AIM THE OF WORK

To spotlight on the new methods of assessing & monitoring depth of anesthesia including Bispectral Index Monitor or BIS,E-entropy and Narcotrend in comparison to the traditional methods in addition to cost effectiveness on patient outcome.

INTRODUCTION

Anesthesia is a balance between the amount of anesthetic drug (s) administered and the state of arousal of the patient. Given that the intensity of surgical stimuli varies throughout surgery, and the hemodynamic effects of the anesthetic drugs may limit the amount that can be given safely ***(Shepherd et al., 2013).***

Depth of anesthesia is a compound of hypnosis, antinociception, suppression of reflexes, and amnesia. Due to its nature, anesthesia depth monitoring requires an indirect parameter. The focus of the monitoring is on the level of hypnosis. Clinical signs of inadequate depth of anesthesia are raised blood pressure level, increased heart rate, and lacrimation. However, these alone are insufficient parameters. Using monitors that estimate the rate of awareness has been shown to reduce intraoperative drug use, speed recovery from anesthesia, and prevent complications such as postoperative nausea and vomiting ***(Ionescu et al., 2013).***

Anesthesia awareness is the explicit recall of sensory perceptions during general anesthesia. Anesthesia awareness is rare, but the incidence may approach 1% in patients at high risk. It can lead to anxiety and post-traumatic stress disorder ***(Liu et al., 2011).***

Intraoperative awareness is defined by both consciousness and explicit memory of surgical events. It occurs in 1 or 2 of every 1, 000 surgical cases, but incidence varies with the patient population, methodology used to study awareness, and time frame of the study. Risk factors include compromise of cardiovascular function as well as acquired or inherited resistance to the sedative or amnesic effects of anesthesia ***(Friedman et al., 2010)***.

Inappropriate titration of the hyponotic components, leading to an excessive depth of anesthesia (DoA) which might compromise the patient outcome. Conversely, underdosing may lead to patient wakefulness under general anesthesia and postoperative recall of events ***(Amornyotin et al., 2011).***

Electroencephalography or EEG is utilized in the evaluation of the hypnotic Component of anesthesia. EEG records the electrical activity of the cerebral cortex via scalp-attached electrodes ***(Lortat-Jacob et al., 2009).***

Bispectral Index Monitor or BIS is an EEG based monitor. Three to four electrodes applied to the forehead register EEG signal, effectively predicts the status of anesthetic metabolism, but neither the transition change from being awake to unconsciousness nor the prediction of the anesthesia depth for anesthetics compound is well assessed ***(Bruhn et al., 2006).***

BIS values range from 0-100, 100 indicating a totally awake and orientated patient and 0 a deeply anesthetized one. Adequate depth of anesthesia for surgical operation is between 40-60 BIS ***(Kymäläinen, 2009).***

The E-Entropy monitor measures irregularity in spontaneous brain and facial muscular activity. It uses a proprietary algorithm to process EEG and frontal (FEMG) data to produce 2 values that indicate the depth of Anesthesia, response entropy (RE) and state entropy (SE). Response entropy (RE), is a fast-reacting parameter based on both EEG and FEMG signals, and is sensitive to facial muscle activation (2-second reaction time). It may indicate the patient's responses to external stimuli and signal early awakening. The second value, state entropy (SE), is a stable parameter based on EEG and may be used to assess the hypnotic effect of anesthetic agents on the brain ***(Shalbaf et al., 2013).***

Highly irregular signals with variation of wavelength and amplitude over time produce high values of entropy and may indicate that the patient is awake. More ordered signals with less variation in wavelength and amplitude over time produce low or zero entropy values, indicating a low probability of recall and suppression of brain electrical activity. The RE scale ranges from 0 (no brain activity) to 100 (fully awake) and the SE scale ranges from 0 (no brain activity) to 91 (fully awake). The

clinically relevant target range for entropy values is 40–60. RE and SE values near 40 indicate a low probability of consciousness ***(Kreuzer et al., 2010).***

The Narcotrend index is a new EEG index, which is based on using spectral analysis to produce a number of parameters. Multivariate statistical methods using proprietary pattern recognition algorithms are then applied to these parameters to provide an automatically classified EEG. The automatic classification functions were developed from visual classification of EEGs. The EEG classification scale is from stage A (awake) to stage F (very deep hypnosis), with stage E indicating the appropriate depth of anesthesia for surgery. As a refinement to the A to F scale, an EEG index (100=awake, 0=very deep hypnosis) is also calculated ***(Christopher, 2009).***

The BIS sensor can be used during induction and airway management with a standalone monitoring system in the anesthetic room, and then used with an integrated BIS system from other manufacturers in the Operating Theatre. Because E-Entropy systems are only available as integrated modular systems and Narcotrend systems are only available as standalone monitors, they do not provide the same flexibility to facilitate comprehensive access between both Anesthetic rooms and Operating Theatres ***(Hemmerling et al., 2011).***

In this review, the neurobiology of consciousness and memory, as well as the incidence, risk factors, sequelae, and prevention of intraoperative awareness will be discussed ***(Mashour et al., 2011)***.

PATHOPHYSIOLOGY OF AWARENESS

Intraoperative awareness requires not only consciousness, but also memory. Although the terms "learning" and "memory" are often considered synonymous, they are not the same process. Learning has been defined as the process of acquiring new information, whereas memory refers to the persistence of learning in a state that can be recalled at a later time. Current research is aimed at understanding the mechanisms underlying the effects of anesthetics on learning and memory processes. The goal is to develop strategies to prevent intraoperative awareness and possible memory deficits in the postoperative period. In turn, much like in consciousness research, anesthetics can be used as powerful probes to gain fundamental insights into the biology and neuronal substrates of memory ***(Squire and Kandel, 2009)***.

Learning and memory take several distinct forms. Explicit (or declarative) memory refers to memories that can be verified as fact and are accessible to the conscious state. Implicit (or nondeclarative) memory accounts for changes in behavior (skills, habits, simple forms of conditioning) that result from experience without the person or animal being consciously aware that learning has caused the change in behavior ***(Squire et al., 2004)***.

For example, implicit memory in humans could result in faster reaction times in response to a stimulus or improved motor skill. Explicit memory has been subclassified into episodic memory, which refers to long-term memory of personal events associated with a specific place and context, and semantic memory, which refers to the recall of known facts about the world, such as the names of objects ***(Mashour et al., 2011)***.

Implicit memory has been subdivided into procedural memory, such as improvements in the ability to ride a bike, and priming, which occurs when a response interval is reduced by previous exposure to a familiar stimulus. Most studies of intraoperative awareness address explicit episodic memory ***(Mashour et al., 2011)***.

One of the most potent actions of general anesthetics is memory blockade. Intravenous and inhalation anesthetics cause memory blockade at doses considerably lower than those required for loss of consciousness and immobility ***(Mashour et al., 2010)***. In human volunteers, the concentration of isoflurane that suppresses learning and memory of verbal cues was approximately one quarter of the dose required for immobilization. In animal studies, subanesthetic concentrations of isoflurane (0.25–0.5 minimum alveolar concentration [MAC]) caused dose-dependent suppression of fear-associated

learning and memory. Interestingly, the relationship between the sedative and amnesic doses differs for different classes of neurodepressant drugs. For example, in human patients, propofol and midazolam caused greater memory blockade than did thiopental or fentanyl at equisedative doses ***(Dutton et al., 2002 and Mashour et al., 2011)***.

The potency of anesthetics for memory blockade also depends on the type of learning. For example, suppression of fear-conditioned memory in response to an auditory tone required twice the concentration of isoflurane (half effective concentration [EC50], 0.47 MAC) that was required to suppress fear-conditioning memory to the environmental context (EC50 0.25 MAC) ***(Mashour et al., 2011)***.

The relative resistance of memory for auditory events to inhaled anesthetics is of particular interest, as patients who experience intraoperative awareness frequently describe auditory perceptions, such as hearing sounds or voices ***(Mody and Pearce, 2004)***.

The relative potencies of the commonly used inhaled anesthetics were compared in rats using a Pavlovian conditioning paradigm known as inhibitory avoidance. In this conditioning paradigm, the animal learns to suppress the natural tendency to enter the darkened compartment of a maze

because entry is associated with a noxious stimulus (a foot shock) ***(Alkire and Gorski, 2004).***

In the study by Alkire and Gorski (2004). this type of learning was impaired by low concentrations of most inhaled anesthetics (0.15% halothane, 0.3% sevoflurane, 1% desflurane) but, surprisingly, was not impaired by isoflurane or nitrous oxide. In contrast, retention of memory (studied after 24 h) was impaired by all anesthetics at relatively low concentrations (0.2% isoflurane, 0.3% sevoflurane, 0.3% halothane, 0.44% desflurane, 20% nitrous oxide) ***(Alkire and Gorski, 2004)***.

Finally, most anesthetics cause antegrade amnesia (loss of memory for a period after administration of the drug) but not retrograde amnesia (loss of memory for events preceding administration of the drug). Intravenous anesthetics, including propofol and etomidate, cause antegrade amnesia and can also interfere with memory consolidation, which refers to the stabilization of memories after the initial acquisition ***(Cheng et al., 2006)***.

Neurobiology of Memory.

The key molecular targets of anesthetics are thought to be the ion channels and neurotransmitter receptors that regulate synaptic transmission and neuronal excitability ***(Hemmings et***

al., 2005). In particular -aminobutyric acid receptor type A ($GABA_A$) receptors are allosterically modulated by most inhaled and intravenous anesthetics, such as etomidate, propofol, barbiturates, many benzodiazepines, ethanol, and neurosteroidbased anesthetics ***(Bonin RP and orser, 2008)***. The GABAA receptors are composed of multiple subunits. At least 19 mammalian genes encode for the various subunits (α_{1-6}, β_{1-3}, $\gamma_{1-3,}$ δ, ε, θ, π, and ρ_{1-3}) ***(Olsen and Sieghart, 2008)***.

The subunit composition of a given GABAA receptor critically determines its cellular expression pattern and pharmacologic properties. For example, $GABA_A$ receptors generate two major forms of inhibition: synaptic inhibition, which is mediated by postsynaptic receptors containing an α_{1-3} subunit, $\beta_{2,3}$ subunits, and a γ subunit, and a persistent or tonic inhibition that is generated predominantly by $\alpha_{4-6}\beta_{1-3}\delta$, and $\alpha 5$ $\beta_{2,3}\gamma_2$ receptors. The receptors that generate tonic inhibition are localized predominantly to the extrasynaptic region of the neurons***(Farrant and Nusser, 2005)***.

Of particular relevance to the memory-blocking properties of anesthetics is a tonic inhibitory conductance generated by 5 subunit-containing $GABA_A$ receptors. These receptors have a restricted pattern of distribution, being expressed predominantly in the hippocampus, where they

represent 20% of all GABAA receptors ***(Caraiscos et al., 2004)***.

The 5GABAA receptors have been strongly implicated in learning and memory processes because compounds that selectively inhibit their activity (specifically, inverse agonists) and genetic manipulations that reduce receptor expression have been associated with improved memory performance in animals. In humans, an inverse agonist for 5GABAA receptors also improved word recall after ethanol-induced memory impairment. A variety of anesthetics, including propofol, isoflurane, and etomidate, enhance the activity of 5GABAA receptors in vitro ***(Martin et al., 2010)***.

In vivo, behavioral studies showed that a low, clinically relevant dose of etomidate impaired performance for memory tasks in wild-type but not null mutant mice lacking the 5 subunit. Etomidate produced similar impairment of motor coordination, loss of righting reflex, and anxiolysis in wild-type, which indicated that 5GABAA receptors are involved in the memory-impairing effects of general anesthetics but not sedation or hypnosis ***(Martin et al., 2009)***.

Low (amnesic) concentrations of anesthetics also target extrasynaptic 4 subunit-containing GABAA receptors, which generate a tonic conductance in the hippocampus and thalamus

(Belelli et al., 2005). Interestingly, the potency of isoflurane in inhibiting fear memory was reduced in α_4 subunit knockout mice, whereas the hypnotic and immobilizing effects of isoflurane were unchanged. The α1 subunit-containing GABAA receptor is abundantly expressed at synapses in the cortex, thalamus, and hippocampus. Knockin mice that expressed an isoflurane-resistant 1GABAA receptor displayed normal sensitivity to the amnesic effect of isoflurane ***(Rau et al., 2009)***.

This result is consistent with the notion that a tonic inhibitory conductance generated by extrasynaptic GABAA receptors regulates memory blockade by anesthetics. Furthermore, the amnesic effects of anesthetics can be dissociated from other behavioral components of the anesthetic state such as sedation or immobility ***(Sonner et al., 2007)***.

The regions of the brain that contribute to explicit episodic memory (memory for facts and events) have been revealed through examination of human patients, who had areas of his temporal lobe surgically resected bilaterally. Such studies on patients or animal models have shown that the medial temporal lobe, which includes the hippocampus, amygdala, and perirhinal, entorhinal, and parahippocampal cortices, plays a critical role in spatial memory, recognition of novelty, and contextual fear ***(Squire et al., 2004 & Mashour et al., 2011)***.

There is a division of function within the medial temporal lobe, and lesions of the hippocampus prevent the acquisition of episodic memory in humans. Memory for emotionally charged content, such as fear, involves the amygdala and the anterior cingulate cortex. The amygdala appears to be particularly important for anesthetic blockade of emotionally charged memory. Lesions of the basolateral nucleus of the amygdala in rats attenuated the amnesic effect of low doses of sevoflurane and propofol for fear-associated aversive learning ***(Alkire and Nathan, 2005)***.

In addition, infusion of a GABAA receptor antagonist into the basolateral amygdala of rats blocked propofol induced amnesia, as well as the loss of activity-regulated cytoskeleton-associated protein, which is induced by synaptic plasticity in the hippocampus ***(Ren et al., 2008)***. Emotional memory in humans can also be blocked by subanesthetic concentrations of sevoflurane (0.25%). In addition, neuroimaging studies involving positron emission tomography in human volunteers showed that 0.25% sevoflurane impaired the functional connectivity between the amygdala and the hippocampus. Brain regions involved in implicit, explicit, and traumatic memory are depicted in (Figure 1) ***(Alkire et al., 2008)***.

At the level of the hippocampus (Figure 1), the mechanism for longterm storage of memories is thought to be

an enhancement of excitatory synaptic transmission, referred to as long-term potentiation (LTP) ***(Kandel, 2009)***. LTP results from functional and structural changes at excitatory synapses, including enhanced activity of AMPA-subtype glutamate receptors, insertion of new AMPA receptors into the postsynaptic membrane, 98 activation of transcription factors, and synthesis of memoryrelated proteins ***(Kandel, 2004)***.

Memory-blocking concentrations of several anesthetics impair LTP64 and the production of memory-related proteins. Various lines of evidence have demonstrated a strong correlation between blockade of LTP by neurodepressive drugs (including anesthetics) and memory impairment. Of particular interest are GABAA receptor subtypes that generate a tonic inhibitory conductance in the hippocampus and cortex ***(Alkire and Guzowski, 2008)***.

An increase in tonic inhibitory conductance by low (amnesic) concentrations of etomidate strongly impaired LTP in hippocampal slices from wild-type.

LTP was first described in animals anesthetized by chloralose and urethane, which suggests that during anesthesia, memory storage can still occur under some conditions ***(Martin et al., 2010)***.

At the forefront of memory-related anesthesia research are studies aimed at understanding how the coordinated activity