Assessing the potential for awareness and learning under anesthesia

The problems of intraoperative learning and awareness during surgery have consequences for both the patient and the medical team. With or without recall, the patient can suffer severe emotional trauma that may result in psychological damage. Successful litigation against the anesthesia professional has been increasing in numbers as failure to provide adequate anesthesia can be considered a breach of the unwritten contract between patient and anesthetist. Balanced anesthesia and its use of muscle relaxants can mask indicators of anesthesia depth such as movement or lacrimation.

To date, means of monitoring real-time levels of intravenous agents have not yet been fully tested and proven. Therefore, monitoring minimum alveolar concentrations of inhaled anesthetics may be the best currently available method of ensuring anesthetic depth. Investigations comparing the correlation between nitrous oxide and isoflurane minimum alveolar concentrations and anesthetic depth have indicated specific levels at which intraoperative learning ceases to occur.

Key words: Awareness, inhaled anesthetics, intraoperative learning, intravenous anesthetics, recall.

Incidence and rationale for concern

Of the 24.5 million surgical cases performed every year in the United States, approximately 18.6 million are performed under general anesthesia. Intraoperative learning may be as high as 40% giving rise to the potential for as many as 7.4 million incidents of intraoperative learning, which would be only a slight improvement over the 50% incidence of awareness reported during the earliest days of anesthesia use.

When low concentrations of potent inhaled anesthetics are given (intentionally or unintentionally) intraoperative learning (with or without recall) is possible. Transition periods or periods of high stimulation during the administration of anesthesia or during the course of the surgery render the patient more susceptible to the occurrence of intraoperative learning and the possibility of memory. The trend toward using “lighter anesthesia” combined with the rising use of intravenous anesthesia may also increase the potential for episodes of intraoperative learning.
In some instances, even when conscious recall for intraoperative events does not exist, patients who hold subconscious memory of intraoperative events may exhibit behavioral modifications initiated outside of conscious activity that indicate memory exists. Even under apparently adequate anesthesia, the auditory system may still register input. Studies have shown that when surgical patients learn under anesthesia, it is through a variety of stimuli including auditory, tactile, and olfactory input, and through response to nociceptive stimuli. Reports of negative sequelae including sleeplessness, anxiety, nightmares, and even of a syndrome similar to post-traumatic stress disorder (including nightmares, flashbacks, etc.) have been documented after episodes of intraoperative learning.

Intraoperative learning and awareness as events are not necessarily problems, depending on the patient's perception of the event and the patient's preparation for its possible occurrence. Intraoperative learning and awareness become problems when the patient perceives a problem or any of the following exist:

- Implicit or explicit memory or intraoperative events, with negative sequelae.
- Overt symptoms (negative behavior modifications) from explicit memory or intraoperative noxious stimuli.
- Covert symptoms (negative behavioral modifications) from implicit memory of intraoperative noxious stimuli.

To facilitate further discussion of this topic, certain definitions must apply (Table I). For the purposes of this discussion, intraoperative learning refers to data input, over time, forming facilitated circuits of latent mental images (engrams) during general anesthesia. This may occur without recall. If so, then the patient was not “aware,” by definition. If postoperative recall exists, then the patient was “aware.” If postoperative negative sequelae (negative behavioral modifications following the operative experience) are determined to exist, then learning may have taken place, and further exploration (such as hypnotherapy) may be necessary to understand the source.

### Table I

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<thead>
<tr>
<th>Anesthesia agent categorical objectives: Definition of terms for intraoperative memory and awareness</th>
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<tr>
<td><strong>Learning:</strong> A relatively long-lasting adaptive behavioral change occurring as a result of experience.</td>
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<td><strong>Implicit memory:</strong> Nondeclarative memory intraoperative learning occurring without recall.</td>
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<td><strong>Awareness:</strong> Memory for events that occurred during general anesthesia, which the patient is able to recall postoperatively (also known as explicit memory).</td>
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<td><strong>Recall:</strong> The process of bringing learning into consciousness.</td>
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<td><strong>Explicit memory:</strong> Declarative memory intraoperative learning accompanied by postoperative recall.</td>
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<td><strong>Secondary memory:</strong> Stored memory occurring upon consolidation and engram formation.</td>
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<td><strong>Negative sequelae:</strong> Negative behavioral adaptations, such as sleeplessness, restlessness, anxiety, hallucinations, nervousness, nightmares, or other post-traumatic stress disorder symptoms, seen postoperatively without preoperative occurrence.</td>
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**Physiology of learning and memory**

There are three types of memory input and storage relevant to time—sensory, primary, and secondary—as defined by perception of stimuli and storage time factors. Sensory memories are input traces that occur for approximately 1 second in the sensory cortices. Primary memories are input continuing over a few seconds to a few minutes. Secondary memories (stored, long-term) occur when input continues, uninterrupted, for a period of 5-10 minutes.

The basis of memory formation begins in the reticular activating system (RAS). The RAS is activated by collaterals from the sensory tracts (particularly pain and proprioceptive impulses). It provokes an arousal reaction in the cerebral cortex and provides a basis for learning. If low-level concentrations of anesthetics are used and their effects are gauged solely by signs of cortical neuron depression, deeper level RAS activity may continue unimpeded and learning may still occur. Consolidation, a process of changes in the synapses following the reaction to stimuli, requires a period of at least 5-10 minutes to establish, and maximum consolidation requires 60 minutes to complete. As consolidation occurs, engrams (Table I) are formed, leading to secondary memory and learning.

If a reaction to stimuli occurs but is followed within that 5-10 minute period by the appropriate deepening of a light plane of anesthesia, consolidation may be prevented. If central nervous system function is not inhibited within these time parameters, consolidation occurs and engrams are formed leading to memory retention.

Although the minimum alveolar concentration (MAC) level of an inhaled anesthetic is a major factor in a continuum of closely monitored endpoints used to gauge depth of anesthesia achieved, MAC alone cannot be relied upon as the sole indi-
cator of whether intraoperative learning potential exists. Similarly, with the use of injected anesthetics, there is no reliable indicator that the patient is beyond the threshold of learning. While there may be indirect indicators of intraoperative learning, such as movement, tachycardia, elevated blood pressure, lacrimation, pupillary dilation, and pronounced perspiration, these indicators are frequently masked due to application of adjunct medications such as beta blockers, muscle relaxants, narcotics, or even the anesthetic itself.

There are no predictable doses nor plasma concentrations of potent opioids that can obviate the patient's hemodynamic responses to noxious stimuli, nor are there any real-time methods to measure serum levels of injected anesthetics in wide use. Likewise, the inclusion of amnestic agents in the anesthesia protocol does not guarantee the lack or intraoperative learning. There is no scientific evidence of amnestic effects of benzodiazepines on iconic (visual) or echoic (auditory) memory, but there is a body of evidence that echoic memory under general anesthesia exists (albeit under "inadequate" or low-level concentration general anesthesia).

**General anesthesia and memory**

The goals of general anesthesia are unconsciousness, muscle relaxation, analgesia, and amnesia. Patients enter into unwritten contracts for these services when they undergo general anesthesia. When these goals are not met, the contract is violated, and patients may consider implementing litigation if the experience is perceived as negative.

Without unconsciousness there is learning. Almost any sensory signal entering the nervous system will cause some degree of RAS activation. Some signals produce a larger degree of activity, especially pain and proprioceptive somatic impulses, both of which are likely to be interpreted as requiring some immediate action by the brain. When sensory signals reach a critical level or threshold, they enter the RAS, and the consciousness arousal reaction is produced. Without the addition of effective doses of anesthetic agent to block the pathways and abort the reaction sequence, consciousness prevails.

Muscle relaxation is an essential component for successful endotracheal intubation as well as for effective access to the surgical site. The trend in recent years, however, has been to use lower doses of anesthetic agent and higher doses or more frequent doses of neuromuscular blocking agent and accompanying narcotic, a situation that can set the stage for and possibly mask the existence of lighter planes of anesthesia and resulting intraoperative learning.

**Analgesia** is a major issue of patient concern. A question often asked by patients undergoing general anesthesia is "Will I feel anything?" In the absence of analgesia, the noxious stimulus of pain will create significant arousal reaction and may interrupt the unconscious state.

Amnesia is another goal of general anesthesia. Failure to provide amnesia has been interpreted to constitute negligence. Although agents such as benzodiazepines are given to achieve this end, there are inadequacies that should be considered which will be discussed later in this column.

**Achieving the goals of general anesthesia**

Each of the agents used in achieving general anesthesia falls into a category of drugs designed to accomplish one or more of the goals of anesthesia listed previously. Premedication and induction with nonopioid and/or opioid agents target analgesia. Amnesia is the main therapeutic goal for benzodiazepines. Neuromuscular blocking agents promote muscular relaxation, and both injectable induction agents and inhalation agents provide unconsciousness. Some of these agent categories have overlapping effects, such as the muscle relaxation that may accompany some of the major inhalation agents or any analgesia which might accompany unconsciousness.

Inherent with the application of any anesthetic are variables unique to the patient, such as the chronic use of alcohol, sedatives, tranquilizers, or narcotics, that result in patient variability in anesthetic requirements. Also, there are additional variables associated with the type of surgery to be performed that become factors in anesthetic depth. In certain procedures, the patient's condition may warrant administering lower doses or concentrations of anesthetics achieving a lighter plane of anesthesia. Commonly, these are procedures that include coronary artery bypass grafting, obstetrics, extensive trauma, or procedures attempted on critically ill patients. The result is that an increased incidence of intraoperative learning has been recorded during these procedures.

As general anesthesia is normally achieved and maintained by various techniques, the agents used in each of these methods should be evaluated for their potential to limit or prevent intraoperative learning.

- **Opioids.** The balanced anesthesia technique has been termed "less forgiving than other techniques," because of the combined effects of various agents used which cannot easily be terminated or reversed. The balanced technique involves the administration of a combination of agents, usually
nitrous oxide and one of the opioid analgesics in combination with a neuromuscular blocking agent. This concept developed with the trend toward same-day surgery and has modified the practice of anesthesia due to the ability of such agents as fentanyl, sufentanil, and alfentanil to produce analgesic effects with rapid onsets of action and minimal side effects.

When used—either alone or in combination—the lighter planes of anesthesia with which these opioid analgesics are likely to be associated have been shown to be related to a greater incidence of intraoperative learning. However, the perception of pain may not be a feature of the experience. Opioid agents are more selective for the cellular opioid receptors that stimulate the body’s own defenses against pain. Predetermined action at targeted opioid receptors can provide analgesia while allowing other sensory and motor modalities to remain intact. Any intraoperative learning experience under opioid/nitrous anesthesia, therefore, may be predominantly an experience of auditory input.

Inhalation anesthetics. The effects of nitrous oxide on implicit memory are difficult to ascertain as it is most commonly used in conjunction with other agents. It may be easier to observe the impact of the fluorinated anesthetics—enflurane, halothane, isoflurane, and desflurane—on implicit memory as the effects of these agents are generally not obscured by coadministered agents. Certain of these inhaled anesthetics have the additional effect of potentiating neuromuscular relaxation. While numerous studies have focused on the ability of various inhaled anesthetics to limit intraoperative learning, an investigation by Dwyer and associates compared intraoperative learning of patients administered isoflurane for elective surgical procedures. The team concluded that end-tidal isoflurane concentrations of \( \geq 0.6 \text{ MAC} \) prevent unconscious learning and conscious recall. Further investigations compared nitrous oxide and isoflurane in healthy volunteers and concluded that isoflurane at \( 0.45 \text{ MAC} \) will prevent intraoperative learning but nitrous oxide at \( 0.6 \text{ MAC} \) will not.

Injectable induction agents. Commonly used as induction agents in general anesthesia, propofol, thiopental, and methohexital are subject to wide variations in pharmacodynamic actions from patient to patient, necessitating constant monitoring within a brief time span as these agents have rapid onsets of action and short durations of action. Consequently, if the rates of distribution and elimination of these agents are not closely matched by the introduction of maintenance agents, a subanesthetic level may exist, enhancing the potential for intraoperative learning, especially during transitional periods. Barbiturate anesthetics cover little analgesia; their exclusive use in the presence of pain may result in excitation.

Neuromuscular blocking agents. These agents enhance muscle relaxation to facilitate endotracheal intubation and to allow an optimal surgical field with lesser amounts of anesthetic. However, in doing so, the addition of neuromuscular blocking agents, such as atracurium and vecuronium, may prevent patient movement in response to noxious stimuli even though intraoperative learning may be taking place. Purposeful attempts by the patient to communicate with the surgical team may be prevented due to the use of these agents.

The inhaled fluorinated anesthetics may offer varying degrees of muscle relaxation or may potentiate the relaxation seen with neuromuscular blocking agents.

Amnestics. Benzodiazepines have been used to produce surgical amnesia with varying degrees of success. These agents have been shown to impair new long-term memory formation, have little influence on other aspects of memory, and spare implicit memory. They do not impair the capabilities for retaining or the ability to recall previously stored information (retrograde amnesia).

Benzodiazepine dose effectiveness varies from patient to patient, and different benzodiazepines have been shown to affect different segments of the learning process. Oral diazepam, for example, appears to work longer than the other drugs in this classification, but its effects are less predictable. Midazolam administered intravenously (5 mg/70kg) appears to prevent the recall of uncomfortable events better than the other benzodiazepines. However, it does not appear as effective at blocking innocuous events. Lorazepam administered intravenously appears to block recall in 70% of patients and has a 4-hour peak efficiency duration. Benzodiazepines are also administered preoperatively for tranquilizing apprehensive patients. It should be remembered, however, that the blocking of recall does not mean that learning did not take place and that there is no implicit memory.

Monitoring intraoperative learning

Positive, direct indicators of potential intraoperative learning are movement or profuse perspiration. Indirect indicators, such as hemodynamic changes, may be used as adjunct data.

While it is possible to track serum and respiratory levels of an agent and there are indirect indicators of the agent's effect, there are several problems with applying the information provided by these
monitors to the possibility of intraoperative awareness and/or learning. Clinical indicators of intraoperative learning, such as movement and hemodynamic changes, may be altered by the administration of both primary anesthetics and adjunct medications. While adequate numbers of studies have not been performed to correlate intraoperative learning with the depth of anesthesia, results achieved by Dwyer et al noting absence of learning at measurable levels of isoflurane have opened the possibility of the potential for learning correlating directly to MAC levels.

Therefore, established techniques used to assess depth of anesthesia are being scrutinized for their value in determining the potential for intraoperative learning (Table II).

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<th>Technique to assess anesthetic depth</th>
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<td><strong>Isolated forearm technique (IFT):</strong></td>
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<td><strong>Electroencephalography (EEG):</strong></td>
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<td><strong>Lower esophageal contractility:</strong></td>
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<td><strong>Surface electromyography (EMG):</strong></td>
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<td><strong>Intraoperative evoked potentials:</strong></td>
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Regardless of the amount of monitoring for the potential of intraoperative learning, the major definitive assessment for ascertaining explicit memory has been the postoperative interview. In addition to determining the possibility of intraoperative learning, the postoperative interview also permits speedy intervention to deter negative sequelae. It is recommended that this interview be conducted as soon as convenient but within 24 hours of the operation. Ideally, the patient should be asked to attempt recollection of the last memory before induction, the first memory upon awakening, any memories of the intraoperative period, and any “dreams” that may have been experienced. Questioning should not be done in any manner that may influence the patient’s response. If the patient reports “dreaming,” it is necessary to determine whether the “dreams” are the result of awareness or merely dreams unrelated to events in the operating room.

To determine the possible existence of implicit memory of intraoperative events, the patient should be asked if he/she has feelings of nervousness or anxiety since the surgery, if there has been a problem sleeping, and other than postoperative pain, if there have been problems with discomfort. Patients who are sufficiently traumatized by an episode of intraoperative learning or awareness may develop negative sequelae as severe as post-traumatic stress syndrome.

Should negative sequelae be suspected or if the patient’s willingness to relate their experiences are in question, a psychiatric consult may be indicated. Hypnosis may be one technique used to determine the extent of implicit intraoperative learning.

**Additional causes of intraoperative learning and memory**

Contributing to the incidence of intraoperative learning and awareness are other factors, including human error and equipment malfunction. Regardless of the efficacy of the individual drugs used to accomplish anesthesia, risk remains in that intraoperative learning may occur due to equipment failure or inappropriate anesthesia administration technique.

According to statistics compiled by the Medical Defence Union (the record-keeping system for medical complications in the United Kingdom), human error was cited in more than 90% of the cases litigated since 1985 with the number one occurrence, faulty anesthetic administration technique, cited in 70% of the cases tracked. Failure to check equipment was cited as the second most common occurrence with 20% of the cases falling under this heading. Only 2.5% of the cases were attributable to equipment malfunction.

**Prevention**

To minimize the potential for intraoperative learning due to operator or equipment error, the following precautions have been recommended:

- Check anesthesia machine function before each case.
- Consider a volatile agent as part of all anesthetic techniques; do not rely on the “nitrous oxide/oxygen/narcotic sequence” alone as the only method to produce unconsciousness.
- Provide adequate premedication, possibly with greater use of amnestics.
- Restrict use of neuromuscular blockade to that which provides a good surgical field.
- Maintain potent inhaled anesthetics at effective MAC concentration.
- Overpressure with a potent inhaled anesthetic during induction and early maintenance.
- Monitor indirect markers (hemodynamics, etc.) to use with other data in determining intraoperative learning potential.

New computer-controlled infusion pumps predicted to be in use by the end of the decade not only will monitor serum levels continuously but rapidly adjust for depletion. To be known at CATIA (computer assisted titration of intravenous anesthesia), this new technology will allow anesthesia professionals to target a patient’s therapeutic window with an indication of the increments required to maintain anesthesia depth. Prevention of intraoperative learning may begin with patient education. The anesthesia professional must identify patient concerns and their origins preoperatively and then offer reassurance and support. The patient must be confident that all measures will be taken to counter events such as intraoperative awakening and pain. In some instances the anesthesia consultant may uncover patient fears related to a previous incident of intraoperative learning.

Expert opinions vary as to the benefits/risks of preoperative discussion of intraoperative memory. Some experts believe that discussion should be limited to those patients who have recall of an intraoperative event during prior surgery. However, other anesthesia professionals profess that such memory occurs with sufficient frequency that the best interests of both the patient and surgical team are served by preoperative counseling and supportive education. Lack of preoperative education has been used to consolidate, the event can be eradicated. There is growing evidence that monitoring end-tidal concentrations may provide the best available indicators of sufficient anesthesia depth to prevent intraoperative learning.

In the procedures where light levels of anesthesia are traditionally used (obstetrics, trauma, and cardiopulmonary procedures), extreme caution must be taken within the operating suite to minimize noxious stimuli, especially auditory stimuli. Conversation between members of the operating team should be kept to a minimum, pertinent only to the surgery and at low vocal levels. There have been studies that suggest verbal personal reinforcement should be directed at the patient during surgery to offset any negative intraoperative learning. Numerous cases of litigation have been initiated because patients recalled unpleasant intraoperative events and derogatory comments made about them.

In one recent case reported by Scripps Howard News Service (January 10, 1993), a Milwaukee woman filed a $275,000 suit for inadequate anesthesia. Her claim was that she heard “disparaging remarks” made about her obesity during cardiovascular surgery. However, despite testimony alleging major damaging remarks that could be attributed to the surgeon, the surgeon was not a defendant in the case. Sole responsibility for the event was placed on the anesthesiologist.

Those administering anesthesia must be aware of the intraoperative learning potential inherent in the various stages of induction and maintenance, with relation to those events where levels of unconsciousness may be interrupted by noxious stimuli or by transition levels of anesthesia. End-tidal monitoring as well as monitoring the indirect markers for reaction to noxious stimuli are recommended.

Owing to the many ramifications of intraoperative learning that may lead to potential postoperative negative sequelae in patients and reactionary litigation, it remains in the best interest of all involved to implement preventive measures.

Summary
Intraoperative learning is a complication of anesthesia that was first documented when Morton applied ether to his first patient in 1846. The advent of neuromuscular blocking agents, which were later to be combined with opioid analgesics permitted practitioners to develop a technique—balanced anesthesia—that relied on lighter levels of anesthesia coupled with pain modulation. Coadministration of muscle relaxants and other adjunct agents, such as the beta blockers, contributed to masking hemodynamic and encephalographic response to stimuli.

The potential for intraoperative learning and memory is both time dependent and dose dependent. If adequate anesthetic depth can be achieved within the 5-10 minute window of stimulation (prior to consolidation), the event can be eradicated. There is growing evidence that monitoring end-tidal concentrations may provide the best available indicators of sufficient anesthesia depth to prevent intraoperative learning. With no current methods for monitoring real-time serum levels of intravenous anesthetics currently available for general use, use of volatile agents may be the optimum practice to minimize the potential for intraoperative learning and awareness.

Data indicate faulty administration technique to be responsible for a majority of the cases brought to litigation. Prevention of the occurrence of intraoperative learning will rely on data to prove the accuracy of indicators for depth and effectiveness for each agent, used singly and in combination.
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