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Anesthetic Considerations for awake Craniotomy in Epilepsy Surgery

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INTRODUCTION

Awake craniotomy represents an essential option for surgical procedures requiring a patient's participation in defining the extent of resection. This includes excision of epileptogenic foci, performed in patients with medically refractory epilepsy. Approximately 2 million Americans with a diagnosis of epilepsy are treated with Antiepileptic Drugs **(AEDs)**, of these 20 percent continue to have seizures accounting for over 75 percent of epilepsy treatment cost in the United States. Surgical intervention can possibly eliminate epilepsy for patients' refractory to medical treatment; however, only a small percentage of potential candidates are referred to epilepsy-surgery centers.

Excision of epileptogenic foci can be performed under general anesthesia or by awake craniotomy, either with local anesthesia and sedation or in an asleep-awake-asleep technique. The anesthetic plan for surgery is largely influenced by the location of the seizure foci and intraoperative cortical mapping. Thesefoci may also be localized preoperatively using noninvasive studies such as MRI, PET and SPECT; however, video-EEG recording is the most important test to define a surgical target before surgery. Localization of epileptogenic foci during surgery can be achieved using intraoperative Electrocorticography **(EcoG)**. EcoG is an invasive electrophysiological modality of directly recording cortical potentials from the surface of the brain. EcoG may be used routinely to localize seizure foci or when preoperative tests fail to do so conclusively. Thus, general anesthesia may be considered if seizure foci are localized with confidence preoperatively and/or cortical mapping is not required.

However, once cortical mapping is necessary or there is a desire to minimize the effects of general anesthetics on EcoG recordings, local anesthesia with sedation in an awake craniotomy is preferred over general anesthesia. Cortical mapping is performedwhen epileptogenic foci are located in close proximity to functionally important (i.e. speech and motor) regions of the cerebral cortex (termed eloquent). This is done by asking the patient to perform certain tasks while stimulating different areas of the brain, thus allowing mapping of the eloquent areas. The patient must therefore be awake and able to cooperate with surgical and anesthesia teams in order to map eloquent areas of the brain prior to lesion resection.

ADVANTAGES OF AWAKE CRANIOTOMY

Awake craniotomy offers several advantages over craniotomy performed under general anesthesia. It represents the relevance of surgical procedures that require patient participation to define the extent of resection. As discussed earlier, awake craniotomy utilizes intraoperative cortical mapping, dynamically testingneurological function. An awake patient provides constantneurologic feedback as a lesion is resected, maximizingchances of a complete resection while preserving neurologic function. This particularsurgery also minimizes the effects of anesthetics on intraoperative electrocorticography, and overall translates intoshorter hospital stays, which in turn decreased hospital expenditures. Awake craniotomy has also been shown to result in lower rates of postoperative anesthetic complications, such as nausea and vomiting. Unique advantages of awake craniotomy for epilepsy surgery are outlined in Table 1.

Table 1: Advantages of Awake Craniotomy.

- Allows for maximal tumor resection
- Accurate intraoperative electrocorticography recordings
- Shorter hospitalization and decreased hospital costs
- Lower rates of postoperative complications

CHALLENGES OF AWAKE CRANIOTOMY

Although awake craniotomy may be preferred over general anesthesia for several reasons, it also presents a multitude of challenges to the anesthesiologist. The anesthetic goal is to provide analgesia and sedation during periods of intense surgical stimulation, while providing conditions that allow the patientlucency during functional testing. Uncontrolled pain during head-holder placement, skin incision, craniotomy, and dura opening may cause hemodynamic instability, emotional distress, and loss of patient's cooperation. Mean while, excessive sedation may result in hypoventilation and hypoxemia, which are extremely hazardous to a patient with an intracranial lesion. An uncooperative, over sedated or agitated patient may require urgent induction of general anesthesia. Controlled ventilation or endotracheal intubations are exceedingly difficult in a patient positioned laterally under surgical drapes with the head immobilized in a head holder. In addition, the anesthesiologist must be aware of other potential complications of awake craniotomy, including unwanted head movement, seizures due to cortical stimulation as well as severe nausea or vomiting. Because many of these issues can be avoided with careful patient selection, the preoperative visit is imperative. The challenges of awake craniotomy are summarized in Table 2.

Table 2: Challenges of awake Craniotomy.

- Requires the patient to be awake and cooperative during functional testing
- Hemodynamic instability due to inadequate pain control
- Hypoventilation and hypoxemia due to excessive sedation
- Difficulty with controlled ventilation or endotracheal intubation due to patient positioning if general anesthesia is urgently required
- High incidence of seizures secondary to cortical stimulation
- Loss of cooperation due to oversedation, nausea/vomiting, or fatigue

PREOPERATIVE EVALUATION AND PREPARATION

The preoperative visit for the patient scheduled for awake craniotomy is of paramount importance, especially in the pediatric population. Because cooperation between the patient and surgical team is required during the operation, individuals should be selected carefully to maximize the potential for success. To avoid intraoperative issues with patient cooperation, it is important that the patient is motivated, mentally mature, and able to follow instructions. The preoperative interview also allows the anesthesiologist to discuss the specifics of intraoperative awakening

with the patient. As the thought of being awake during surgery is undoubtedly worrisome, the anesthesiologist must ensure the patient's complete comprehension regarding deep sedation during the initial and final parts of the operation, which also tend to be most painful. In addition, it should be stressed that the anesthesiologist would be at bedside throughout the procedure to monitor the patient and alleviate any pain or discomfort. Table 3 summarizes the objectives of the preoperative interview.

Table 3: The objectives of the preoperative visit.

- Identify a motivated patient with good psychological profile
- Establish a relationship of confidence and trust
- Inform the patient what to expect (e.g., detailed verbal description, video tape)
- Emphasize that a patient would be deeply sedated for the most painful episodes
- Reassure the patient that the anesthesiologist will be at bedside throughout the procedure
- Avoid premedication with long-acting sedatives

Patients presenting for epilepsy surgery are often on multiple Antiepileptic Drugs **(AEDs)**. Thus, it is important for the anesthesiologist to be familiar with AEDs, namelythe effects of anesthetic medications on seizure threshold, and the pharmacodynamics of AEDs and anesthetic medications. Phenytoin, phenobarbital and carbamazepine were the mainstay of AEDs for many years, but the past 30 years have shown many advances with newer drugs offering fewer side effects. Table 4 lists frequently used AEDs as well as their common side effects.

Table 4: Common Side Effects of Antiepileptic Drugs.

Drug (Trade Name)	Side Effects
Phenytoin (Dilantin)	Gingival hyperplasia, folate deficiency, peripheral neuropathy, blood dyscrasia, and rare hypersensitivity hepatitis
Phenobarbital	Sedation, folate deficiency, hepatitis (rare)
Valproic Acid (Depakote)	Tremor, thrombocytopenia, rare fatal hepatitis
Carbamazepine (Tegretol)	Elevated liver enzymes, leucopenia, rare aplastic anemia, ataxia
Clonazepam (Klonopin)	Muscle weakness, sedation
Oxcarbezepine (Trileptal)	Weight gain, hyponatremia, somnolence
Lamotrigine (Lamictal)	Rash, blood dyscrasia
Levetiracetam (Keppra)	Headache, asthenia
Topiramate (Topomax)	Anorexia, renal stones
Gabapentin (Neurontin)	Well tolerated
Zonisamide (Zonergan)	Weight gain, rare Steven-Johnson syndrome
Primidone (Mysoline)	Metabolized to Phenobarbital: less sedation

INTRAOPERATIVE ANESTHETIC MANAGEMENT

In many centers, a surgery which entails resection of a lesion situated in the eloquent area is a two-stage procedure. The first stage involves implantation of intracranial electrodes under general anesthesia. Epidural and depth electrodes can be inserted via burr holes, while insertion of grid electrodes over a large cortical surface area requires a full craniotomy with removal of a bone flap. Accurate placement of depth electrodes intraoperatively may require the preoperative placement of a stereotactic head frame under local anesthesia. Since the head-frame limits optimal head positioning for direct laryngoscopy, a fiberoptic endotracheal intubation may be required. Postoperatively, the patients are monitored in specialized units to map the seizure focus using a newly implanted grid (ECoG). The same grid is used to demarcate eloquent regions of the cortex. The second stage of the procedure entailsremoval of the electrodes and awake resection of the lesion.

Following placement of the subdural electrodes, AEDs are discontinued to increase seizure frequency for diagnostic purposes. Acute AED withdrawal can also lead to partial or generalized seizures, altered localization of seizure foci, increased interictal spiking rate, and in rare cases, status epilepticus orpostictal mental confusion. Thus, familiarity with seizure presentation and symptoms is of utmost importance in recognizing perioperative seizures.

Positioning

Undergoing electrocorticography, functional testing, craniotomy and resection while awake makes for a tumultuous and tiresome day for the patient. Thus, every effort should be made to assure patient comfort. Proper positioning, scalp block, and adequate local analgesic infiltration will facilitate patient tolerance of the operation. Since the left hemisphere usually controls language, the patient is routinely placed in a right semi-lateral position with a gel roll or blanket under the shoulder, ensuring proper padding. A urinary catheter should be placed during the asleep phase of the procedure to minimize patient discomfort. If a cranial fixation device is used, local analgesics should be injected near the pin sites. Surgical drapes need to be tented away from the patient's face to facilitate communication with providers and to allow visualization of brain-mapping, if so desired.

Anesthetic Techniques

The primary goal of anesthetic management during awake craniotomy is to have an alert, cooperative patient during cortical mapping. Of equal importance, the patient should also be comfortable throughout the procedure, which could last up to 8 hours. Drugs administered during the procedure should provide an adequate level of sedation and analgesia for bone flap removal, placement of the head holder and skin and dura opening, but must not interfere with functional testing or electrocorticography. Thus, various intraoperative management strategies have been proposed to achieve these goals.

The anesthetic techniques commonly used for the awake craniotomy include local analgesia (no sedatives), monitored conscious sedation, and asleep-awake-asleep approach. The current trend in is to use deep sedation or general anesthesia ("asleep") during the opening and closing phases of the procedures, only awakening the patient intraoperatively for cortical mapping ("awake"). This approach became popular with the introduction of short acting, titratable drugs, and more recently, monitors of sedation depth (i.e. BIS).

Airway management during the "asleep" phase of the procedure varies among institutions. Some allow the patients to spontaneously ventilate with supplemental oxygen and a nasal airway under deep sedation using propofol infusion. Others advocate controlling airway with an endotracheal tube or Laryngeal Mask Airway **(LMA)**.

The LMA has proven to be particularly useful for an asleep-awake-asleep craniotomy. With its ease of insertion even with semi-lateral patient positioning, and head immobilization in a cranial fixation device, the LMA has proven its value. Also, the airway is secured and ventilation can be controlled during deep levels of anesthesia, thereby preventing hypoventilation and hypercarbia. In retrospective analysis, hypoventilation and airway obstruction were less common using LMA compared to unsecured airways with intravenous sedation. If intubation is necessary for airway control, an endotracheal tube should be modified to allow for local analgesic delivery to the airway to prevent coughing or straining during intraoperative extubation. This can be achieved by attaching a pilot catheter that allows lidocaine to be injected around the endotracheal tube. After awake testing the patient is reintubated over a tube changer that was left in place during intraoperative extubation. The patient can also be reintubated fiberoptically. It is important to note that endotracheal intubation during a craniotomy may be extremely difficult due to limited airway access and sub-optimal head position.

Intraoperative Monitoring

Routine intraoperative monitors for an awake craniotomy consist of noninvasive blood pressure measurements, pulse oximetry, uremeter, electrocardiogram, and capnography. In addition, the author routinely uses an intra-arterial line for continuous blood pressure measurements. Although some experts advocate the use of invasive monitoring when clinical circumstances warrant (i.e. patients with a significant co-morbidity, procedures with a significant blood loss, such as arteriovenous malformation), we believe that most craniotomies are associated with a highly variable level of painful stimuli and, consequently, with a significant hemodynamic instability. Emergent hypertension is common to most intracranial procedures and should be treated aggressively, while postoperative hypertension is associated with a higher incidence of intracranial hemorrhage.

Anesthetic Agents

Many sedation techniques have been described for awake craniotomy. A combination of droperidol and opioids (termed neuroleptanalgesia) has been traditionally used to produce a state

of indifference, immobility, and analgesia. The combination is difficult to titrate because droperidol has a slow onset of action (6-8 min) and lasts up to 12 hours. Moreover, neuroleptanalgesia may promote a dysphoric feeling, adrenergic blockade, extrapyramidal symptoms, and anticholinergic effects. Also, the recent FDA "black box" warning related to fatal dysrhythmias associated with the drug led to almost complete abandonment of this technique.

Several reports have endorsed the use of propofol for sedation during awake craniotomy. The rapid onset and a fast redistribution of propofol offer flexibility and ease of titration. In addition, the use of propofol reduced the incidence of seizures and nausea/vomiting. However, oversedation and respiratory depression are an ever-present concern. Obesity was a consistent risk factor and a reason to require a secure airway. Other complications included hypotension, tachycardia, and seizures (rare).

A combination of propofol and remifentanil has been successfully used for the awake brain lesion resection.Remifentanil's context-sensitive half-life is less than 5 minutes and independent of infusion duration. These characteristics allow a rapid modulation of analgesia and sedation that is required during the course of the surgery. The adverse effects of remifentanil, however, are similar to those of all fentanyl congeners and include respiratory depression, oversedation, and nausea. Additional complications of this technique include intraoperative seizures, and disorientation, while one retrospective chart review of awake craniotomies under propofol-remifentanil anesthesia found an ever higher incidence of respiratory than with opioid alone.

Dexmedetomidine **(DEX)**, a highly specific alpha-2 adrenoreceptor agonist, has been recommended for use during awake craniotomy, as it does not suppress ventilation. The sedation produced by this drug class, unlike that by traditional sedatives such as benzodiazepines and propofol, does not depend primarily on activation of the Gamma-Aminobutyric Acid **(GABA)** system. Furthermore, the primary site of alpha-2 agonist sedative action does not appear to be the cerebral cortex, as would be the case with GABA-mimetic drugs. Perhaps because of a non-cortical site of action, alpha-2 agonists appear to engender a different type of sedation when compared to GABA-mimetic drugs. DEX produces an unusually cooperative form of sedation, where patients easily transition from sleep to wakefulness and task performance when aroused, falling back asleep when not stimulated. Moreover, disinhibition, cited as a common problem for propofol and the benzodiazepines, has not been described for DEX. It is possible that DEX appears to exert its sedative action at the locus coeruleus, or wakefulness and anxiety center, thus cognitive compromise and accompanying disinhibition is less prominent. This theory is consistent with healthy volunteer data indicating that cognitive integrity is well preserved in patients receiving the medication. Dexmedetomidine or propofol with remifentanil is the most commonly chosen regimen for seamless transition from asleep or sedated state to alertness and back intraoperatively.

Regional scalp blockade supplemented with field blocks are commonly used to reduce pain associated with the bone flap removal and dura opening. Techniques for regional analgesia are well

described and include blockade of the greater and lesser occipital, auriculotemporal, supraorbital, and zygomaticotemporal nerves. Bupivacaine 0.5% with epinephrine 1:200,000, 2.5 cc is usually injected at each site. In addition, approximately 40 cc of bupivacaine 0.33% with epinephrine 1:200,000 is injected along the incision line prior to commencing surgery. Ropivacaine, 0.5%, is less cardiotoxic, but has a pharmacological profile similar to that of bupivacaine, providing a good alternative. The regional block is done at least one hour prior to skin incision to allow maximal diffusion of anesthetic agent and minimize local anesthetic toxicity.

Table 5: Anesthetics commonly used in Awake Craniotomy.

Drug (s)	Advantages	Disadvantages
Droperidol/fentanyl	Cooperative patient	Slow onset of action, prolonged wakeup, FDA "black box" warning.
Propofol	Rapid onset and offset of action, good titratability, antiemetic effect	Respiratory depression, confusion, hypotension
Propofol/Remifentanil	Favorable pharmacokinetics (i.e. both drugs are short acting), blunted hemodynamic responses	Respiratory depression, hypotension, bradycardia
Dexmedetomidine	"Cooperative sedation", analgesia, minimal respiratory depression	Bradycardia, hypotension

A number of intraoperative problems may occur during the awake testing that necessitate an induction of general anesthesia (Table 6). Patients may become uncooperative due to excessive pain, anxiety or postural discomfort. Seizures may be triggered during electrical stimulation of the cerebral cortex leading to postictal confusion. Patients may become nauseated during temporal lobe and dura manipulation. Excessive sedation may alsolead to airway obstruction, hypoxia, hypercarbia, and inadequate operating conditions. Retrospective chart reviews of patients who have undergone awake craniotomy indicate that the main reasons behind conversion to general anesthesia and/or inadequate mapping were inadequate communication with the patient and/or intraoperative seizures. Failure of an awake craniotomy was associated with a compromised resection of the lesion and increased postoperative morbidity. Therefore, most anesthetic protocols include prophylaxis with antihypertensives, anticonvulsants, and antiemetics.

Table 6: Common Complications of an Awake Craniotomy.

- Respiratory depression
- Airway obstruction
- Aspiration
- Seizures and postictal confusion
- Excessive sedation interfering with testing
- Pain
- Dysphoria and anxiety
- Nausea and Vomiting

PATIENT ACCEPTANCE OF AWAKE CRANIOTOMY

Most studies suggest that patients tolerate awake craniotomy well and that they would tolerate this procedure again if necessary. Moreover, patients who underwent tumor removal under general anesthesia stated "they would be willing to undergo an awake craniotomy if their surgeon recommended it". In one recent study, about 87% of patients felt at ease during surgery while twenty four percent experienced some discomfort. Fifty six percent of patients reported no postoperative pain and eighty four percent of patients were content with timing of their discharge. The suggested areas for improvement include provision of written information, enhancing post-discharge support and allowing more time for discussion with the anesthesiologist.

SUMMARY

A number of studies suggest that aggressive resection of certain brain lesions (e.g. tumors, epileptic foci, etc.) can reduce neurologic deficits and prolong survival. When these lesions are located near eloquent areas, an awake craniotomy is a preferable way to maximize sparing of these highly functional regions of the brain. Modern awake craniotomy with functional brain mapping is a safe and well-tolerated approach for removal of lesions located in close proximity to these areas. Successful management of a patient undergoing an awake craniotomy requires familiarity with specific technical strategies including scalp block, advanced airway management, unconventional sedation protocol, and dexterous hemodynamic control during highly variable levels of stimulation. Currently, propofol with opioid (usually remifentanil) or, alternatively dexmedetomidine, are the most commonly used regimens for the awake craniotomy. The anesthesiologist must strive to attain a nexus of careful patient selection and extensive preoperative evaluation, thus forming the foundation for a seamless procedure.

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