attenuated over time. This is a grave situation with almost uniformly poor outcome. A variety of acute neurological insults (encephalitis, stroke, trauma, and post-cardiac arrest) may also present with coma and electrographic seizures on EEG ***(37)***

**6. Summary**

**Epilepsy:** A brain disease defined by any of the following conditions: At least two unprovoked (or reflex) seizures occurring > 24 hours apart; One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; Diagnosis of an epilepsy syndrome.

It is extremely difficult to confirm the exact cause of epilepsy and only in 25‑35% of the patients, one can possibly be sure of the exact aetiology. Following are few of the known causes of epilepsy Genetic, Trauma, Tumor, Infection Cerebral degeneration, Cerebrovascular disease, Multiple sclerosis,. Alcohol, Metabolic disorders.

The standard management of adults with a confirmed diagnosis of epilepsy is antiepileptic drugs therapy. The AEDs are divided into first, second, and third generation AEDs.

There are important pharmacokinetic and pharmacodynamics interactions between AEDs and drugs commonly used in anaesthesia. These affect both drug efficacy and the risk of seizure activity intraoperatively. Also Many of the Anesthetic agents used possess both pro-convulsant and anticonvulsant properties, which could impact on the choice of anaesthetic agents.

Surgical options include implantation of a vagal nerve stimulator to reduce seizure frequency, curative respective surgery suchas ananterior temporal lobectomy, or disconnective procedures that interrupt the propagationof seizures suchas a corpus callosotomy or a multiple pial transection

Status epilepticus should be managed as early as possible as it is associated with significant morbidity and mortality. Benzodiazepines are the drug of choice for out-of-hospital treatment. Since IV access may not be possible in the home setting, other modes of administration such as rectal, buccal and nasal are advised.

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