An Update of Neuroanesthesia for Intraoperative Brain Mapping Craniotomy

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The perioperative multidisciplinary team approach has probably been best exemplified by the care of awake craniotomy patients. Advancement in anesthesia and meticulous perioperative care has supported the safety and complexity of the surgical and mapping efforts in glioma resection. The discussions in this review will emphasize on anesthetic and perioperative management strategies to prevent complications and minimize their effects if they occur, including current practice guidelines in anesthesia, updates on the applications of anesthetic medications, and emerging devices. Planning the anesthetic and perioperative management is based on understanding the pharmacology of the medications, the goals of different stages of the surgery and mapping, and anticipating potential problems.

KEY WORDS: Neuroanesthesia, Awake craniotomy, Mapping

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Since the1980s, the recent approaches in awake craniotomy for function mapping in tumor resection have been strongly supported by modern neuroanesthesia with the advancement and safety in anesthesia practice guidelines, agents, equipment, techniques, and monitoring.[1-5] In the last 3 decades, compelling evidence has suggested improvement in overall patient survival and malignancy progression-free survival after maximizing brain tumor resection facilitated by intraoperative mapping of language and sensorimotor function in the eloquent areas.[6-9] As the mapping techniques evolved from cortical mapping to continuous subcortical mapping,[10-12] and new treatment paradigms were developed for the previously nonoperable insular gliomas through trans-sylvian or transcortical resection,[13] neuroanesthesia care has advanced to ensure patient safety and comfort in support of neurosurgical advances.

The aim of this article is to review recent updates of anesthesia care for awake craniotomy, with emphasis on anesthesia plans, monitoring, medication choices, and intraoperative challenges. The specific anesthesia planning, including design of sedative regimens, and any special airway support equipments, should always be created according to the individual patient characteristics, and tailored to the surgery and functional mapping needs.

ABBREVIATIONS: ASA, American Society of Anesthesiologists; **GA,** general anesthesia; **HFNC,** high-flow nasal cannula; **LMA,** laryngeal mask airway; **MAC,** monitored anesthesia care

PREOPERATIVE ASSESSMENT AND PREPARATION

In addition to a routine anesthesia preoperative evaluation, there are crucial factors and steps pertinent to a successful awake craniotomy, including appropriate patient selection and preparation, as well as strategic anesthetic planning tailored to each individual patient.

For selection criteria, the only absolute contraindications to performing awake craniotomy are patient refusal and inability to cooperate, for instance, confusion or decreased level of consciousness, baseline moderate to severe dysphasia or aphasia, language barrier, or inability to lay still. Challenging patient characteristics may include uncontrolled preoperative seizure, obesity with obstructive sleep apnea or features suggestive of difficult airway, chronic cough, severe gastroesophageal reflux, and history of anesthesia emergence delirium.[14] In addition, tumor pathologies, such as large lesions with marginal intracranial compliance, deep-seated tumors likely to require significant surgical retraction, and highly vascular lesions, may render surgical challenges in a spontaneously breathing awake patient.[13] Meanwhile, these newly developed surgical approaches for the previously nonoperable gliomas will demand extra attention from anesthesia care.

INTRAOPERATIVE ANESTHETIC TECHNIQUES

The American Society of Anesthesiologists (ASA) has clearly delineated the continuum of depth of sedation in their practice guidelines to provide the "Definition of General Anesthesia (GA) and Levels of Sedation/Analgesia" (https://www.asahq.org/standards-and-guidelines/continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedationanalgesia). The key difference is that as the level of anesthesia deepens, the need and level of airway intervention increase.

Various anesthetic management plans for awake resection of brain tumors have been described over the years.[15-17] Different anesthetic options reflect a continuum encompassing variable depth of anesthesia with periods of wakefulness during function mapping and testing. The 2 ends of the spectrum represent the "asleep-awake-asleep" technique involving GA and the monitored anesthesia care (MAC) practice, called "conscious sedation" by some, respectively. Under the "asleep-awake-asleep" plan, the patient undergoes GA before mapping, and wakes up intraoperatively for mapping and testing, and then GA or sedation for the tumor resection.[16] The MAC practice means that the patient is under mild to moderate, or at most in deep sedation, but arousable throughout the surgery.[15,17] During testing and resection, continuous support with communication and reassurance can help to alleviate the patient's anxiety. However, occasionally, an addition of mild sedation may be necessary. Various anesthesia techniques differ mainly in 3 aspects: (1) the depth of sedation outside the mapping period, (2) the choice of anesthetic agents, and (3) the method and level of airway support when the patient is not awake for the mapping.

The advantage of the "asleep-awake-asleep" technique is the control of the airway and ventilation during the painful parts of the surgery. The facilitation of brain relaxation through regulating carbon dioxide level in controlled ventilation is particularly useful in tumor surgery, if lesions are deep seated with significant mass effect or hypervascularity. Airway management during the asleep phase is commonly accomplished with supraglottic airways, such as laryngeal mask airway (LMA), but endotracheal tube or other airway devices have been used.[18] The main challenge of this technique occurs at the emergence from GA and extubation. The key to success is to promote a smooth transition from asleep to awake state. Short-acting anesthetic agents are discontinued to allow their hypnotic effects to wear off. Full precautions need to be exercised as for any postanesthesia recovery, such as emergence agitations, hemodynamic fluctuations, residue anesthetics, unrecognized pain and discomfort, shivering, or nausea vomiting. As with the MAC technique, a suitable airway plan is essential if emergent airway control is necessary thereafter.

The MAC technique aims to provide varying levels of sedation and quick transitions matching the surgical stimulation and mapping correspondingly. The strength of this technique is the avoidance of excessive airway intervention and any associated physiological disturbance such as agitation, coughing, or hypertension during emergence from anesthesia. However, oversedation, airway obstruction, and respiratory depression are more common. The challenge is to achieve a fine balance of sedation and respiratory function. In addition to continuous close coordination and high vigilance of the care team, the anesthesiologists are prepared to quickly adjust anesthesia agents to fine-tune the sedation level while providing appropriate support for the airway. A comprehensive plan for supporting or securing the airway emergently should be in place. Airway obstruction can be alleviated with insertion of nasopharyngeal airway.[19] But if the problem aggravates rapidly to critical situations, assisted ventilation with a supraglottic airway, or endotracheal tube intubation if indicated, can be life-saving.

A systemic review and meta-analysis comparing the outcome of 4 common complications from 47 studies in awake craniotomy, including 18 using "asleep-awake-asleep" technique with GA and 27 with MAC, did not reveal any difference in the outcome based on the anesthesia technique.[20] It concluded that both techniques are feasible and safe. The consensus on the choice of anesthesia plan seems to remain largely as a decision based on the local neurosurgery and anesthesia practice.[21,22]

PATIENT MONITORING

All patients undergoing awake craniotomy should be, at a minimum, monitored according to the ASA Basic Anesthetic Monitoring Standards (https://www.asahq.org/standards-and-guidelines/standards-for-basic-anesthetic-monitoring).

Specifically for the purpose of the intraoperative functional mapping, monitoring core temperature will guide efforts to maintain the patient's comfort with normal body temperature and help to ensure suboptimal low body temperature or shivering do not interfere with the mapping. Shivering can render unbearable stress to the patient, resulting in mapping difficulty, leading to prolonged testing and surgical procedure, possibly also tachycardia and hypertension from acute increase of sympathetic outflow.[23] Addition of dexmedetomidine to the anesthesia regimen may mitigate the problem, as it was shown to prevent shivering after anesthesia by changing the threshold.[24,25] Ondansetron has also been suggested to have anti-shivering effect by central inhibition of serotonin reuptake at the level of the preoptic anterior hypothalamic region.[26]

Additional monitoring the depth of anesthesia based on processed electroencephalography, such as the Bispectral Index, has been reported to assist in the titration of sedative drugs and to assess the return of consciousness and readiness to begin neurological testing, if the monitor strip is not obstructive to the surgical field for craniotomy.[27] However, it would not replace clinical assessment of the sedation and conscious level, which provides the most timely and valuable information. Recent evidence has further revealed that subjective methods for assessing wakefulness during awake craniotomies may be insufficient. The administration of objective measures of wakefulness just prior to language task administration may be needed to ensure that patients are ready for testing.[28]

ANESTHESIA AND ANALGESIA

To plan the anesthetic regimen for managing tumor resection with function mapping, both the benefits and downsides of the medications need to be taken into consideration (Table). The desirable pharmacokinetics of anesthetics for awake craniotomy would be quick onset and short duration, as titratability is the key given the dynamic nature and frequent transition of depth of anesthesia during the surgical procedure. Currently, most neurosurgical centers utilize intravenous agents for sedation and anesthesia in awake craniotomy.[5]

Midazolam is a common choice of anxiolytics for preparing the patient to start the course of anesthesia. It provides sedation, amnesia, and anticonvulsant effects. In addition to concerns of prolonged sedation and respiratory depression, excitation or disinhibition has been reported, especially in elderly patients.[29] More specific to the concerns of function mapping, Lin et al[30] have shown that midazolam might induce motor coordination deficits in both contralateral and ipsilateral limbs of patients with eloquent area glioma. In the same study, they have also demonstrated that the midazolam-induced neurological deficits could be reversed by flumazenil, an antagonist of midazolam's - gamma-aminobutyric acid (GABA) receptor, suggesting the possible mechanism of the exposure of abnormal brain connectivity by the anesthetic agent. This observed pharmacologic sedation strategy has led to the inspiration for a "brain stress test" to assess neural reserve in neurologically vulnerable patients for treatment stratifications.[31]

Propofol has become a widely utilized hypnotic for awake craniotomy since it became available in the 1990s.[2] It has a quick onset time within 1 min after a bolus dose, and its rapid clearance allows fast and clear emergence from sedation and GA. In some countries, target-controlled infusion system is used to deliver propofol to maintain the desired hypnotic level by adjusting its effect-site concentration.[32,33] Some patients may also experience euphoria, excitation, or disinhibition while on low-dose propofol.[29]

A newer agent, dexmedetomidine, has become available for use in awake craniotomy after approval for sedation in nonintubated patients by the FDA in 2008. It is a selective α2-agonist with dose-dependent sedative, anxiolytic, and analgesic effects.[34,35] Dexmedetomidine was associated with fewer respiratory adverse events. Its ability to promote sleep-like arousable sedation while maintaining respiratory drive makes it an attractive choice for conscious sedation. A randomized trial to compare the quality of intraoperative brain mapping and efficacy of sedation showed that dexmedetomidine was similar to propofol-remifentanil combination during awake craniotomy for supratentorial tumor resection.[5] Dexmedetomidine-based anesthesia and scalp block were reported to facilitate awake craniotomy without any requirement for urgent airway intervention or unplanned conversion to a full GA.[36] Compared to propofol, ventilation suppression is less by dexmedetomidine, although it does act synergistically with other hypnotic agents.[37]

Good local anesthesia of the scalp minimizes the need for excessive intravenous sedatives and its associated complications, such as the risk of altered mental status, airway compromise, or hypercapnia. Adequate regional anesthetization can be achieved with either a nerve scalp block[38] or in forms of local anesthetic field infiltration to provide a circumferential block of the incision sites and pin sites.[17] The regional nerve scalp block (Figure A) selectively anesthetizes the major nerves innervating the scalp covering the craniotomy incision, while the local field infiltration of circumferential scalp block (Figure B) is performed through injecting anesthetics surrounding the incision line. Both techniques have been shown to provide analgesia for surgical incision and reduce the need for other medication for pain control, such as the narcotics, while the comparison of superiority of efficiency remains in debate, especially in terms of postoperative pain control.[39,40] In either technique, the total dose of local anesthetic agents should not exceed the toxic dose.

INTRAOPERATIVE CHALLENGES

Airway Support

Airway support is crucial in the core anesthesia management for awake craniotomy. The incidence of airway- and ventilation-related complications has been reported to be 1.8% to 4%.[41] In various published series, however, there is a lack of uniformities in patient comorbidities, duration of mapping, anesthetic technique utilized, degree of expertise, and definition of complications. Airway obstruction and respiratory depression can be both a sign and a cause of patient obtundation. Hypercapnia and oxygen desaturation can raise the danger of cerebral hyperemia and secondary hypoxemic injury.

Preoperative evaluation of conventional airway comorbidities, such as obesity, obstructive sleep apnea, and history or signs of difficult airway, in addition to surgical challenges in resection of the complex glioma,[13] would promote extra preparation of strategies and plans of airway intervention in anticipation of the greater risk. To facilitate any potential emergency airway rescue when needed, mindful surgical positioning is important to avoid extreme rotation of the head and neck, and to leave adequate space for the mobility of the jaw and the lower chin to allow full mouth opening. For airway devices, nasal cannula is commonly used to deliver supplemental oxygen in MAC technique. For

TABLE. Comparison of Intravenous Sedative Agents Used in Awake Craniotomy for Function Mapping

Drug	Onset and duration	Effects	Cautions
Midazolam	Onset (IV bolus): 1 to 5 min; duration: <2 h	Anxiolytic, amnesia, anticonvulsant	Excitation or disinhibition, may induce motor discoordination, respiratory suppression
Propofol	Onset (IV bolus): 9 to 51 s; duration: 3 to 10 min	Hypnotic, amnesia, anticonvulsant, antiemetic, blunts airway reflexes	Respiratory suppression, hypotension, may induce euphoria, excitation or disinhibition
Dexmedetomidine	Onset (IV loading): 5 to 10 min; duration: 60 to 120 min	Hypnotic, anti-delirium, mild analgesia, no interference with electrocorticography	Respiratory suppression, hypotension or hypertension, bradycardia, slows gastrointestinal motility, prolonged duration
Remifentanil	Onset: 1 to 3 min; duration: 3 to 10 min	Analgesia	Respiratory suppression, bradycardia, nausea, may induce hyperalgesia

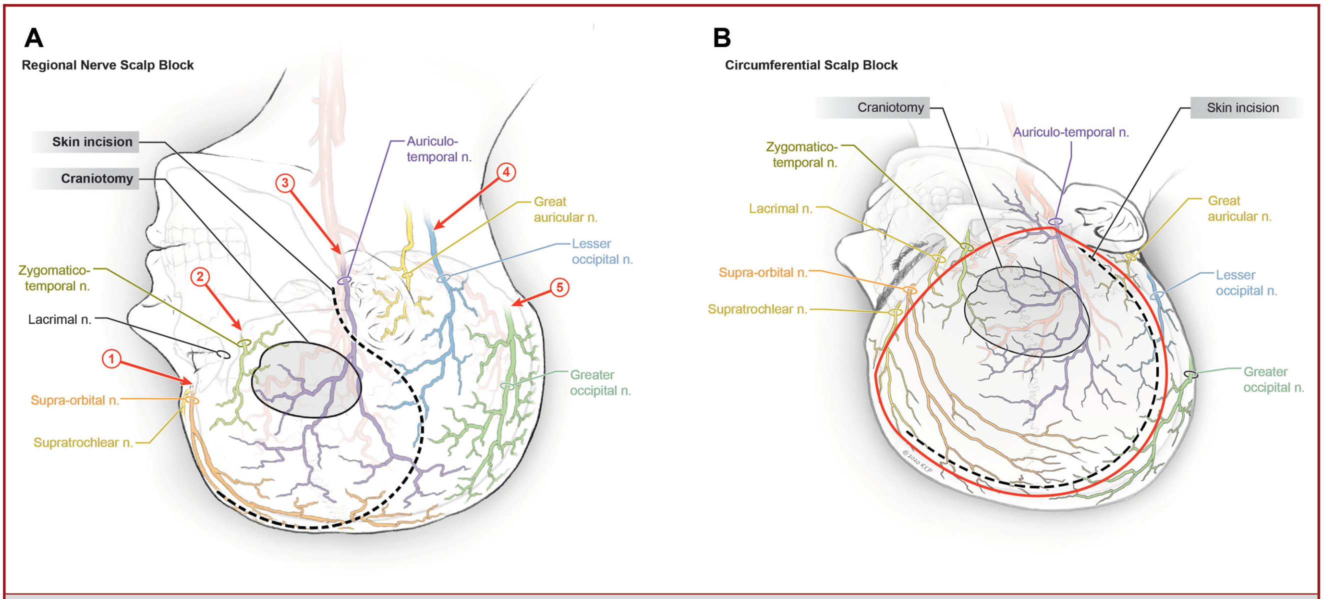

FIGURE. *Comparison of scalp block techniques.* **A**, *Regional nerve scalp block. Numbers 1 through 5 indicating the common nerves anesthetized for awake craniotomy: supraorbital, zygomaticotemporal, auriculotemporal, lesser occipital, and greater occipital nerves, respectively.* **B**, *Circumferential scalp block. The bold line in red color illustrating the infiltration of local anesthetics in the surgical field surrounding the incision line.*

minor airway obstruction or oxygen desaturation, gentle patient stimulation and jaw thrust, decreasing the anesthetic dose, and increasing oxygen supplementation may suffice. Nasal airways can be inserted to mitigate upper airway obstruction and are usually well tolerated.[19] High-flow nasal cannula (HFNC) is an air-oxygen blender supplying humidified air and oxygen mixture with control of FiO_2 from 0.2 to 1.0. It has recently been reported to facilitate awake craniotomy in the morbid obese patients.[42,43] HFNC is mainly favorable to oxygenation, while the control on ventilation or brain relaxation might be less optimal during tumor resection. If the patient continues to show inadequate respiratory effort, assistance by mask ventilation, or even a more sustained intervention by placement of a supraglottic airway, such as the LMA, may be needed. Recent advances in technology have brought innovations in the designs of supraglottic airway devices, aiming for quicker placement, guarding against aspiration, and including built-in intubation conduit to facilitate endotracheal tube intubation as further indicated.[44] There have been reports that newer devices, such as the i-Gel® (Intersurgical Ltd, Wokingham, United Kingdom)[45,46] or the Air-Q® Intubating Laryngeal Airways (ILA™, Cookgas® LLC, Mercury Medical, Clearwater, Florida) might be a choice for consideration in emergency airway rescue.[47] Using the fiberoptic bronchoscope, or LMA, as a conduit has been shown to be useful in awake intubation for difficult airways or when the head is fixated on a Mayfield (Integra LifeSciences) during craniotomy.[18,48]

Laryngospasm and aspiration can potentially occur, especially at emergence from anesthesia in "asleep-awake" approach or during emergency airway instrumentations. Every effort should be taken in anesthesia planning and management to prevent these complications from occurring. It is important to note that hypnotics and opioids act synergistically. Oversedation can lead to upper airway collapse and obstruction regardless of the choice of primary sedative agent. ASA has provided practice guidelines for management of the difficult airway for both ventilation and intubation algorithms.[49]

Intraoperative Seizures

Intraoperative seizure is a top cause of failed awake craniotomies.[14] The incidence of stimulation-induced seizure has been reported to be between 2.1% and 21.5%.[14,17,50,51] In view of preoperative patient vulnerabilities, it is associated with preoperative history of seizures and tumor location,[52] which highlights the need to optimize seizure control before elective tumor resection. During the awake stage of craniotomy, the combination of absence of anticonvulsant effect from anesthetics and the electrical stimulation during mapping would also increase the risk of seizures. If iatrogenic seizure is initiated by electrical stimulation, a preconvulsive state with after-discharges may be detected by simultaneous intraoperative electrocorticography monitoring, and treatment may be initiated before clinical convulsion ensues.[53] Electrical stimulation should be withheld immediately, and if the after-discharges persist, prompt treatment is necessary. Immediate actions include irrigation of cortex with ice-cold Ringer's solution and increasing supplementary oxygen concentration.[54] If this fails to abort the seizure, small boluses of propofol (0.5-1.0 mg/kg) can be given. Other anticonvulsants, such as benzodiazepam, may not be optimal, since slower clearance and possible interference on function testing may hinder further mapping.[30] Some degree of postictal drowsiness, respiratory depression, and hypotension may occur, necessitating support from the anesthesiologists. Transient focal neurological deficit after a convulsion can occur. It is often possible to resume mapping after a brief period if the patient recovers. However, reassurance should be provided to the patient before further mapping is performed. Rarely, for patients whose seizures are refractory and are evolving into generalized convulsion or status epilepticus, additional loading dose of antiepileptic agents can be administered.

Nausea Vomiting

Nausea vomiting can occur both during the awake surgery and postoperatively.[20] Brain surgery is a known risk to nausea vomiting. On the other hand, nausea vomiting during the awake surgery is a serious safety concern since it may contribute to inadvertent brain swelling and increased risk of aspiration, in addition to discomfort and distress in an awake patient. It is preferable to plan the propofol infusion, for its excellent anti-emetic property, unless it is contraindicated to the mapping purpose. Prophylaxis would be a preferable strategy, especially in patients presenting with characteristics of moderate risk, such as young female, nonsmoker, history of motion sickness or postoperative nausea vomiting, or increased risk of aspiration. Using multiple anti-nausea medications from different pharmacological mechanisms, in the beginning of the procedure, may help to achieve optimal outcome.[55] Other measures may include gentle manipulation of the dura and limitation of narcotic doses.

POSTOPERATIVE CARE

Patients undergoing awake craniotomy have been reported with less postoperative complications, compared with those under GA.[56] The neurological and hemodynamic monitoring, as well as care requirements, should be held the same after the surgery regardless of anesthesia type. Target blood pressure range needs to be maintained in the transition from intraoperative to postoperative care, since uncontrolled high blood pressure has been associated with prolonged hospital stay and increased mortality resulted from intracranial bleeding after craniotomy.[57,58]

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