**Anesthesia for Intraoperative Brain Mapping and Deep Brain Stimulation in Children**

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**Introduction to Brain Mapping**

Intraoperative brain mapping is an essential tool for neurosurgical procedures that involve lesions near functional or “eloquent” cortex. Eloquent areas include primary motor cortex, primary somatosensory cortex, language areas such as Broca and Wernicke’s, primary visual areas, angular gyrus, and mesial temporal regions for memory. When tumors or epileptic foci are located adjacent to these areas of functional cortex, both intraoperative electrophysiological monitoring and neurocognitive testing aid in aggressive resection of the pathological lesion while attempting to minimize neurological deficits.

The demands of electrophysiological monitoring have a profound effect on the anesthetic technique and agents that can be used during the procedure. In some instances the patient must be awake, such as when language testing is being performed. Electrocorticography and motor mapping can be performed under general anesthesia. Anesthetic goals include providing adequate surgical conditions, minimizing interference on intraoperative brain mapping, and maintaining patient comfort and safety throughout the procedure $^1$.

Any procedure involving brain mapping requires constant communication between the anesthesia team and surgeon. Preoperatively, this ensures that the entire team understands the surgical and anesthetic plan; and intraoperatively, neurophysiologic monitoring may require adjustments of anesthetic depth and anesthetic agents.

Adding to the difficulty of providing anesthesia to these patients is the lack of prospective, randomized trials comparing anesthetic techniques. Most evidence involves case-series or retrospective analysis. These studies can be confusing to an anesthesiologist naïve to the technical neurophysiology language, and the available studies form conclusions that are sometimes contradictory and inconsistent. This has resulted in protocols that vary by institution, and there is no consensus as to the optimal anesthetic technique for mapping procedures.

**Brain Mapping Techniques and Anesthetic Issues**

**Electrocorticography**

Electrocorticography is utilized during epilepsy surgeries to help identify abnormal EEG patterns that result from epileptogenic foci. These spike waves identify the seizure focus and allow precise resection. After resection, ECoG recordings can be performed again to ensure there is no further spike activity.
Most anesthetics affect intraoperative ECoG recordings, yet ECoG has successfully been performed with local anesthetic only, monitored anesthetic care, and general anesthesia. The commonly used agents, including volatile anesthetics, nitrous oxide, propofol, dexmedetomidine, and opioids will now be discussed in greater detail.

**Volatile Agents**

Volatile agents are commonly used for maintenance of general anesthesia when patients are not candidates for an awake craniotomy. However, their use still varies between institutions. For instance, sevoflurane has been shown to significantly reduce spike activity in epileptic patients at 1.5 MAC. However, this study was performed with patients under the effects of a fentanyl-based anesthetic. Fentanyl, like many opioids, has been shown to induce spike wave activity especially at high doses and may have increased spike activity at the baseline recordings for this study. Other studies have shown that sevoflurane can increase spike activity at higher concentrations, just prior to causing burst suppression. One can see the confusion as one agent, sevoflurane, has both epileptic and antiepileptic properties. Indeed, some institutions’ protocols avoid volatile agents altogether for fear that they may make reliable ECoG impossible, while others have attempted to use the epileptogenic properties of higher dose sevoflurane to localize seizure foci.

As shown by Kurita et al, sevoflurane’s ability to increase epileptiform activity may help in accurate resection of seizure foci. This study showed that ECoG at 0.5MAC sevoflurane were similar to recordings at ictal onset in the awake state, whereas at 1.5 MAC the ECoG recordings were more similar to the interictal period in the awake state. These interictal spikes correspond to “irritative” zones, whereas the ictal onset zone is the area where a seizure originates, and is the gold standard for localizing the epileptogenic zone, the smallest area needed to be resected to prevent further seizures. Higher sevoflurane levels may increase the “volume” of the recordings; however, may not increase the specificity of recordings which allow for resection of the smallest area necessary. Isoflurane, like sevoflurane, does appear to have the same epileptogenic potential, but not to the same degree. When used to maintain general anesthesia during ECoG monitoring, low levels of volatile anesthetic combined with higher dose opioid administration should not interfere with electrocorticography. At our institution, a dexmedetomidine infusion is commonly added to further lower the volatile agent needed to maintain an adequate level of anesthesia.

**Nitrous Oxide**

Nitrous oxide is often used in neurosurgical procedures. It has been shown to attenuation spike activity on ECoG especially when combined with volatile anesthetics. Despite this, nitrous oxide is a key part of many successful anesthetic protocols for epilepsy surgery. If used, it should not be combined with additional volatile agent, but rather with a liberal opioid administration. Opioid and nitrous oxide alone should not interfere with ECoG.
Of note, when patients already have an ECoG grid in place and are returning for resection, one should avoid using nitrous oxide until the dura is open to prevent pneumocephalus\textsuperscript{11}.

**Propofol**

As with sevoflurane, propofol has been shown to have both epileptic and antiepileptic properties that appear to be dose dependent. In low doses, propofol causes activation of EEG activity\textsuperscript{12,13}. It may even cause background activity, which may resemble epileptiform spiking\textsuperscript{14}. Larger doses lead to slowing and attenuation of spike activity, and at sufficient doses may lead to burst suppression and isoelectricity.

Both Herrick\textsuperscript{14} and Soriano\textsuperscript{15} showed that propofol did not affect the ability to obtain ECoG recordings if terminated at least 20 minutes prior to the start of ECoG. In light of the evidence, propofol should be discontinued prior to the start of ECoG.

**Dexmedetomidine**

Dexmedetomidine has minimal effect on ECoG and can be continued during recordings at low infusion rates\textsuperscript{16}. Because of its minimal respiratory depression, titratability, and ability to provide a cooperative, relaxed patient, dexmedetomidine is an excellent anesthetic for procedures that require a patient to be awake during a portion of the procedure. In addition, dexmedetomidine has been shown to provide hemodynamic stability during neurosurgical procedures\textsuperscript{17}. Modest reductions in blood pressure and heart rate are secondary to alpha-2 mediated adrenoreceptor activity. Reductions in circulating catecholamines result in a decreased incidence of tachycardia and hypertension during the perioperative period\textsuperscript{18}.

When used for maintenance of general anesthesia in combination with sufentanil, dexmedetomidine did suppress epileptiform activity\textsuperscript{19}. However, at Texas Children's Hospital high infusion rates of dexmedetomidine are typically used throughout brain mapping procedures with adequate ECoG recordings. We perform almost all these procedures under general anesthesia, and volatile agents and/or propofol are discontinued prior to ECoG. During the time of very “light” anesthesia, we supplement an opioid infusion with a dexmedetomidine infusion up to 1 mcg/kg/hr during electrocorticography, and have experienced no difficulty with neurophysiologic monitoring.

**Opioids**

Opioids are a mainstay of neuroanesthesia, and this is particular true with brain mapping procedures performed under general anesthesia. Because both volatile agents and propofol are discontinued or used in very low doses during brain mapping, there is potential for patient awareness, discomfort, and movement. Using large doses of short-acting opioids, one can maintain patient comfort, minimize the chance of patient movement, and not
affect brain mapping. During awake craniotomies, opioids help manage pain and discomfort that may occur despite an adequate scalp block with local anesthesia. Opiates do not alter seizure threshold or interictal spike activity. Moderate doses may result in muscle rigidity without EEG spiking, and extremely high doses will induce seizures. Patients with partial complex epilepsy given moderate doses of fentanyl, may experience increases in IIS that is not confined to the previously identified seizure foci. Alfentanil, an opioid with a shorter terminal half-life than fentanyl, has been used in bolus dosage to increase IIS activity for mapping foci. Remifentanil has a similar effect on IIS but its duration of action is much shorter than fentanyl, making it a better choice during awake craniotomy when ventilation cannot be mechanically supported.

Direct Cortical Stimulation

Direct cortical stimulation is the process of applying direct electrical stimulation to the cortex to help map eloquent areas responsible for motor function, language, vision, or sensation. Of these, only motor mapping may be performed under general anesthesia, as all other forms of mapping inherently require the patient to be awake to participate in testing and provide feedback while testing is being performed.

Motor mapping has few limitations on anesthetic agents, the main limitation being that cortical motor evoked potential (cMEPs), just like transcranial motor evoked potentials, are especially sensitive to volatile agents. Concentrations as low as 0.2-0.4 MAC have been shown to interfere with the ability to obtain adequate recordings. Intravenous agents and an awake anesthetic technique have less interference with motor mapping than the use of volatile agents and general anesthesia.

Motor mapping may be performed by the surgeon stimulating the cortex, and either the anesthesiologist or another member of the operating team assessing whether there is a visually observed motor response to a particular area, such as hand, foot, or face. This allows for mapping of the functional motor cortex during the operation so that it may be spared during resection.

For motor mapping to be performed, the patient cannot receive neuromuscular blocking agents.

Protocols for Brain Mapping Procedures

Awake or Asleep

The decision to perform either a general anesthetic or an awake craniotomy is complex, dependent on patient factors, institutional culture, surgeon preference, and anesthesia provider’s familiarity and comfort with various techniques. Some basic rules are evident that may make this decision a little more simple.

1. Language/Sensory testing can only be performed in an awake patient.
2. General anesthesia can be performed during ECoG and motor mapping.
3. Less anesthetic=less interference with neurophysiologic monitoring. So, if a patient is a candidate for an awake craniotomy, one should strongly consider it.
4. Do not perform an awake anesthetic on a patient that cannot be expected to cooperate.

This puts the anesthesiologist in a unique situation. On the one hand, what might be best for the surgical excision of the lesion (awake patient minimizing the chance of interference with neuromonitoring or neurological deficit), might not be best for the patient (traumatic experience from awake craniotomy or risks from lack of cooperation/movement).

While these rules are helpful, they ignore the complexity of the challenges involved in patient selection and the risk/benefit ratio inherent to the decision to perform an awake craniotomy or general anesthetic.

**Patient Selection**

Some institutions have absolute age cut-offs for performing an awake craniotomy. At our institution this does not exist and each case is taken on a case-by-case basis. Ideally, this decision involves many team members including surgeon, patient and parents, anesthesiologist, neurologist, and if possible someone with expertise in helping ascertain whether a patient is mature and capable of dealing with the procedure, such as a child psychiatrist. The importance of a thorough preoperative assessment and communication with the child cannot be overemphasized. The patient should have a clear understanding of what will be done, what he/she will experience, and reassured that they will be kept comfortable and safe. **Other issues which can make the decision more clear cut include comorbidities such as anxiety disorder, developmental delay, obesity, obstructive sleep apnea, and anything that would make conversion to general anesthesia challenging (difficult airway).** Such comorbidities are strong contraindications for performing an awake craniotomy.

**Risk/Benefit Ratio**

Adding to the difficult decision as to whether an awake or general anesthetic is more appropriate are the opposing risks and benefits of both techniques. To simplify, an awake anesthetic will benefit aggressive surgical excision of the tumor or seizure focus and allow for neurocognitive assessment to look for neurological deficits during resection. However, inherent to this technique is a certain loss of control of parameters that as anesthesiologists we are accustomed to maintaining. These include the ability to precisely control hemodynamics and ventilatory status (blood pressure control, secure airway, adjustment of CO₂). These parameters not only allow us to feel more comfortable, but they benefit surgical conditions by preventing a “tight brain” and ensuring patient cooperation. By performing a general anesthetic, the risk of interference with mapping techniques and neural deficits postoperatively may be increased. As one can see, the decision as to anesthetic choice can be quite complex, and requires communication between surgeon, anesthesiologist, and patient.
General Anesthesia

These are some examples of protocols for epilepsy surgery involving brain mapping with electrocorticography and cortical mapping under general anesthesia. The basic premise is to minimize anesthetic agents that may interfere with mapping procedures (volatile agents, propofol, benzodiazepines), yet still ensure patient safety and comfort. To do this, one should consider opioid administration as the backbone of the anesthetic technique.

**Protocol**

1. Minimal or no benzodiazepines for premedication

2. Opioid Infusion: Sufentanil 0.3-1mcg/kg/hr or Remifentanil 0.1-0.5mcg/kg/min (higher end of dose range during ECoG if volatile agent is turned off)

3. Volatile Agent <0.5 MAC. (At our institution, we attempt to completely discontinue volatile agent during ECoG)

   OR

   N₂O substituted for volatile agent

   OR

   Propofol infusion 100-250 mcg/kg/min (turn of prior 20-30 min prior to ECoG)

4. Motor mapping: no neuromuscular blockade, low volatile agent (0.2-0.4MAC) but may still attenuate cortical MEPs

5. Consider adding Dexmedetomidine 0.2-0.7 mcg/kg/hr for all variations of this protocol. This has minimal effect on ECoG recordings while helping deepen the anesthetic while other agents are discontinued.

6. Local Anesthetic: as general anesthesia during ECoG is a time when the patient may be “light” one should consider the scalp block just as important as during an awake craniotomy. This may lower the chance of patient discomfort or movement during this time.

**Methods to Improve ECoG**

Despite strict attention to anesthetic technique, sometimes poor signals are still present. The following are some drugs that have been used to increase epileptiform activity.

1. Methohexital 0.3-0.5 mg/kg
2. Etomidate 0.1-0.2 mg/kg
3. Alfentanil 50 mcg/kg
4. Remifentanil 2.5 mcg/kg
Awake Craniotomy

Two common methods for “awake craniotomy” include local with conscious sedation and the Asleep/Awake/Asleep (AAA) technique whereby general anesthesia is induced and then completely stopped during the time of mapping. The benefits of the AAA include shortened time needed for patient cooperation, increased depth of anesthesia during stimulating portions of the procedure (craniotomy), and more control of ventilation if an airway is in place. The disadvantages include the need to remove an airway during the procedure with limited access to reacquire it and the chance of patient bucking or delirium on awakening.

All combinations of anesthetic agents have been used successfully for all anesthetic techniques during awake craniotomy. The most popular agents for sedation include propofol and dexmedetomidine. These agents have been used alone or in combination with an opioid, with both fentanyl and remifentanil being the most popular. Volatile agents have also been used during the asleep portion of AAA techniques. When deciding on which agents to choose the following should be considered:

1. **Dexmedetomidine** causes minimal respiratory depression and has been shown to provide stable hemodynamics during craniotomy\(^\text{17}\). It also allows for smooth emergence from anesthesia and provides a cooperative patient that is easily arousable. Typical infusion rates during the asleep portion range from 0.5-1 mcg/kg/hr and during the awake portion from 0.1-0.5 mcg/kg/hr\(^\text{16}\).

2. **Propofol** is widely used during awake craniotomies because of its easy titratability. Its antiemetic properties are also beneficial for an awake patient. It does cause dose dependent ventilatory depression, and should be terminated 20-30 min prior to ECoG to prevent attenuation of spike activity\(^\text{15}\).

3. **Remifentanil** is easily titratable, allowing for rapid emergence from anesthesia. In this author’s opinion, these characteristics make it an ideal opioid for an AAA technique.

**Tips for Awake Craniotomy**

The success or failure of an awake craniotomy is dependent on many variables. However, with attention to detail and proper planning, most patients tolerate the procedure very well.

1. Local Anesthetic for scalp block is essential for patient comfort
2. Antiemetic: nausea from opioids, hypotension, hypovolemia, or from pulling on the dura may occur.
3. LMA for less straining/bucking on emergence
4. If endotracheal intubation, local anesthetic to trachea may prevent bucking/straining
5. BIS monitor may help with timing of removal of airway
6. Patient padding and positioning are crucial to patient comfort while awake

lications for Awake Craniotomies in Epilepsy Surgery\textsuperscript{35}

Anesthetic Issues with Deep Brain Stimulation (DBS)
An excellent review of the issues associated with DBS was written by Venkatraghavan\textsuperscript{36}. The most common indications for DBS in the pediatric population include movement disorders such as dystonia and Tourette’s. The challenge with DBS procedures concerns balancing the desire for an awake patient with a patient population that, because of their disease process, can be difficult to manage with an awake technique. Additionally, microelectrode recordings place many limitations on anesthetic agents.

Surgical Procedure
DBS involves the placement of electrodes into deep nuclei of the brain, with common targets including the globus pallidus internus (GP\textsubscript{i}) and subthalamic nuclei (STN). The procedure has two parts; the insertion of electrodes, and then internalization of the connecting wires and pacemaker. These can be done on the same day of surgery are separated into a two part procedure.

The first step is placement of the head frame, which in pediatric patients is usually done after induction of anesthesia. An MRI or CT is then performed, and for the initial surgery burr hole(s) are placed. If DBS insertion is bilateral, then bilateral
burr holes are made. After that, electrode placement begins. There are three methods by which proper electrode placement in the target nuclei is achieved. First is the frame-based imaging, which calculates depth and trajectory to get electrodes close to the target nuclei. Second, neurophysiological monitoring via microelectrode recordings further guides electrodes to the proper placement, and third is macrostimulation. Microelectrode recordings (MER) record electrical activity of individual neurons, and can distinguish between such tissue as globus pallidus externa, interna, and even the border between the two. MER is started about 10mm away from the target, and then the probe is inserting millimeter by millimeter as recordings are taken. This is a painstaking process, and may take hours. After this, macrostimulation of an awake patient occurs. The patient needs to be awake in order to express if there is alleviation of his/her symptoms and if there are any side effects during stimulation of the electrodes.

After the electrode is in place, the rest of the procedure involves placement of the wires and pacemaker (usually subclavicular) and this portion can be performed under any anesthetic technique.

With newer technology, some DBS insertions are being performed with just MRI based imaging. This cuts out the need for MER and an awake patient, and relieves many of the limitations on anesthetic agents.

**Anesthetic Agents and MER**

Anesthetic agents have a profound effect on MER, although the mechanisms by which are not completely understood. The effects appear dependent on both the target nuclei (GPI vs STN) and disease process\(^37,38,39\). MER is less affected in dystonia than in Parkinson's disease, and the GP\(_i\) is more sensitive to anesthetic agents than the STN. This may be due in part to higher GABA input to the GP\(_i\).

All GABA agents affect MER, despite this, propofol is the most widely used agent for these procedures. Agents with the least effect include the opioids remifentanil and fentanyl, as well as dexmedetomidine and ketamine, likely due to their non-GABAergic action\(^40,41\).

Volatile agents have also been used for DBS, yet most success has been shown in procedures where the STN was the target\(^42-44\). Unfortunately for the pediatric anesthesiologist, the primary target of dystonia patients is the GP\(_i\). Information as to acceptable concentrations of volatile agents, or whether one agent is preferable over another, is lacking.

MER have been successfully recorded with commonly used anesthetic agents such as propofol, volatile agents, opioids, ketamine, and dexmedetomidine. However, any agent with GABA agonism may attenuate MER. Benzodiazepines have been shown to abolish MER and propofol may attenuate MER. As such, our protocol for DBS relies heavily on combinations of dexmedetomidine, remifentanil, and ketamine. In our experience, these agents cause minimal interference with MER, and allow for an awake and comfortable patient during macrostimulation.
**Macrostimulation**

Macrostimulation involves an awake and cooperative patient. The benefit of performing macrostimulation is that it allows for confirmation of correct placement of electrodes by relief of symptoms and assessment of side-effects such as rigidity, nausea, pain, and parasthesia.

**Example of Protocol for DBS**

1. **Dexmedetomidine:** Bolus 1mcg/kg over 20-30 minutes
   Continuous infusion 4 mcg/cc, @ 0.1-2 mcg/kg/hour
2. **Ketamine:** Infusion @ 5 – 30 mcg/kg/min. 1-2 mg/kg/hr
3. **Remifentanil:** Continuous infusion , 50 mcg/cc, @ 0.05 – 0.1 mcg/kg/min asleep
   0.005 – 0.01 mcg/kg/min awake.
4. **Nicardipine:** 0.1 mg/cc @ 0.5 – 5.5 mcg/kg/min (systolic BP < 140, risk of parenchymal hemorrhage during insertion of electrodes).
5. **Decadron**
6. **Antiemetics**
7. Avoid all drugs that affect the GABA–receptor activity. AVOID Propofol, benzodiazepines, barbiturates and etomidate.

DBS can be a long, tedious procedure with a long period where the patient must be awake if macrostimulation must be performed. An asleep/awake/asleep technique is employed at our institution, but DBS has been performed under conscious sedation in pediatric patients with success using combinations of dexmedetomidine/propofol.

**REFERENCES**


