



# Intraoperative Stimulation Mapping in Neurosurgery for Anesthesiologists, Part 2: The Anesthetic Considerations

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## Abstract

Intraoperative language and sensorimotor function mapping with direct electrical stimulation allows precise identification of functionally important brain regions. Direct electrical stimulation brain mapping has become the standard of care for the resection of brain lesions near or within eloquent regions with various patient outcome benefits. Intraoperative stimulation mapping (ISM) is commonly performed in an awake patient for language and motor assessments. However, motor mapping under general anesthesia, termed asleep motor mapping, has been increasingly performed over the last two decades for lesions primarily affecting the motor areas of the brain. Both asleep-awake-asleep and monitored anesthesia care have been successfully used for awake craniotomy in modern neuroanesthesia. Each anesthetic agent exerts varying effects on the quality of ISM, especially under general anesthesia. Careful selection of an anesthetic technique is crucial for the successful performance of ISM in both awake and asleep conditions. A comprehensive search was performed on electronic databases such as PubMed, Embase, Cochrane, Scopus, Web of Science, and Google Scholar to identify articles describing anesthesia for awake craniotomy, intraoperative brain mapping, and asleep motor mapping. In the second part of this narrative review, we summarize the effects of different anesthetic regimes and agents on ISM, causes of the failure of awake craniotomy and mapping, and outline the anesthetic considerations for ISM during awake craniotomy and asleep motor mapping.

## Keywords

- ▶ direct electrical stimulation
- ▶ intraoperative stimulation mapping
- ▶ awake craniotomy
- ▶ asleep motor mapping
- ▶ monitored anesthesia care
- ▶ neuroanesthesia

## Introduction

Awake craniotomy (AC) with intraoperative direct electrical stimulation (DES) brain mapping has been performed since more than a century ago pioneered by Bartholow<sup>1</sup> leading to

the landmark paper by Penfield describing the sensorimotor homunculi in 1937.<sup>2</sup> Modern neurosurgery has progressed significantly thereafter, especially with the advancement of neuroimaging modalities. Yet, intraoperative stimulation mapping (ISM) remains the gold standard for real-time,

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precise localization of eloquent brain regions due to inherent variability in the anatomic and functional regions<sup>3</sup> and intraoperative brain shifts.<sup>4</sup> ISM has been shown to allow safe and tailored resections of eloquent regions with various patient outcomes benefits.<sup>5</sup> In the past two decades, there has been a rising trend in asleep motor mapping, which was made possible through the work of Taniguchi et al.<sup>6</sup> Various anesthesia drugs and regimes have been used over the years during AC. But to date, no studies have directly examined the effects of anesthetic agents on DES of the brain. This review article summarizes the evidence on the anesthetic considerations for ISM in awake and asleep conditions.

## Methods

A comprehensive electronic search was performed in the following databases from their inception to June 2023: PubMed, Embase, Cochrane, Scopus, Web of Science, and Google Scholar. The literature search was performed using specific keywords: anesthesia AND awake craniotomy OR intraoperative stimulation mapping OR direct electrical stimulation, and asleep motor mapping OR direct cortical motor evoked potential (dcMEP). To date, there are no articles describing anesthesia considerations during intraoperative stimulation brain mapping. Articles were screened and included if it described the anesthesia management during intraoperative brain mapping either AC or asleep motor mapping, the effects of different anesthetic agents on the quality of mapping, and the causes of failure of AC. Articles that described extraoperative mapping and AC without ISM were excluded. Data were then extracted and organized to be presented in a cohesive manner.

## Anesthesia Considerations for Intraoperative Stimulation Mapping

### Choice of Anesthetic Technique for Awake Craniotomy with Intraoperative Stimulation Mapping

The main goal in AC is a patient who is calm, responsive, and able to perform the tasks required during stimulation mapping to accurately identify eloquent structures. Both the asleep-awake-asleep (SAS) technique (with general anesthesia [GA] during the asleep phase) and conscious sedation (or monitored anesthesia care [MAC]) can be used for ACs with ISM, provided that adequate local anesthesia (LA) is administered to the scalp, short-acting anesthetic drugs are used, and sedative infusions are stopped or reduced ahead of the mapping.<sup>7</sup> (► **Table 1**) Some of the anesthetic consideration for electrocorticography (ECoG) may apply to ISM and has been described previously.<sup>8</sup>

A meta-analysis by Stevanovic et al did not identify significant differences between SAS and MAC techniques with regard to the rate of mapping failure, intraoperative seizures (IOSs), and new neurological deficits.<sup>9</sup> A recent meta-analysis by Natalini et al concluded that the MAC technique had fewer AC failures and shorter procedure time, while the SAS technique had a lower incidence of IOSs.<sup>10</sup> Nevertheless, both these meta-analyses are flawed

by bias due to the inclusion of a large number of observational and retrospective studies. Therefore, anesthesia management in ACs remains primarily guided by local practice preferences, and no one technique is superior with regard to the quality of ISM. Some authors have suggested that the SAS technique could be beneficial in more prolonged procedures (more than 4 hours) to limit patient fatigue during mapping. However, to date, no evidence supports this affirmation.<sup>11,12</sup>

### Choice of Anesthetic Drugs for Awake Craniotomies

Many different drug regimens have been used in the setting of AC.<sup>7,10,11</sup> A commonly used anesthesia regime, as described by Sanai et al in their landmark paper on outcomes after language mapping for glioma resection, includes premedication with low doses of midazolam and fentanyl, followed by sedation with propofol or dexmedetomidine with remifentanyl and cessation of all anesthetics after removal of the bone flap.<sup>13</sup> If an SAS technique is chosen, either total intravenous anesthesia (TIVA) or volatile may be used during the asleep phases of surgery, with most studies reported using TIVA.<sup>9–11</sup> Recently, Kulikov et al described the use of xenon anesthesia during the first asleep phase of SAS for AC with the advantage of a short awakening time of approximately 5 minutes.<sup>14</sup>

Dexmedetomidine has been proposed for theoretical and practical benefits in awake procedures, notably because it maintains spontaneous breathing and patient cooperation<sup>15</sup> while allowing reliable, functional mapping and ECoG recordings.<sup>16</sup> In patients with supratentorial brain mass lesions, midazolam and propofol exacerbate or unmask neurologic deficits more than dexmedetomidine at clinically equivalent sedation levels,<sup>17</sup> which could, in theory, make dexmedetomidine less likely to induce false positives during intraoperative mapping. Another retrospective study also reported more postoperative neurological deficits in the subgroup of patients who received benzodiazepines during their AC, partly related to the unmasking of their preoperative deficits.<sup>18</sup>

A randomized controlled trial (RCT) by Goettel et al found that the efficacy of sedation and mapping quality was similar between propofol-remifentanyl and dexmedetomidine for conscious sedation during AC for supratentorial tumor resection. However, patients in the dexmedetomidine group had a lower rate of adverse respiratory events.<sup>19</sup> Another RCT by Elbakry and Ibrahim comparing propofol-remifentanyl with propofol-dexmedetomidine sedation for AC for epilepsy surgery reported a higher sedation score in the propofol-remifentanyl group at the cost of more side effects such as nausea, vomiting, oxygen desaturation, and respiratory depression.<sup>20</sup> A recent meta-analysis concluded that dexmedetomidine provided better surgeon satisfaction during AC with no significant differences with propofol in other outcomes (intraoperative adverse events, patient satisfaction, and procedure duration). However, one of the three RCTs included in their analysis used the SAS technique; thus, the generalizability of their results is questionable.<sup>21,22</sup>

An older observational study reported the use of a ketamine-propofol combination (ketofol) in a 1:1 ratio mixture as part of their MAC technique during AC for tumor resection.

**Table 1** Summary of anesthesia considerations for intraoperative stimulation mapping

	Awake craniotomy	Asleep motor mapping
Anesthesia technique	Monitored anesthesia care (MAC) OR Asleep-awake-asleep (SAS) Similar outcomes and quality of mapping, but SAS may be advantageous in longer procedures	Total intravenous anesthesia (TIVA) preferred
IV anesthetic agents	Various combinations may be used for sedation: Propofol-remifentanyl Propofol-dexmedetomidine Dexmedetomidine has the advantage of lower adverse respiratory events, improved patient cooperation, and surgeon satisfaction Benzodiazepine may unmask preoperative neurological deficits	Propofol-remifentanyl combination is commonly used during TIVA
Volatile agents	N/A	Minimum Alveolar Concentration less than 0.5 may be used if a triple motor mapping technique is performed (DES, dcMEP, and tcMEP)
Muscle relaxants	N/A	Avoid after intubation

Abbreviations: DES, direct electrical stimulation; dcMEP, direct cortical motor evoked potentials; IV, intravenous; N/A, not available; tcMEP, transcranial motor evoked potentials.

Adverse events occurred in 53.6% of their patient, which included hemodynamic events (10.7%), respiratory events (7.1%), oversedation (7.1%), and seizures (7.1%).<sup>23</sup> These results are comparable to those reported in propofol or dexmedetomidine-based MAC techniques. However, they did not report on the quality of ISM during the AC.<sup>10,21</sup> Although the technique sounds promising, there is inadequate evidence currently to support this technique.

#### Failure of Awake Craniotomy and Intraoperative Mapping

Failure of AC is defined as an unplanned conversion to GA or a premature cessation of intraoperative mapping. AC failures are low, reported around 2 to 3%, irrespective of the anesthesia technique.<sup>9,10</sup> The main causes of failure of AC were intraoperative agitation or lack of compliance during mapping (35%), followed by IOSs (13%), drowsiness or oversedation (9%), and acute neurological deficit (7%).<sup>10</sup> Agitation and reduced compliance during mapping may be caused by factors such as significant preoperative deficits, impaired cognitive status, poor motivation or tolerance for the procedure, and fatigue from prolonged mapping. These factors can be reduced by strict patient selection criteria, adequate patient preparation, and the presence of a skilled multidisciplinary team.<sup>5,10</sup>

The incidence of IOSs range from 5 to 8%,<sup>24,25</sup> with only 0.5% leading to failure of AC.<sup>9</sup> Most IOS resolved without adverse effects to the patient.<sup>9</sup> A large proportion of IOS is triggered by DES of the brain.<sup>24,25</sup> A retrospective study found that risk factors for IOS include frontal tumor location, preoperative history of seizures, preoperative radiotherapy, and, interestingly, intraoperative use of dexmedetomidine.<sup>25</sup> Another retrospective analysis also reported that IOS detected via ECoG occurred more in dexmedetomidine compared with propofol, but was not statistically significant on univariate regression analysis with similar epilepsy outcomes at 1 year in both groups.<sup>24</sup> Further studies are needed

to delineate the association of dexmedetomidine with the occurrence of IOS during AC.

IOS is usually self-limiting with cessation of the ISM. Rapid irrigation of the cortex with cold saline will abort the seizure in most other patients, allowing the resumption of mapping after a brief rest period. However, refractory seizures are usually treated with intravenous benzodiazepines, propofol bolus, and antiepileptic drugs. Rarely conversion to GA with invasive airway management may be required.<sup>5,11,26</sup> Overall, the combined evidence supports the notion that AC with ISM is a safe procedure with a high success rate.<sup>10</sup>

#### Anesthesia Considerations for Motor Mapping under General Anesthesia

In recent years, there has been a growing number of studies that compare motor mapping in awake patients versus patients under GA. Two recent meta-analyses of mainly observational studies found similar results with either technique with regard to neurological deficits (both early and late) and severe morbidity. However, there was a trend toward a greater mean extent of resection in AC compared with GA (90.1% vs. 81.7%)<sup>27</sup> and a lower rate of permanent deficit in AC compared with GA (10.8% vs. 12.7%).<sup>28</sup> Both these meta-analyses concluded that glioma resection in or near the motor areas can be safely performed with either technique.

To date, no studies have compared volatile to TIVA anesthetic technique in asleep motor mapping. Most recent studies on motor mapping under GA reported using a TIVA protocol, usually consisting of propofol and remifentanyl infusions with muscle relaxants avoided after intubation.<sup>29–34</sup> TIVA is recommended as the optimal anesthetic regime in the literature<sup>35</sup> because of the well-recognized dose-dependent effects of volatile anesthetics on transcranial MEP (tcMEP) amplitudes,<sup>36–39</sup> which many authors postulate to elicit similar effects during direct cortical

stimulation of MEP. Low doses of volatile agents (Minimum Alveolar Concentration < 0.5) allow acceptable tcMEP recordings for clinical interpretation in some patients.<sup>40</sup> Thus, volatile agents compatible with tcMEP testing<sup>41</sup> will likely enable the measurement of responses to cortical or subcortical DES, as resistance to stimulation will be reduced by bypassing the skull (–Table 1).

Nevertheless, earlier studies on asleep motor mapping used volatile anesthetic techniques. Wood et al attempted to localize the somatosensory and motor cortex using the low frequency (LF) stimulation paradigm described by Penfield. They successfully localized the somatosensory and motor cortex under LA but could not localize the motor cortex under volatile anesthesia.<sup>42</sup> Similarly, Vitaz et al obtained successful motor stimulation in only 50% of their patients under volatile anesthesia using the LF paradigm, even when higher thresholds were used.<sup>43</sup>

The high frequency (HF) stimulation paradigm developed by Taniguchi et al was able to overcome the inhibition of volatile anesthetic to synaptic transmission at the anterior horn of the spinal cord by using a stimulus of 300 to 500 Hz in trains of 5, at a much lower total charge than those produced by LF paradigm. They theorized that this repetitive stimulation caused an accumulation of corticospinal excitatory postsynaptic potentials in motor neurons to achieve firing thresholds even under GA. This also allowed the detection of motor responses without causing apparent patient movement via electromyogram recording of evoked muscle potentials.<sup>6</sup> Following this, Kawaguchi et al found that short-train HF stimulation successfully evoked intraoperative MEP under isoflurane or sevoflurane anesthesia but not single-pulse HF stimulation. They also found that intraoperative MEP changes were still detectable under partial neuromuscular block conditions in 50% of patients.<sup>44</sup>

It should be highlighted that studies on subcortical HF motor mapping that detailed their anesthetic regime have used only TIVA (propofol-remifentanyl) regime. Thus, the correlation between motor threshold (MT) intensity and distance from the corticospinal tract (CST) may not apply to a volatile anesthetic technique.<sup>30–32</sup> If low MTs are reached, the CST is expected to be very close, and depression of the MEP response secondary to volatile anesthetics could, in theory, lead to damage to these tracts. Two recent small retrospective studies showed that asleep motor mapping (cortical and subcortical) can be safely performed using triple motor mapping (using DES, tcMEP, and dcMEP) and volatile anesthetic regime with either sevoflurane, desflurane, or isoflurane in 50 to 70% nitrous oxide at less than 0.5 minimum alveolar concentration and remifentanyl,<sup>45</sup> or a mixed TIVA and sevoflurane technique with an end-tidal average of 0.7%.<sup>46</sup> Since HF subcortical motor mapping is still a developing technique, the inclusion of volatile agents during GA with motor mapping should be discussed with the neurosurgical team. It may be justifiable if the triple motor mapping technique is employed.

Ketamine and etomidate have been successfully used during tcMEP in spine surgery.<sup>47–50</sup> Two recent RCTs in

elective spine surgery reported that ketamine in subanesthetic dose (0.5 mg/kg/h) and ketofol (in 1:4 mixture) improved tcMEP amplitudes without affecting latency when compared with dexmedetomidine and propofol.<sup>51,52</sup> On the contrary, a 1 mg/kg bolus dose of ketamine significantly suppressed tcMEP.<sup>53</sup> Extrapolating these findings from tcMEP, low-dose ketamine may have a role in augmenting dcMEP signals, especially during intraoperative loss of signals after optimizing all other physiological parameters. Nonetheless, these agents have not been directly investigated during asleep motor mapping.

Somatosensory evoked potential (SSEP) signals are less sensitive to anesthetics, and reliable signals can be obtained with lower MAC concentrations of volatile agents. Since SSEP phase-reversal uses an electrode grid directly applied to the cortex, recorded signals are more reliable than transcortical SSEP.<sup>42,54</sup> Reliable SSEP phase reversal has been performed using 0.5 to 1.0% isoflurane with 60% N<sub>2</sub>O.<sup>42,54</sup> Muscle relaxants can improve the quality of SSEP signals but are generally avoided during SSEP phase reversal since motor mapping with DES usually follows.

## Conclusion

ISM is the gold standard for resection of lesions within or adjacent to eloquent brain tissue with various outcome benefits. AC with MAC is frequently utilized during ISM due to the feasibility of intraoperative language, motor, and neurocognitive testing. Various anesthetic regimens are compatible with awake functional mapping, although dexmedetomidine may have an advantage over other sedative agents. On the contrary, intraoperative motor mapping can be performed both under awake and asleep conditions. While TIVA has been the standard anesthetic regimen of choice in most recent studies in asleep motor mapping, the role of low-dose volatile anesthetics could be found in this clinical context, especially with the high-frequency stimulation paradigm and triple motor mapping. Further studies are required to investigate the effects of volatile anesthetics on subcortical motor mapping and find its role in future asleep motor mapping.

## Conflict of Interest

None declared.

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