Austin Journal of Anesthesia and Analgesia

Austin Publishing Group

Open Access Full Text Article

Review Article

Anesthesia-Related Perioperative Seizures: Pathophysiology, Predisposing Factors and Practical Recommendations

Alix Zuleta-Alarcon[1]*, Karina Castellon-Larios[1], Kenneth R Moran[1], Suren Soghomonyan[1], Lakshmi N Kurnutala[1] and Sergio D Bergese[1,2]

[1]Department of Anesthesiology, Ohio State University, USA

[2]Department of Neurological Surgery, Ohio State University, USA

***Corresponding author:** Alix Zuleta-Alarcon, Department of Anesthesiology, Wexner Medical Center, The Ohio State University, Doan Hall N 411, 410 W 10th Ave, Columbus, OH. 43210, USA

Received: April 10, 2014; Accepted: May 26, 2014; Published: May 31, 2014

Abstract

Epilepsy is one of the most prevalent neurological disorders both in the United States and worldwide. It is present in 0.5-1% of the population, with a 10% lifetime risk of experiencing a single seizure. Anesthesiologists are frequently faced with the management of seizures in epileptic and nonepileptic patients in the intraoperative, emergency, or intensive care unit settings. This review aims to provide an update on the pathophysiology, clinical presentation and treatment strategies of perioperative seizures and the pro- and anti-convulsant properties of anesthetic agents, focused on neurosurgical populations.

Many aspects of anesthesia may affect seizure incidence in the perioperative setting, including changes in antiepileptic drug regimen causing sub therapeutic antiepileptic drug (AED) blood levels, nil per os (NPO) status, anxiety, sleep deprivation, and drug interactions. Several general anesthetics and drugs used during anesthesia possess pro-convulsant properties that may trigger clinical seizures at induction or emergence. Anesthetic-induced epilepsy has been described during anesthesia with sevoflurane, isoflurane, etomidate, local anesthetics, opioids, propofol, as well as other anesthetics and auxiliary drugs. In neurosurgical patients, perioperative seizure risk is highly relevant, especially in patients with brain tumors, subarachnoid hemorrhage (SAH) and traumatic brain injury (TBI). Although common in practice, routine antiepileptic prophylaxis in neurosurgical patients remains controversial.

Keywords: Neurosurgery; Anesthesia; Seizures; Perioperative; Anticonvulsants

Introduction

Seizures are the clinical manifestation of the brain's abnormal electrical activity with enhanced synchrony. They emerge from a hyper excitable focus within the brain where synchronized electrical activity has been formed [1,2]. Epilepsy can be defined as recurrent seizures unprovoked by acute systemic or neurologic insult [2].

Worldwide, around 50 million people suffer from epilepsy. In developing countries the annual rate of new cases reaches 6-10 per 1000 of population [3]. Since the introduction of anesthesia in medical practice, numerous reports of perioperative seizures have been published in medical literature. Many anesthetic agents have been shown to either increase or decrease seizure threshold. Nonetheless, the incidence, risk factors, pathophysiological mechanisms and prophylactic measures of anesthetic drug-induced seizures are still not fully understood.

This review focuses on the pathophysiology, clinical presentation and treatment strategies of perioperative seizures and the pro- and anticonvulsant properties of anesthetic agents.

Pathophysiology

Central nervous system (CNS) synchronicity and excitability are controlled by multiple factors. Excitatory and inhibitory neurotransmitters like glutamate and GABA, interact with specific receptors, (NMDA, AMPA and GABA) to control signal conduction, neurocircuit activity and neuronal synchronization within the CNS [4-6].

Understanding the pathophysiology of seizures and epilepsy is the initial step in exploring the pro- or anticonvulsant effects of anesthetic drugs and establishing rational therapeutic measures [7].

Epileptogenesis is a sequence of events that turn the normal neuronal network into a hyperexcitable one. Progression to neuronal hyperexcitation results in functional reorganization at the synaptic and network levels and predisposes to structural changes [8]. The underlying biological mechanisms of these changes are not fully understood and studied. Complex intracellular and extracellular ionic shifts, osmolar changes, neuro-glial and synaptic deregulation, neuroactive substance and cytokine release, alterations in gene expression and action of micro RNAs all contribute to the development and maintenance of the hyperexcitable state [6].

Neuronal hyperexcitability is facilitated by acute changes in transcellular electrolyte balance. With increases in intracellular sodium (Na^+) and calcium (Ca^{2+}) concentrations, decrease in extracellular chloride (Cl^-), and blockage of rectifier potassium currents as well as decreased GABA-ergic inhibition. Metabolic changes induced

Citation: Zuleta-Alarcon A, Castellon-Larios K, Moran KR, Soghomonyan S, Kurnutala LN and Bergese SD. Anesthesia-Related Perioperative Seizures: Pathophysiology, Predisposing Factors and Practical Recommendations. Austin J Anesthesia and Analgesia. 2014;2(4): 1026.

by tissue hypoxia and ischemia, hypoglycemia and other factors, may further increase the epileptogenic potential in the brain [6,9]. Massive ionic fluxes and excessive depolarization may result in simultaneous neuronal discharges and synchronized oscillations of the membrane potentials [6]. Important potential master regulators of epileptogenesis have emerged in recent years, including brain-derived neurotrophic factor (BDNF)–tropomyosin-related kinase B (TRKB) also known as NTRK2 signaling, the mammalian target of rapamycin (mTOR) pathway and the RE1-silencing transcription factor (REST) pathway [10,11].

In addition to up regulation of specific transcription factors, substantial structural changes develop in brain tissue during formation of the epileptogenic focus. These include neurodegeneration, neurogenesis, local gliosis, axonal damage or sprouting, dendritic plasticity, blood–brain barrier disruption, local recruitment of inflammatory cells, reorganization of the extracellular matrix and molecular architecture of individual neuronal cells [8].

Excitotoxic cell damage during epilepsy is one of the major mechanisms determining disease progression and treatment outcome. Uncontrolled release of excitatory neurotransmitters triggers massive transmembrane Ca^{2+} influx and its release from the intracellular storage compartments. This initiates a cascade of downstream reactions resulting in structural membrane damage, edema, apoptosis and necrosis. Additional contributors to progression of the disease and irreversible tissue damage include hypermetabolism and mismatch between the demand and supply of oxygen and nutrients, metabolic and respiratory acidosis, hypoxemia, and cerebral ischemia [6,12].

Increased neuronal synchrony in thalamocortical neurons both during anesthesia and sleep is one of the proposed mechanisms for the development of anesthetic drug-induced seizures. These events happen more commonly during induction and emergence from anesthesia [7,13]. Synchronous patterns happen typical during the sleep period and can be detected on the electroencephalogram (EEG) as slow cortical oscillations (<1 Hz) and delta activity (<4 Hz). Similar patterns can be registered during induction and maintenance of anesthesia [7].

Sleep spindles appear in response to inactivation of low-threshold Ca^{2+} spikes and hyper polarization of cortical and thalamocortical neurons, mainly those of the reticular nucleus of the thalamus. Increased cortical oscillation and synchrony are intimately associated with spike-wave seizures. During wakefulness, sleep oscillations are suppressed and low-amplitude rapidly irregular frequency alpha (8-13 Hz) and beta (14-30 Hz) bands dominate the EEG tracing [14].

Gowers [15] observed an exclusively nocturnal occurrence of generalized seizures in 20% of patients. He also observed a peak occurrence around bedtime and waking up hours, 9-11 pm, and 3-5 am respectively. This time pattern was also observed in an analysis of two large series of patients with tonic-clonic generalized seizures [16,17]. A high incidence of seizures during the awakening period was found, also called 'awakening epilepsies' [14].

Besides sleep patterns, there are other factors associated with an increased risk for seizures in the perioperative setting: anesthetic usage, electrolyte abnormalities, hypoglycemia, medication withdrawal, patient age, hyperventilation, and changes in usual AED regimens [18].

Classification

Seizures can be classified in two major groups according to the extent of the electrical disturbance [11]. (Table 1).

Implications in the perioperative setting

Intraoperative seizures may evoke patient movement during surgery, interfere with airway patency and ventilation, induce cerebral and systemic acidosis, increase intracranial pressure, and cause cerebral edema [2]. In severe cases, status epilepticus (SE) may develop [2]. This is a serious condition that carries a short-term mortality of up to 22% and long-term mortality of 43% [19]. Multiple factors related to perioperative patient management may contribute to seizure development. For example, changes in antiepileptic drug regimen due to patient noncompliance or NPO status sleep deprivation, fatigue, stress, surgical pain, adverse drug reactions and

Table 1:

International Classification of Seizures	
Partial Seizures	
Simple partial seizures (consciousness not impaired)	- With motor symptoms - With sensory symptoms - With autonomic symptoms - With psychic symptoms
Complex partial seizures (with impaired consciousness)	- Simple partial seizures followed by impairment of consciousness - With impairment of consciousness at seizure onset
Partial seizures evolving to secondary generalized seizures	- Simple partial secondarily generalized - Complex partial secondarily generalized - Simple partial evolving to complex partial evolving to generalized
Generalized Seizures	
- Absence seizures (formerly called petit mal) - Myoclonic seizures - Clonic seizures - Tonic seizures - Tonic clonic seizures (formerly called grand mal) - Atonic seizures (drop attacks)	

interactions between anesthetics and anticonvulsants [2,20].

In 2005, Akavipat [21] identified a perioperative seizure incidence of 3.1 per 10,000 patients. According to the authors, up to 67.9% of cases were related to surgery, 54.72% were attributed to patient-related factors, and 30.19% of cases were directly associated with anesthesia.

Niesen [20] retrospectively studied 6-years of medical records for 641 patients with a preexisting seizure disorder, who were admitted to the hospital for at least 24 hours after anesthesia for non-neurological procedures. Among those patients, 3.4% experienced perioperative seizures. Clinically significant factors associated with increased risk were younger age (40.3 ± 22.2 vs 53.3 ± 22.6 years; P=0.011), more frequent seizures at baseline, and a shorter length of time between the last seizure and hospital admission ($p < 0.001$). Perioperative seizure activity of these patients was related to sub therapeutic blood levels of AEDs.

A multidisciplinary approach might be required to effectively manage the patients at risk of perioperative seizures, including those requiring multiple medications to achieve seizure control and patients with a history of frequent or recent seizures [20,22]. It is important to determine baseline AED blood levels to ensure perioperative drug compliance and prevent sub therapeutic levels. Special attention is needed on patients in which medications that alter AED absorption and metabolism are prescribed, such as, rifampin, carbapenems, sucralfate, antacids, cisplatin, etoposide and other chemotherapeutic drugs [23,24]. Anesthesia providers should have sufficient knowledge and expertise to assess the blood levels of AED medications, existing options of antiepileptic therapy and the possibility of adverse drug interactions [20].

Once a seizure takes place, measures must be taken to prevent its progression into SE. The most common causes of perioperative SE are AED withdrawal, alterations in dosing, switching to alternative drugs, and comorbid conditions including cerebrovascular disease, epilepsy, fever, systemic infections, malignancy, metabolic disorders and drug toxicity [19].

Benzodiazepines are considered first line drugs for termination of convulsive status epilepticus (CSE). Initial management of CSE includes general resuscitative measures to support the cardiovascular and respiratory function, securing adequate intravenous (IV) access, and IV administration of a benzodiazepine [2]. In the operating room, thiopental and propofol can also be considered as reasonable first choices [25]. 50 ml of 50% dextrose should be administered if hypoglycemic seizures are suspected or 250 mg thiamine and glucose (dosage) if impaired nutrition or alcohol abuse is suspected [2].

Seizures lasting over 5-30 minutes are considered established status epilepticus and phenytoin, fosphenytoin, valproate, phenobarbital, and levetiracetam should be considered for treatment. If SE persists after therapy with 2 AEDs, a refractory SE is diagnosed, and general anesthesia should be administered. Propofol, thiopental and ketamine infusions, as well as inhalational anesthesia with isoflurane or desflurane, have been shown to be effective in the management of refractory status epilepticus. Continuous EEG monitoring is required to assess epileptic activity and to monitor weaning. Maximal therapy should be maintained until twelve to twenty four hours after the last clinical or electrographic seizure [2]. Thereafter, a gradual tapering of IV AEDs with a switching to enteric route is carried out.

AEDs and anesthetic drugs

Anesthetic agents do not significantly alter AED pharmacokinetics [2]. However many AEDs induce or inhibit the expression of cytochrome P450 isoenzymes thus modifying the metabolism of many drugs used in general anesthesia [23]. Phenytoin, carbamazepine, phenobarbital, and primidone stimulate the metabolism of fentanyl, vecuronium and other non-depolarizing neuromuscular agents, as well β-blockers, (propranolol, and metoprolol), and calcium channel antagonists, (nifedipine, felodipine, nimodipine, and verapamil). Other medications affected include psychotropic medications, immunosuppressants, and antibacterials [23].

In contrast, new generation AEDs such as gabapentin, lamotrigine, levetiracetam, tiagabine, topiramate, vigabatrin, and zonisamide do not have clinically significant enzyme-inducing properties. Valproic acid is an enzyme inhibitor and may inhibit the metabolism of amitriptyline and nortriptyline, which could lead to overdose and seizure precipitation [23,26].

Generally, perioperative AED drug blood level monitoring is not required. However, in critically ill patients admitted to the intensive care unit (ICU), antiepileptic therapy in conjunction with closely monitored blood concentrations may be a safe and reliable approach [2,27].

NPO and AED therapy

Niesen [20] underscored the importance of maintaining inpatient dosing regimens as close as possible to what the patient is accustomed to as an outpatient. Preoperative consultation with a neurologist may become necessary in those cases requiring multiple medications or when a parenteral formulation is unavailable. Assessment of the potency of parenteral formulations is necessary to avoid perioperative seizures related to in-hospital alterations of the antiepileptic regiments [20].

Wichards [28] reviewed the currently available parenteral options for AED substitution during the perioperative period. They divided the AEDs into groups based on the availability of equivalence data for parenteral or rectal dosage forms. Drugs such as benzodiazepines (clonazepam, diazepam, lorazepam), phenobarbital, phenytoin, valproic acid, gabapentin, lacosamide and levetiracetam have equivalence data for parenteral or rectal dosage forms [28].

Drugs with little data on parenteral administration include clobazam, nitrazepam, carbamazepine, ethosuximide, primidone, lamotrigine, oxcarbazepine and topiramate. AEDs without available parenteral replacement require use of alternative medications. In these cases, parenteral benzodiazepines may prevent withdrawal seizures [28]. In cases where combination therapy is justified for seizure control or when perioperative substitution with intravenous agents is required, interaction between various AEDs needs to be taken into account and dose adjustments made. Regular therapy with oral medications should be resumed as soon as the patient can tolerate the oral intake [28].

Sleep deprivation

Sleep deprivation (SD) predisposes to clinical seizures as well as epilepticform discharges on the EEG [29] even in patients with no prior seizure history.

Transcranial magnetic stimulation studies suggest increased cortical excitability in sleep-deprived patients. Selective rapid eye movement (REM) SD significantly reduces silent period duration and intracortical inhibition [30,31]. These SD modifications in cortical excitability may be mediated by GABA ergic neurons. As SD is associated with seizure induction as well as increased intensity and duration of seizures [32], it seems rational to promote healthy sleep for at-risk patients undergoing anesthetic procedures. Such an approach is especially important for patients with underlying seizure disorder [32].

Fatigue and Stress

Patients report stress and tiredness as factors that precipitate seizures and increase their frequency. Nakken [33] studied the relationship between different precipitating factors and the occurrence of seizures in 1677 adult patients. In their series, emotional stress and tiredness were among the three most commonly reported factors (20.9% and 9.5% respectively) with equal distributions between generalized and partial seizures [33]. In children, however, the most common precipitants reported were illness and fever (32%) [34].

Mechanisms on how the stress can predispose to seizures are not fully understood. Nevertheless, perioperative stress reduction, although difficult, should be taken into consideration as a non pharmacologic means of seizure prevention. In addition to direct antiepileptic effects, preoperative benzodiazepines may also promote anxiolysis and relieve stress.

Hyperventilation

Hyperventilation is associated with a decline in PCO_2 and subsequent decrease in cerebral blood flow. These changes tend to decrease the normal alpha and beta activity on the EEG and induce a synchronous delta activity (<4 Hz). The epileptogenic effects of hypocapnia have been used as a diagnostic tool during electrophysiological diagnosis of epilepsy [35].

Children are especially sensitive to PCO_2 variations. Hyperventilation-induced EEG changes occur in 95% of epileptic children compared to 40% of epileptic adults [35].

In contrast, voluntary hyperventilation studies in epileptic patients have shown a low incidence (5%) of epilepticform EEG changes which rarely manifest clinically in adults and adolescents [36]. According to Holmes [36] only 0.52% of patients with localized epilepsy and no patient with generalized seizures developed clinical seizures in response to hyperventilation. Interictal electrical discharges, increased in 12.2% of patients with generalized epilepsy and 3.4% with focal epilepsy.

Thus, currently available data recommends avoiding hyperventilation in patients prone to development of epileptic seizures, particularly, in pediatric patients and in patients undergoing induction of anesthesia with sevoflurane [37]. During induction in epileptic patients, slow preoxygenation is preferable compared to a fast oxygenation technique, as the latter may trigger a clinical seizure (unpublished own data).

Anesthetics

In 1990, Modica [38,39] analyzed the pro- and anticonvulsant properties of anesthetic and analgesic medications. Following their publication, the epileptogenic potential of anesthetic drugs has been widely studied. Pro-convulsant properties have been mainly attributed to local anesthetics, volatile agents, opioids, ketamine, etomidate, propofol and low doses of methohexital.

Local anesthetics

CNS compromise resulting from the local anesthetic-induced systemic toxicity (LAST) is well recognized. The overall estimated incidence of perioperative seizures related to local anesthetic toxicity is 120 per 10,000 [40].

Since the early 1900's, many studies have demonstrated both the pro- and anticonvulsant properties of local anesthetics [19,39]. In lower doses, local anesthetics produce an antiepileptic action, while proepileptic effects become more pronounced after increasing the dose and plasma concentration. One of the explanations of the neurotoxic effects of local anaesthetics is their ability to rapidly cross the blood–brain barrier [41] and decrease seizure threshold in the hippocampus, cerebral cortex and amygdala, predisposing the patient to seizures. In lower concentrations, they act as anticonvulsants by depressing cerebral electrical activity, metabolism, and blood flow [18,42].

Kopp [43] found a 5.8% frequency of perioperative seizures in patients with a history of seizure disorder undergoing regional anesthesia (epidural, caudal, or peripheral nerve blocks). Nevertheless, they concluded that this type of regimen is not contraindicated in epileptic patients.

Anesthesia providers should focus on increasing patient safety and implementing strategies that decrease LAST incidence during regional anesthesia. In patients predisposed to seizures, current recommendations include utilization of lowest effective anesthetic doses, using less toxic anesthetics, such as lidocaine or mepivacaine, and providing postoperative analgesia with opioid infusion [44]. In case of LAST, treatment recommendations include prompt airway management and lipid emulsion therapy with an initial bolus of 1.5 mL/kg of 20% lipid emulsion followed by an infusion of 0.25 mL/kg/min, not exceeding 10 mL/kg over 30 minutes. Concomitantly, benzodiazepines, propofol, or thiopental should be administered. If seizures persist despite benzodiazepines, small doses of succinylcholine or another neuromuscular blocker should be considered to minimize the motor manifestations of seizures and reduce acidosis and hypoxemia [45].

Neuraxial anesthesia, as well as high brachial plexus blocks, should be performed with monitoring for the possibility of inadvertent intrathecal injection of high doses of local anesthetics. In such cases, seizures and other symptoms of neurotoxicity may develop following injection. The rate of this complication can be minimized by adequate training, continuous patient monitoring during the injection, avoidance of high drug concentrations, and application of test doses prior to administration of the full anesthetic dose [46,47].

Volatile agents

The pro-convulsant potential of volatile agents is explained by their ability to destabilize the cortex and delay inhibitory circuits [7].

Voss [13] compared the cortical effects of desflurane and other volatile anesthetic agents in sheep to investigate their ability to produce interictal spike discharges that could potentially translate into clinical seizure. They demonstrated that desflurane produced less cortical spikes compared to other inhalational anesthetics at a maintenance dose. The agents could be ranked by their relative ability to cause spike activity: enflurane >> sevoflurane > isoflurane = desflurane [13].

Studies with sevoflurane have demonstrated subclinical paroxysmal cortical electrical excitability in epileptic and nonepileptic patients at surgical levels of minimum alveolar concentration (MAC) [28,48]. Constant [49] analyzed the EEG epileptic activity of sevoflurane and suggested clinical practice guidelines to limit the expression of the epilepticform phenomena. The epilepticform discharges were shown to be proximal to burst suppression periods, and spikes increased at MAC >1.5 in a dose-dependent manner.

During sevoflurane anesthesia in children, the authors recommend keeping the maintenance doses below 1.5 MAC and premedicating the patients with benzodiazepines to avoid cortical hyper excitation and development of seizures [49,50].These recommendations can be applied to all patients at high risk or a history of seizures who undergo inhalational anesthesia.

Intravenous agents

Propofol at low doses can induce both epilepticform activity on EEG and overt seizures during anesthesia induction and emergence. This may be explained by rapid changes of propofol concentration in the brain at the beginning or end of anesthesia [51]. Glycine antagonism and specific $GABA_A$ receptor agonism appear to mediate the epileptogenic potential of propofol [51]. According to Hadipour-Jahromy and Daniels [51], propofol increases the inhibition of GABA ergic thalamopetal inputs to the thalamus, generates thalamo-cortical oscillations and promotes high-voltage spike and wave spindles and clinical seizures in animal models.

As with many anesthetic agents, higher doses of propofol exhibit anticonvulsant properties attributed to NMDA antagonism and inhibition of neural firing by GABA [51,52]. Propofol selectively suppresses the L-type high-voltage-activated Ca^{2+} and Na^{+} currents, thus modulating neuronal excitability [53]. In cortical pyramidal neurons, propofol has been shown to decrease the duration and number of action potentials [52]. It also has been recommended, in combination with midazolam, for the management of seizures and refractory SE due to its $GABA_A$ activity, rapid titratability and short duration [54,55].

Etomidate: Etomidate acts on $GABA_A$ receptor β2 and β3 subunits. The mechanism of its pro-convulsive action may be related to excessive activation of GABA ergic β2 receptors located on GABA ergic interneurons [7]. Another proposed mechanism is its effect on KCC2 co-transporter, chloride dominating $GABA_A$ influx currents, and excitatory response to GABA [7] Recent studies of epileptogenic properties of etomidate in patients undergoing electroconvulsive therapy showed longer seizure duration measured by EEG and motor activity compared to other anesthetics. It is considered the drug of choice in patients undergoing electroconvulsive therapy owing to its ability to induce high quality spikes on EEG [56].

Ketamine: Ketamine acts on NMDA glutamate receptor as a noncompetitive antagonist. Although some cases of ketamine induced seizures have been published in animals, multiple case reports suggest ketamine as an effective second-line strategy in the management of status epilepticus. It is suggested that during status epilepticus there is a down regulation of synaptic GABA receptors while NMDA receptor expression increases. These changes may lead to prolonged SE due to a decreased response to GABA agonists and increased glutamate stimulation respectively. Besides the ability of ketamine to act independently of GABA receptors and to antagonize NMDA receptors, ketamine therapy produces less hypotension. Further studies are required to determine the optimal use of ketamine in seizure management [57,58].

Methohexital's: Methohexital's epileptogenic potential and ability to induce interictal spiking has been used to localize the epileptic focus during intra operative electrocorticography and epilepsy surgery. Methohexial has been shown to increase the duration of seizures in electroconvulsive therapy. During preoperative intracarotid barbiturate testing, performed occasionally for language and memory lateralization, methohexital injection may confer a higher risk of seizures in epileptic patients [59].

Opioids: Multiple mechanisms have been suggested to explain the epileptogenic effects of opioid analgesics. Neuro excitatory activity has been described for hydromorphone, morphine, meperidine, remifentanil and fentanyl [60,61]. Experimental models suggest that neuronal excitation is mediated via selective stimulation of κ and μ opioid receptors in a dose-dependent manner, decreased GABA ergic interneuronal inhibition of pyramidal neurons [62] and inhibition of hyperpolarization-activated K^{+} currents [7]. The ability of opioids to increase the epilepticform activity and duration of the seizure is routinely being used to localize the epileptogenic zone in patients undergoing electroconvulsive therapy and surgery for seizures [62,63].

In the perioperative setting, opioid-induced agitation, myoclonus, and seizures should be avoided. The excitatory activity of opioids is concentration-dependent. Low opioid doses with addition of adjuvant medications may help to prevent or decrease the incidence of perioperative seizures. Preventive and treatment options for opioid-induced seizure activity include facilitation of drug clearance, administration of benzodiazepines and opioid rotation [64].

Neurosurgery

Brain tumors

Up to 60% of patients diagnosed with brain tumors develop seizures after diagnosis or already suffer from it at the time of presentation [65]. In patients with high risk of seizure development for example patients with gliomas, AED treatment with initial monotherapy at minimal effective dose is recommended. First-line agents include valproic acid, phenytoin, and levetiracetam. In a case of treatment failure, alternative AEDs, combination and / or adjunct therapy are indicated [66].

Perioperative antiepileptic prophylaxis in patients with a brain tumor and without a prior history of seizures remains controversial. In 2009, a Cochrane review [65] estimated the effectiveness and rates of adverse events with AED-based (phenobarbital, phenytoin, and divalproex) seizure prophylaxis in patients diagnosed with brain tumors. They found no difference in first seizure prevention between intervention and control groups. However, an increased risk of adverse events, nausea, skin rash, sore gums, myelo suppression, vertigo, blurred vision, tremor, and gait unsteadiness, was found in patients receiving AEDs (Number Needed to Harm 3; RR 6.10, 95% CI: 1.10-34.63; P = 0.046).

The benefits of routine antiepileptic prophylaxis for neurosurgical patients are not obvious. Wu [67] recently conducted a prospective trial to study phenytoin as a prophylactic antiepileptic drug versus placebo in patients undergoing brain tumor resection. Patients received the investigational drug for 7 days after the surgery. The trial was terminated early after an interim analysis demonstrated no clinically significant difference in the incidence of seizures between the prophylaxis and the control groups (p=0.51) or the incidence of early seizures between both groups (p=0.62). The authors concluded that the overall incidence of seizures is low in patients undergoing brain tumor surgery. Furthermore, there was a significantly higher rate of adverse events in the phenytoin group (p<0.01). Future well designed prospective studies may help to define the subgroup of patients that will benefit from prophylactic antiepileptic therapy [65].

Subarachnoid hemorrhage

The estimated incidence of seizures in patients with aneurysmal subarachnoid hemorrhage (SAH) is 5-8%. Up to 26% of seizures occur during the acute phase [26]. Patients at higher risk include those with cerebral infarcts, primary lesions located in the territory of the middle cerebral artery, hydrocephalus and intraparenchymal hematomas [68]. Multiple studies have demonstrated unfavorable outcomes in stroke patients receiving AED prophylaxis. In 2009 Resengart [68] analyzed 3552 patients with SAH. Among them, up to 65% received AEDs prophylaxis, phenytoin being the most commonly prescribed medication (52.8%). The patients who received prophylactic AED showed a higher risk of unfavorable 3-month outcome. Naidech [69,70] also linked phenytoin prophylaxis with poor cognitive and functional outcome.

Chumnanvej and colleagues [46] conducted a retrospective analysis of 453 patients and showed that a 3-day phenytoin prophylaxis prevented seizures in cases of SAH. In contrast to previous reports, they found a significant reduction in the complication rate with prophylactic therapy (p=0.002).

According to the Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage, Special Writing Group of the Stroke Council, American Heart Association (2009) [71], administration of prophylactic anticonvulsants may be considered in the immediate posthemorrhagic period (Class IIb, Level of Evidence B). However, the routine long-term use of anticonvulsants is not recommended (Class III, Level of Evidence B) but may be considered for patients with risk factors such as prior seizures, parenchymal hematomas, infarcts, or middle cerebral artery aneurysms (Class IIb, Level of Evidence B).

SAH-induced seizures must be recognized by the anesthesia care team as an indicator of severe SAH. All available risk factors should be taken into consideration to assess the potential benefits and risks of prophylactic anti-seizure therapy in patients diagnosed with aneurysmal SAH.

Brain stimulation

Cortical stimulation is essential in neurosurgical tumor resection. Intra operative mapping of the motor cortex and descending cerebrospinal pathways helps to preserve the motor function and avoid inadvertent trauma to the brain. Szelényi [72] showed that stimulation-associated seizures are a common occurrence with an incidence of 9.5% with 60-Hz stimulation and 1.2% with the train-of-five technique (p<0.001). According to the authors, stimulation-associated seizure risk is not affected by previous symptomatic epilepsy.

Seizures are less likely with brief high-frequency pulse trains and have not been reported with single pulses [73]

Stimulation-induced seizures are mostly self-terminating. However, any focal seizure developing after electrical stimulation can be effectively treated with topical application of cold Ringer's lactate solution or IV administration of barbiturates. [Sartorius and Berger, as cited in [72]]. Increases in post-discharge activity may be indicative of impending seizure, and will justify interruption of direct cortical stimulation.

Traumatic brain injury

Posttraumatic epilepsy is one of the most common causes of acquired epilepsies. The likelihood of posttraumatic seizures (PTS) increases with the severity of the injury. Devastating lesions of brain parenchyma, such as intracranial hemorrhage and SAH, increase the risk of seizures. The incidence of early posttraumatic seizures (<7days) varies between 2.1-16.3%, and the risk of late posttraumatic seizures ranges from 2.1% to 25.3% [53].

Seizures increase local and systemic metabolic requirements, causing hyperemia, tissue hypoxia and release excitatory neurotransmitters. It may significantly compromise respiration and airway patency, and in refractory cases, intracranial hypertension may develop. Thus, development of clinical seizures in patients suffering from severe TBI justifies early intervention to prevent progressive metabolic derangement and further tissue injury [74].

The American Academy of Neurology and Brain Trauma Foundation recommend using prophylactic phenytoin or carbamazepine during the first 7 days following severe TBI [75]. However, such therapy is not recommended for late PTS prophylaxis [75]. The major advantage of phenytoin is the lack of sedation in therapeutic doses which is beneficial in TBI patients requiring frequent neurological assessment. The risk of short-term side effects of phenytoin is considered to be low [76].

Levetiracetam is an alternative to phenytoin for PTS prophylaxis. Recent studies suggest that the drug has an equivalent prophylactic potential [77] although it can induce epilepticform activity on EEG [78,79].

Conclusion

The risk for development of perioperative seizures increases with fluctuations in AED intake and with many precipitating factors like hyperventilation, fever, electrolytic abnormalities, intra operative manipulations (transcranial stimulation) and other factors [20]. In high risk patients, epileptogenic properties of commonly used anesthetic drugs should be taken into consideration, as well as the possibility of adverse pharmacological interactions [7,25]

EEG is diagnostic for seizures and helps adjust therapy based on the individual requirements of each patient. Intraoperative electrocorticographic monitoring allows for identification of the epileptogenic foci during epilepsy surgery as well as safer and more radical resection of tumors located in highly eloquent cortical regions.

The rationale for routine antiepileptic prophylaxis in neurosurgery is debatable, and more research is required to identify the patients who will benefit from such therapy. Antiepileptic prophylaxis is indicated early in severe TBI, while prophylactic AED administration is generally not recommended in patients with brain tumors, SAH, or TBI during the later phase of treatment [80].

Perioperative seizures may occur in patients with or without any history of epilepsy. Anesthesiologists should be familiar with the pathophysiology, risk factors and management strategies of perioperative seizures and should be able to undertake appropriate prophylactic measures in high risk patients.

Disclosure

The authors have not received any funding and have no conflict of interests related to this publication.

References

1. Huff JS, Fountain NB. Pathophysiology and definitions of seizures and status epilepticus. Emerg Med Clin North Am. 2011; 29: 1-13.
2. Perks A, Cheema S, Mohanraj R. Anaesthesia and epilepsy. Br J Anaesth. 2012; 108: 562-571.
3. World Health Organization. Epilepsy. 2012.
4. Kingsley RE. Electromechanical Signaling. In Concise text of neuroscience. 2nd edn. Lippincott Williams & Wilkins. 2000; 91-145.
5. Kingsley RE. Electrical Signaling. In the Concise text of neuroscience. Chap 3. Lippincott Williams &Wilkins. 2000.
6. Schwartzkroin PA, Baraban SC, Hochman DW. Osmolarity, ionic flux, and changes in brain excitability. Epilepsy Res. 1998; 32: 275-285.
7. Voss LJ, Sleigh JW, Barnard JP, Kirsch HE. The howling cortex: seizures and general anesthetic drugs. Anesth Analg. 2008; 107: 1689-1703.
8. Pitkänen A, Lukasiuk K. Mechanisms of epileptogenesis and potential treatment targets. Lancet Neurol. 2011; 10: 173-186.
9. Maranhão MV, Gomes EA, de Carvalho PE. Epilepsy and anesthesia. Rev Bras Anestesiol. 2011; 61: 232-24, 242-54, 124-36.
10. Goldberg EM, Coulter DA. Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. Nat Rev Neurosci. 2013; 14: 337-349.
11. Epilepsy Foundation of Kentuckiana
12. Patel PM, Drummond JC. Cerebral Physiology and the Effects of Anesthetic Drugs. 7th edn. Miller's Anesthesia.
13. Voss LJ, Ludbrook G, Grant C, Sleigh JW, Barnard JP. Cerebral cortical effects of desflurane in sheep: comparison with isoflurane, sevoflurane and enflurane. Acta Anaesthesiol Scand. 2006; 50: 313-319.
14. Kotagal P, Yardi N. The relationship between sleep and epilepsy. Semin Pediatr Neurol. 2008; 15: 42-49.
15. Gowers WR. Epilepsy and Other Chronic Convulsive Diseases. London: Williams Wood. 1885; 1.
16. Janz D. Epilepsy and the sleeping-waking cycle. Vinken PJ, Bruyn GW, editors. In: The Epilepsies, Handbook of Clinical Neurology, Amsterdam: North-Holland. 1974; 15: 457.
17. JANZ D. The grand mal epilepsies and the sleeping-waking cycle. Epilepsia. 1962; 3: 69-109.
18. Brown DL, Ransom DM, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth Analg. 1995; 81: 321-328.
19. Murdoch D. Mechanisms of status epilepticus: an evidence-based review. Curr Opin Neurol. 2007; 20: 213-216.
20. Niesen AD, Jacob AK, Aho LE, Botten EJ, Nase KE, Nelson JM, et al. Perioperative seizures in patients with a history of a seizure disorder. Anesth Analg. 2010; 111: 729-735.
21. Akavipat P, Rungreungvanich M, Lekprasert V, Srisawasdi S. The Thai Anesthesia Incidents Study (THAI Study) of perioperative convulsion. J Med Assoc Thai. 2005; 88: S106-112.
22. Benish SM, Cascino GD, Warner ME, Worrell GA, Wass CT. Effect of general anesthesia in patients with epilepsy: a population-based study. Epilepsy Behav. 2010; 17: 87-89.
23. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. Lancet Neurol. 2003; 2: 473-481.
24. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. Lancet Neurol. 2003; 2: 347-356.
25. Kofke WA. Anesthetic management of the patient with epilepsy or prior seizures. Curr Opin Anaesthesiol. 2010; 23: 391-399.
26. Perucca E. Clinically relevant drug interactions with antiepileptic drugs. Br J Clin Pharmacol. 2006; 61: 246-255.
27. Hauser WA, Hesdorffer DC. Epilepsy: frequency, causes, and consequences. New York: Demos Publications; 1990.
28. Wichards WS, Schobben AF, Leijten FS. Perioperative substitution of anti-epileptic drugs. J Neurol. 2013; 260: 2865-2875.
29. Badawy RA, Curatolo JM, Newton M, Berkovic SF, Macdonell RA. Sleep deprivation increases cortical excitability in epilepsy: syndrome-specific effects. Neurology. 2006; 67: 1018-1022.
30. Placidi F, Zannino S, Albanese M, Romigi A, Izzi F, Marciani MG, et al. Increased cortical excitability after selective REM sleep deprivation in healthy humans: a transcranial magnetic stimulation study. Sleep Med. 2013; 14: 288-292.
31. Scalise A, Desiato MT, Gigli GL, Romigi A, Tombini M, Marciani MG, et al. Increasing cortical excitability: a possible explanation for the proconvulsant role of sleep deprivation. Sleep. 2006; 29: 1595-1598.
32. Benbadis SR, Kotagal P, Rothner AD. Supplementary motor area seizures presenting as stumbling episodes. Seizure. 1995; 4: 241-244.
33. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav. 2005; 6: 85-89.
34. Fang PC, Chen YJ, Lee IC. Seizure precipitants in children with intractable epilepsy. Brain Dev. 2008; 30: 527-532.
35. Constant I, Seeman R, Murat I. Sevoflurane and epileptiform EEG changes. Paediatr Anaesth. 2005; 15: 266-274.
36. Holmes MD, Dewaraja AS, Vanhatalo S. Does hyperventilation elicit epileptic seizures? Epilepsia. 2004; 45: 618-620.

37. Yli-Hankala A, Vakkuri A, Särkelä M, Lindgren L, Korttila K, Jäntti V. Epileptiform electroencephalogram during mask induction of anesthesia with sevoflurane. Anesthesiology. 1999; 91: 1596-1603.

38. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part II). Anesth Analg. 1990; 70: 433–444.

39. Modica PA, Tempelhoff R, White PF. Pro- and anticonvulsant effects of anesthetics (Part I). Anesth Analg. 1990; 70: 303–315.

40. Kopp SL, Wynd KP, Horlocker TT, Hebl JR, Wilson JL. Regional blockade in patients with a history of a seizure disorder. Anesth Analg. 2009; 109: 272-278.

41. Greensmith JE, Murray WB. Complications of regional anesthesia. Curr Opin Anaesthesiol. 2006; 19: 531-537.

42. Kopp SL, Wynd KP, Horlocker TT, Hebl JR, Wilson JL. Regional blockade in patients with a history of a seizure disorder. Anesth Analg. 2009; 109: 272-278.

43. Kopp SL, Wynd KP, Horlocker TT, Hebl JR, Wilson JL. Regional blockade in patients with a history of a seizure disorder. Anesth Analg. 2009; 109: 272-278.

44. Faccenda KA, Finucane BT. Complications of regional anaesthesia Incidence and prevention. Drug Saf. 2001; 24: 413-442.

45. Weinberg GL. Treatment of local anesthetic systemic toxicity (LAST). Reg Anesth Pain Med. 2010; 35: 188-193.

46. Chumnanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. Neurosurgery. 2007; 60: 99-102.

47. Liu SS, Lin Y. Local anesthetics, in Paul G. Barash, Bruce F. Cullen, Robert K. Stoelting, Michael Cahalan M. Christine Stock: Clinical Anesthesia. 6th edn. Philadelphia: Lippincott Williams & Wilkins, 2009; 542.

48. Jääskeläinen SK, Kaisti K, Suni L, Hinkka S, Scheinin H. Sevoflurane is epileptogenic in healthy subjects at surgical levels of anesthesia. Neurology. 2003; 61: 1073-1078.

49. Constant I, Seeman R, Murat I. Sevoflurane and epileptiform EEG changes. Paediatr Anaesth. 2005; 15: 266-274.

50. Akeson J, Didriksson I. Convulsions on anaesthetic induction with sevoflurane in young children. Acta Anaesthesiol Scand. 2004; 48: 405-407.

51. San-juan D, Chiappa KH, Cole AJ. Propofol and the electroencephalogram. Clin Neurophysiol. 2010; 121: 998-1006.

52. Martella G, De Persis C, Bonsi P, Natoli S, Cuomo D, Bernardi G. Inhibition of persistent sodium current fraction and voltage-gated L-type calcium current by propofol in cortical neurons: implications for its antiepileptic activity. Epilepsia. 2005; 46: 624-635.

53. Lowenstein DH. Epilepsy after head injury: an overview. Epilepsia. 2009; 50 Suppl 2: 4-9.

54. Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol. 2011; 10: 922-930.

55. Shearer P, Riviello J. Generalized convulsive status epilepticus in adults and children: treatment guidelines and protocols. Emerg Med Clin North Am. 2011; 29: 51-64.

56. Hoyer C, Kranaster L, Janke C. Sartorius A. Impact of the anesthetic agent ketamine, etomidate, thiopental, and propofol on seizure parameters and seizure quality in electroconvulsive therapy: a retrospective study. Eur Arch Psychiatry Clin Neurosci. 2014; 264: 255-261.

57. Abend NS, Dlugos DJ. Treatment of refractory status epilepticus: literature review and a proposed protocol. Pediatr Neurol. 2008; 38: 377-390.

58. Kramer AH. Early ketamine to treat refractory status epilepticus. Neurocrit Care. 2012; 16: 299-305.

59. Loddenkemper T, Möddel G, Schuele SU, Wyllie E, Morris HH 3rd. Seizures during intracarotid methohexital and amobarbital testing. Epilepsy Behav. 2007; 10: 49-54.

60. Fodale V, Schifilliti D, Praticò C, Santamaria LB. Remifentanil and the brain. Acta Anaesthesiol Scand. 2008; 52: 319-326.

61. Tempelhoff R, Modica PA, Bernardo KL, Edwards I. Fentanyl-induced electrocorticographic seizures in patients with complex partial epilepsy. J Neurosurg. 1992; 77: 201-208.

62. Saboory E, Derchansky M, Ismaili M, Jahromi SS, Brull R, Carlen PL, et al. Mechanisms of morphine enhancement of spontaneous seizure activity. Anesth Analg. 2007; 105: 1729-1735.

63. Akcaboy ZN, Akcaboy EY, Yigitbasł B, Bayam G, Dikmen B, Gogus N et al. Effects of remifentanil and alfentanil on seizure duration, stimulus amplitudes and recovery parameters during ECT. Acta Anaesthesiol Scand. 2005; 49: 1068-1071.

64. Thwaites D, McCann S, Broderick P. Hydromorphone neuroexcitation. J Palliat Med. 2004; 7: 545-550.

65. Tremont-Lukats IW, Ratilal BO, Armstrong T, Gilbert MR. Antiepileptic drugs for preventing seizures in people with brain tumors. Cochrane Database Syst Rev. 2008; CD004424.

66. Englot DJ, Berger MS, Chang EF, Garcia PA. Characteristics and treatment of seizures in patients with high-grade glioma: a review. Neurosurg Clin N Am. 2012; 23: 227-235.

67. Wu AS, Trinh VT, Suki D, Graham S, Forman A, Weinberg JS, et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. J Neurosurg. 2013; 118: 873-883.

68. Rosengart AJ, Huo JD, Tolentino J, Novakovic RL, Frank JI, Goldenberg FD, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. J Neurosurg. 2007; 107: 253-260.

69. Naidech AM, Kreiter KT, Janjua N, Ostapkovich N, Parra A, Commichau C, et al. Phenytoin exposure is associated with functional and cognitive disability after subarachnoid hemorrhage. Stroke. 2005; 36: 583-587.

70. Lanzino G, DÙrso PI, Suarez J. The Participants in the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Seizures and anticonvulsants after aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011; 150: 247-256.

71. Bederson JB, Connolly ES, Batjer HH Jr, Dacey RG, Dion JE, Diringer MN, et al. Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage: A Statement for Healthcare Professionals from a Special Writing Group of the Stroke Council, American Heart Association. Stroke. 2009; 40: 994-1025.

72. Szelényi A, Joksimovic B, Seifert V. Intraoperative risk of seizures associated with transient direct cortical stimulation in patients with symptomatic epilepsy. J Clin Neurophysiol. 2007; 24: 39-43.

73. Macdonald DB, Skinner S, Shils J, Yingling C; American Society of Neurophysiological Monitoring. Intraoperative motor evoked potential monitoring - a position statement by the American Society of Neurophysiological Monitoring. Clin Neurophysiol. 2013; 124: 2291-2316.

74. Arndt DH, Lerner JT, Matsumoto JH, Madikians A, Yudovin S, Valino H et al. Subclinical early posttraumatic seizures detected by continuous EEG monitoring in a consecutive pediatric cohort. Epilepsia. 2013; 54: 1780-1788.

75. The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Role of antiseizure prophylaxis following head injury. J Neurotrauma. 2000; 17: 549-553.

76. Debenham S, Sabit B, Saluja RS, Lamoureux J, Bajsarowicz P, Maleki M et al. A critical look at phenytoin use for early post-traumatic seizure prophylaxis. Can J Neurol Sci. 2011; 38: 896-901.

77. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. Neurocrit Care. 2010; 12: 165-172.

78. Jones KE, Puccio AM, Harshman KJ, Falcione B, Benedict N, Jankowitz BT. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. Neurosurg Focus. 2008; 25: E3.

79. Inaba K, Menaker J, Branco BC, Gooch J, Okoye OT, Herrold J, et al. A

prospective multicenter comparison of levetiracetam versus phenytoin for early posttraumatic seizure prophylaxis. J Trauma Acute Care Surg. 2013; 74: 766-771.

80. Klimek M, Dammers R. Antiepileptic drug therapy in the perioperative course of neurosurgical patients. Curr Opin Anaesthesiol. 2010; 23: 564-567.

Austin J Anesthesia and Analgesia - Volume 2 Issue 4 - 2014
ISSN : 2381-893X | www.austinpublishinggroup.com

Citation: Zuleta-Alarcon A, Castellon-Larios K, Moran KR, Soghomonyan S, Kurnutala LN and Bergese SD. Anesthesia-Related Perioperative Seizures: Pathophysiology, Predisposing Factors and Practical Recommendations. Austin J Anesthesia and Analgesia. 2014;2(4): 1026.