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Novel Incorportation Of Biomedical Engineering Algorithms (bispectral Index Guided Or Anesthetic Concentration Guided) In Real-Time Decision Support To Prevent Intraoperative Awareness Using An Electronic Anesthesia Information Mananagement System

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NOVEL INCORPORATION OF BIOMEDICAL ENGINEERING ALGORITHMS (BISPECTRAL INDEX GUIDED OR ANESTHETIC CONCENTRATION GUIDED) IN REAL-TIME DECISION SUPPORT TO PREVENT INTRAOPERATIVE AWARENESS USING AN ELECTRONIC ANESTHESIA INFORMATION MANAGEMENT SYSTEM

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DEDICATION

To my wonderful parents, John and Mavis Shanks, for whom I am blessed to have in my daily life and who continuously and graciously, give me their love, support, and encouragement.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter 1

Chapter 2

TABLE OF EQUATIONS

CHAPTER 1 – Intraoperative Awareness: Incidence, Epidemiology, Risk Factors, and Consequences

Experiencing and remembering the trauma of surgery is a feared complication and is often referred to as intraoperative awareness or anesthesia awareness (AWR). "Awareness" in this context is defined as the consciousness and explicit recall of events during an operation (between time of anesthesia induction and emergence from anesthesia) that can include auditory, sensory, and/or nociceptive stimuli. AWR occurs while a patient is intended to be under general anesthesia (GA). GA is defined as a drug-induced loss of consciousness during which a patient cannot be aroused even by a painful stimulus (ASA Task Force, 2006). A balanced anesthetic technique can include the use of amnesic drugs, neuromuscular blocking agents (paralytics), narcotics, and inhaled or intravenous anesthetics. These medications are titrated to maintain stable physiologic parameters based on the patient's co-morbidities.

The incidence of AWR is low and reported to be between 0.1 – 0.2%. Sebel et al. demonstrated an incidence of 0.13% (Sebel et al., 2004) for definite AWR at seven medical centers in the United States, which is consistent with an earlier study in Europe finding an incidence of 0.16% (Sandin et al., 2000). Collectively, these studies suggest an incidence of approximately 1-2cases/1000. However, if the potential or possible AWR reports in the Sebel et al. study were included, the incidence rose to 0.36% (Sebel et al., 2004). In high-risk cases the incidence may be as high as 1%.

The incidence of AWR changes in different healthcare environments around the world. Ranta et al. investigated all patients undergoing GA for a one year period in Finland and found an incidence of 0.4% of definite AWR and an incidence of 0.3% for possible AWR (Ranta et al., 1998). They noted that the AWR patients received a statistically smaller dose of anesthetics

based on hand review of the medical records. Psychiatric evaluations were performed on five of the AWR patients and it was determined that three of the five patients had a history of major depression (Ranta et al., 1998). Myles et al. performed a patient satisfaction survey the first day after an operation in Australia and noted a self-reported AWR incidence similar to the United States of 0.11% (Myles et al., 2000). More recently, Errando et al. prospectively evaluated 4,001 patients in Spain and noted a very high incidence of 1.0% which is about 5 times that of the reported rate in the United States (Errando et al., 2008). Xu et al. conducted a descriptive cohort study from 25 medical centers in China which included data on 11,101 patients (Xu et al., 2009). They showed an incidence of 0.41% of definite AWR and 0.41% of possible AWR cases which is about double the reported rate in the United States. The United Kingdom and Irish pubic hospitals have performed national audits on the event of "accidental awareness" (Pandit et al., 2014). The most recent NAP5 (5^{th} National Audit Project) used a patient reporting system of accidental AWR over a one year time period and reported an incidence of certain or probable and possible AWR cases of 1 out of every 19,600 anesthetics (Pandit et al., 2014). The NAP5 project is different from the other previously described studies since this was a self-reporting system by the patient with no specific constraints on the time of the report in relation to the operation and no formal interviews conducted.

Data derived from internal quality assurance or improvement programs have also been retrospectively analyzed to determine the incidence of anesthesia AWR. Pollard et al. used data from a quality improvement program over a three year period (2002-2004) at eight locations to investigate the incidence of AWR (Pollard et al., 2007). Patients were interviewed within a 48 hour window after GA. They reported a far lower incidence of awareness across the 8 participating centers: 0.0068% or 1 of every 14,560 patients (Pollard et al., 2007). Mashour et

al. in turn also reviewed three years of quality assurance data at a large academic institution (Mashour et al., 2009c). Patients were interviewed on post-operative day one following anesthesia by a member of the anesthesia team or a nurse via a postoperative interview. Patients were not specifically asked about AWR but rather a general open ended question regarding problems with anesthesia. They found a higher incidence than Pollard et al. (2007) of 0.023% or 1 of every 4,401 patients (Mashour et al., 2009c). Mashour et al. highlighted that the retrospective approach was likely insufficient for optimal capture of awareness events (Mashour et al., 2009c). Mashour et al. resolved the controversies in the literature regarding AWR incidence by comparing prospective, structured interviews and spontaneous patient reports in a *single* cohort. They found a significantly higher capture for awareness events with structured interviews (Mashour et al., 2013).

In the United States there are approximately 21 million patients that receive general anesthesia per year, which equates to 20,000 to 40,000 associated cases of AWR (JACHO, 2004). Even though AWR is a low incidence event, due to the large number of general anesthetics performed each year there is a significant number of patients adversely affected. The literature states a complex list of experiences reported by patients during the awareness event including: auditory perceptions, visual perceptions, tactile stimuli, pain, paralysis, helplessness, anxiety, fear, extreme panic, terror and feeling of abandonment (Cook et al., 2014; Domino et al., 1999; Ghoneim et al., 2009; Moerman et al., 1993; Osterman et al., 2001; Schwender et al., 1998). After the event, patients report anxiety, nightmares, unpleasant dreams, flashbacks, and post-traumatic stress disorder (PTSD) (Cook et al., 2014; Domino et al., 1999; Ghoneim et al., 2009; Moerman et al., 1993; Osterman et al., 2001; Schwender et al., 1998). The Joint Commission on Accreditation of Hospital Organizations reviewed the literature on AWR and

reported 48% related to auditory stimuli, 48% percent related to the sensation of not being able to breathe and 28% related to pain (JACHO, 2004). Several small cohort samples have also been reported in the literature. Moerman et al. noted that 70% of the patients studied experienced sleep disturbances, nightmares, flashbacks and anxiety due to the awareness experience (Moerman et al., 1993). Schwender et al. (interviewed 45 awareness patients from Germany and noted that 22 of the 45 patients experienced negative unpleasant effects after the event (Schwender et al., 1998). Mashour et al. have developed a classification instrument to aid the analysis of qualitative experiences, as well as the experience of distress during an anesthesia awareness event (Mashour et al., 2010).

Patients who do experience explicit awareness have reported significant psychological sequelae including posttraumatic stress disorder (PTSD). PTSD is developed after a traumatic experience and has three significant components; re-experiencing of the event, avoidance of cues or triggers related to the event, and physiological hyperarousal (Osterman et al., 2001; Whitlock et al., 2014). There is significant emotional, social, and economic impact of patients with psychological sequelae following an intraoperative AWR event and therefore the need to minimize such events (although rare) is important in the medical community. From a small cohort report of awareness patients, PTSD was shown in 3 of 45 patients (Schwender et al., 1998). The patients were interviewed on average 0.84 years (range 0.1-5.0) after the AWR event (Schwender et al., 1998). Osterman et al. sought to determine the development of PTSD after AWR by investigating 16 AWR patients and 10 control patients (Osterman et al., 2001). All patients were administered the Clinician Administered PTSD Scale (CAPS) (Blake et al., 1995). CAPS scores patients on a scale from 0 to 136 (Blake et al., 1995). A score 45 or greater meets the diagnostic criteria for PTSD (Blake et al., 1995). Osterman et al. found that 56.3% of the

AWR patients and no control patients met the diagnostic criteria for PTSD (Osterman et al., 2001). Of the PTSD patients, the patients met the criteria with an average 17.9 years after the event (Osterman et al., 2001). Three factors were significantly associated with developing PTSD; intraoperative experience "that you left your body at some point" and "that at some point you could mentally escape" as well as postoperative feeling "that you left your body at some point" (Osterman et al., 2001). Osterman et al. and Schwender et al. both determined that patients experience PTSD years after the actual awareness event (Osterman et al., 2001; Schwender et al., 1998). Leslie et al. further validated the high incidence of PTSD after awareness and showed an incidence of 71% (Leslie et al., 2010). The Psychological Sequelae of Surgery (Psych SOS) study used a cohort of AWR patients from three large clinical trials investigating the prevention of AWR with control patients on age, sex, type of surgery, and risk of AWR (Whitlock et al., 2014). A total of 68 AWR patients were matched with 418 control patients and were administered the PTSD Checklist-Specific (PCL-S) and/ or the modified Mini International Neuropsychiatric Interview with a median time of two years past the date of the operation. These techniques were aimed at identifying patients that exhibited symptoms of PTSD (Whitlock et al., 2014). Whitlock et al. demonstrated 43% of patients with AWR met the criteria for PTSD using the PCL-S and 14% of the AWR patients scored consistently with the DSM-IV diagnosis of PTSD (Whitlock et al., 2014). More recently, the NAP5 reported that 47% of their self-reported AWR cases were associated with distress to the patient (Cook et al., 2014). Since the NAP5 is the most recent study on negative experiences of patients that experience AWR, the actual incidence of PTSD is unknown. However, the authors did state that via patient self-report experiences of "re-experiencing the event through 'flashbacks' and nightmares, hyperarousal (increased anxiety, sleep disturbances) and avoidance" (Cook et al., 2014).

Therefore, it is not unreasonable to conclude that some of these patients have or will develop PTSD after the AWR event. Thus, there are serious consequences to AWR that highlight the need for its prevention.

To date no prospective large scale clinical trials have been performed to determine independent risk factors for an AWR event. However, quality assurance closed claims databases have been examined to try to identify such risk factors retrospectively. Domino et al. reviewed the national database from the American Society of Anesthesiologists Closed Claims Project (Domino et al., 1999). This database is a compilation of closed medical claims from the United States. Although this not an inclusive list of all AWR cases seen in the United States it is representative of the type of patients who seek a malpractice claim. Of the 4,183 claims reviewed, 1.5% were due to a complaint of awareness (Domino et al., 1999). Women (77%) and patients under 60 years of age (89%) were more likely to file an AWR claim (Domino et al., 1999). The majority of patients (68%) who filed an AWR claim were healthy (American Society of Anesthesiologists class I or II on a I-V scale) and undergoing elective surgery (87%) (Domino et al., 1999). After review of the medical records that were available, Domino et al. determined that 33% of the AWR patients received standard of care while a surprising 43% received sub-standard care (Domino et al., 1999). A logistic regression model was developed to look for independent risk factors associated with malpractice claims of AWR. They found that using no volatile anesthetic (adjusted odds ratio (AOR) 3.20 95% confidence interval (CI) 1.88-5.46), female gender (AOR 3.08, 95% CI 1.58-6.06), intraoperative opioid use (AOR 2.12, 95% CI 1.20-3.74) and intraoperative muscle relaxant use (AOR 2.28, 95% CI 1.22-4.25) were independent predictors of AWR claims (Domino et al., 1999). Although these data are interesting, Domino's work is limited to only those cases that actually filed a complaint and

therefore is not a complete picture of all types of patients who have had an experience of AWR and therefore the independent predictors may not translate to a representative sample. More recently, NAP5 also contributed to the literature potential risk factors based on the 300 self-reported events of AWR. They noted that factors that may pre-dispose a patient to AWR were: females (65% of reports), younger adults, obesity (3-fold effect), level of training of the anesthesiologist, history of awareness during a previous anesthetic, operations not occurring during normal business hours, emergent operations, obstetric surgery, cardiothoracic surgery, and the use of neuromuscular blockade agents during the operation (Pandit et al., 2014). Due to the small sample size of AWR patients within the NAP5, no predictive modeling could be performed. However, when comparing Domino's study using closed claimed data and the NAP5 both female sex and the use of neuromuscular blockade during the case are documented as potential indicators that put patients at risk for AWR.

Since so little is known about the mechanisms, true incidence, and risk factors of anesthesia awareness, the Joint Commission on Accreditation of Hospital Organizations issued a sentinel event on anesthesia awareness in 2004 and noted that "Anesthesia awareness is under-recognized and under-treated in health care organizations" (JACHO, 2004). The Joint Commission recommends the development and implementation of AWR policies to educate clinicians, develop a risk profile to determine high risk patients, and discuss the risk factors with patients prior to undergoing anesthesia. They also recommend use of effective anesthesia monitoring tools and appropriate post-operative follow-up by the anesthesiology team for all patients that undergo a general anesthetic. For patients that do have a documented explicit AWR event, the Joint Commission recommends the facilitation of proper counseling avenues. In 2006, the American Society of Anesthesiologists (ASA) followed the Joint Commission and developed

a task force to “stimulate the pursuit and evaluation of strategies that may prevent or reduce the frequency of intraoperative awareness and provide guidance for the intraoperative use of brain function monitors as they relate to intraoperative awareness” (ASA Task Force, 2006).

Causes of Intraoperative Awareness

There are several main causes of AWR documented in the literature from previously described cases; overly “light” anesthesia (87% of AWR cases), increased anesthetic requirements (7% of AWR cases) and malfunction (5% of AWR cases) or misuse of anesthesia delivery systems (4% of AWR cases) (Ghoneim et al., 2009). The NAP5 also introduced several additional potential causes of AWR; the use of neuromuscular blocking drugs (93% of AWR cases) without the use of a nerve stimulator to monitor the actual muscular blockade (9% of AWR cases used the nerve stimulator), type of anesthetic agents used to induce GA, and total intravenous anesthesia (Pandit et al., 2014).

Light anesthesia is necessary in some types of surgical cases (such as trauma) or when the patient is not medically tolerant of the anesthetic dose but the operation is emergent (Ghoneim, 2010). However, light anesthesia can also occur by error in the delivery system with either mechanical malfunction or the clinician not being aware that there is insufficient anesthetic delivery (Ghoneim, 2010). Situations associated with an inability to tolerate normal doses of anesthesia include high risk patients (ASA class IV or V), hypovolemia, patients with limited cardiac reserve, cardiac or trauma operations, and cesarean sections (Ghoneim, 2010).

Some patients require higher than normal anesthetics requirements. Age and hypothermia affect the minimum alveolar concentration (MAC), which is commonly used as a tool to determine adequate anesthesia. The MAC decreases by approximately 6% per decade of

age (Mapleson, 1996). MAC was also determined to be lower for two commonly used inhaled anesthetics (halothane and isoflurane) in hypothermic piglets (Satas et al., 1996). Recently a distinct phenotype (red hair) has been linked to a specific genotype demonstrating that red-haired patients require significantly more inhaled anesthetic requirements (desflurane) than dark-haired patients (Liem et al., 2004). Smith et al. found that rodents showed a rapid tolerance to the inhalational anesthetic nitrous oxide, a phenomenon referred to as tachyphylaxis (Smith et al., 1979). Research on rodents has also shown that chronic exposure to sub-anesthetic doses of nitrous oxide causes tolerance, which is no longer seen six days after the termination of exposure (Koblin et al., 1979). For humans, an acute tolerance to nitrous oxide within 10 to 60 minutes of administration was shown in some patients but the reason was not clear (Ramsay et al., 1992). From the pharmacologic perspective, chronic alcohol and opioid use also increase requirements (McQuay et al., 1982; Shafer et al., 1983; Tammisto and Takki, 1973). Tammisto and Takki reviewed the records of 151 chronic alcoholics and determined that they required higher doses of anesthetics and also 20% of the patients exhibited signs of inadequate anesthesia (Tammisto and Takki, 1973). Arguably, the most important reason for a patient's increase for anesthetic requirements is a history of AWR (Aranake et al., 2013; Ghoneim et al., 2009). Aranake et al. demonstrated a relative risk of 5.0 (95% Confidence Interval 1.3-19.9) to experience another AWR event when a patient had a history of AWR (Aranake et al., 2013). Patients with a history of AWR from three clinical trials focused on AWR prevention were matched with patients who did not have a history (Avidan et al., 2011; Avidan et al., 2008; Mashour et al., 2012); importantly, the control group patients also had at least one risk factor for AWR.

The malfunction or misuse of anesthesia delivery systems are generally due to either lack of servicing, neglect of the care provider to check for proper machine functionality prior to use,

and lack of vigilance by the anesthesia care provider. Increased vigilance of the anesthesia care provider has been shown in one study to decrease the incidence of AWR in cardiac surgery patients (Ranta et al., 1996). Ranta et al. performed a two phase study to address vigilance and anesthesia awareness (Ranta et al., 1996). In phase one, patients were interviewed to determine the incidence and identify the patients who experienced AWR. These findings were reported back to the care providers for high risk cardiac patients including the administration of anesthetics given. For phase two of the study they interviewed patients for documented AWR and noted a decrease in the incidence from 4% to 1.5% between the two phases (Ranta et al., 1996). Ranta et al. concluded that with education and increased vigilance the documented incidence rate in a high risk population can be decreased (Ranta et al., 1996).

There are also several risk factors in addition to the stated known causes that also will put a patient at increased risk for AWR: duration of laryngoscopy and intubation, history of difficult intubation or anticipated difficult intubation, chronic pain patient presenting using high dose opioids, planned use of relaxants during the maintenance of GA, absence of volatile anesthetic or propofol use during maintenance of anesthesia (Ghoneim et al., 2009) and total intravenous anesthesia (ASA Task Force, 2006; Ghoneim, 2010; Pandit et al., 2014).

Techniques for Monitoring Anesthetic Depth: MAC and EEG

The first public demonstration of a surgery under GA occurred in 1846 and approximately one year later the “stages” of GA were described by Snow. The stages of anesthesia essentially used the patient as the “monitor,” basing anesthetic depth on respiratory patterns, muscle tone, and pupillary responses. Because the stages of anesthesia were

qualitative, the potency of anesthetic drugs could not be readily compared to one another (Mashour, 2006).

In 1965 a turning point for modern anesthesia arose with the concept of minimum alveolar concentration (MAC). MAC was developed as a way to quantify the anesthetic effect of inhalational agents (Eger et al., 1965). MAC is defined as the minimum alveolar concentration of inhaled anesthetic that will prevent movement from a noxious stimulus in 50% of subjects (Eger et al., 1965). This concept worked well to quantify differences between different inhalational anesthetics (anesthetic vapors), as potency could be related to a single behavioral endpoint.

MAC is defined in terms of one atmospheric pressure and serves as an indicator for the concentration of the anesthetic (Gelb, 2009). Specifically, the MAC represents the partial pressure of the inhaled anesthetic vapor in the alveoli of the lungs (Gelb, 2009; Quasha et al., 1980). When the partial pressure of any vapor is at equilibrium in the body, all tissues of the body will have the same partial pressure of the vapor, including the alveoli of the lung, the brain, and the blood (Quasha et al., 1980). Therefore, the MAC is a representation of the partial pressure of the vapor in the brain but not the actual concentration of the vapor (Quasha et al., 1980). However, the measurement of the expired partial pressure of the anesthetic vapor is proportional to the actual anesthetic concentration affecting the brain of the specific anesthetic vapor (Gelb, 2009).

To calculate the MAC for a specific time-point for a specific inhaled anesthetic vapor: (Eger, 2001; Gelb, 2009; Quasha et al., 1980).

$$\text{MAC} = \frac{\text{End-tidal expired partial pressure (captured by the attached gas analyzer)}}{\text{Known MAC value constant for that specific inhaled anesthetic vapor}}$$

The MAC for each specific inhaled anesthetic vapor is set for the age of 40. However, MAC decreased by decade of life and therefore the MAC is age adjusted depending on the age of the patient (Eger, 2001; Gelb, 2009; Mashour et al., 2009a; Quasha et al., 1980).

Some common limitations of MAC are: neuromuscular blockade that is commonly used during surgery obscures the behavioral endpoint of MAC, MAC is specific to inhaled agents, and anesthetic effects on mobility are mediated in the spinal cord rather than the brain (Mashour, 2006). In regards to anesthetic monitoring to minimize the probability of consciousness, MAC is not directly related to the neuroanatomic substrate of consciousness (Mashour, 2006). However, MAC monitoring is the standard of care currently for measuring depth of anesthesia. Since MAC has limitations, this has led to a renewed interest in electroencephalographic (EEG) assessment of anesthetic depth, which was suggested by Gibbs et al. in 1937 (Gibbs, 1937).

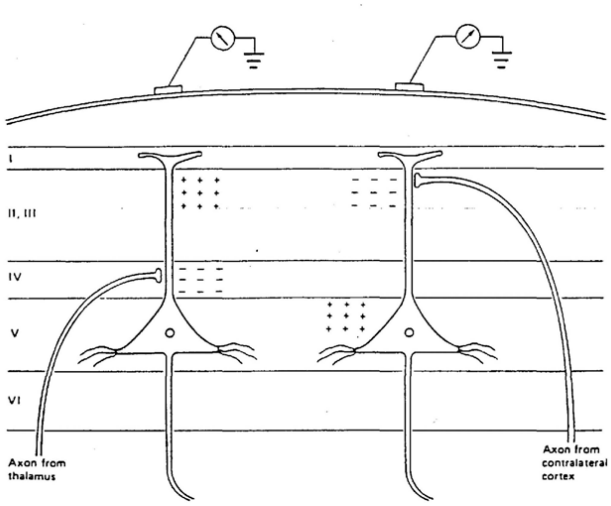


Figure 1: Schematic representation of the synapses, dendrites, of the pyramidal layers of the outer cortex of the brain with the external electrode placement on the scalp. (Reprinted from Olejniczak, P., 2006. Neurophysiologic Basis of EEG. Journal of Clinical Neurophysiology 23 (3), 186-189 with permission from Wolters Kluwer Health)

EEG monitoring was the next logical step for assessing anesthetic depth because while MAC is a pharmacologic measure, the EEG reflects activity of the end-organ of interest, the brain. The EEG signal on the scalp is from the synaptic activity of the pyramidal cells in the superficial layers of the cerebral cortex (Figure 1) (Olejniczak, 2006; Rampil, 1998; Sloan, 2006; Teplan, 2002; Walczak, 2009). Pyramidal cells are a major neuronal cell type in the cortex. They have a long straight dendrite that extends from the cell body up through the cortical layers directly to the surface of the pial surface of the gyrus (Jameson and Sloan, 2006; Rampil, 1998; Teplan, 2002; Walczak, 2009). If the neighboring pyramidal cells have similar altered membrane potentials they combine additively in the extracellular fluid to create a larger current flow that is detected on the scalp (Olejniczak, 2006; Rampil, 1998; Sloan, 2006; Teplan, 2002; Walczak, 2009). Therefore, pyramidal cells can be affected by other local synaptic activity as well as from other neural activity, specifically from the thalamus (Jameson and Sloan, 2006; Sloan, 2006; Teplan, 2002; Walczak, 2009). The EEG electrodes on the scalp register changes in voltage, which can fluctuate with changes in the current that flows between the dendrites and the cortical pyramidal cells (Olejniczak, 2006; Sloan, 2006; Teplan, 2002; Voss and Sleigh, 2007; Walczak, 2009). The voltages are attenuated and smeared by the passage through the cranium and the scalp, which in turn will allow higher voltages to become dominant readings on the EEG (Voss and Sleigh, 2007). Therefore, the EEG monitors used for depth of anesthesia monitoring report a frequency-distorted measure of mean dendritic currents of cortical pyramidal neurons (Sloan, 2006; Teplan, 2002; Voss and Sleigh, 2007; Walczak, 2009).

There are five EEG frequency bands that are influenced by anesthetic administration: gamma, beta, alpha, theta and delta. Gamma waves (25-50 Hz) are traditionally associated with higher cognition and the processing of sensory stimulation in the awake brain (Jameson and

Sloan, 2006; John and Prichep, 2005). Beta waves (12-24 Hz) are traditionally associated with the alert state (Freye and Levy, 2005; Sloan, 2006). Alpha waves (8-12 Hz) are seen when patients are awake but with their eyes closed or in a relaxed state (Freye and Levy, 2005; Jameson and Sloan, 2006; Sloan, 2006; Teplan, 2002). Theta waves (4-8 Hz) are normally seen in sleep (Freye and Levy, 2005; Jameson and Sloan, 2006; Sloan, 2006). Delta waves (below 4 Hz) are traditionally demonstrated in deep sleep (Jameson and Sloan, 2006; Sloan, 2006).

The changes in EEG patterns are drug specific and not consistent across all anesthetics. Numerous studies have been conducted to determine how commonly used anesthetics affect the EEG. Long et al. investigated the EEG determinants of 14 patients emerging from GA with thiopental, nitrous oxide-oxygen, and vecuronium and supplemented either isoflurane (inhaled) or fentanyl (intravenous) (Long et al., 1989). Patients in the supplemented isoflurane group showed “obvious changes” in their EEG before the patient responded to verbal commands to open their eyes (Long et al., 1989). This was not seen in patients supplemented with fentanyl during emergence of GA (Long et al., 1989). Long et al. concluded that when using isoflurane, EEG determinants can be used to guide when a patient will emerge from GA but not when a fentanyl-supplemented GA is used (Long et al., 1989). Drummond et al. investigated the median frequency, spectral edge frequency, frequency band power ratio, total power, and dominance shift of the EEG recording to determine if one specific component can be a predictor of the depth of anesthesia during the emergence phase from isoflurane-nitrous oxide based anesthesia in 15 surgical patients (Drummond et al., 1991). The conclusion was that no one specific component of the EEG can be used as predictor for the depth of anesthesia and that at best, the EEG components can only be used as a trend when used in conjunction with other commonly used clinical signs to measure the depth of anesthesia (Drummond et al., 1991). Sebel et al.

investigated movement on surgical incision (noxious stimuli) in patients with GA induced with thiopental but maintained with three different MACs of isoflurane and found that for patients who did not move, there was a statistically significant difference in their delta power on the EEG (Sebel et al., 1995). Rundshaen et al. further validated the change in the delta power on the EEG during intubation (noxious stimuli) when thiopental and fentanyl were used (Rundshagen et al., 2004). Sakai et al. sought to investigate the use of ketamine and propofol infusions in 48 patients. Patients received either propofol infusion or ketamine plus propofol infusion in varying doses. They concluded that when ketamine is included with propofol, less propofol is needed to have clinical significant endpoints for hypnosis (Sakai et al., 1999). Although the addition of ketamine decreases the dose of propofol to reach hypnosis endpoints, it did not depress the EEG in proportion to the hypnotic effects (Sakai et al., 1999). Gamma waves were shown to be significantly decreased when propofol induction was used in surgical patients, whereas ketamine had the opposite effect (Lee et al., 2009). Ketamine increased the power in the gamma bandwidth and decreased the power in the alpha wave on the EEG (Lee et al., 2013). In human subjects, alpha oscillations appear prominently in the occipital lobe in the resting state with eyes closed. However, alpha power and coherence is reduced in the occipital lobe and increased in the frontal lobes in association with propofol-induced unconsciousness (Purdon et al., 2013). This reverses with return of consciousness. Propofol and sevoflurane, when used as a GA for maintenance of anesthesia, both demonstrated alpha oscillations on the EEG (Akeju et al., 2014). Sevoflurane, but not propofol, demonstrated increased power in the theta component of the EEG (Akeju et al., 2014). The evidence presented suggests that there is not one specific component of the EEG that changes uniformly under anesthesia that could serve as the sole predictor of the

depth of anesthesia. Therefore, when using the EEG, either processed or un-processed, the type of anesthetic used must be considered when interpreting the relevant changes in the EEG.

EEG Transformation to Bispectral Analysis for Anesthesia Depth Monitoring

The EEG is one of several voltage waveforms present on the scalp of a patient. In the awake patient there is an electrocardiogram (ECG) from the carotid artery in the neck, electromyography (EMG) from the muscles of the face, and electrooculography (EOG) from the muscles around the eye. The patient's body also acts as an antenna and the different voltage waveforms interact with the EEG. Therefore, a well-designed amplifier is needed to remove or attenuate the unwanted signals. For example, the EMG has some overlap with the EEG in the gamma bandwidth. To rectify this, the raw EEG tracing is amplified and then put through a band-pass filter to quantify and separate the EEG from the EMG. Some depth of anesthesia monitors report the EMG with the EEG.

Signal processing is mandatory to remove any artifacts that are attributable to other electrical activities. For the EEG, an analog signal must be transformed into a digital signal. By definition, analog signals are continuous and smooth where digital signals represent discrete points in time and the values are set to a specific time point (Rampil, 1998). The EEG varies smoothly over a set time and is therefore an analog signal on the scalp (Rampil, 1998). When an analog signal is translated to digital, it occurs at a specific time point (sampling interval) which is known as sampling or digitizing (Figure 2) (Schwilden, 2006). There is a loss of fidelity of the smooth continuous EEG signal when digitizing occurs at set specific time points. The number of time points is selected using a sample rate (expressed in hertz (Hz)) which is the reciprocal of the sampling interval (Rampil, 1998). The sampling interval is determined using Nyquist-Shannon's

sampling theorem which states that the sampling rate should be more than twice the highest expected frequency of the EEG signal (Rampil, 1998; Schwilden, 2006). Current systems that process EEG from an analog to a digital signal recommend setting a sampling rate that is 4 to 10 time higher than the highest expected frequency as well as to use a low pass filter (high frequency filter) to remove any frequencies outside the known range of EEG frequencies (0.5-30 Hz) (Rampil, 1998; Sloan, 2006; Walczak, 2009).

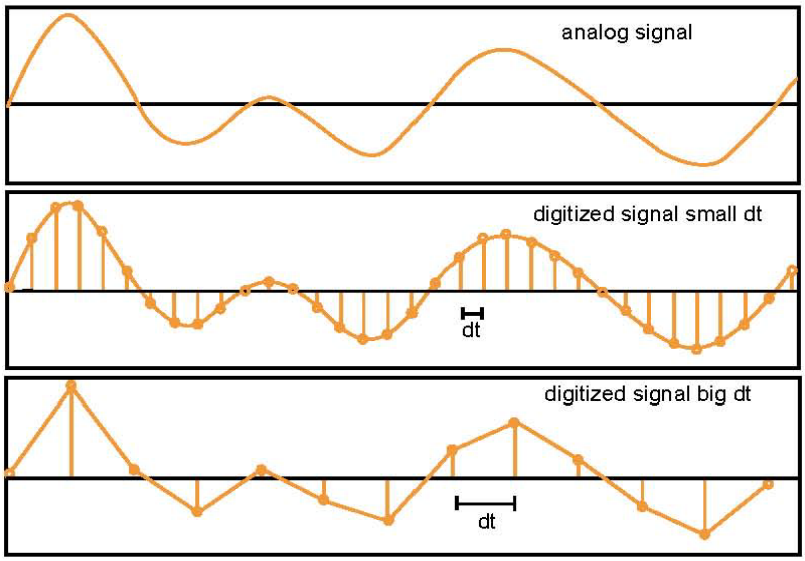


Figure 2: Transformation from an analog to digital sample resulting in a loss of fidelity. Using Shannon's sampling theorem this sample was digitized using a sampling rate of twice the highest expected frequency. (Reprinted from Best Practice & Research Clinical Anaesthesiology, Vol 20, No 1, Schwilden, H., Concepts of EEG processing: from power spectrum to bispectrum, fractals, entropies and all that, 31-48 (2006), with permission from Elsevier)

A time domain analysis is one way to analyze the EEG by examining how the voltage changes over time (Rampil, 1998; Sigl and Chamoun, 1994). Any signal can be expressed in terms of its sinusoids components (sin and cosine waves) (Sigl and Chamoun, 1994). The sin and cosine wave can be expressed as a function of time, t, and described by their amplitude, frequency and phase angle with the formula: (Rampil, 1998; Sigl and Chamoun, 1994)

$$x(t) = \text{amplitude} * \sin [\text{phase angle} + 2\pi(\text{frequency})(\text{time})]$$

where: amplitude = one half the peak to peak voltage

frequency = number of complete cycles per second

phase angle = offset of the wave signal from time 0

Complex EEG waveforms which may represent all five common frequencies bands can be transformed from the time domain to a frequency domain using Fourier transformation (or spectral analysis) based off of Fourier's Theorem (Rampil, 1998; Sigl and Chamoun, 1994; Tonner and Scholz, 2006). Fourier's Theorem allows any waveform to be shown as the sum of its respective sin waves with different frequencies, amplitudes, and phase angles (Walczak, 2009). The Fourier Transformation is composed of discrete points that correspond to a specific frequency (Equation 1) (Sigl and Chamoun, 1994). The range of the frequency for equation one is determined by the sampling rate (fs) and will span from a frequency of 0 to $fs/2$ (Sigl and Chamoun, 1994). Every component frequency will have a power. The frequency domain transformation is normally presented graphically as the magnitude of the frequency that component contributed to the signal (or power). The power of each component is then used to compute the power spectrum (Equation 2) (Sigl and Chamoun, 1994). The result of the Fourier transformation, with the power spectrum, is the generation of a frequency spectrum as a function of power (Figure 3), which will allow the user to quantify the extent to which frequency

$$X(f) = 2/M \sum_{k=0}^{M-1} x(k)\, e^{-ik2\pi f}.$$

Equation 1: Fourier Transformation where the time domain component of the EEG is transformed into a frequency range component of the EEG. M = number of samples, i = $\sqrt{(-1)}$, and x(k) = the original signal (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., equation 3 with kind permission from Springer Science and Business Media)

$$P(f) = |X(f)|^2.$$

Equation 2: Power spectrum of the Fourier Transformation (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., equation 4 with kind permission from Springer Science and Business Media)

components are present in the EEG signal (Freye and Levy, 2005; Rampil, 1998; Sigl and Chamoun, 1994; Tonner and Scholz, 2006). Fourier transformation is quite laborious, even with a computer, so in 1965 Cooley and Tukey published an algorithm for Fourier series computation of digitized data, which was called Fast Fourier Transformation and is now used for processing of EEG signals (Freye and Levy, 2005; Rampil, 1998).

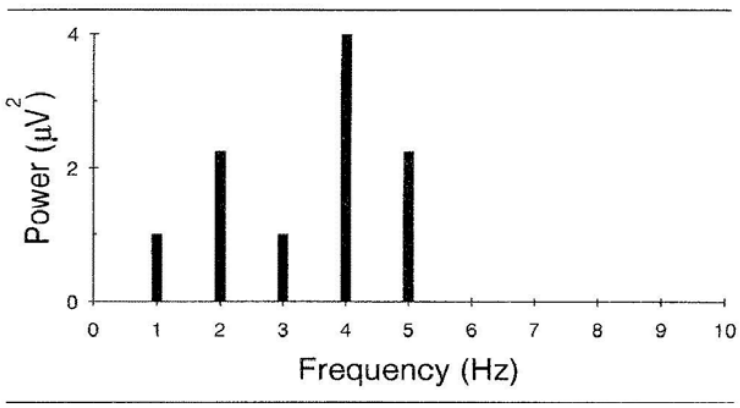


Figure 3: Power spectrum transformation from the Fourier Transformation and shows the frequency distribution of the component sinusoid as a function of power. (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Figure 5 with kind permission from Springer Science and Business Media)

Since the EEG is a complex signal and is non-linear in nature, one sinusoid component may interact with another sinusoid component and therefore is not a function of just one frequency. This interaction is referred to as phase coupling. For example, assume a simple non-linear system where the output is the square of the input signal (Equation 3) (Sigl and Chamoun, 1994). In the output, ($f1$ + $f2$), ($f1$ - $f2$), $2f1$, and $2f2$ are all dependent on the input

$$y(k) = x^2(k).$$

$$\begin{aligned} \textit{INPUT:}\quad x(k) &= \cos(f_1 k + \theta_1) \\ &\quad + \cos(f_2 k + \theta_2) \\ \textit{OUTPUT:}\quad y(k) &= 1 + \cos[(f_1 + f_2)k + (\theta_1 + \theta_2)] \\ &\quad + \cos[(f_1 - f_2)k + (\theta_1 - \theta_2)] \\ &\quad + \tfrac{1}{2}\cos(2f_1 k + 2\theta_1) \\ &\quad + \tfrac{1}{2}\cos(2f_2 k + 2\theta_2), \end{aligned}$$

Equation 3: Intermodulation Products [($f1$ + $f2$), ($f1$ - $f2$), $2f1$, and $2f2$] are dependent on $f1$ and $f2$. The representative phase angles of the intermodulation products are also dependent on the input. Therefore, they are termed "Phase Coupled." (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Equations 5 and 6 with kind permission from Springer Science and Business Media)

signal $f1$ and $f2$. Therefore, these are termed intermodulation products (IMP) (Sigl and Chamoun, 1994). The corresponding phase angles of the IMP output signal are also dependent on the input signal and are termed phase coupled. Phase coupling implies that the sinusoidal components may have a common generator (Rampil, 1998). Phase coupling is typical in the brain and you can use the degree of phase coupling to investigate relationships in changes to the level of sedation seen with the use of anesthetics. To quantify the amount of phase coupling in the system, a bispectral analysis is performed, which reflects the phase coupling across two frequencies (Hagihira et al., 2001).

The bispectrum of the EEG measures the correlation of phases between different frequency components and quantifies the relationship among three sinusoidal frequencies (the triplet): frequencies $f1$ and $f2$ and modulation component at frequency $f1 + f2$ (Rampil, 1998; Sigl and Chamoun, 1994). For each triplet, the bispectrum, $B(f1,f2)$, is calculated based on the Fourier transformation (Equation 4) (Rampil, 1998; Sigl and Chamoun, 1994). When computing the bispectrum, the signal is divided into relatively short epochs for calculation and then averaged over a number of epochs to provide a stable estimate of the true bispectral values (Rampil, 1998). Therefore, the bispectrum reflects the phase coupling between the component sinsuoids as well as the power information (Rampil, 1998; Sigl and Chamoun, 1994).

$$B(f_1, f_2) = \left| \sum_{i=1}^{L} X_i(f_1)\, X_i(f_2)\, X_i^*(f_1 + f_2) \right|,$$

Equation 4: The Bispectrum – Represents the actual amount of phase coupling between the component sinusoids. (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Equation 8 with kind permission from Springer Science and Business Media)

At any specific frequency you can have a single sinusoid component or intermodulation products resulting from phase coupling. There is no way for the system to tell them apart from one another, but the interest really lies in how much phase coupling is in the signal. Therefore, to quantify the amount of phase coupling in the signal, the bicoherence is needed. To calculate the bicoherence, you first need to calculate the maximum amount of phase coupling that is possible. This is referred to as the real-triple product (RTP) (Equation 5) (Sigl and Chamoun, 1994). The bicoherence (BIC) is therefore calculated as a ratio of the actual amount of phase coupling in the system (bispectrum) to the square root of the maximum amount of phase coupling possible (RTP) (Equation 6) (Sigl and Chamoun, 1994). The bicoherence is presented as a percentage of phase coupling from 0% to 100% (Sigl and Chamoun, 1994). Figure 4 is a representation of the signal transformation from a time domain, to frequency domain, to bispectrum analysis of a patient prior to induction of anesthesia.

$$\mathrm{RTP}(f_1, f_2) = \sum_{i=1}^{L} P_i(f_1)\, P_i(f_2)\, P_i(f_1 + f_2).$$

Equation 5: Real Triple Product – Represents the maximum amount of phase coupling the sample can have. (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Equation 9 with kind permission from Springer Science and Business Media)

$$\mathrm{BIC}(f_1, f_2) = 100\, \frac{B(f_1, f_2)}{\sqrt{\mathrm{RTP}(f_1, f_2)}}.$$

Equation 6: Bicoherence – Represents the normalized amount of phase coupling in the sample. (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Equation 10 with kind permission from Springer Science and Business Media)

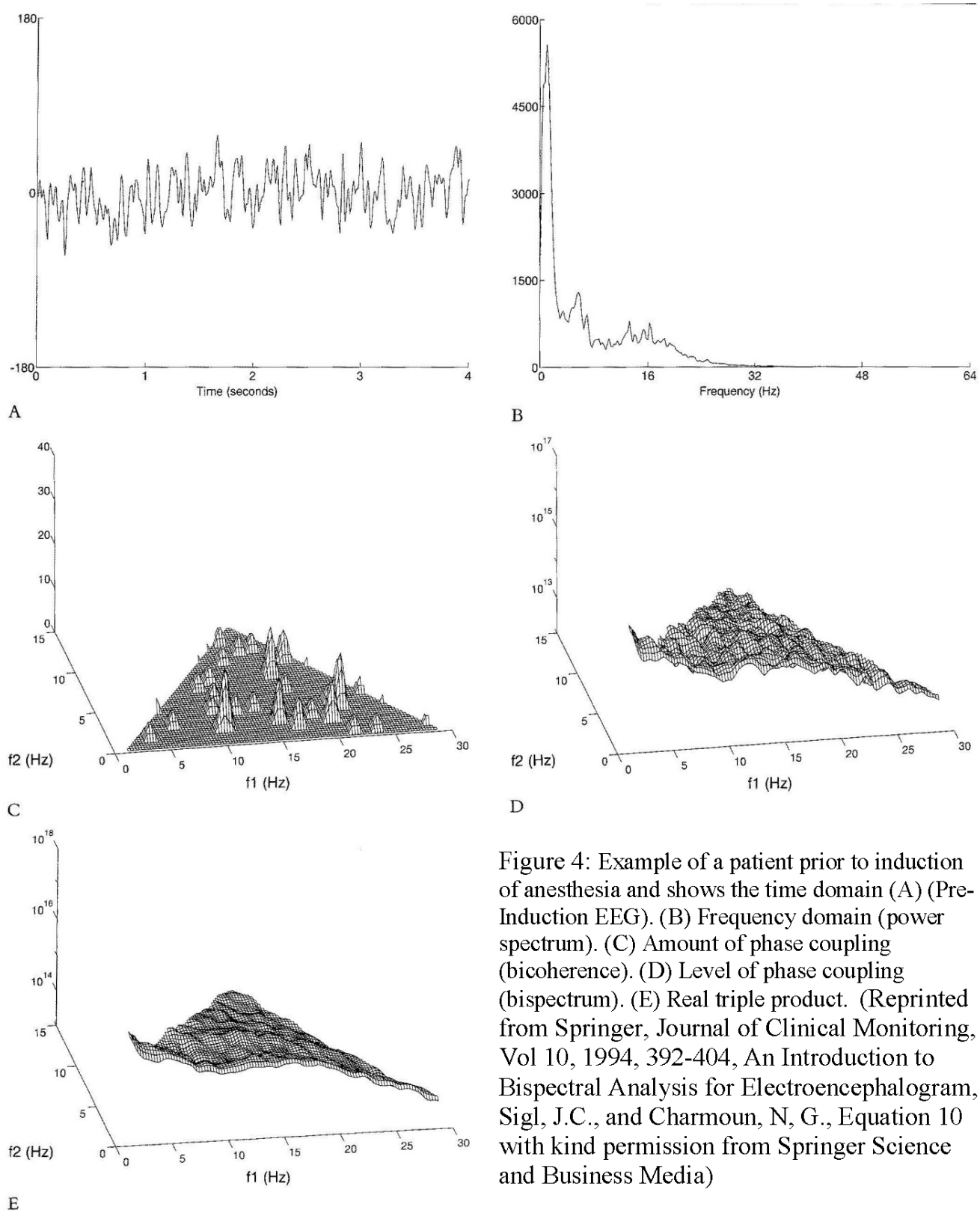


Figure 4: Example of a patient prior to induction of anesthesia and shows the time domain (A) (Pre-Induction EEG). (B) Frequency domain (power spectrum). (C) Amount of phase coupling (bicoherence). (D) Level of phase coupling (bispectrum). (E) Real triple product. (Reprinted from Springer, Journal of Clinical Monitoring, Vol 10, 1994, 392-404, An Introduction to Bispectral Analysis for Electroencephalogram, Sigl, J.C., and Charmoun, N, G., Equation 10 with kind permission from Springer Science and Business Media)

Calculation of the Burst Suppression to be Used in Anesthesia Depth Monitoring

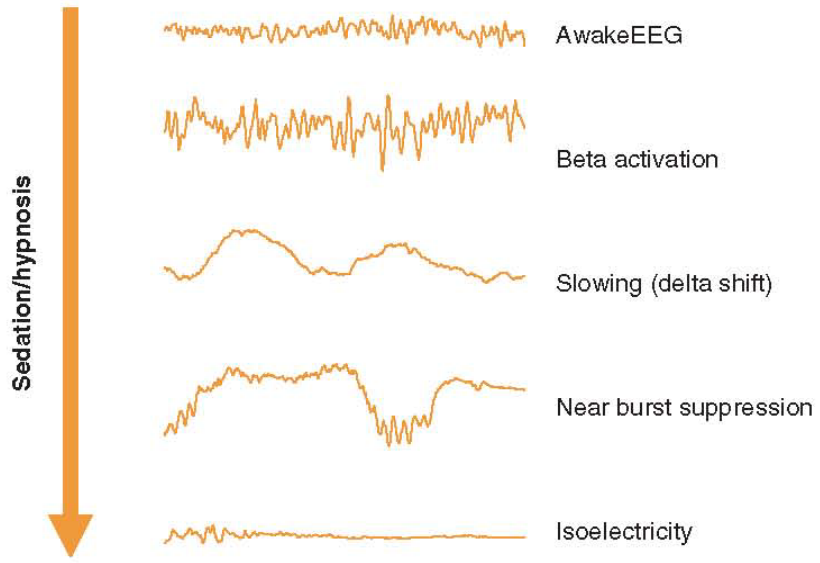


Figure 5: EEG changes induced by anesthetics from awake to near burst suppression. (Reprinted from Best Practice & Research Clinical Anaesthesiology, Vol 20, No 1, Tonner, P.H., Bein, B., Classic electroencephalographic parameters: Median frequency, spectral edge frequency etc, 147-159 (2006), with permission from Elsevier)

During levels of deep anesthesia, burst suppression is seen in the time domain signal; an EEG morphology that—unlike other features of the EEG during anesthesia—is not observed during natural sleep. Burst suppression is defined as periods of high or normal voltage alternating to periods of time with low or isoelectric voltages (Rampil, 1998; Sigl and Chamoun, 1994; Tonner and Bein, 2006).

Burst suppression is induced by large doses of anesthetic and can be quantified by reporting the burst suppression ratio (Figure 5) (Rampil, 1998; Sarkela et al., 2002; Tonner and Bein, 2006). The burst suppression ratio equals the total time of burst suppression divided by the epoch length used to analyze the sample (Sarkela et al., 2002).

Calculation of the Bispectral Index based on EEG Transformation

The Bispectral Index (BIS) is a complex parameter that is composed of a time domain (burst suppression analysis), frequency domain (power spectrum, bispectrum interfrequency phase relationships) and high order spectral subparameters and is proprietary in nature (Johansen, 2006; Rampil, 1998). To calculate the BIS, based on the EEG transformation

principles discussed earlier, the EEG is filtered to exclude the high and low frequency artifacts of the signal (Rampil, 1998). After the first filter pass, the signal is divided into epochs of 2 seconds in length (Rampil, 1998). There are a series of algorithms that the signal is processed through with the goal to remove or ignore artifacts (Rampil, 1998). These algorithms can remove ECG or pacemaker spikes from the signal and interpolate the missing EEG data. These epochs can therefore still be used in the processing of BIS. Eye blinking from the EOG is considered noise and is excluded from the analysis. The remaining epochs are then checked for low-frequency electrode noise and if some are detected another filtering process is applied to reject the low frequencies. The variance is also calculated for each epoch of the EEG (Rampil, 1998). The variance of a specific epoch is investigated by looking at the average of the previous recent epochs of the raw EEG waveform. If there is a difference, the new epoch will be marked as noisy and discarded from the analysis; however, that epoch variance will be incorporated into making a new updated average. This change in the running average of the epoch variances will allow for a slow adaptation to changes of new variances. Once the EEG epoch is artifact free or corrected, the degree of burst suppression is calculated using the time domain of the epoch. The degree of burst suppression calculation into the BIS

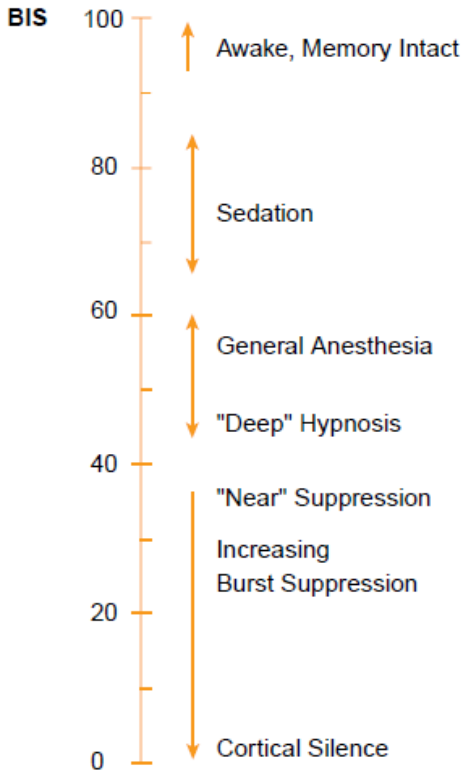


Figure 6: Dimensionless BIS value from 0 (cortical silence) to 100 (fully awake and memory intake). (Reprinted from Best Practice & Research Clinical Anaesthesiology, Vol 20, No 1, Johansen, J.W., Update on Bispectral Index Monitoring, 81-99 (2006), with permission from Elsevier)

is done with two separate algorithms; burst suppression ratio (BSR) as described earlier and QUAZI suppression index (detects burst suppression in the presence of wandering baseline voltages) (Rampil, 1998). Next, the waveform data are ready to be converted to the frequency domain per the Fast Fourier Transformation processes and the bispectrum is calculated. The actual calculation of the BIS number is a proprietary combination of the EEG subparameters already explained. The BIS value was derived from experimental data on approximately 5,000 hours of recording on 1,500 anesthetics that varied in the mode and type of drug given (Sigl and Chamoun, 1994). The BIS reports a dimensionless number from 100 (awake) to 0 (isoelectric) that decreases continuously with decreasing levels of consciousness and that incorporates the power, frequency, beta activation, burst suppression, and bicoherence (Figure 6) (Gelb, 2009; Johansen and Sebel, 2000; Rampil, 1998). The BIS that is presented to the observer is an average value that is derived from the previous 60seconds of usable data (Rampil, 1998).

BIS Placement

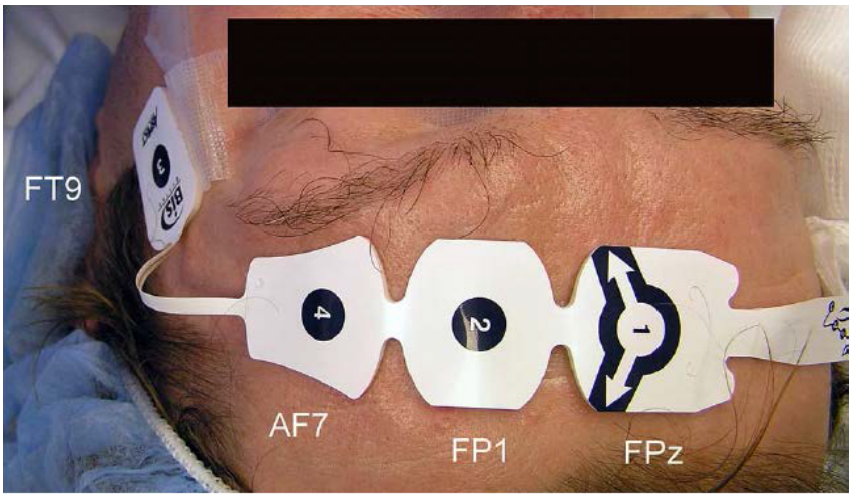


Figure 7: Patient positioned supine with the BIS monitor adhered to the anterior-superior view of the forehead. (Reprinted from Best Practice & Research Clinical Anaesthesiology, Vol 20, No 1, Johansen, J.W., Update on Bispectral Index Monitoring, 81-99 (2006), with permission from Elsevier)

Clinically, the BIS was approved by the Food and Drug Administration for human subjects use in 1996 and uses a series of four electrodes that are placed along the forehead of the patient according to the international 10-20 electrode nomenclature placement to monitor two channels of the EEG in a proprietary ipsilateral frontal-

temporal montage configuration (Figure 7 and Figure 8) (1991; Johansen, 2006; Teplan, 2002; Watson et al., 2008). The four electrodes are placed on different coronal lines of the brain: frontoparietal (FPz amd FP1), anterior frontal (AF7) and frontotemporal (FT9) (1991; Johansen, 2006). The sensor placed on AF7 (lead 4) is the grounding electrode and measures the electromyography of the frontalis muscle of the forehead (Johansen, 2006). The electrodes are placed in a montage configuration that allows for amplification of electrical activity in the brain based on a pair of scalp electrodes (Sloan, 2006). The proprietary BIS sensor montage is from lead 1 to lead 3 and lead 2 to lead 3 (Figure 7) (Johansen, 2006). Each electrode is encased in a small plastic sponge that is embedded in a conductive gel to have good electrical contact with the patient's skin. The electrode impedance can be less than 5kohms if the skin is prepped via an alcohol wipe prior to placement (Glass et al., 1997; Rosow and Manberg, 2001). The four electrode configuration allows the monitor to perform an automatic impedance check (Rosow and Manberg, 2001). The electrodes are connected to the BIS module via a single cable for display to the clinician.

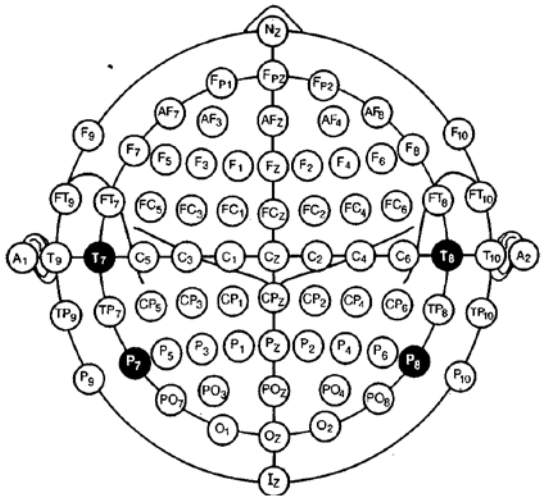


Figure 8: Superior view of the international 10-20 electrode nomenclature placement on the head. (Reprinted from Sharbrough, F., 1991. American Electroencephalographic Society Guidelines for Standard Electrode Position Nomenclature. Journal of Clinical Neurophysiology 8 (2), 200-202 with permission from Wolters Kluwer Health)

Anesthetic Effects on the BIS

The BIS is purported to measure a state of the brain and not the concentration of a specific anesthetic drug. It is therefore necessary to interpret how the BIS value will change

depending on the medication type correlated to the sedation level of the patient. The raw EEG component change with a specific anesthetic, therefore the processed EEG in the BIS value also reacts differently depending on the anesthetic of choice.

GA is associated clinically with a decrease in the average EEG frequency and the increase in the average power (Rosow and Manberg, 2001). However, most drugs used in GA do not have a simple monotonic relationship to dose response in respect to the cases in EEG frequency and power (Rosow and Manberg, 2001). The Bispectral analysis in the BIS is advantageous to this situation since it is using the harmonic and phase relationship (bicoherence) of the EEG.

In 1997, shortly after the approval for patient use, Glass et al. sought to determine the sedation levels in relationship to the BIS values and drug concentrations in the blood for four commonly used anesthetics and analgesics: propofol, midazolam, isoflurane, and alfentanil in healthy volunteers (Glass et al., 1997). Each patient had a recorded BIS value and level of drug concentration in the blood to correspond to the modified observer's assessment of alertness/sedation scale which ranges from 0 (does not respond to noxious stimulus) to 5 (responds readily to name spoken in normal tone) (Glass et al., 1997). Glass et al. determined that for propofol, the BIS value correlated significantly better to levels of sedation than the blood concentration (Glass et al., 1997). For midazolam and isoflurane, the BIS value was equally as effective as the blood concentration levels in predicting levels of sedation (Glass et al., 1997). No patients lost consciousness from alfentanil and therefore were excluded from the analysis (Glass et al., 1997). All three subsequent group data were then pooled for BIS values to determine the BIS value at which unconsciousness was induced. 50% of patients were unconscious at a BIS value of 67 and 95% of patients were unconscious at a BIS value of 50

(Glass et al., 1997). Glass et al. was the first group to prove that BIS may be a valuable tool in monitoring sedation and unconsciousness in patients under anesthetics. It is therefore common practice to titrate anesthetics to a BIS value of 40-60 (Glass et al., 1997).

Since Glass et al. published the first article assessing the utility of the BIS monitor, several other investigators have assessed the usability of the BIS monitor in different clinical situations using a variety of commonly used anesthetics. Liu et al. sought to evaluate the effectiveness of BIS in determining the level of consciousness for patients under propofol

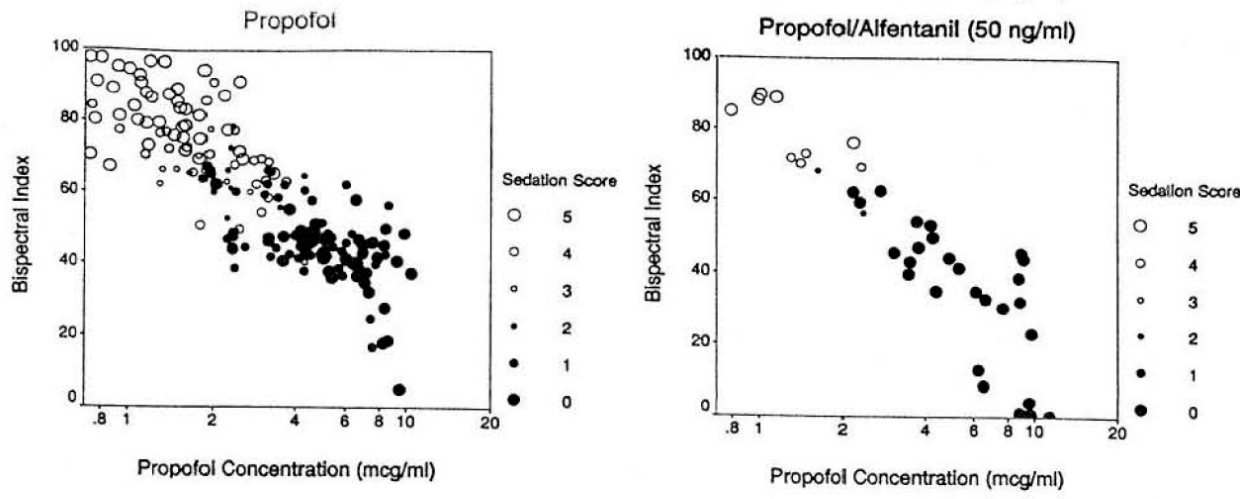


Figure 9: The BIS value correlates well with Propofol alone and Propofol with an opioid (Alfentantil) and the level of sedation. Level of sedation = 0 means no response to noxious stimuli (trapezius squeeze). (Reprinted from Iselin-Chaves, I.A., Flaishon R., Sebel, P.S., 1998. The Effect of the Interaction of Propofol and Alfentanil on Recall, Loss of Consciousness, and the Bispectral Index. Anesthesia and Analgesia 87, 949-955 with permission from Lippincott Williams & Wilkins International Anesthesia Research Society)

sedation for regional anesthesia procedures (Liu et al., 1997). They determined that BIS was a useful tool and showed that both BIS and explicit recall decreased with increasing levels of sedation (Liu et al., 1997). Iselin-Chaves et al. evaluated the BIS value when an anesthetic (propofol) plus an opioid (alfentanil) were used in conjunction with one another in healthy volunteers (Figure 9) (Iselin-Chaves et al., 1998). They concluded that BIS correlated well with level of sedation even in the presence of an opioid (Iselin-Chaves et al., 1998). Interestingly,

Iselin-Chaves et al. also discovered that BIS responds to painful stimuli by increasing in value (Iselin-Chaves et al., 1998). However, this response can be ablated by giving opioids or increasing the propofol concentration to control the pain from the stimuli (Iselin-Chaves et al., 1998). Nitrous oxide is a commonly used gas during GA and therefore the use of nitrous oxide as it relates to the BIS value was a necessary area of research. Rampil et al. sought to determine the effects on the BIS and EEG when healthy young adult volunteers where given nitrous oxide in five different concentrations (Rampil et al., 1998). It was determined that nitrous oxide does cause an increase in the theta and beta waves in the EEG, however, the BIS values did not change and the volunteers remained responsive (Figure 10) (Rampil et al., 1998). Barr et al. shared the interpretation that nitrous oxide does not affect the BIS values even when the subject is rendered unconscious (Barr et al., 1999). Puri followed up these finding on nitrous oxide and published a case report on two patients who underwent open heart surgery with nitrous oxide and isoflurane for anesthesia (Puri, 2001). The BIS values were high when nitrous oxide was used but decreased when the nitrous oxide was stopped and then increased again once re-initiated (Puri, 2001). This suggests that perhaps the use of nitrous oxide

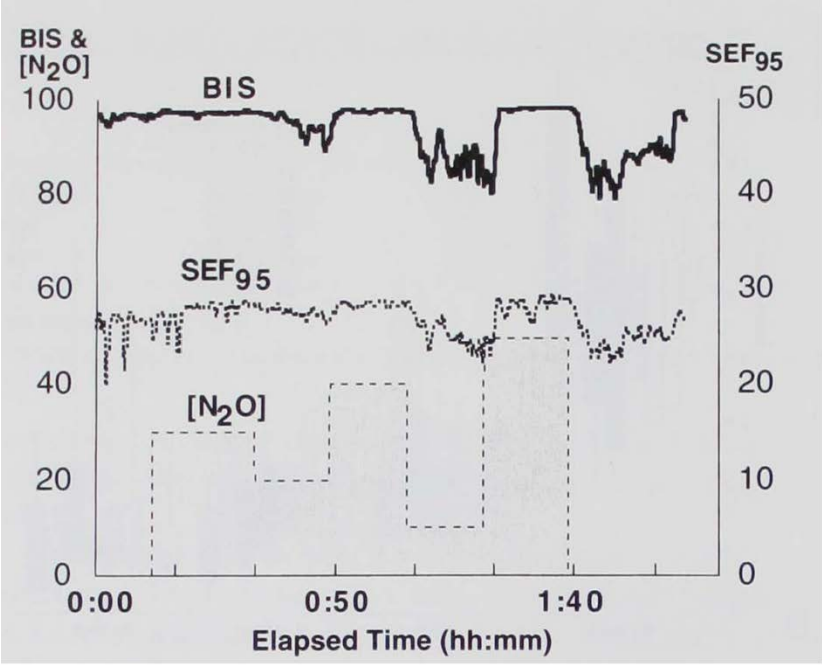


Figure 10: BIS values relatively unchanged after nitrous oxide administration in healthy volunteers (Reprinted from Rampil, I.J., Kim, J., Lenhardt. R. Bispectral EEG Index during Nitrous Oxide Administration. Anesthesiology 89 (3), 671-677 with permission from Wolters Kluwer Health)

in conjunction with other inhaled anesthetics may change the BIS values to a higher value and therefore should not be used to guide a clinician's decision making process to measure adequate depth of anesthesia. Sevoflurane, which is another commonly used anesthetic vapor during GA, did show a decrease in the BIS value when the subject was rendered unconscious (Figure 11) (Barr et al., 1999).

Although not an anesthetic, the effect of neuromuscular blockade medications on the BIS must also be understood. Neuromuscular blockade agents are commonly used for part of or the entire surgical case. Messner et al. sought to determine the relationship between electromyographic activity and the BIS value (Messner et al., 2003). It was discovered that fully awake volunteers had a substantial decrease in BIS (down to 9) due to the use of muscle blockade and concluded that BIS may not be a reliable marker for assessing sedation in patients where neuromuscular blockade is needed (Messner et al., 2003).

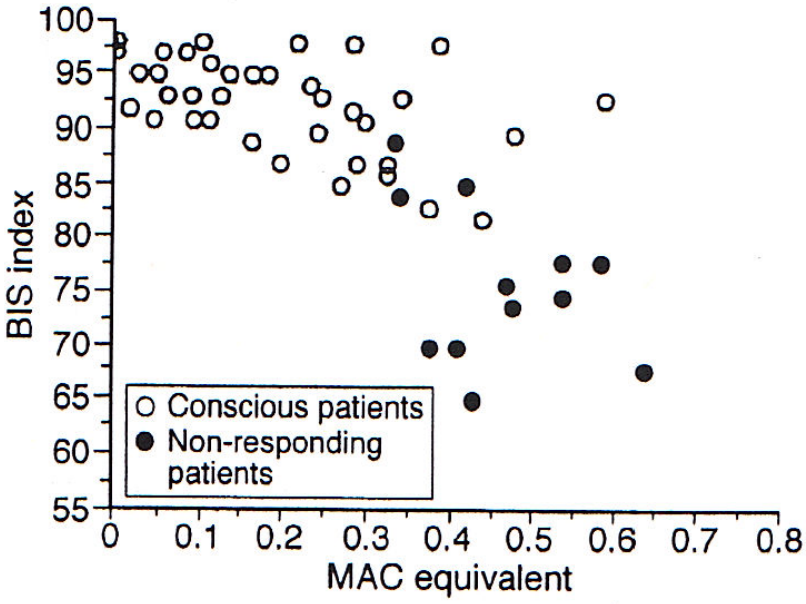


Figure 11: Decrease in BIS index with the use of sevoflurane when the subject was rendered unconscious (Reprinted from Barr, G., Jakobsson, J.G., Owall, A., Anderson, R.E., Nitrous oxide does not alert bispectral index: study with nitrous oxide as sole agent and as an adjunct to i.v. anaesthesia , British Jounral of Anaesthesia, 1999, 82 (6), 827-830, by permission of Oxford University Press)

Around the same time, investigators hypothesized that BIS monitoring could help to decrease emergence times from anesthesia since the care provider could titrate the anesthetic to a targeted BIS value and ensure the patient did not have excessive anesthesia that would delay

emergence. Gan et al. developed a prospective trial in which all patients received the same anesthetic protocol consisting of propofol, alfentanil and nitrous oxide (Gan et al., 1997). Half of the patients received BIS monitoring titrating anesthetics to reach BIS values between 40 and 60 during the case and half did not. They found that patients in the BIS monitoring groups received less propofol during the case and had significantly faster recovery times than the traditional monitoring group (Gan et al., 1997). This could be a potentially important finding to help with the increasing cost in medical care. However, Yli-Hankala et al. also studied 80 patients undergoing surgery (Yli-Hankala et al., 1999). Half of the patients were randomly allocated to BIS monitoring and half the patients were monitored per standard of care. Yli-Hankala et al. also found that the patients receiving BIS monitoring had a decrease in the use of anesthetics (propofol and sevoflurane) and quicker recovery times but concluded the observed benefit did not justify the cost of the monitoring system (Yli-Hankala et al., 1999). Johansen et al. analyzed profiles of 1,552 adult patients emerging from GA on and determined that when the BIS was targeted and maintained between 50-65, patients had reduced emergence and recovery times (Johansen et al., 2000). These studies suggest that with BIS monitoring targeted to a specific value, the patients may need less anesthetic, emerge from anesthesia quicker and having a faster post-anesthesia recovery profile. However, the results of these small efficacy trials have not been validated by effectiveness data (Gan et al., 1997; Johansen et al., 2000; Yli-Hankala et al., 1999).

The BIS monitor, along with other EEG-based modules, has limitations. There are several commonly used drugs or devices that can interfere with the BIS function in routine clinical care: use of depolarizing muscle relaxant, activation of electromagnetic equipment or devices, patient warming systems or planned hypothermia induction (ASA Task Force, 2006).

Also, drugs such as ketamine and nitrous oxide have different receptor targets than the more commonly used GABAergic drugs and may be associated with erroneous values (Jameson and Sloan, 2006). Rampil et al. determined that although the EEG changes during nitrous oxide administration for sedation, the BIS value did not change (Rampil et al., 1998). The patient's pre-existing co-morbidities may also may confound BIS values. Patients with Alzheimer's disease, severe hypoglycemia, cerebral ischemia, and neurologic diseases have been shown to have lower BIS values (Mashour, 2006; Schnider et al., 1998). Some unforeseen intraoperative events such as cerebral ischemia or hypoperfusion, gas embolism, and unrecognized hemorrhage may also produce a rapid change in BIS values even though the anesthetic regimen remained unchanged (ASA Task Force, 2006).

BIS Prospective Clinical Trials

The correlation of BIS values with sedation levels has been established in healthy volunteers or in closely controlled trials. However, the utility of the BIS monitor in preventing AWR had not been addressed until 2004. Since that time there have been three large randomized trials investigating the utility of BIS when compared to standard of care monitoring in clinical practice and targeted end-tidal anesthetic concentrations for high risk surgical patients under general anesthesia: the B-Aware trial, the B-Unaware trial, and the BAG-RECALL trial.

The B-Aware trial assessed whether BIS monitoring decreases the incidence of AWR in high risk surgical patients compared to standard of care monitoring techniques (Myles et al., 2004). This was a multi-center double-blinded randomized trial in which patients were randomly assigned to BIS monitoring or routine care. All patients received GA per their anesthesia care provider and there were no set anesthetic protocols for the study. All patients received a BIS

electrode placed regardless of randomization but only those that were randomized to BIS monitoring were actually connected to the BIS monitors for intraoperative monitoring. For patients allocated to the BIS group, anesthesia was adjusted to maintain a targeted BIS value between 40 and 60 during the surgical case from laryngoscopy (intubation) to surgical closure. BIS was recorded per the anesthesia care provider every 5 minutes for the first hour and every 10 minutes after the first hour. All patients were interviewed for AWR post-operatively at 2-6 hours, 24-36 hours and 30 days. Any potential AWR patients were further evaluated by a committee of three experienced anesthesiologists. The patients were coded as awareness, possible awareness or no awareness. 2,503 patients were enrolled but 40 were excluded due to various reasons (Myles et al., 2004). All patient baseline characteristics were similar between the two groups. At the 30 day post-operative interview, the BIS group (n=2, 0.17%) had a significantly lower incidence of AWR than the standard of care group (n=11, 0.91%) (Myles et al., 2004). The combination of possible or definite AWR events showed no statistical difference between the groups: 22 in the BIS group (1.8%) and 27 in the standard of care group (2.2%) (Myles et al., 2004); however, “possible awareness” cases at that time included patients who dreamt under anesthesia, which is no longer thought to be a “near-miss” awareness event (Samuelsson et al., 2008). Myles et al. concluded that their B-Aware trial proved that BIS monitoring could reduce the relative risk of awareness by 82% (95% CI 17-98%) in high risk general anesthesia surgical patients (Myles et al., 2004). They also noted that the BIS patients did not have a significant difference in the time to recover from GA than patients with normal standard of care monitoring. Although this trial was performed in a routine clinical setting and therefore the data are generalizable to the high risk surgical population, it is not generalizable to patients at all risk levels of awareness. Myles et al. therefore suggested the use of BIS

monitoring is warranted in patients at high risk of AWR that are undergoing a general anesthetic (Myles et al., 2004).

The B-Unaware trial assessed whether a BIS-based anesthetic protocol is better than a protocol based on the measurement of end-tidal anesthetic concentration (MAC) for decreasing AWR in high risk surgical patients undergoing GA (Avidan et al., 2008). This was a single-center, prospective study in which consecutively numbered patients were pre-randomized in blocks of 50 to BIS monitoring or 50 to MAC based monitoring. All patients received the BIS sensor but for those patients randomized to the MAC group, the clinicians were not able to see BIS values. MAC was visible to both group's clinicians during the surgical case. For the BIS group, an alert sounded if the BIS exceeded 60 or fell below 40; there were no set MAC alerts. For the MAC group, an alert sounded if the concentrations fell below 0.7 MAC or exceeded 1.3 MAC. BIS and MAC concentrations were recorded every second and data were downloaded into a computer system for analysis. All patients were interviewed three times (within 24 hours, between 24-72 hours, and 30 days after extubation) using the Brice awareness interview. Any patient interview that reported remembering something between "going to sleep" and "waking up" via the Brice interview was hand-reviewed by an independent panel to determine if the patient had definite awareness, potential awareness, or no awareness. 2000 patients were enrolled but only 1941 completed the study due to various reasons; there were 967 in BIS group and 974 in MAC group (Avidan et al., 2008). The patients in the MAC group had a statistically significant larger population with underlying neurologic disease than the BIS group (Avidan et al., 2008). Otherwise, the two groups had similar baseline co-morbidities. The B-Unaware trial found that four patients had definite AWR; two in the BIS group and two in the MAC group (Avidan et al., 2008). The overall incidence of definite AWR in this trial is 0.21% (Avidan et al.,

2008). Five patients had possible AWR; four in the BIS group and one in the MAC group. The overall incidence of definite or possible AWR in this trial was 0.46% (Avidan et al., 2008). Avidan et al. concluded that a structured BIS intraoperative protocol is not superior to a MAC based monitoring approach nor did it reduce the administration of volatile anesthetic gases when compared to a protocol based on MAC (Avidan et al., 2008). They noted that the BIS values were persistently under 60 during the period of awareness for the majority of the definite and possible AWR cases. Avidan et al. emphasized the point that these data cannot be extrapolated to patients under total intravenous anesthesia since all patients received volatile agents for this trial; importantly, approximately 43% of patients in the original B-Aware trial received total intravenous anesthesia (Avidan et al., 2008). Avidan et al. concluded that BIS based protocol is not superior to MAC based protocol in preventing AWR (Avidan et al., 2008).

The BAG-RECALL trial expanded upon the B-Unaware methodology in order to determine definitively whether a BIS guided alerting system is superior to a MAC guided alerting system in prevention of AWR (Avidan et al., 2011). The investigators prospectively randomized 6,041 adult patients at high risk for AWR across three surgical centers (Avidan et al., 2011). All patients received a BIS monitor but those randomized to the MAC guided alerting system, the BIS values were blinded from the anesthesia provider. For patients randomized to the BIS guided alerting system, both the BIS values and MAC values were visible to the anesthesia provider. In the BIS guided group, an audible alarm was generated if the BIS value when above 60 or fell below 40. There were no alarms set for the MAC values in this group. In the MAC guided group, an audible alarm was generated if the MAC fell below 0.7 or exceeded 1.3 using an age-adjusted formula, since MAC values change with age. Data were electronically captured at a minimum of 1 minute intervals. Patients were interviewed for awareness within 72

hours after surgery and at 30 days after tracheal extubation. Nine patients were found to have definite AWR (0.16% incidence) and 27 patients were found to have definite or possible AWR (0.47% incidence) (Avidan et al., 2011). When investigating the incidence of definite AWR by randomization group, seven of the nine patients were allocated to the BIS targeted group (Avidan et al., 2011). Nineteen of the 27 patients who were found to have definite or possible AWR were in the BIS targeted group (Avidan et al., 2011). It was therefore concluded that alerts based on BIS values are not superior to MAC-guided alerting system.

The B-Aware, B-Unaware, and BAG-RECALL all show that those patients randomized to BIS monitoring have similar incidence of AWR (approximately 0.2%), which is lower than what would be predicted in a high-risk population (approximately 1%). The studies differ in that the B-Unaware and BAG-RECALL trials suggest that a MAC-based protocol may be as efficacious as a BIS-based protocol in patients receiving inhaled anesthetics. However, the role of BIS monitoring in reducing the incidence of anesthesia awareness still needs further investigation, specifically as it relates to patients at all levels of risk undergoing anesthesia with both intravenous and inhalational agents.

Decision Support Alerting Systems Driving Provider Actions

An advantage of having a processed EEG signal transformed into a numerical index is that there is can be a quantitative threshold for decision support alerts to be implemented. Decision support alerting is relatively new to the medical community and is based upon the use of an automated clinical documentation system that is programmed to alert clinicians to a potential adverse event. These alerts are designed to drive a change in clinical practice by

making the provider aware of the potential for an adverse event based upon set threshold criteria for which going above or below could increase risk of patient harm.

Kucher et al. were one of the first investigative teams to use an electronic alert system to alter an adverse event: venous thromboembolism in hospitalized patients (Kucher et al., 2005). They hypothesized that electronic alerts sent to the provider would increase the rate at which patients were administered prophylaxis against deep-vein thrombosis (DVT). The hospital electronic database was queried in real time for patients at risk of DVT and determined if the patient was on adequate prophylactic measures. For those patients that did not have adequate prophylactic measures in place, they were randomly allocated to the clinician receiving an electronic alert about DVT prophylactic measures or no alert sent to the treating clinician. Kucher et al. found that the electronic alert reduced the risk of DVT or pulmonary embolism at 90 days by 41% (Kucher et al., 2005). This served as a proof of concept that a simple programming technique could impact the adverse event rate of patients.

O'Reilly et al. were among the first investigators to use an anesthesia information system (AIMS) to improve timely administration of prophylactic antibiotics (O'Reilly et al., 2006). AIMS is an electronic record of all perioperative documentation and monitoring. These systems can be as simple as having an automated history and physical section or as advanced as having an intraoperative system that captures electronically all physiological variables, all medications, and all surgical events. O'Reilly et al. saw a need for timely administration of prophylactic antibiotics to decrease surgical site infections (O'Reilly et al., 2006). This was accomplished by programming the AIMS to remind the anesthesiologist to administer the antibiotics within one hour of the surgical incision. The program tracks the time of surgical incision and therefore could remind the clinician when one hour had lapsed without an input of antibiotic

administration into the system. If the antibiotic was not administered the anesthesiologist was prompted to answer why. The study was designed so clinician feedback was available and compliance rates were posted around the operating rooms. Those with poor compliance were specifically targeted by team members. A manual chart review prior to implementation of the AIMS showed a 69% compliance rate (O'Reilly et al., 2006). After one year, the compliance rate increased to 92% (O'Reilly et al., 2006). This study supported the concept that a simple programming change can affect patient care and decrease adverse events.

Kheterpal et al. the following year at the same institution used the AIMS to improve compliance for documentation of arterial line placement (Kheterpal et al., 2007). Documentation of arterial line placement is important to professional fee reimbursement as well as to the need for completeness of the medical record. Once again the AIMS was programmed into two groups; the experimental group received alpha-numeric text messages and emails for up to 2 days after a stated operation to document the arterial line and the control group received no text messages or emails. The AIMS could determine if an arterial line was placed for the patient and used during the surgical operation and could also determine if a professional note used for fee reimbursement was drafted into the system. If the patient had the arterial line but not the professional note for fee reimbursement the case was considered non-compliant. Prior to the study commencement, there was an 80% compliance rate for documentation. After the complication of the study, the experimental group showed a 93% compliance rate compared to an 84% compliance rate in the control group ($p<0.001$) (Kheterpal et al., 2007). Due to the statistical increase in compliance, the department decided to implement the system for all patients, which increased the departmental compliance to 99% and showed a profit of $151,000

in professional fee charges (Kheterpal et al., 2007). This study proves that alert systems are beneficial.

The use of AIMS is now widely adapted across the country which lends itself to developing and implementing new research technologies that use provider entered point-of-care comorbidity information on a specific patient into the system and then integrate a risk profile with the actual dynamic physiologic changes that occur during an operation to alert the clinician to potential adverse outcomes. The research that has been previous completed using AIMS, has proved the utility in the framework that the use of an AIMS can drive changes in provider care and hopefully minimize adverse outcomes in surgical patients. Such technology therefore has the potential to minimize complications such as intraoperative awareness.

Research Hypothesis: Anesthesia Information System alerting based on a novel anesthetic concentration algorithm (incorporating the use of intravenous anesthetics) or an EEG-guided algorithm will reduce the known incidence of intraoperative awareness

Specific Aim 1: Development of an age-adjusted minimum alveolar concentration (MAC) alerting protocol within an Anesthesia Information System incorporating the inhalational vapor MAC with common intravenous anesthetic infusions that may have been given to the patient.

Rationale: MAC is the current standard of care in monitoring anesthetic depth of patients while under general anesthesia. The age-adjusted MAC value measures the actual partial pressure of the inhaled anesthetic vapor in the alveoli of the lungs which is the partial pressure of the anesthetic vapor in the brain. Therefore MAC is not directly related to the neuroanatomic substrate of consciousness, the brain (Mashour, 2006). In addition, the MAC does not incorporate intravenous anesthetic use. Therefore, to adequately alert clinicians in the prevention of awareness, a "MAC Equivalent" is developed that uses the actual age-adjusted MAC and incorporates the use of two commonly used intravenous anesthetic agents.

Specific Aim 2: Conduct a prospective randomized comparative effectiveness trial to determine if either the anesthetic concentration alerting protocol (using the MAC equivalent alerting algorithm) or a BIS alerting protocol is superior in the prevention of definite intraoperative awareness in an unselected adult surgical population.

Rationale: To date, there have been no comparative effective trials investigating the use of anesthetic concentration monitoring and BIS monitoring in the prevention of intraoperative awareness. The previous trials were performed on patients classified at high-risk for

intraoperative awareness (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004) and used only inhalational MAC monitoring compared with BIS monitoring.

Specific Aim 3: Identification of a specific population-based threshold using both age-adjusted MAC and BIS for the prevention of intraoperative awareness using discrete continuous anesthesia information system monitoring data.

Rationale: The protocols for MAC and BIS monitoring that have been previously used were not determined using prospectively collected discrete data elements in the prevention of intraoperative awareness. Therefore, using the unselected adult surgical population and the discrete monitoring data electronically extracted from the anesthesia information system, a specific threshold can be determined that maximizes sensitivity and specificity in the prevention of intraoperative awareness.

Chapter 2: Bioinstrumentation and Data Acquisition/Extraction System

The University of Michigan Health System uses the Centricity® (General Electric (GE) Healthcare®) Anesthesia Information System (AIMS) and AISYS Anesthesia Machines® (GE Healthcare®). Physiologic variables (heart rate, blood pressure, BIS values) are displayed on the GE Marquette Solar 9500® monitor (GE Healthcare®). Anesthetic monitoring variables are displayed on the AISYS display monitor (GE Healthcare®). All BIS electrodes (Aspect Medical®) were placed while the patient was awake in the pre-operative holding area. Upon entry into the operating room, the electrodes were connected via a single cable to the BIS tram module (Aspect Medical®). The tram module interfaced with the GE Marquette Solar 9500® monitor (GE Healthcare®). A complete picture of the anesthesia monitoring set-up can be found in Figure 1.

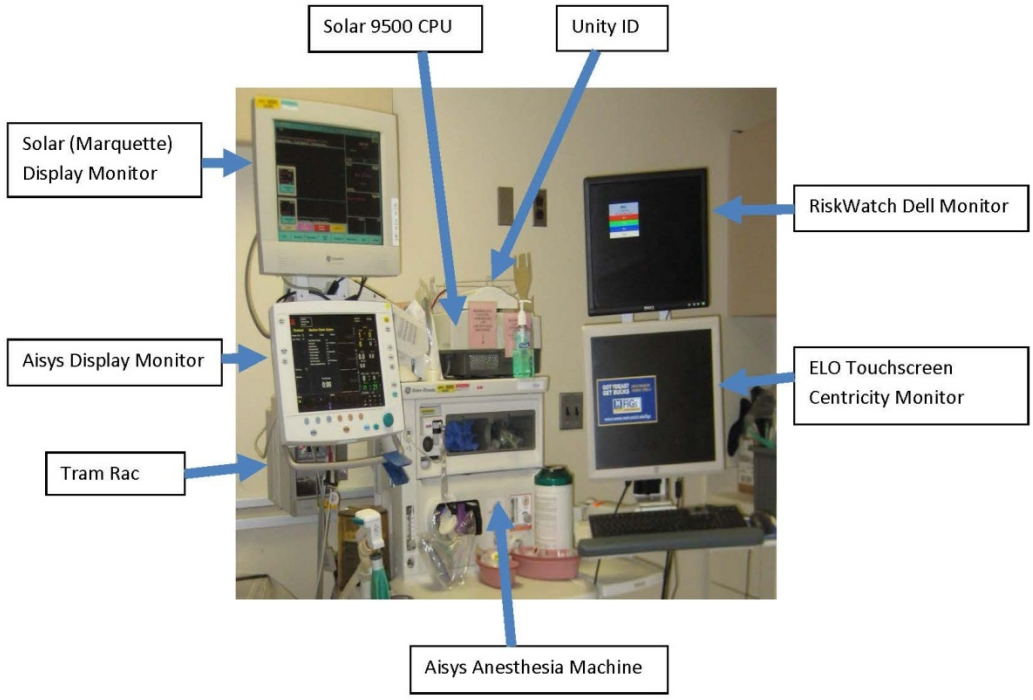


Figure 1: Anesthesia Monitoring Configuration

The physiologic variables displayed on the GE Marquette Solar 9500® monitor and the anesthetic variables from the AISYS Anesthesia Machines® are transmitted electronically every 30 seconds to one of many servers to be saved into databases over GE Unity Network (GE Healthcare ®). A unity network interface device (ID) (GE Healthcare ®) is used as a communication bridge between the different devices. The Unity Network ID (GE Healthcare ®) connects the different devices via a device identification communication adapter (DIDCA) automatically (Figure 2 and 3).

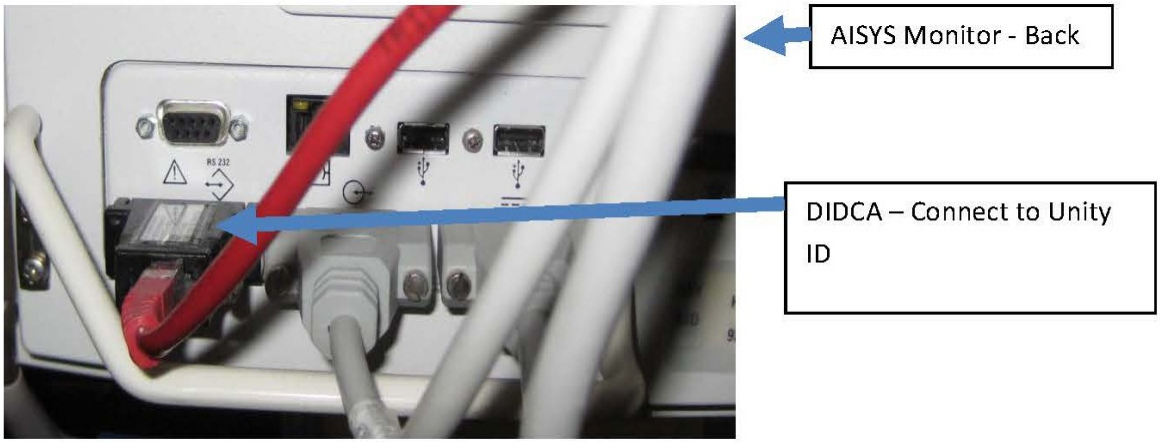


Figure 2: DIDCA connection to the Unity ID

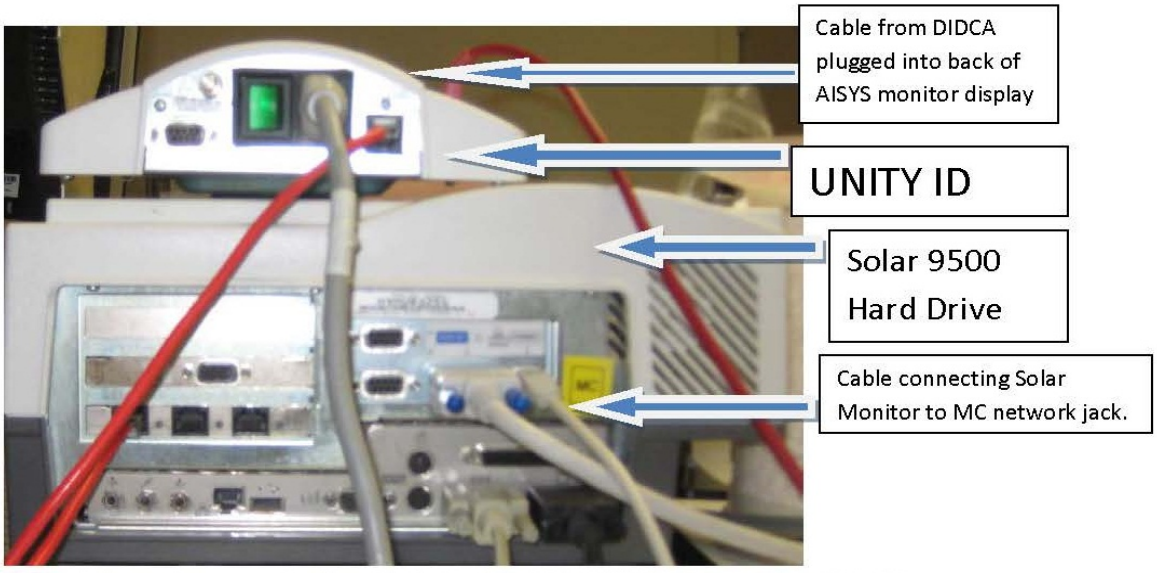


Figure 3: Connection examples from the back of the Solar 9500 Monitors and the Unity ID

Figure 4:Tram Rack

For this specific research, depth of anesthesia was monitored using the BIS. The BIS module tram (Aspect Medical®) is inserted into the tram rack and connected to the GE Marquette Solar 9500® monitor (Figure 4). The BIS values are transmitted over the Unity Network the same as the other physiologic variables displayed on the GE Marquette Solar 9500® monitor.

The AIMS system (Centricity Perioperative Anesthesia (CPA) (GE Healthcare®)) is installed and runs on a personal computer (PC) within each operating room. The AIMS CPA can also be installed and run on any PC that is logged into the firewalled hospital network. The AIMS CPA features a pre-operative history and physical, an intraoperative management, and a post-operative recovery room section. The pre-operative history and physical is completed by the anesthesia care provider prior to the operation. Information is entered at the point-of-care using co-morbidity specific pull-down menus. Every selection has a discrete code that is stored within the Centricity Clinical Data Repository (CDR) database (GE Healthcare®). In addition, the provider has an option to hand-type in any additional information as warranted. These selections can then be retrospectively queried and coded to be used for research. The demographic and laboratory data are automatically fed into the CDR and displayed on the AIMS CPA using interfaces with the hospital information system.

The AIMS CPA intraoperative section provides three distinct features of intraoperative care management. First, there is an anesthetic script that is a pre-selected guideline of events

expected to occur during the case. The script elements can be selected via a touchscreen in the operating room which is then transmitted into the database with a specific date and time stamp. Due to the nature of the operating room, the provider can adjust the time of a selection if there was not the opportunity to document the event in real-time. Each specific script element is also stored with a discrete value and can be queried retrospectively. The script elements define important parts of the operation such as anesthesia start and end, type of intubation (if any), and the type of anesthetic used along with the time the doses were administered (Figure 5). Second, the precise values of the physiologic variables from both the monitor and the anesthesia machine are displayed in table format. This allows the clinician to review the intraoperative record and determine if the patient received a general anesthetic via inhalational of intravenous agents (Figure 6 and 7). Finally, the physiologic waveforms from the monitor are also displayed on the AIMS CPA screen.

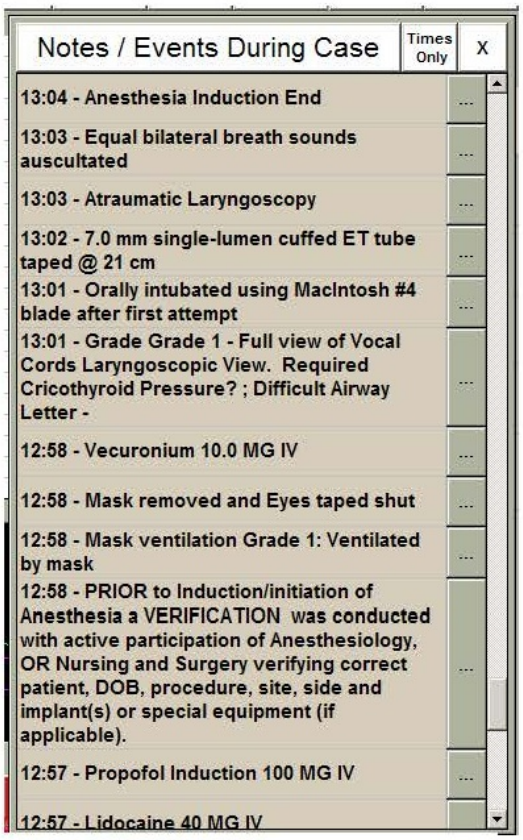


Figure 5: Example of anesthesia script elements

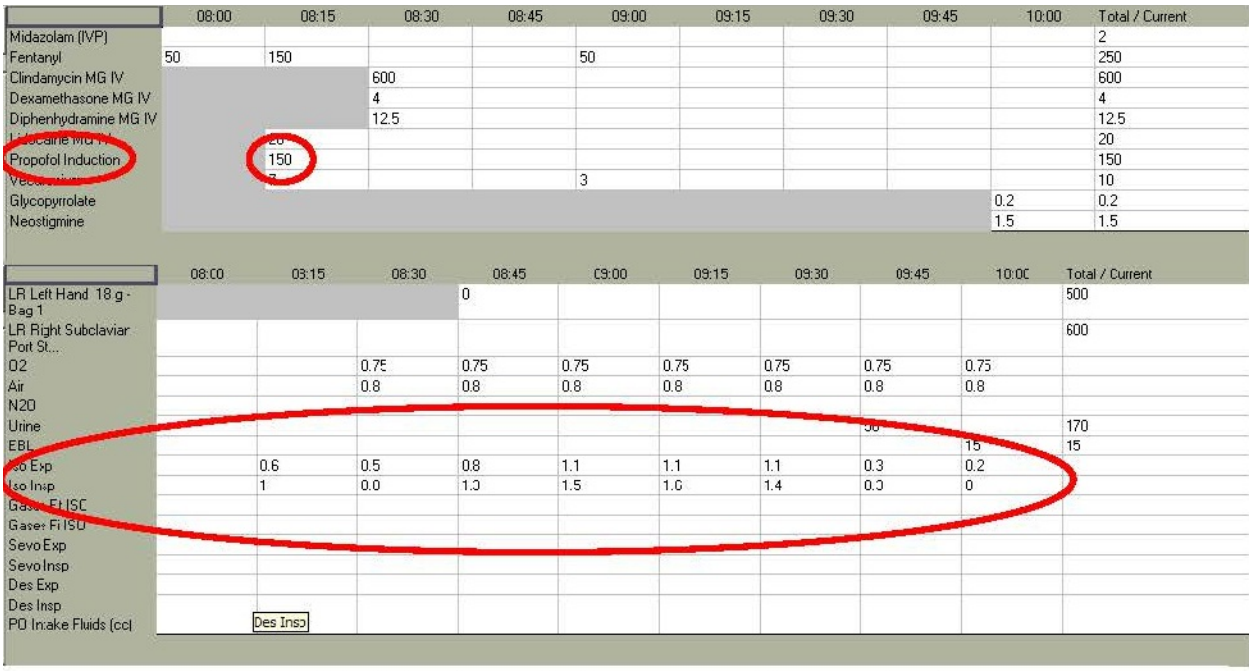


Figure 6: Example of an inhalational anesthetic (bottom) with a one-time intravenous induction agent (top).

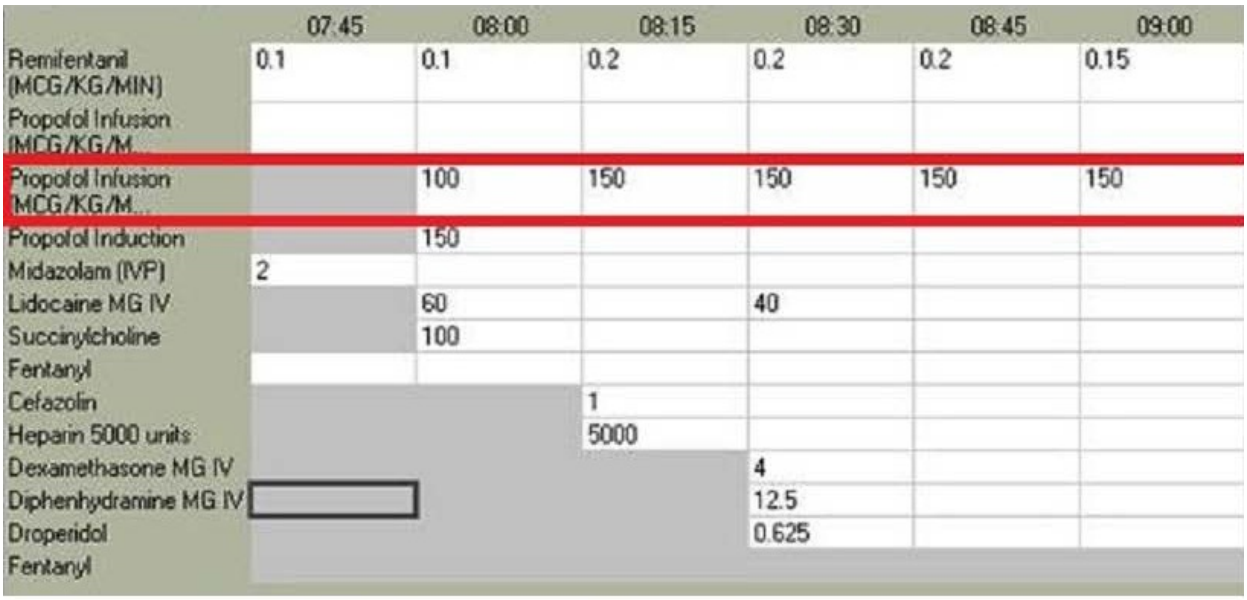


Figure 7: Example of total intravenous anesthesia (TIVA)

The transformation of monitor-capture to visualization on the AIMS CPA requires numerous data transmission and data truncating steps (Figure 8, steps A-G described below). The entire data acquisition system is running behind a firewalled password-protected system within the University of Michigan Health System, which is monitored and regulated by the Clinical Application Systems (CAS) team within the Department of Anesthesiology. The monitors from the AISYS Anesthesia Machines® and GE Marquette Solar 9500® monitor (A) are receiving information from the various physiologic variables being collected during the operation. The physiologic variables that are collected can either be continuous or discrete. For example, heart rate is collected each time the patient's heart beats while a blood pressure taken with a blood pressure cuff may only be taken every 3 to 5 minutes. The data from the monitors (A) is then transmitted via the GE Unity Network (which is the monitor capture interface) to one of many servers that is running GE's monitor capture software (GE Healthcare®) (B). Each server running the monitor capture software has two Ethernet connections. The first is a unity network connection that is able to pull physiologic variables from the GE Marquette Solar 9500® monitor and the AISYS anesthesia machine and transmit those data to the hospital network. The second Ethernet connection transmits data from the hospital network to the hospital server. This monitor capture software (B) uses the IP address from each operating room monitor and every 30 seconds pulls data from the monitors that is being transmitted over the unity network. The data are inserted into a local database (C). Both the monitor capture interface and the local database (B and C) reside on the same server. The 30-second data pulled from the monitors via the monitor capture interface is then transmitted to a hospital level central database (D) via a DataLink interface. The hospital level central database (D) holds the data collected every 30-second off the unity network. Data are continuously being pulled and placed

into the hospital level central database regardless of whether an operation is occurring. Due to the massive amount of discrete data points, this centralized hospital database is purged once a week. The CAS team has developed a structured query language (SQL) (E) to extract data from the centralized hospital database (D) into the Centricity CDR database (F). The data are extracted from the centralized hospital database (D) into the Centricity CDR (F) for an actual operation. Instead of the more granular 30-second data pull, this SQL code asks for data to be pulled into Centricity CDR every 60 seconds. In addition, the data are also aggregated into 15-minute snap-shots that are represented graphically in the intraoperative record in a table format for the clinician to review in the AIMS CPA (Figures 6 and 7). As previously stated, the AIMS CPA application is running (G) on a standard PC in the operating room at the patient's bed side. The AIMS CPA application (G) samples the Centricity CDR (F) for data every minute to update the screen on the AIMS CPA application (G) that is visible to the clinicians. The clinicians' hand-entered information into the AIMS CPA application (G) in real-time such as script elements for start and end of operation or medications administered, is transmitted back to the CDR database (F). There are continuous data transmissions between the CDR and AIMS CPA application until the case has been ended by the clinician within the AIMS CPA application. The CDR database (F) now holds continuously collected data at a rate of every 60-seconds, all individual data entries (e.g., blood pressure by cuff) and any user entered information at the point-of-care in the operating room into the AIMS CPA application such as script elements or medications. All data transmitted to the CDR database (F) are kept indefinitely and considered the patient's medical record.

For research purposes the CDR database (F) can be queried using SQL. The SQL query is extracted and entered in any statistical package for analysis at a later time. Each SQL query is

developed by the investigative team but written and executed by the CAS programmers. Since all preoperative history and physical elements are stored as discrete variables, the investigator can identify a specific co-morbidity of interest and code the data into binary (yes/no) or categorical concepts for analysis. Continuous intraoperative physiologic variables can be extracted either minute to minute as they are captured, a median over a set time-point, or a high/low value during the operative case. All intraoperative data can be queried or alerts can be generated by set anesthesia script elements that are time-stamped. For the research presented in this dissertation, the script elements of "anesthesia induction end" to "surgical dressing end" were used as the timestamps to capture all depth of anesthesia monitoring variables and to determine when to alert the clinician. These script elements were used to document the exact time that anesthesia was induced for the specific patient, who should thereafter be adequately anesthetized; to the time that anesthesia would be reversed or turned off. In addition, to determine any monitor capture interface issues with data transmission into the CDR database, queries were developed to determine if standard measures from the anesthesia machine were invalid. If the CPA application had a documented start and end of the surgical case time-stamped but the anesthetic depth value for MAC and the end-tidal carbon dioxide were both zero, those cases were classified as monitor capture interface issues.

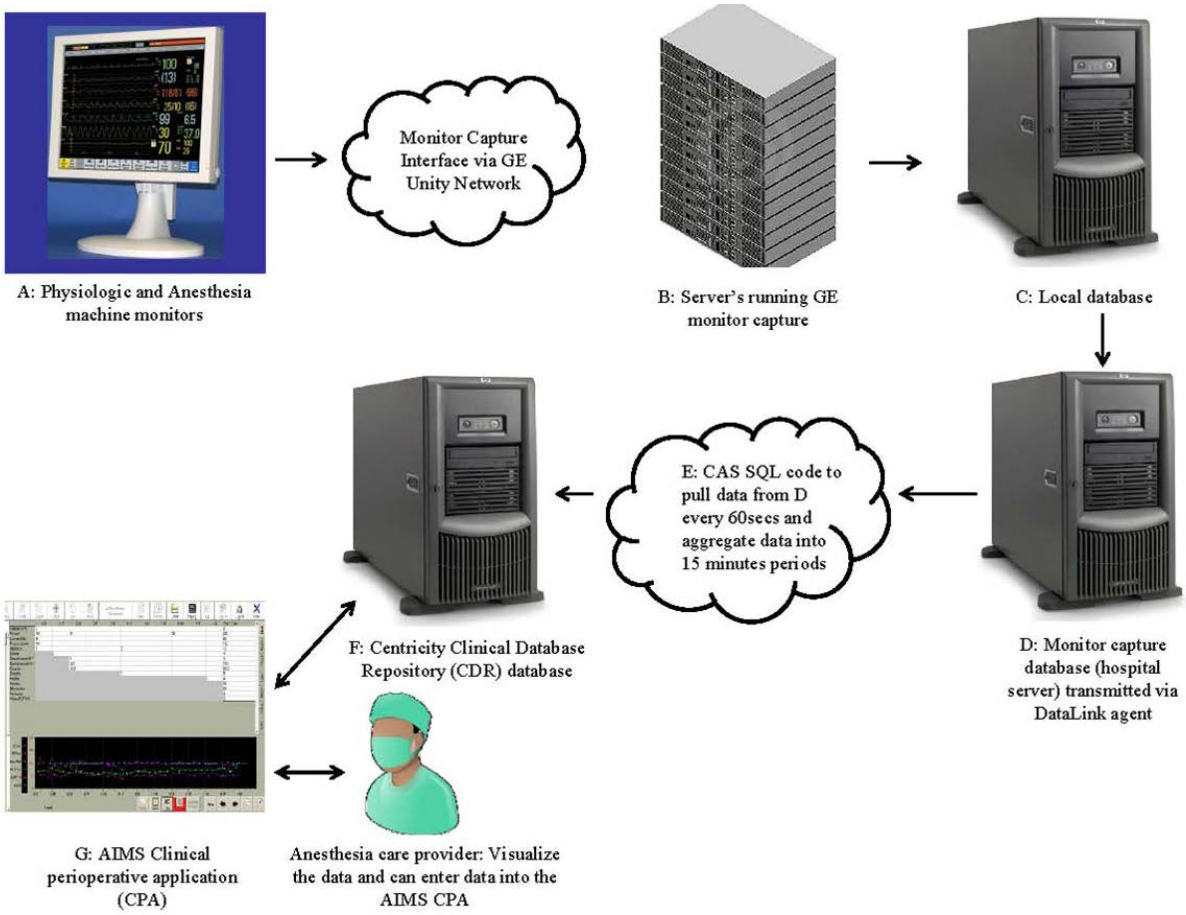


Figure 8: Overview from monitor-capture to visualization on the AIMS CPA

Chapter 3 – Development of a Novel Electronic Algorithm for Detecting Potentially Insufficient Anesthesia: Implications for the Prevention of Intraoperative Awareness

With growing recognition of the problem of intraoperative awareness (AWR), there is a strong impetus to develop effective methods of detecting insufficient levels of anesthesia. Assessment of anesthetic depth has evolved from stages and planes of anesthesia, to the concept of minimum alveolar concentration (MAC), to more recent techniques based on electroencephalography (EEG) (Mashour, 2006). There is still controversy, however, regarding the efficacy of EEG-based technology in the prevention of awareness. The B-Aware trial was a prospective study of high-risk patients that demonstrated a benefit of Bispectral Index (BIS) monitoring compared to a routine care group (Myles et al., 2004). One limitation of this trial was that the BIS-guided approach was not compared to another protocol-based anesthetic. The recent B-Unaware trial was a prospective study that instead compared a BIS-guided anesthetic to a protocol based on >0.7 MAC end-tidal anesthetic gas concentrations (Avidan et al., 2008). The B-Unaware study did not demonstrate any benefit of a BIS-guided protocol compared to a MAC-guided protocol. One limitation of the B-Unaware trial was that it was restricted to inhalational agents. Since the BIS monitor is sensitive to the effects of intravenous anesthetics, a protocol that incorporates the MAC-sparing effects of such agents may be a better comparator to the EEG-based approach.

Methods

We developed an electronic algorithm that employs our anesthesia information management system to calculate a "MAC equivalent" based on total inhalational MAC, as well as documented infusions or boluses of intravenous agents. The algorithm for analysis of an

active case is as follows, with an associated electronic pager alert triggered if implemented in real time.

- Conditions for an "active case" are:
    1. data capture is possible (i.e., not a paper record)
    2. data capture is active (i.e., "patient in room" has been electronically entered and end-tidal [Et] CO_2 is detected)
    3. case has been identified as a general anesthetic
    4. "anesthesia induction end" has already been documented
    5. request for recovery room bed or transport to an intensive care unit has not been documented
    6. surgical dressing completion has not been documented
- The alerting system checks the most recent value (within a specified time period) of:
    1. Et Sevoflurane (MAC=2.0)
    2. Et Isoflurane (MAC=1.2)
    3. Et Desflurane (MAC=6)
    4. Et Nitrous Oxide (MAC=105)

  and compares it to the MAC of each agent. It adds the resulting MAC values together for "current total MAC."
- The system then checks for a charted propofol infusion in mcg/kg/min and divides by 150, assuming that 150 mcg/kg/min is "1.0 MAC" for propofol. The analogous concept of MAC for propofol is "Cp50"- the plasma or blood concentrations at which 50% of patients do not move in response to a noxious stimulus (Smith et al., 1994). Since we do not have the technology at our institution to calculate Cp50 or Cp50-awake, we have chosen the above propofol dose as an initial value based on clinical experience. The resultant MAC equivalent is added to current total MAC.
- The system next checks for a dexmedetomidine infusion with a rate of 0.2 mcg/kg/hour or greater. If present, it multiplies the current total inhalational MAC by 2, as dexmedetomidine can reduce MAC by 50% (Aantaa et al., 1997).
- At this point, the "current total MAC" is defined as: Et Sevo /2 + Et Iso /1.2 + Et Des/6 + Et Nitrous /105 + propofol rate (in mcg/kg/min)/150. If dexmedetomidine is $\geq$0.2 mcg/kg/hour, inhalational MAC is multiplied by 2.
- If this total MAC is below a set threshold, the system assesses whether a bolus of propofol, midazolam, etomidate, or thiopental has been documented in the preceding 10 minutes.
- The system then triggers an alert if total age-adjusted MAC is below the assigned threshold AND no bolus has been documented in the preceding 10 minutes. Age adjustment for MAC is only performed for volatile agents and is based on calculations derived from prior literature (Eger, 2001; Nickalls and Mapleson, 2003) (**Table 1**).
- If implemented, the clinician electronically signed into the case receives an alphanumeric page stating "Potentially insufficient anesthesia, please check vaporizers and intravenous lines."

Table 1: Age-adjustment ranges for minimum alveolar concentration (MAC).

Age (years)	1 MAC (%)
Des: 18-39	**7.0**
40-59	**6.0**
60-79	**5.2**
80-99	**4.5**
Sevo: 18-39	**2.4**
40-59	**1.7**
60-79	**1.5**
80-99	**1.2**
Iso: 18-39	**1.3**
40-59	**1.1**
60-79	**1**
80-99	**0.8**

Des= Desflurane, Sevo= Sevoflurane, Iso= Isoflurane

After Institutional Review Board approval (HUM 4487, University of Michigan Health System), we retrospectively applied the algorithm to the electronic intraoperative data of adult general anesthesia cases at our University Hospital from 2/07 through 1/08 in which no awareness was reported. In order to assess a differential frequency of alerting, we retrospectively analyzed electronically documented cases of AWR that occurred from 1/04 through 1/08 using the same age-adjusted MAC thresholds. AWR were identified through routine postoperative interviews assessing any problems related to anesthesia, rather than an explicit query such as the Brice interview. Age, gender, body mass index (BMI), American Society of Anesthesiologists (ASA) classification status, use of total intravenous anesthesia,

emergent cases, and cardiac cases were assessed and compared between the two groups (awareness vs. no awareness). Comparisons were made using Chi-Square, Fischer's Exact Test, or Mann Whitney U Test, where appropriate. P values <0.05 were considered statistically significant.

The B-Unaware trial used 0.7 MAC as a threshold; we started above this value and decreased thresholds until they approached MAC awake (Eger, 2001). The threshold for analysis was set to <0.8, <0.7, <0.6, <0.5, <0.4 age-adjusted MAC. After calculating the incidence of alert triggering in cases with or without awareness, positive and negative likelihood ratios were calculated.

Results

From 2/07 through 1/08, we identified 15,091 cases valid for analysis that had no documented AWR. From 1/04 through 1/08, we identified 12 cases of AWR for which electronic data were available (9 of these are discussed and documented in Mashour et al, 2009). Demographic data from the two groups are demonstrated in **Table 2**. The only significant difference between the two groups was an increased incidence of ASA 3, 4, and 5 patients in the awareness group (75%) compared to the non-awareness group (40%) (P=0.02).

In all cases analyzed, the incidence of triggers decreased as MAC thresholds were decreased (**Table 3**). The AWR, however, demonstrated a higher frequency of alert triggers at all MAC thresholds. The <0.8 age-adjusted MAC threshold was most sensitive to AWR and had the best negative likelihood ratio, since it triggered in 12/12 cases. The threshold of <0.5 age-adjusted MAC was associated with the best positive likelihood ratio.

Table 2: Demographic data for the study population.

	-Awareness n=15,091	**+Awareness n=12**	**P value**
Age	52.2 ± 16.6	60.3 ± 15.3	0.10
Male Gender	47.7% (7,192)	58.3% (7)	0.46
BMI	28.8 ± 7.1	29.1 ± 8.4	0.94
ASA 3,4 or 5	39.9% (6,015)	75% (9)	**0.02**
TIVA	1.7% (259)	0% (0)	1.00
Emergent	6.9% (1,041)	8.3% (1)	0.58
Cardiac	1.8% (279)	0% (0)	1.00

P values were calculated either using Chi-Square, Fischer's Exact Test, or Mann Whitney U Test. BMI= Body mass index, ASA= American Society of Anesthesiologists classification, TIVA= Total intravenous anesthesia

Table 3: **Assessment of trigger frequency in a retrospective study of 15,091 patients without awareness and 12 patients with awareness.**

Trigger Thresholds	**% Trigger -Awareness n=15,091**	**% Trigger +Awareness n=12**	**Positive Likelihood Ratio**	**Negative Likelihood Ratio**
<0.8 aa-MAC	85.3%	100%	1.17	0
<0.7 aa-MAC	78.7%	91.7%	1.17	0.39
<0.6 aa-MAC	69.2%	91.7%	1.33	0.27
<0.5 aa-MAC	57.8%	83.3%	1.44	0.4
<0.4 aa-MAC	48.9%	66.7%	1.36	0.65

Minimum alveolar concentration (MAC) thresholds were age-adjusted (aa) and incorporated the infusion of the intravenous agents propofol and dexmedetomidine

Discussion

Electronic alerts have been developed and employed at our institution and have been shown to increase compliance with both clinical and administrative tasks (Kheterpal et al., 2007; O'Reilly et al., 2006). To our knowledge, this is the first report of an electronic algorithm and alert system designed to detect potentially insufficient anesthesia. Empirically-derived refinement of both the algorithm and alert threshold will help further determine the optimal "signal-to-noise" ratio (i.e., tradeoff between sensitivity and specificity) for detecting insufficient anesthesia related to true intraoperative awareness events. It is important to note that the present findings are consistent with clinically relevant investigations in AWR. Our alert system would have triggered in 78.7% of cases with a threshold of <0.7 effective MAC, which is comparable to the 74.5% incidence of end-tidal gas concentrations <0.7 MAC in the B-Unaware study (Avidan et al., 2008).

One advantage of the system is its ease of installation and cost efficiency: assuming that an anesthesia information management system is in place, the algorithm can be employed readily. A second advantage is that a more comprehensive assessment of anesthetic agents can be accomplished, in contrast to the limited MAC calculation available on many monitors. MAC-sparing infusions or boluses are common and should be accounted for in a MAC-based protocol. A third advantage is that the algorithm can be readily modified and could potentially include data from EEG-based monitors as well.

One disadvantage of the algorithm is that it only incorporates intravenous infusions or boluses that have been electronically *documented*. In general, poor documentation could lead to under- or over-alerting. For example, a mechanical malfunction of an intravenous line that resulted in no anesthetic delivery would not be detected if not charted, as there is no direct

information from the patient as in the case of end-tidal gas concentrations. Another disadvantage is that in our protocol, the MAC equivalent for propofol is established by convention rather than a physiologic measure such as Cp50 (Smith et al., 1994). In the future, both of these disadvantages may be compensated for if the use of end-tidal propofol concentrations becomes a standard of practice (Takita et al., 2007). Furthermore, we cannot attest to the complete absence of awareness cases in the control group, as a prospective approach to awareness detection was not used (Mashour et al., 2009c). Nonetheless, even assuming the reported incidence of awareness cases at 0.15% in the control group, it would likely not affect the outcome given the awareness incidence of 100% in the test group. Finally, this algorithm obviously requires an anesthesia information management system and alphanumeric paging system already in place.

The exclusion of opiates from our algorithm merits discussion. It is well known that, beyond a certain dosing threshold, opiates have a MAC-sparing effect. A combination of premedication, intermittent boluses, and continuous infusions—often with different agents—is common in the perioperative setting. Incorporating this heterogeneous practice would add considerable complexity to the algorithm in this initial phase of development. It is important to note that cases traditionally conducted with high-dose opiates, such as cardiac surgery, are still associated with a high incidence of intraoperative awareness (Avidan et al., 2008; Myles et al., 2004). It is also important to note that current practice does not typically include even a simple MAC alarm (Umesh et al., 2009). Thus, the development of an automated, modifiable alerting system that can be programmed at different thresholds of age-adjusted MAC—and that is inclusive of selected intravenous sedative-hypnotic agents—is already a major advance compared to existing technology. A large clinical trial testing the algorithm in comparison to the

BIS monitor is currently being conducted (clinical trial NCT00689091), which will help elucidate empirically whether opiates need to be included in the next iteration of the algorithm.

In conclusion, we have developed a novel electronic algorithm and alerting system that may help detect insufficient anesthesia and that is more sensitive to cases of intraoperative awareness. The prospective study of such an electronic alert system may be useful as a standard of comparison for EEG-based systems and warrants further investigation as an adjunct in the prevention of awareness during general anesthesia.

Reprinted in entirety from Springer: Journal of Clinical Monitoring and Computing (23) 2009: 273-277, A Novel Electronic Algorithm for Detecting Potentially Insufficient Anesthesia: Implications for the Prevention of Intraoperative Awareness, Mashour G.A., Esaki, R.K., Vandervest, J.C., **Shanks A**., Kheterpal, S. Entire text with tables with kind permission from Springer Science and Business Media

Chapter 4 – Prevention of Intraoperative Awareness with Explicit Recall in an Unselected Surgical Population: A Randomized Comparative Effectiveness Trial

Intraoperative awareness with explicit recall (AWR) of surgical events is a potentially devastating event associated with post-traumatic stress disorder (Leslie et al., 2010) and has an incidence of approximately 0.15% for all risk levels (Sandin et al., 2000; Sebel et al., 2004). Processed electroencephalographic monitors have been developed to assess anesthetic depth and potentially prevent AWR, which is considered a sentinel event by the Joint Commission (JACHO, 2004). The Bispectral Index® (BIS) monitor (Covidien, Boulder, CO) processes a frontal electroencephalographic channel to calculate a dimensionless number from 100 (awake) to 0 (no detectable brain activity) in order to provide a measure of the patient's level of consciousness; a BIS range of 40 to 60 is suggested to be consistent with the state of general anesthesia (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004).

Past efficacy trials have evaluated the role of protocols based on the BIS monitor (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004) and anesthetic concentrations (Avidan et al., 2011; Avidan et al., 2008) for the prevention of AWR. However, these studies were performed exclusively in patients at high risk for the complication. A large cohort study did find that BIS monitoring decreased the incidence of AWR in a broad surgical population compared with historical controls, but was limited by its observational design, changing practice patterns regarding end-tidal anesthetic concentration monitoring, and exclusion of patients not receiving neuromuscular blockers (Ekman et al., 2004). As such, there are currently no comparative effectiveness data to guide the decisions of providers or policy makers as they attempt to prevent AWR in the >200 million major surgeries performed worldwide each year (Weiser et al., 2008).

Similarly, there are no effectiveness data supporting the claim that anesthetic consumption is reduced with the use of a BIS monitor, which has been suggested to decrease inhaled anesthetic use by up to 38% (Song et al., 1997). These data are reinforced by meta-analyses of small efficacy trials of both inhaled and intravenous anesthesia (Liu, 2004; Punjasawadwong et al., 2007). It has recently been argued that decreased anesthetic use and the ensuing clinical benefits such as faster recovery or reduced nausea and vomiting make the BIS monitor cost-effective and that it should therefore be routinely incorporated (Klopman and Sebel, 2011).

Here we describe a comparative effectiveness study with active comparators and a two-sided superiority design. This randomized controlled trial compared alerting protocols based on either anesthetic concentration or BIS values in an unselected surgical population at three hospitals within a tertiary academic medical center. The primary outcome was the incidence of definite AWR; prespecified secondary outcomes included the incidence of definite or possible AWR, as well as anesthetic usage and recovery variables.

Materials and Methods

A detailed description of the experimental protocol for the Michigan Awareness Control Study (ClinicalTrials.gov number NCT00689091) has been previously reported (Mashour et al., 2009b). The conduct of the study and the reporting of results followed the Consolidated Standards of Reporting Trials guidelines (Schulz et al., 2010).

Participants

The study received approval from the Institutional Review Board of the University of Michigan, Ann Arbor, (HUM00013626) and was deemed to be of minimal risk. A full discussion

of the risks and benefits was conducted with each patient approached. Patient consent to interventions and follow-up was electronically documented in our perioperative information system (Centricity®, General Electric Healthcare, Waukesha, WI). Patients were recruited from three hospitals of the University of Michigan Health System from May 2008 until May 2010. Inclusion criteria were age >18 years, general anesthesia using inhalational or intravenous technique for any surgical case that did not involve the forehead, and availability for follow-up interviews. Exclusion criteria were intracranial procedures, adhesive allergy, psychosis, or history of traumatic brain injury. All patients enrolled in the study were blinded to group assignment and had the BIS electrode applied to the left side of the forehead by a member of the research staff prior to entering the operating room.

To detect a reduction in the incidence of AWR from 0.15% to 0.04% (Ekman et al., 2004), we calculated a need for 14,072 per group or a total n = 28,144 with 80% power and a significance level of 5%. We targeted a total recruitment of 30,000 patients, with a pre-specified interim analysis after 20,000 patients were recruited (2/3 target sample) (Mashour et al., 2009b). A constant likelihood group sequential method with formal futility boundaries was used with a two-sided O'Brien-Fleming stopping rule. There was no contingency for early termination for efficacy. An acceptance region plot (or a futility region plot) was generated using SAS statistical software (SAS version 9.2, Carey, NC). The two-sided futility boundary (for the differences in proportions between the BIS and the anesthetic concentration group) at the planned interim analysis was from -0.0005434 to 0.0005434. The difference between the proportions observed at the interim analysis was 0.0003275422 (11/9376 cases of definite awareness in the anesthetic concentration group minus 8/9460 cases of definite awareness in the BIS group), which is within the stopping boundary for futility.

Study Design

The University of Michigan Health System utilizes the Centricity® electronic perioperative information system in all of its operating rooms. Using this system, automated real-time analysis of BIS values or minimum alveolar concentration (MAC) was performed every five minutes, with the transmission of provider-specific electronic alphanumeric paging alerts in less than 60 seconds. Operating rooms were randomized every three months based on even- or odd-numbered operating rooms to either (1) electronic alerts in the event of median BIS values >60, or (2) electronic alerts for median age-adjusted MAC level of <0.5. The threshold of age-adjusted MAC <0.5 was chosen based on a retrospective analysis of electronically documented cases with and without awareness that occurred prior to the onset of the study (Mashour et al., 2009a), as well as the high frequency with which thresholds of higher MAC are crossed (Avidan et al., 2008). In addition to the age-adjusted MAC of standard inhaled anesthetics, alerting based on anesthetic concentrations also reflected documented intravenous anesthetic infusions and bolus doses (Mashour et al., 2009a). Paging alerts to the clinician electronically signed into and physically present during the case reported either the median BIS value or anesthetic concentration level for the prior 5 min epoch, followed by "Potentially insufficient anesthesia-please check vaporizers and intravenous lines." (Specific coding for the electronic alerts can be found in Appendix I.)

In the BIS-targeted rooms, BIS values appeared on the main monitoring screen and were automatically recorded. In the anesthetic alert-targeted rooms, BIS values neither appeared on the monitor nor were accessible intraoperatively. Other aspects of anesthetic care (e.g., choice of anesthetic agents, benzodiazepines) were not standardized for this study.

Randomization and Blinding

Randomization was performed using a random-number, computer-generated block scheme based on even or odd operating room number. The blocks were defined within a specific year of the study based on the original start date of recruitment. The study year was divided into four quarters by calendar month (three months per quarter). Within a specific study year, the odd-numbered operating rooms and even-numbered operating rooms were randomized to BIS alerting two times and anesthetic concentration alerting two times. If the odd-numbered operating rooms were randomized to one alerting protocol, the even-numbered operating rooms were randomized to the alternative alerting protocol for that quarter of the study year. Patients, postoperative interviewers, and all case reviewers were blinded to group assignment. Practitioners receiving pages regarding BIS or MAC values were not blinded to group assignment. However, practitioners were not made aware of the randomization scheme or dates for randomization change during the study.

Technical Factors

The BIS monitors used in the Michigan awareness control study were not free-standing devices, but modules that interfaced with the Solar 9500 (General Electric®) anesthetic monitors used in our institution's operating rooms. During scheduled quality control checks within the first two months of the trial, it became clear that in some instances there was a failure of BIS values to be generated. Technical representatives from both manufacturers confirmed this as a known software interface problem. Since the study was designed as an effectiveness trial, the decision was made to proceed and use the population receiving neither the BIS nor anesthetic concentration protocol as a *post hoc* "no intervention" group for the purpose of secondary

analysis. Failure to generate BIS values was similar in both even (17%) and odd (19%) numbered operating rooms, which was the randomization scheme for alerting protocols.

Main Outcome Measures

Blinded, trained interviewers used the modified Brice interview (Brice et al., 1970) employed in other studies of intraoperative awareness (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004; Sebel et al., 2004) to screen patients 28 to 30 days after surgery via telephone. A single interview was performed in contrast to past trials (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004) due to the high number of patients recruited; the 28 to 30 day interview was chosen because it would likely detect the most clinically significant awareness events. If patients could not be reached by telephone after multiple attempts, a written form of the interview was sent to the patient. Any patients reporting AWR during the Brice interview had a more detailed interview by an anesthesiologist committee member blinded to the intervention. All patients reporting AWR were offered psychiatric care.

For those patients who reported AWR, three blinded experts independently determined whether the reported event was definite, possible, or no awareness based on the data obtained from the first two interviews (Brice screening and follow-up). These individuals also reviewed awareness events for the BAG-RECALL trial (ClinicalTrials.gov number NCT00682825) (Avidan et al., 2011; Avidan et al., 2009). We compared inter-rater agreement using Fleiss's Kappa statistic for the three blinded assessments of awareness, which showed fair agreement (0.25). In the event of a conflict, a fourth blinded expert reviewer from another institution made the final determination; this expert reviews cases for the American Society of Anesthesiologists Anesthesia Awareness Registry. The qualitative aspects of the awareness report were classified

using the Michigan Awareness Classification Instrument (Mashour et al., 2010). Class 1 is defined as isolated auditory perceptions, class 2 is tactile perceptions, class 3 is pain, class 4 is paralysis and class 5 is paralysis and pain. If an event is also associated with distress, the class number is modified with a "D."

Anesthetic usage, time to meeting recovery room discharge criteria, and incidence of postoperative nausea/vomiting were prespecified secondary outcomes (Mashour et al., 2009b). Postanesthesia care unit discharge criteria include (among other variables): oxygen saturation >92% or preoperative baseline (at appropriate levels of supplemental oxygen), core temperature between 36^0 and 38^0 Celsius, normal heart rate and rhythm (or no worse than baseline status), other hemodynamic vital signs within normal physiologic range for age or within 20% of baseline values, normal neurological evaluation, pain score ≤ 4, postoperative nausea and vomiting ≤ 2. BIS values, MAC values, and doses of propofol, midazolam, fentanyl and morphine were assessed across all groups.

Statistical Analysis

The primary outcome was the incidence of definite AWR in the anesthetic concentration and BIS groups using modified intention-to-treat analysis. Modified intention-to-treat was defined as a patient who was randomized and was interviewed at 30 days. Prespecified secondary analysis was conducted to determine the combined incidence of definite and possible AWR as well as the classification of events. Significance was assessed using a two-tailed Pearson chi-square test. Confidence intervals were calculated using Newcombe's method without continuity correction (Newcombe, 1998). The average number of paging alerts

generated in the groups was compared with the incidence of definite or possible AWR events using a linear regression R-Squared test.

Patient characteristics, comorbidities, and risk factors for awareness (Table 1) were analyzed to determine if there were statistically significant differences between the anesthetic concentration and BIS groups in the modified intention-to-treat analysis. The Kolmogorov-Smirnov statistic was used to determine normality for the two continuous variables (age and body mass index). If the p-value was significant (<0.05), the assumption of normality was violated and nonparametric analyses (e.g., Mann-Whitney U test) were used. Nonparametric data are presented as median and interquartile range [25^{th} to 75^{th} percentile]. Parametric data are presented as mean ± standard deviation. For categorical variables, a two-tailed Pearson chi-square test was used, where a p-value of <0.05 was considered statistically significant. All categorical data are presented as number (percentage). For ease of interpretation we have defined cardiovascular disease as having one or more of the following conditions: history of myocardial infarction, congestive heart failure, valvular heart disease, dysrhythmia, endocarditis, peripheral vascular occlusive disease, angina or orthopnea. We have defined lung disease as having one or more of the following conditions: history of pulmonary hypertension, chronic obstructive pulmonary disease or dyspnea. We have defined liver disease as having one or more of the following conditions: history of cirrhosis, acute liver failure, or chronic liver failure. We have defined neuropsychiatric disease as having one or more of the following conditions: history of stroke or transient ischemic attack, seizures, depression, bipolar disorder, anxiety disorder, or posttraumatic stress disorder. We have defined alcohol abuse as having 3 or more drinks daily and/or high withdrawal potential.

For the other key secondary outcomes, all continuous elements were assessed for normality as described. We chose to use the *post hoc* grouping variable (anesthetic concentration, BIS, and no intervention) to assess the secondary outcomes and therefore *post hoc* comparison testing was employed for elements in Table 2. The median BIS values were compared between the BIS and anesthetic concentration groups using a Mann-Whitney U test; a Kruskal-Wallis test was used to compare median anesthetic dosages and discharge times among the anesthetic concentration, BIS, and no intervention groups. A two-tailed Pearson chi-square test was used to compare the outcomes of nausea or vomiting among the three groups. Bonferroni adjustments were used for the Mann-Whitney U test variables. For the variables that were analyzed using the Kruskal-Wallis test, pair-wise comparisons using a series of Mann-Whitney U tests were performed if the omnibus test was significant. For the Bonferroni adjustment, we started at an alpha level of 0.05. Based on the number of comparisons required, the new alpha level to measure significance was 0.002. We calculated a total of 22 comparisons based on the number of embedded Mann-Whitney U tests that were performed for Kruskal-Wallis tests with significant omnibus tests. Only those pairwise comparisons with a p-value <0.002 were reported in Table 2 as statistically significant differences. If there were no statistically significant pairwise comparisons, “NS” (no significance) was reported for ease of interpretation. Statistical software IBM SPSS statistics version 19 (IBM Corp, Somers, NY) was used.

Results

Recruitment and patient characteristics

A total of 21,601 patients were enrolled in the study at the time of interim analysis, with a 97% recruitment rate (Figure 1). As described in the methods, the study was terminated due to futility. Of the study cohort, 18,836 or 87% of the patients were available for postoperative interview assessing awareness at one month; 9460 patients were randomized to the BIS group and 9376 patients were randomized to the anesthetic concentration group (Figure 1). Patient characteristics and comorbidities for the modified intention-to-treat BIS and anesthetic concentration groups are demonstrated in Table 1. There were no adverse events related to the study.

Figure 1: Flow diagram of recruitment and follow-up interviews. BIS=Bispectral Index

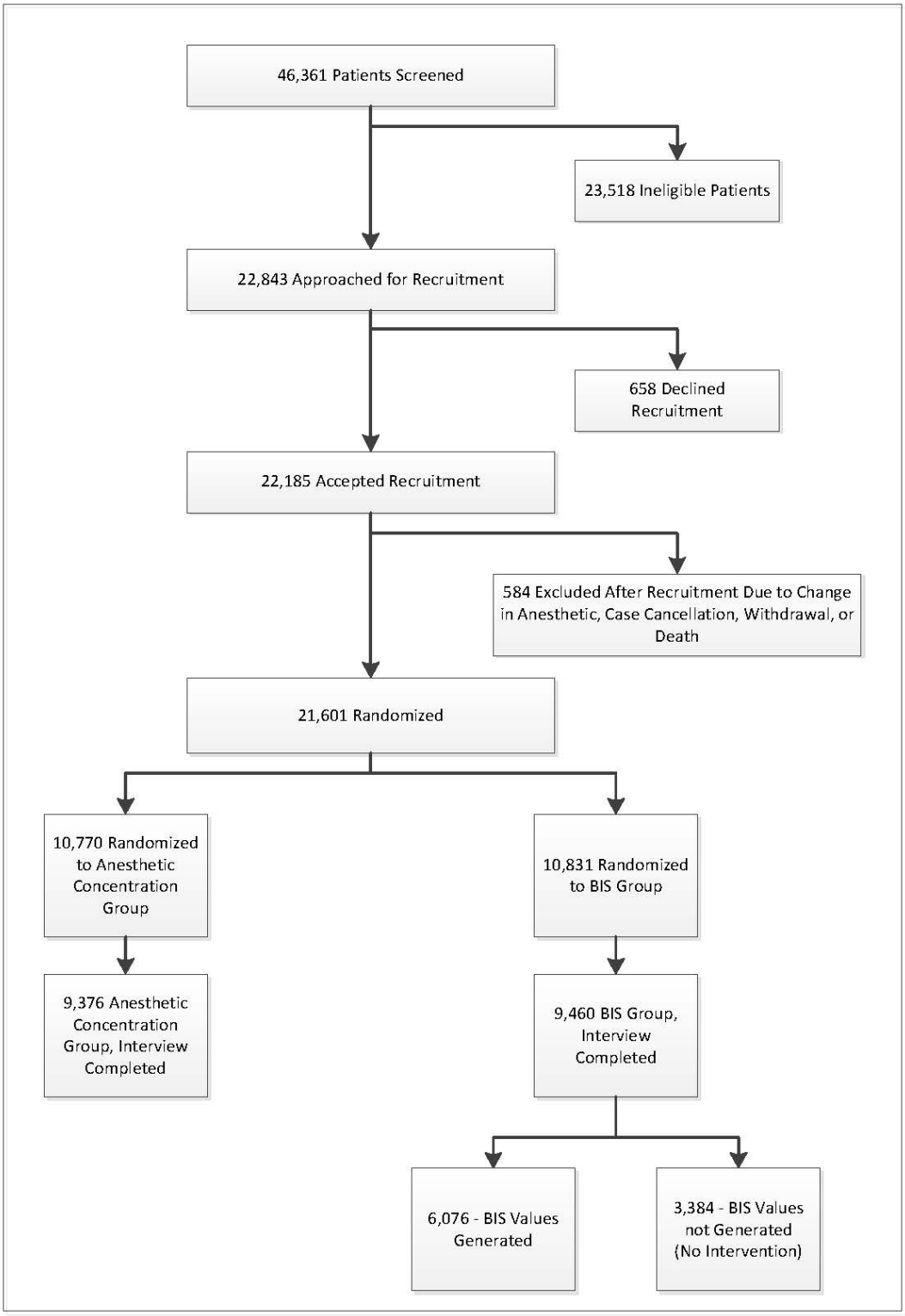


Table 1: Patient characteristics, comorbidities, and risk factors for awareness

	Anesthetic concentration n (%) (N=9,376)	**Bispectral Index n (%) (N=9,460)**	**p-value**
Male Sex	4,199 (45)	4,237 (45)	0.99
Age in years*	53 [41 to 64]	53 [41 to 64]	0.79
Body Mass Index (kg/m^2)*	28 [25 to 33]	28 [24 to 33]	0.50
Cardiovascular Disease	1,702 (18)	1,723 (18)	0.91
Lung Disease	950 (10)	967 (10)	0.84
Renal Disease	601 (6.4)	612 (6.5)	0.87
Liver Disease	88 (0.9)	58 (0.6)	0.01
Neuropsychiatric Disease	2,003 (21)	2,053 (22)	0.57
History of Awareness	50 (0.5)	59 (0.6)	0.41
History of Difficult Intubation	45 (0.5)	40 (0.4)	0.56
Narcotic Dependency	9 (0.1)	11 (0.1)	0.67
Alcohol Abuse	205 (2.2)	180 (1.9)	0.17
Current Anti-Convulsant Therapy	222 (2.4)	202 (2.1)	0.28
Current Benzodiazepine, Barbiturates, or GABA agonist	3,490 (37)	3,438 (36)	0.21

*Non-parametric data presented as median [25^{th} to 75^{th} percentile interquartile] range.

All categorical data elements are presented as number (%)

Of the 9460 patients randomized to the BIS intervention and successfully interviewed, 3384 or 36% did not have BIS data recorded due to technical issues described in Materials and Methods (Technical Factors). This population was used for secondary analysis only as a *post hoc* control group because it had neither intervention; there were more females ($p<0.001$) and more patients with lung disease ($p=0.002$) in this group. Neither female sex nor lung disease were shown to be associated with an increased incidence of intraoperative awareness in our recent companion randomized controlled trial (Avidan et al., 2011).

Incidence of intraoperative awareness events

The overall incidence of definite awareness in the study cohort was 19/18,836 or 0.1%. By modified intention-to-treat analysis, the incidence of definite AWR was 11/9376 or 0.12% (95% CI 0.07 to 0.21%) in the group randomized to the anesthetic concentration protocol and 8/9460 or 0.08% (95% CI 0.04 to 0.16%) in the group that was randomized to receive BIS monitoring ($p=0.48$, Figure 2).

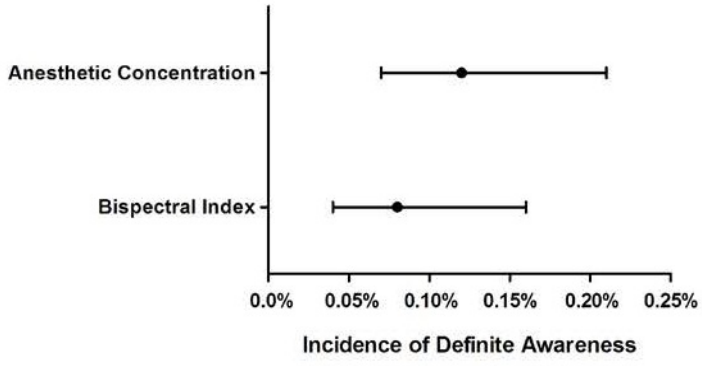


Figure 2: Primary outcome of definite awareness in modified intention-to-treat groups

Using the Michigan Awareness Classification Instrument, no statistical differences in event or distress classes were found between the groups. *Post hoc* power analysis revealed that 102,951 patients in each group would be required to detect a difference between the two interventions. The 13% of recruited patients who did not complete interviews (e.g., due to death or lack of response) were unlikely to skew the reported incidence of AWR. Assuming the same

incidence rates found in the modified intention-to-treat groups, 100,000 simulations were run to generate cumulative distribution functions that demonstrate the probability of a significant difference of outcome if the 2765 patients not interviewed were included. Using a Fisher's exact test, the likelihood of a significant difference with inclusion of this population was 0.016%.

By *post hoc* analysis, the incidence of definite AWR was 11/9376 or 0.12% in the anesthetic concentration group, 3/6076 or 0.05% in the group that actually received BIS monitoring, and 5/3384 or 0.15% in the no intervention group (p=0.27). Based on the 0.12% awareness incidence in the anesthetic concentration group and the 0.05% awareness incidence in the group that received BIS monitoring, a *post hoc* power analysis revealed that 29,996 patients in each group would be required to detect a difference between the two interventions. The combined incidence of definite *and* possible AWR cases was 0.08% in the group that received BIS monitoring, 0.20% in the anesthetic concentration group and 0.38% in the no intervention group (p=0.006, Figure 3). By *post hoc* analysis, the cohort receiving no intervention had 4.7 times more definite or possible awareness events compared to the cohort receiving the BIS protocol (p=0.001; 95% CI 1.7 to 13.1). Of patients with definite or possible awareness receiving BIS monitoring, 50% had no 5-min epoch of BIS values <60 during the case and 50% had at least one 5-min epoch of median BIS value >60.

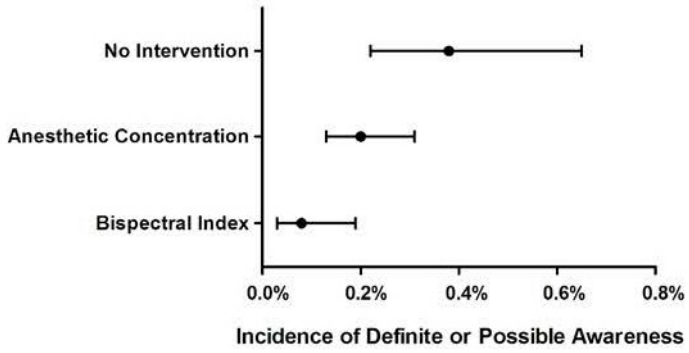


Figure 3: Secondary outcomes of definite or possible awareness in *post hoc* groups.

By secondary analysis using *post hoc* grouping, the average number of alerts in the no intervention group (0/case), anesthetic concentration group (1/case), and BIS group (2.2/case) varied inversely with the incidence of definite and possible awareness events (r^2=0.951).

BIS Values, Anesthetic Usage, and Recovery

The secondary outcome measures of anesthetic use and recovery times were performed using the *post hoc* comparison groups of anesthetic concentration, BIS, and no intervention. Since the decision was made to present the data using the three *post hoc* groups instead of the modified intention-to-treat grouping (BIS or anesthetic concentration), Bonferroni adjustments were performed as described in the *Statistical Analysis* section of the Materials and Methods. Data are presented in Table 2, with only significant pair-wise comparisons reported. There was a statistically significant difference in the median MAC for pairwise comparisons of anesthetic concentration to no intervention groups and also for BIS to no intervention groups. Intraoperative propofol bolus dosing showed a significant pair-wise comparison between the BIS and no intervention groups. The total midazolam dose showed no statistically significant differences. Total fentanyl and total morphine use had statistically significant pair-wise comparisons for all combinations of the three grouping variables. Although statistically significant, the clinical relevance of these differences is unclear.

Median time to meeting recovery room discharge criteria was 98 min (interquartile range 66 to 140) for anesthetic concentration group, 95 min (interquartile range 64 to 138) for the BIS group, and 94 min (interquartile range 64 to 133) for the no intervention group. There was a significant pair-wise comparison between the no intervention and anesthetic concentration groups. There was no evidence for reduced recovery time in patients receiving BIS monitoring

compared to no intervention. There was no statistically significant difference among the three groups for reduced nausea or reduced vomiting upon first assessment in the recovery room (Table 2).

Table 2: Anesthetic use and recovery variables

	Anesthetic concentration (N=9,376)	**Bispectral Index (N=6,076)**	**No intervention (N=3,384)**	**p-value**
BIS Values* % complete data (n)	40 [34 to 46] 41% (3,885)	40 [35 to 44] 100% (6,076)	N/A N/A	NS
MAC Values** %complete data (n)	0.9 [0.8 to 1.1] 98% (9,170)	0.9 [0.8 to 1.1] 99% (5,988)	0.9 [0.8 to 1.1] 98% (3,303)	<0.001 (Pairwise-comparisons of No Intervention to Anesthetic Concentration AND No intervention to BIS)
Propofol Intraoperative Bolus (mg)** % complete data (n)	170 [130 to 200] 100% (9,376)	180 [130 to 200] 100% (6,076)	170 [120 to 200] 100% (3,384)	<0.001 (Pair-wise comparison of No intervention to BIS)
Midazolam (mg)** % complete data (n)	2 [2 to 4] 100% (9,376)	2 [2 to 4] 100% (6,076)	2 [2 to 4] 100% (3,384)	NS
Fentanyl (µg)** % complete data (n)	175 [100 to 250] 100% (9,376)	200 [100 to 250] 100% (6,076)	150 [100 to 250] 100% (3,384)	<0.001 (All pairwise comparisons)
Morphine (mg)** % complete data (n)	0 [0 to 5] >99.9% (9,374)	0 [0 to 5] >99.9% (6,074)	0 [0 to 3] >99.9% (3,383)	<0.001 (All pairwise comparisons)
PACU Discharge Readiness (min)** % complete data (n)	98 [66 to 140] 91% (8,527)	95 [64 to 138] 91% (5,521)	94 [64 to 133] 90% (3,043)	0.001 (Pairwise comparison No intervention to anesthetic concentration)
No Nausea (% of patients) (n)*** % complete data (n)	92% (6,184) 72% (6,787)	93% (4,042) 72% (4,403)	93% (2,286) 74% (2,506)	NS
No Vomiting (% of patients) (n) *** % complete data (n)	99% (7,149) 78% (7,329)	99% (4,617) 77% (4,707)	99% (2,608) 79% (2,687)	NS

Note: Bonferroni adjustments were made due to *post hoc* comparisons (α=0.002). All data using the Kruskal-Wallis test also had pair-wise comparisons using a series of Mann-Whitney U tests if the omnibus test was significant. Only p-values < 0.002 in the pairwise comparisons were reported as statistically significant differences for these *post hoc* tests.

*Non-parametric data presented as median [25^{th} to 75^{th} percentile interquartile] ranges and evaluated using Mann-Whitney U test .**Non-parametric data presented as median [25^{th} to 75^{th} percentile interquartile] ranges and evaluated using Kruskal-Wallis test. ***Categorical data evaluated using Pearson chi-square.

BIS=Bispectral Index, MAC=minimum alveolar concentration, TIVA=total intravenous anesthesia, PACU=postanesthesia care unit.

Discussion

This is the largest prospective randomized controlled trial ever conducted on the prevention of AWR and the only such effectiveness trial. This negative study was unable to determine if an alerting protocol based on BIS values or anesthetic concentration was superior in preventing definite intraoperative awareness. Other conclusions of the study are that (1) comparative effectiveness trials with definitive results regarding the prevention of AWR in unselected patients will likely not be feasible, (2) *post hoc* secondary analysis suggests that a protocol based on the BIS monitor probably reduces awareness events compared to routine care without a protocol, (3) increased provider alerting is a possible mechanism for decreasing awareness events when comparing two protocols, (4) the BIS monitoring protocol used in this trial is not associated with a reduction in the use of anesthetic drugs in routine clinical practice, and (5) the BIS monitoring protocol used in this trial is not associated with reduced recovery time or incidence of nausea and vomiting in routine clinical practice.

The B-Aware study demonstrated that a BIS-guided protocol significantly reduced the incidence of AWR in a high-risk population compared to no intervention (Myles et al., 2004). Subsequently, the B-Unaware study demonstrated no difference between a BIS-guided and

MAC-guided protocol in the high-risk population (Avidan et al., 2008), a finding supported by the recent BAG-RECALL trial (Avidan et al., 2011). The current study differs from all past trials in that it assessed AWR prevention in an unselected, representative surgical population as opposed to the high-risk population alone. The primary results of our study are consistent with the B-Unaware and BAG-RECALL trials in that no statistically significant difference in the prevention of AWR could be demonstrated between anesthetic concentration and BIS monitoring protocols. However, the results of the *post hoc* secondary analysis are consistent with the B-Aware trial (Myles et al., 2004) in that the BIS monitor showed a trend toward reducing the incidence of awareness events compared to a group with no intervention. One methodological similarity of the current trial, the B-Aware trial (Myles et al., 2004) and the observational study by Ekman et al., 2004 is that anesthetic administration was not restricted to potent inhaled agents alone, as it was in the B-Unaware and BAG-RECALL trials (Avidan et al., 2011; Avidan et al., 2008). Our study supports the conclusion of a recent Cochrane database review suggesting that the BIS monitor may reduce AWR when compared to assessing clinical signs alone, but not when compared to a protocol based on anesthetic concentration (Punjasawadwong et al., 2007).

The use of the BIS monitor in the current study generated approximately twice as many alerts as that of the anesthetic concentration protocol. Therefore, increased alerting could potentially be a mechanism of decreased definite or possible AWR events, an interpretation supported by the results of our companion trial. In the BAG-RECALL study, the alarm frequency based on anesthetic concentration was approximately 2-fold higher than that based on BIS values; the higher alarm rate with the anesthetic concentration protocol was associated with fewer definite and possible AWR events. The different alerting threshold in BAG-RECALL (0.7MAC) and the current trial (0.5MAC) likely explains the ostensibly disparate outcomes. It is

important to note that there was a high incidence of false positive alerting, which mitigates any conclusion regarding alerting protocols as a method of preventing AWR.

Efficacy trials and meta-analyses have suggested that the BIS monitor can significantly reduce consumption of anesthetic drugs, which leads to improved outcomes such as faster recovery or reduced nausea and vomiting. These data have been used to argue that the BIS monitor is cost-effective and should be routinely adopted for every general anesthetic (Klopman and Sebel, 2011). The BIS protocol used in the current study was not shown to reduce anesthetic dosing, which is in contrast to the recent Cochrane database review (Punjasawadwong et al., 2007). Furthermore, the BIS protocol used in the current study was not associated with reduced recovery time or reduced incidence of nausea and vomiting compared to routine care. One hypothesis to explain the discrepancy is that conclusions derived from efficacy trials or meta-analyses based on such trials are not sufficiently robust to hold in a test of effectiveness. Another hypothesis to explain the discrepancy is that the difference in BIS-guided protocols between the current and past studies led to disparate outcomes.

Limitations of our study include insufficient numbers to answer with precision whether and to what extent there is a difference in the definite AWR incidence between protocols based on BIS values and anesthetic concentrations. This limitation likely reflects the rarity of AWR in an unselected surgical population and is informative regarding the future investigation of protocols to reduce AWR. Another limitation of the trial was the proportion of patients randomized to the BIS protocol who did not receive BIS monitoring. However, this unplanned technical issue has yielded useful secondary findings and is mitigated by the following considerations: (1) even complete compliance would almost certainly not have been sufficient to detect a significant difference in the modified intention-to-treat groups, (2) the population

receiving neither intervention yielded useful information regarding the effect of anesthetic protocols compared to routine care, a matter of recent controversy,(Crosby, 2011) (3) the incidence of definite and possible AWR events in the no-intervention group was equivalent to that previously reported (Punjasawadwong et al., 2007; Sandin et al., 2000; Sebel et al., 2004), which validates the methodology of the trial and suggests that a single interview at 30 days was sufficient to detect clinically relevant AWR, and (4) the number of prospectively-studied patients who received BIS monitoring nonetheless exceeds all major efficacy trials combined (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004).

In conclusion, this effectiveness study could not detect a difference between BIS and anesthetic concentration protocols in reducing the incidence of definite AWR with explicit recall. By *post hoc* analysis, we demonstrated that the BIS monitor may play a role in reducing AWR compared to no intervention. These findings are consistent with conclusions of a Cochrane review based on various efficacy studies (Punjasawadwong et al., 2007). In contrast to the Cochrane review, the BIS protocol used in this study was not associated with improved recovery.

This is my primary body of work and was previously published in full with tables and figures by Wolters Kluwer Health Lippincott Williams & Wilkins: **Shanks AM**, Mashour GA, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, Picton P, Schueller C, Morris M, Vandervest JC, Lin N, Avidan MS. *Prevention of Intraoperative Awareness with Explicit Recall in an Unselected Surgical Population: A Randomized Comparative Effectiveness Trial.* Anesthesiology 2012, 117 (4) 717-725.

Chapter 5 – Systematic Review for Alerting Thresholds for the Prevention of Intraoperative Awareness with Explicit Recall

Intraoperative awareness with explicit recall (AWR) of surgical events can be a devastating complication for patients, with significant psychological sequalae (Domino et al., 1999; Ghoneim et al., 2009; Leslie et al., 2010; Moerman et al., 1993; Osterman et al., 2001; Schwender et al., 1998). The incidence of definite AWR in patients undergoing general anesthesia is reported to be between 1 and 2 out of 1,000 cases and as high as 3 to 4 of 1,000 cases for both possible and definite AWR events (Mashour et al., 2012; Sandin et al., 2000; Sebel et al., 2004); in patients at high risk for AWR, the incidence approaches 1% (Myles et al., 2004). It has been posited that the primary reason for AWR is insufficient anesthesia (Ghoneim et al., 2009; Nickalls and Mahajan, 2010), suggesting that alerting protocols could prevent AWR if a specific threshold was identified.

Two common surrogates for anaesthetic depth are minimum alveolar concentration (MAC) measured by end-tidal anesthetic concentration (ETAC), and the Bispectral Index® (BIS). Alerting algorithms based on either MAC or BIS values can be implemented easily to notify the provider of potentially insufficient anesthesia. The rapid expansion of electronic Anesthesia Information Systems (AIMS) allows for enhanced use of alerting algorithms with the potential to combine demographic, co-morbidity, physiologic and anesthetic concentration variables. In addition, the AIMS allow the provider to be notified via pager for potentially insufficient anesthesia even when the alarms on the primary monitoring system have been silenced.

Clinical trials investigating the prevention of AWR (Avidan et al., 2008; Mashour et al., 2012; Myles et al., 2004; Zhang et al., 2011) used specific thresholds for potentially insufficient

anesthesia, with the provider either being instructed to keep the BIS value between 40 and 60 or with audible alarms if the BIS or MAC values fell outside defined ranges. The MAC and BIS values chosen were based on previously published work, but to date, there has been no systematic study of the appropriate threshold for MAC or BIS alarms for the prevention of AWR based on prospectively collected data.

The parent trial for this study (Mashour et al., 2012) investigated whether the use of alerting algorithms in cases randomized to either anaesthetic concentration or BIS values decreased the incidence of AWR. It did not investigate the discrete MAC or BIS data elements to determine whether there is a specific value that would maximize the sensitivity and specificity in the prevention of AWR or explore any changes in provider behaviour when alerts are generated. Therefore, the objective of this study was to test the hypothesis that there is an evidence-based alerting threshold for MAC or BIS values that would maximize the sensitivity and specificity of alarms aimed at preventing AWR. In addition, we sought to determine if alerting the provider changes behaviour with respect to anaesthetic management in the prevention of AWR.

Materials and Methods

This study is a pre-specified secondary analysis of the Michigan Awareness Control Study (MACS) (ClinicalTrials.gov No. NCT00689091) (Mashour et al., 2012). The parent trial and this secondary analysis were approved by the Institutional Review Board (IRB HUM 13626, initial study approval 8/14/2007) of the University of Michigan, 2800 Plymouth Road, Building 520 Room 3214, Ann Arbor, MI 48109 (Chairmen: Drs Michael Geisser and John Weg). In brief, we screened all adult patients between May 2008 and May 2010 presenting to a

multihospital healthcare system for surgery in which general anaesthesia using inhaled or intravenous anaesthetic. A detailed discussion with each patient took place and verbal informed consent was obtained and documented in our AIMS. Patients were excluded if the use of a BIS monitor was impractical (e.g. intracranial procedures, adhesive allergy, surgery involving the forehead) or underlying brain disorder rendered the BIS a questionable measure of consciousness (e.g., history of traumatic brain injury). The BIS Quatro sensor (Covidien, Boulder, Colorado, USA) was attached preoperatively in all patients by a member of the research staff. Alerts to notify the provider of potentially insufficient anaesthetic dosing were based on either the age-adjusted MAC (aaMAC) (Nickalls and Mapleson, 2003) or BIS values. For the parent trial, aaMAC was calculated based on pre-specified age groups (Mashour et al., 2009a).

A detailed description of the randomisation and blinding is explained elsewhere (Mashour et al., 2012; Mashour et al., 2009b) and is briefly summarized here. The study was divided into eight quarters (eight 3-month periods over 2 years), with MAC and BIS alerting algorithms randomly assigned for each quarter. For the MAC alerting rooms, the real-time BIS values were hidden from the provider's view. In addition, if the median ETAC for a 5-min epoch was less than 0.5 aaMAC, an alphanumeric paging alert was sent to the provider in the room. For the BIS alerting group, the BIS values were visible to the provider. In addition, if the median BIS value for a 5-min epoch was greater than 60, an alphanumeric paging alert was generated. A study team member contacted each patient and administered the modified Brice interview 28-30 days after surgery (Abouleish and Taylor, 1976; Brice et al., 1970). As described previously, after the modified Brice interview and additional interviews of potential AWR patients (Mashour et al., 2012) were performed, each event was categorized as no AWR, possible AWR or definite AWR. Data from other trials in which the authors were involved

(Avidan et al., 2011; Avidan et al., 2008) could not be included due to differences in data acquisition systems and incomplete records of alarm delivery.

For the MACS trial, Centricity® (GE Healthcare, Madison, Wisconsin, USA) was the AIMS system used for programming alerts and notifying providers via alphanumeric text paging. Centricity® interfaces with the haemodynamic monitors (GE Marquette Solar 9500, Milwaukee, Wisconsin, USA) and also with the anaesthesia machine (AISYS Anesthesia Machine, GE Healthcare). ETAC values were automatically calculated in real time from the expired volatile anaesthetic concentrations that were collected by the AISYS anaesthesia machine and transmitted to Centricity®. BIS and ETAC data elements were electronically captured for every patient by the AIMS every 60s and were available for later study extraction and analysis.

For this secondary analysis, we included cases in which inhaled volatile agents were used as the primary anaesthetic. We excluded total intravenous anaesthetic (TIVA) cases, any case for which a propofol infusion was used in conjunction with a volatile anaesthetic and any case with missing volatile anaesthetic data due to infrequent AIMS data interface issues.

Secondary Analysis Methodology

All cases were reviewed to ensure complete data for ETAC and BIS values from an electronically documented time of “anesthesia induction end” to the time of “request for postanaesthesia care unit (PACU) bed” or “transport to the ICU.” For this secondary analysis, aaMAC was calculated on the basis of the age documented in the AIMS at the time of operation and not on the pre-specified age groups as in the parent trial (Nickalls and Mapleson, 2003). The surgery was divided into 5-min epochs (during the AIMS timestamps listed previously) and the median ETAC was calculated for each of those 5-min epochs. The overall median ETAC

was also calculated for each case. The same technique was used for patients with valid BIS monitoring data.

Data were analyzed two different ways to determine a single threshold for the prevention of AWR for ETAC and BIS values. First, the data were dichotomised by whether any 5-min epoch was below (aaMAC) or above (BIS) a set value throughout the case. The maximum sensitivity, specificity and Youden's Index were calculated. Second, the median ETAC and BIS values for the case were analysed using a receiver operating characteristic curve c-statistic. If the c-statistic demonstrated adequate discriminating capacity (> 0.70), then the value with the maximum sensitivity and specificity would be computed and retrospectively applied to the database to determine a single threshold for the prevention of AWR.

To investigate whether the alerting algorithm changes provider behaviour, we first calculated the percentage of the case during which the anaesthetic concentrations triggered the alarm. This percentage was calculated by dividing the number of 5-min epochs that met the ETAC alerting threshold by the number of 5-min epochs overall. We chose to present the data as the percentage of the case duration instead of total minutes of the case to account for the variance in length of procedures. A control group that had no real-time alerting interventions, distinct from the ETAC and BIS groups, was used to explore whether there is a behavioural effect by retrospectively applying the ETAC alerting algorithm. This group received neither BIS nor MAC alerts yet was still assessed for AWR; the anaesthetic was delivered on the basis of routine clinical and hemodynamic variables. The control group resulted from technical interface issues from the parent trial and was not prespecified (Mashour et al., 2012). However, as there was a "no intervention" group that resulted from MACS, we could assess whether there was a behavioural effect attributable to having alerts generated throughout the case. This was

accomplished by retrospectively applying the ETAC alerting algorithm to the "no intervention" group and calculating what percentage of time the case would have triggered an alarm if an algorithm had been active in real time. The percentage of the case during which the anaesthetic triggered the ETAC alerting algorithm was then compared between the original ETAC intervention arm and post hoc control group. The mean percentage of the case that triggered an alarm was also examined for change in behaviour across the study period for both the ETAC and BIS arms. If the mean percentage changed across the quarters, this would indicate that anesthetic delivery behaviour had changed.

Statistical Analysis

Due to the low incidence of definite AWR in the parent trial and the potential psychological impact of possible AWR, we combined definite and possible AWR events into one category for this secondary analysis. To determine whether there was a single threshold that maximises sensitivity and specificity for the prevention of AWR, aaMAC for all cases was dichotomised by whether the case did or did not have any 5-min median epochs in which the aaMAC was less than 0.4, less than 0.5, less than 0.6, less than 0.7, less than 0.8 or less than 0.9. The same dichotomising technique was used for cases with valid BIS data that had at least one 5-min median epoch with BIS more than 60, more than 70, BIS more than 80 or more 90. The baseline BIS threshold was set at 60 because this generally represents the threshold between general anesthesia (<60) and sedation or wakefulness (>60) (Glass et al., 1997). Sensitivity, specificity and Youden's Index were then calculated to determine whether there was an optimal threshold for the prevention of AWR for either aaMAC or BIS. The Youden's Index was calculated as (sensitivity + specificity – 1) (Bewick et al., 2004). A Youden's Index of 1 would indicate the threshold is perfect and a Youden's index of 0 would indicate the threshold has no

diagnostic value in the prevention of AWR (Bewick et al., 2004). Next, a c-statistic was calculated from a receiver operating characteristic curve to determine whether there is a single diagnostic threshold for either ETAC or BIS that can be quantified for prevention of AWR. If the c-statistic was deemed adequate (>0.70), then the continuous data for both aaMAC and BIS would be analysed to determine the specific threshold in the prevention of AWR.

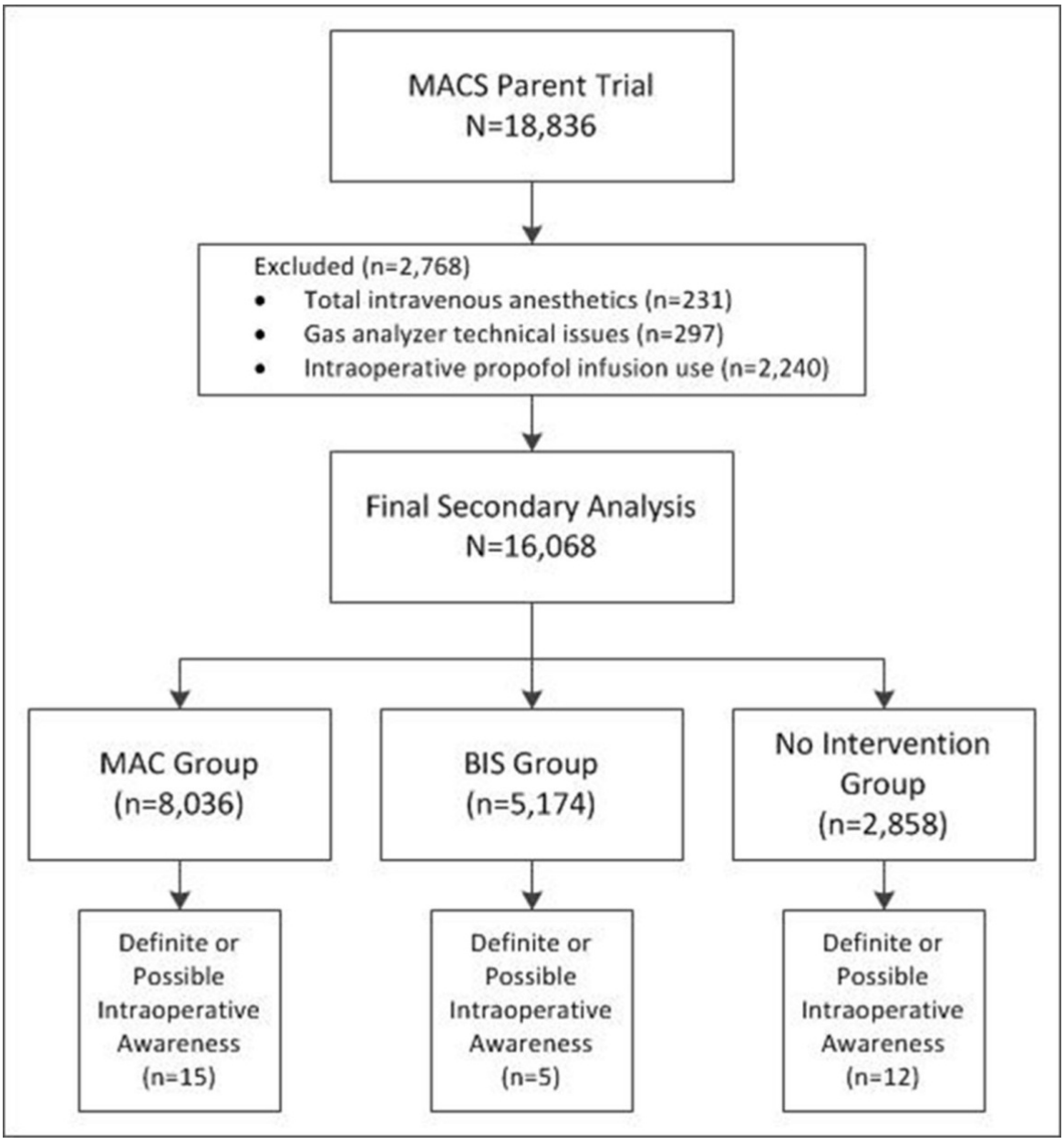
A Mann-Whitney U test was performed to assess whether providers receiving the original MAC alerts differed statistically when compared to the "no intervention" (i.e. no alert) group for the entire time period and by quarter of the study. To determine whether there was a behavioural change, as documented by a significant difference in the percentage of the case that triggered an alert for potentially insufficient anaesthesia, a Kruskal-Wallis test was performed for both MAC and BIS arms across the study period. Data are displayed as the mean percentage of the case to trigger an alert ± 2x SEM.

SPSS® version 20 (IBM® Corp, Armonk, New York, USA) was used for all analyses. Data extraction from AIMS was completed using structured query language. A p-value of less than 0.05 was considered statistically significant throughout.

Results

The parent trial had a total of 18,836 patients with complete information on the AWR outcome. We excluded 231 cases because of the use of TIVA, 297 for agent analyser device technical issues and 2,240 for use of an adjunct intraoperative propofol infusion. This resulted in the dataset of 16,068 patients, with a total of 32 definite or possible AWR events (Figure 1).

Figure 1: Flow Diagram from Parent Study to Secondary Analysis



Youden's Index did not demonstrate a single threshold for aaMAC or BIS values in the prevention of AWR (Table 1). The c-statistic for median aaMAC was 0.431 ± 0.046 and 0.491 ± 0.056 for BIS, indicating that there is not a specific threshold that can be calculated for the prevention of AWR when using either aaMAC or BIS values. There were 10 patients who experienced an AWR event with BIS values <60 (median for 5-min epoch) for the entire case.

Table 1: Sensitivity, Specificity, and Youden's Index for each case that had valid measurements for End-tidal Anesthetic Concentration and Bispectral Index values

aaMAC

	Sensitivity (95% CI)	Specificity (95% CI)	Youden's Index
aaMAC <0.4	0.28 (0.14-0.47)	0.79 (0.79-0.79)	0.07 (-0.06 – 0.26)
aaMAC <0.5	0.38 (0.22-0.56)	0.71 (0.71-0.71)	0.08 (-0.08-0.27)
aaMAC <0.6	0.44 (0.27-0.62)	0.59 (0.59-0.60)	0.03 (-0.14-0.24)
aaMAC<0.7	0.59 (0.41-0.76)	0.45 (0.45-0.45)	0.05 (-0.14-0.21)
aaMAC<0.8	0.78 (0.60-0.90)	0.30 (0.30-0.30)	0.08 (-0.10-0.20)
aaMAC<0.9	0.81 (0.63-0.92)	0.18 (0.18-0.18)	-0.01 (-0.19-0.10)

BIS

	Sensitivity (95% CI)	Specificity (95% CI)	Youden's Index
BIS ≥ 60	0.09 (0.01-0.43)	0.72 (0.72-0.72)	-0.19(-0.28-0.15)
BIS ≥ 70	0.00 (0.00-0.32)	0.91 (0.91-0.91)	-0.09 (-0.09-0.24)
BIS ≥ 80	0.00 (0.00-0.32)	0.97 (0.97-0.97)	-0.03 (-0.03-0.29)
BIS ≥ 90	0.00 (0.00-0.31)	0.99 (0.99-0.99)	-0.01 (-0.01-0.31)

aaMAC = age-adjusted MAC; BIS = Bispectral Index; CI = Confidence Interval

When applying the ETAC alerting algorithm retrospectively to the "no intervention" (i.e. no alerts) cases, we determined that cases randomised to MAC alerting had a statistically shorter mean percentage of the case that generated an alert for potentially insufficient anaesthesia than the "no intervention" cases (2.4% ± 7.5% versus 3.1% ± 8.5%, p=0.009). Four of the eight quarters demonstrated these findings, although the remaining quarters did not reach statistical significance (Figure 2). In the trend analysis by study period, the mean percentage of the case that triggered a potentially insufficient anaesthetic alert in the ETAC arm increased significantly (p <0.001) (Figure 3). However, the mean percentage of the case that generated a BIS alert via the alerting algorithm did not change across the study period (p=0.38) (Figure 4).

Figure 2: Comparison of end-tidal anesthetic concentration alerting and 'no intervention'

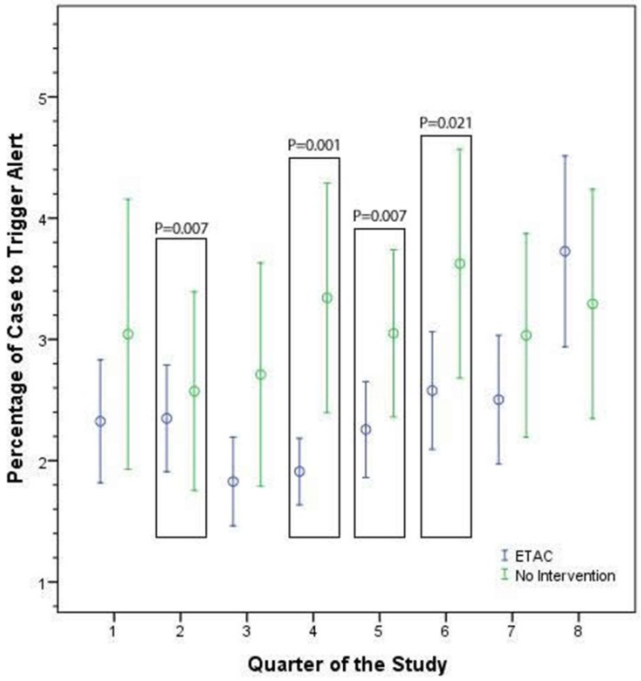


Figure 3: End-tidal anesthetic concentration alerting trend analysis

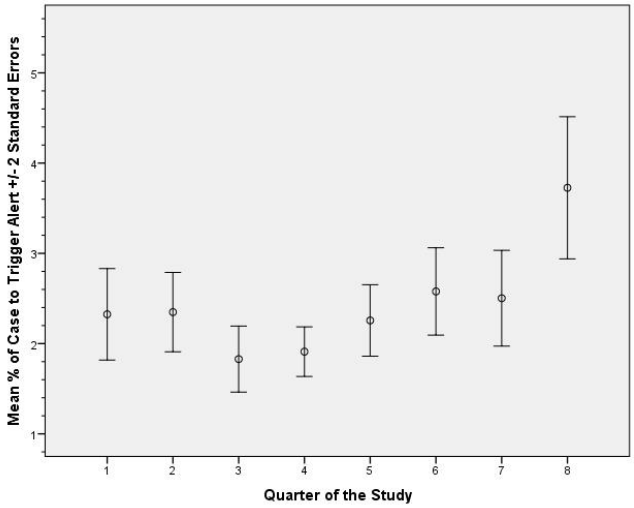
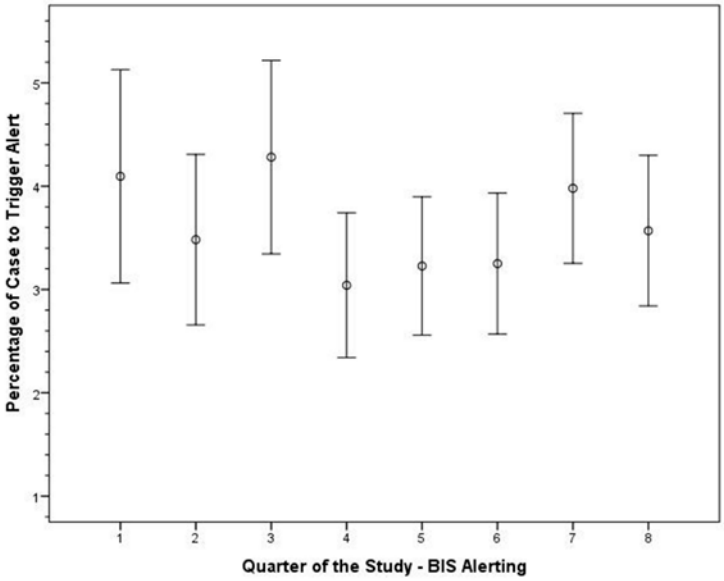


Figure 4: Bispectral Index alerting trend analysis



Discussion

Population-based alerting in the prevention of AWR is important to consider because retrospective evidence shows that approximately 87% of all AWR cases are attributable to insufficient anaesthesia (Ghoneim et al., 2009). An editorial by Nickalls and Mahajan (Nickalls and Mahajan, 2010) presented a parsimonious approach by stating that all cases of AWR are attributable to insufficient anaesthesia unless there is compelling evidence to the contrary. They suggested that a population-based adequate dose for anaesthetics should be identified and implemented for the prevention of AWR (Nickalls and Mahajan, 2010). In the present study, we analysed discrete surrogate metrics of anesthetic depth (ETAC and BIS) in order to identify a single diagnostic threshold for the systematic prevention of AWR. We have demonstrated that, in patients undergoing general anaesthesia in which only volatile anaesthetics were used, there is no population-based threshold that could be used as an alert in the prevention of definite or

possible AWR for either ETAC or BIS. The population data from Youden's index suggest that the thresholds studied would not result in the eradication of AWR.

The thresholds that we selected were representative of what would be considered standard of care aaMAC for patients under general anaesthesia. Concentrations higher than 1.0 aaMAC were excluded from this analysis because of very high false positive alarms at thresholds of at least 0.7 MAC (Mashour et al., 2009a). It is important to note that Youden's index incorporates data on both sensitivity and specificity. As Table 1 indicates, lower alerting thresholds (e.g., higher anaesthetic concentrations) increase sensitivity at the cost of decreasing specificity. Thus, including thresholds of AWR alerting beyond 1 MAC would further increase sensitivity, but would probably not increase Youden's index due to the concomitant decrease in specificity. In addition, the c-statistics indicated that, for both aaMAC and BIS, there was approximately a 50% chance (essentially random) of determining the correct threshold in the prevention of AWR using a population-based approach (Bewick et al., 2004).

To date, multiple randomised controlled trials have been conducted using a population-based alerting (or monitoring) strategy in which a specific alarm or range for ETAC or BIS was established for the prevention of AWR (Avidan et al., 2011; Avidan and Mashour, 2013; Avidan et al., 2008; Mashour et al., 2012; Myles et al., 2004). Myles et al. found that BIS monitoring (maintained between 40 and 60) was associated with a relative risk reduction of 82% in surgical patients at high risk for AWR when compared to routine monitoring (Myles et al., 2004). The next two trials used audible alerts to notify the provider of potentially insufficient anesthesia in patients at high risk for AWR. Avidan et al. found that both BIS and ETAC alarms reduced observed awareness events compared to the expected incidence (Avidan et al., 2011; Avidan et al., 2008). Mashour et al. included unselected surgical patients requiring general anesthesia and

demonstrated that BIS alerting protocols reduced the incidence of definite or possible AWR compared to no intervention (Mashour et al., 2012). The persistence of AWR in previous trials suggests that population-based alerting approaches for insufficient anaesthesia will not eradicate AWR. The current study adds to the literature by suggesting that it was not simply the empirical or arbitrary determination of alerting thresholds in past trials that failed to eradicate AWR because our systematic analysis and comparison suggest that no one threshold exists. Rather than arguing that BIS or ETAC alerts are not useful, we would instead encourage clinicians to choose some threshold to prevent egregious causes of AWR (such as an empty vaporiser). Past randomised controlled trials demonstrate that alerts are, in fact, associated with reduced AWR.

At an individual level, we know that there is a specific threshold at which the patient will be likely to experience AWR. The identification of such a threshold will, in the future, probably be guided by risk factors for AWR coupled with more sophisticated monitoring. Previous work has reported specific patient-based risk factors for AWR. Further identification of risk factors, in conjunction with developments in monitoring the neural substrates of consciousness, must ultimately be incorporated into prevention strategies for AWR at an individualised level.

Fundamentally, individualised-based alerting strategies would not be beneficial without establishing evidence that real-time alarms are capable of changing behaviour. We have demonstrated that real-time alerting alters the administration of anaesthetics. When retrospectively applying the MAC alerting algorithm to the “no intervention” cases in the parent trial, the providers that were not alerted to potentially insufficient anesthesia had lower MAC values throughout the case than those that were actually alerted in real time. This indicates that the providers receiving alerts were statistically more likely to keep the anesthetic concentration within the stated range for the trial and, we infer, changed their behaviour to do so. These results

confirm other previously published studies that providing clinicians with alerts can drive a change in clinical care (Bates et al., 2001; Eden et al., 2009; Kheterpal et al., 2007; Kooij et al., 2008; Kucher et al., 2005; O'Reilly et al., 2006; St Jacques et al., 2005; Wax et al., 2007).

When alerting is used to notify providers to change behaviour, there is the potential for alert fatigue, which is defined as the provider becoming less responsive due to an alarm becoming bothersome or ineffective. Alert fatigue is an increasingly prevalent phenomenon in the medical community, especially with the rapid advancement of electronic medical records (Baker, 2009; Kesselheim et al., 2011; Lee et al., 2010). Block et al. surveyed anaesthesiologists practising in the USA and found that 70% of the time alarms were silenced was due to the perception of a false alarm (Block et al., 1999). Only 16% of providers stated that they never turn off alarms (Block et al., 1999). Therefore, it is imperative to minimise false alarms—and, consequently, alert fatigue—in developing an alerting strategy for AWR, a difficult task given the rarity of the outcome. This is one reason why the current study focused on sensitivity and specificity. We found evidence of alert fatigue as well as possible desensitisation to ETAC alerts across the study period. The mean percentage of the case that generated an ETAC alert changed significantly during the last quarter of the trial, with alerts having increased approximately 1.2% from the previous quarter and 1.5% from the beginning of the study. These data could indicate that the providers thought the alerts were false alarms and therefore were becoming desensitised and fatigued as the study continued (delayed alert fatigue). However, these findings were only found in the last quarter of the study and could also be an outlier. The BIS alerting rate was consistent throughout the study and showed no evidence of generating desensitisation or alert fatigue.

The main limitation of this study was the small number of AWR outcomes in our population (n=32). To move towards an individualized alerting approach, a multinomial logistic regression model must be developed that incorporates patient-specific risk factors (such as history of AWR (Aranake et al., 2013)) along with anaesthetic concentrations and, if possible, neurophysiologic indices. Furthermore, we used the median from a 5-min period and must acknowledge that individual BIS or MAC values could have nonetheless fluctuated in a way that might not be detected with our methodology. Finally, the current study only investigated a threshold using general anaesthesia with inhaled anaesthetics and is therefore not generalisable to cases performed using TIVA.

In conclusion, we could not identify a single practical threshold of ETAC or BIS values that can be chosen for the eradication of definite and possible AWR in a broad surgical population. Although alerts have been demonstrated to prevent AWR, future work must move towards an individualised patient-based approach incorporating specific risk factors as well as monitoring the neural substrates of consciousness. Indeed, recent studies have demonstrated promise in identifying correlates of anaesthetic-induced unconsciousness based on the neurobiology of consciousness (Casali et al., 2013; Lee et al., 2013). Finally, we were able to demonstrate that providing alerts via an AIMS can influence intraoperative care, but ETAC alerting has the potential for desensitisation and alert fatigue.

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Chapter 6 - Intraoperative Awareness Monitoring and Past Research Overview

By conducting the largest prospective clinical trial on AWR in an unselected surgical adult population, it was determined that BIS alerting did not appear to be superior to MAC-based alarms incorporating IV anesthetics at preventing AWR events. Through a secondary analysis of the traditional MAC calculations and investigating individual BIS values, it was demonstrated that there is no single population-based alerting algorithm using either the MAC or BIS values to alert the clinician in the prevention and eradication of AWR. Therefore, the field of anesthesiology must move past the population-based approach in alerting for the eradication of AWR and develop a patient-based alerting system.

Over the past decade, the medical community has recognized the need to develop enhanced monitoring techniques with the aim of preventing intraoperative awareness with recall (AWR). The Joint Commission on Accreditation of Hospital Organizations issued a sentinel event in 2004 stating that "anesthesia awareness is under-recognized and under-treated" (JACHO, 2004). They specifically recommended use of effective anesthesia monitoring tools to aid in the prevention of AWR (JACHO, 2004). The American Society of Anesthesiologists (ASA) developed a task force in 2006 to "provide guidance for the intraoperative use of brain function monitors as they relate to intraoperative awareness" (ASA Task Force, 2006). Since this time, several large prospective trials have been completed to determine superior methods of alerting clinicians to the possibility of insufficient anesthesia, which is the most common cause of AWR, using both anesthetic concentration monitoring and brain function monitoring (such as the Bispectral Index [BIS]) (Avidan et al., 2011; Avidan et al., 2008; Mashour et al., 2012; Myles et al., 2004; Zhang et al., 2011).

Anesthetic depth has traditionally been quantified for the clinician as “minimum alveolar concentration” (MAC). MAC represents the concentration of anesthetic that will suppress movement in response to a noxious stimulus in 50% of the population, was developed for inhalational anesthetics only and quantifies differences in potency among the different inhalational agents (Eger et al., 1965). MAC represents the partial pressure of the inhaled anesthetic vapor in the alveoli of the lungs (Gelb, 2009; Quasha et al., 1980). The partial pressure of any vapor in the body, when at equilibrium, will be the same in all tissues in the body, including the brain. Therefore, the MAC represents the partial pressure of the vapor in the brain, but not the actual concentration of the anesthetic vapor (Quasha et al., 1980). Brain wave monitoring, derived from a processed electroencephalographic (EEG) wave, reflects the activity of the end organ of interest in AWR, the brain, and is not based on a pharmacologic measure. However, there is not one specific component of the processed EEG that can used as a predictor of the depth of anesthesia and the type of anesthetic used affects the EEG interpretation (Drummond et al., 1991).

Starting in 2004, several prospective randomized trials were completed to investigate if anesthetic concentration monitoring (MAC) or EEG-based monitoring (BIS) were superior in prevention of AWR (Avidan et al., 2011; Avidan et al., 2008; Myles et al., 2004). The B-Aware trial compared BIS monitoring to routine clinical care in a high risk surgical population for the prevention of AWR (Myles et al., 2004). Myles et al. concluded that BIS monitoring reduced the relative risk of AWR by 82% and suggested all high risk patients should be monitored with the BIS (Myles et al., 2004). The B-Aware trial did not alert the clinicians when the BIS values were outside a targeted range and had no active comparator in the control group. Therefore, in 2008 the B-Unaware trial investigated if BIS, when compared to MAC monitoring, had a lower

incidence of AWR in the high risk surgical population using targeted alerting mechanisms (Avidan et al., 2008). Avidan et al. demonstrated no statistically significant difference in the incidence of AWR between the two monitoring techniques and suggested the B-Unaware trial did not support routine use of BIS monitoring in high risk surgical population (Avidan et al., 2008). Avidan et al. followed up on this finding with a multi-center BAG-RECALL trial to compare BIS and MAC monitoring in the prevention of awareness in high risk surgical patients with targeting alerting mechanisms (Avidan et al., 2011). Once again, the superiority of BIS, when compared to MAC, could not be established (Avidan et al., 2011).

The B-Aware, B-Unaware, and BAG-RECALL trials all investigated different AWR monitoring techniques in the high risk surgical population. The targeted BIS values for each trial were based on validated research that showed 95% of patients were unconsciousness when the BIS value was 50 and recommended that anesthetics should be titrated to a BIS value between 40 and 60 to prevent AWR (Glass et al., 1997). The targeted MAC values for the B-Unaware and BAG-RECALL trials were based on the assumption that 0.7 MAC would general suppress consciousness and memory for surgical events. The value of 0.7 MAC was chosen because when several anesthetic volatile agents are used in conjunction with one another an end-tidal anesthetic concentration (ETAC) is equated since the MAC equivalents for each agent are additive. Research has demonstrated that 50% of subjects will lose responsiveness to a command when the ETAC is one-third of the MAC (Eger, 2001). Therefore, if the ETAC is maintained above the 0.7 MAC, this may reduce AWR (Ghoneim, 2010; Gonsowski et al., 1995). The B-Unaware and BAG-RECALL trials restricted their anesthetics to inhalational agents only. Furthermore, the B-Aware, B-Unaware, and BAG-RECALL trials did not focus on unselected surgical patients at all risk levels for AWR. Finally, since many surgical cases are

now using a combined technique between IV and inhalational anesthetics, an “anesthetic concentration” concept was needed when investigating AWR prevention alerting techniques.

Development of the Anesthetic Concentration Alert Incorporating IV Anesthetics

To adequately assess if alerting techniques based on MAC or BIS are superior in the prevention of AWR, the traditional MAC concept must also include IV anesthetics in addition to the inhaled anesthetics used. Intravenous anesthetics are known to have a “MAC sparing” effect (Mashour et al., 2009a). Therefore, we developed a “MAC equivalent” alert that incorporated the inhalational anesthetic vapor MAC with IV agents (Mashour et al., 2009a). The algorithm for the “MAC equivalent” alert was based on clinical experience and was not validated or verified by independent measures. Using a retrospective review, we identified 15,091 cases that did not have AWR and 12 cases of AWR from a generalized surgical population at a large tertiary academic hospital (Mashour et al., 2009a). We retrospectively applied our “MAC equivalent” algorithm for both AWR and non-AWR cases to determine at which MAC equivalent (age-adjusted) threshold would demonstrate optimal sensitivity and specificity in the detection of AWR.

In the selection of the proper threshold to use for anesthetic concentration alerting for future prospective trials that incorporate the effects of IV anesthetics on the MAC value, an optimal signal-to-noise ratio must be determined that results in a tradeoff between sensitivity and specificity. We concluded that a threshold of <0.8 was most sensitive to the detection of AWR and had the best negative likelihood ratio but the threshold of <0.5 was associated with the best positive likelihood ratio (Mashour et al., 2009a). Therefore, we selected <0.5 age-adjusted MAC

equivalent to be used as the alerting threshold for the Michigan Awareness Control Study (clinical trial NCT00689091) (Mashour et al., 2012).

Michigan Awareness Control Study

The Michigan Awareness Control Study (MACS) sought to determine if a BIS or anesthetic concentration (adjusted for IV anesthetic effects) alerting for possible insufficient anesthesia would decrease the incidence of AWR in an unselected and broad surgical population (Mashour et al., 2012). The results demonstrated that BIS and MAC alerting techniques did not differ with respect to the prevention of AWR. However, when BIS alerting was compared against routine standard of care (i.e. no alerting to clinicians), we demonstrated a 4.7-fold reduction in definite or possible AWR (Mashour et al., 2012). Therefore, MACS findings support the conclusions found in the B-Aware, B-Unaware, and BAG-RECALL trials even though the patient populations were different and the anesthetic concentration alerting adjusted for the effects of IV anesthetics. For this trial, the anesthetic concentration alerting was based upon the "MAC equivalent" algorithm and is not directly comparable to the B-Unaware and BAG-RECALL trials.

Systematic Analysis of Alerting Thresholds in the Prevention of AWR

There have been no systematic analyses of appropriate thresholds to develop population-based alerting algorithms in the prevention of AWR. Three trials (Avidan et al., 2011; Avidan et al., 2008; Mashour et al., 2012) specifically investigated AWR between two empirically derived alerting protocols with pre-defined thresholds. However, there was no principled approach to determining the optimal alerting threshold for each of these techniques. Therefore, we sought to identify a threshold for AWR alerting for both BIS and MAC monitoring using granular

continuous data electronically captured during the MACS trial (Shanks et al., 2014). Since the "MAC equivalent" alert has not been validated, this study only used age-adjusted MAC (aaMAC) values. All cases that were performed under total IV anesthesia or any case that used an IV infusion with an inhalational anesthetic were removed for this secondary analysis (Shanks et al., 2014).

Two techniques were employed to determine an appropriate threshold for both BIS and aaMAC alerts using the granular data. First, data were dichotomized based on whether a 5-minute epoch during the surgical case was below (for aaMAC) or above (for BIS) clinically relevant thresholds. The sensitivity, specificity, and Youden's Index were also calculated. Second, the median MAC and BIS values were individually analyzed using a receiver operator characteristic (ROC) curve c-statistic. If the c-statistic was deemed adequate to demonstrate a discriminating capacity (>0.70), then the value for MAC and BIS with the maximum sensitivity and specificity would be calculated and retrospectively applied to the database.

Youden's index did not demonstrate a single threshold for either aaMAC or BIS in the prevention of AWR (Shanks et al., 2014). Neither c-statistic reached discriminating capacity to determine a threshold based on the median continuous aaMAC and BIS data (Shanks et al., 2014). Therefore, we have demonstrated that in patients receiving only volatile anesthetics, no population-based threshold can be used to alert clinicians in the prevention of AWR (Shanks et al., 2014).

Future Directions of a Patient-Based Monitoring Approach in the Prevention of AWR

The prospective clinical trials on the prevention of AWR (Avidan et al., 2011; Avidan et al., 2008; Mashour et al., 2012; Myles et al., 2004) and the secondary systematic analyses of

granular data (Shanks et al., 2014) have demonstrated that the field of anesthesiology must move beyond the population-based approach in prevention of AWR and towards an individualized patient-based approach. The specific neuroscientific mechanisms of anesthetic-induced unconsciousness are beyond the scope of this project. However, to discuss a patient-based monitoring approach in the prevention of AWR, a brief discussion of consciousness and unconsciousness within brain networks is warranted.

Consciousness is a complex process that is poorly understood. One current theory suggests that that there is a feedback of information from the frontal cortex to more primary sensory areas in the brain that helps select neural information for representation and "broadcasting" (Changeux, 2012; Dehaene and Changeux, 2011; Dehaene et al., 1998). This model is referred to as the Global Neuronal Workspace (GNW). Specifically, the GNW states that to form a conscious experience, there is a set of long-range excitatory axons originating with the pyramidal cells of the prefrontal cortex that extend towards the thalamocortical loops (Changeux, 2012; Dehaene and Changeux, 2011; Dehaene et al., 1998). In support of this and other theories related to information synthesis in the brain, anesthetics disrupt this feedback connectivity from the frontal cortex in association with unconsciousness (Lee et al., 2013). This finding is consistent with the cognitive unbinding paradigm of general anesthesia (Changeux, 2012; Lee et al., 2009; Mashour, 2004, 2013).

To determine accurately that a patient is unconscious during exposure to a general anesthetic, practical assessment of connectivity disruption is needed. Recently Lee et al. studied frontal-parietal feedback connectivity disruption in surgical patients anesthetized with three commonly used anesthetics: ketamine, propofol and sevoflurane (Lee et al., 2013). Eight-channel EEG recording was conducted and normalized symbolic transfer entropy was used as an

analytic technique assessing directed connectivity (Lee et al., 2013). The authors demonstrated that each of these molecularly and neurophysiologically diverse anesthetics disrupted feedback connectivity (Lee et al., 2013). Another technique for identifying the breakdown of cortical connectivity and communication is the perturbational complexity index (PCI). PCI assesses the EEG's response to transcranial magnetic stimulation and is an index of the level of information contained in the response of the brain to the perturbation of the stimulus (Casali et al., 2013). The findings indicated that PCI successfully demonstrated the breakdown of cortical communication in anesthetized patients (Casali et al., 2013). These two recent studies have demonstrated that in humans undergoing anesthesia, it is possible to demonstrate a disruption of cortical connectivity and communication across all major classes of anesthetics.

Patient Monitoring Towards the Eradication of Awareness – The Next Steps

We have demonstrated that there is no discriminating threshold at the population-based level below which (aaMAC) or above which (BIS) AWR is eradicated (Shanks et al., 2014). Therefore, it is imperative to revise the assumptions that there is one set value for all patients to prevent AWR towards an individualized patient-based approach. This study has demonstrated the need for patient-based algorithms in the prevention of AWR and the need to incorporate the neurobiology of consciousness (and unconsciousness). One way to develop and validate a patient-based alerting algorithm, is to use a multivariate logistic regression model that will determine independent predictors of AWR. Individual risk factors that have already been associated with an increased incidence of AWR will be covariates in the model, including: patient history of AWR (Aranake et al., 2013), high risk surgery, volume status, chronic use of alcohol, chronic use of opioids (either as a Boolean concept or the morphine equivalents for current opioid consumption), chronic use of sedative hypnotics, acute use of amphetamines,

female sex, age (binned by decade of life), obesity (categorized by the World Health Organization standards) and multiple approaches to assessing depth of anesthesia (Schneider et al., 2014). The multivariate logistic regression model would need to be developed on a set of patients with prospectively collected data in an AIMS as well as post-operative Brice interviews to document the AWR event. This would require a minimum of 200 AWR patients in the development database as well as another 200 patients in the validation database to follow the rule of 10 which was developed to prevent overfitting the logistic regression model and states that for every covariate placed into a model, there must be at least 10 patients with the outcome of interest (AWR) (Harrell et al., 1984). When a model is overfit, the results may be "fitting" the noise and not the actual signal or the true underlying covariates that are independent predictors of AWR and can be used in patient-based alerting algorithms. Currently there are no trials that have been conducted that would allow this level of modeling to be performed properly. Once the data are available, the independent risk factors that are identified, and validated, can then be programmed into an AIMS system to risk-adjust and alert clinicians on a patient-based level for the prevention of AWR.

Appendix I: Actual SQL code for Alerting Algorithms

Below is the actual SQL code running in real-time within the Centricity (GE Healthcare®) database to alert providers when the median anesthetic concentration <0.5 or the median BIS value was >60 for a 5 minute period

Anesthetic Concentration Alert Algorithm

```
IF @age_in_years <= 39
   SELECT  @sevo_mac = 2.4 ,
         @iso_mac = 1.3 ,
         @halo_mac = 0.9 ,
         @des_mac = 7.0 ,
         @nitrous_mac = 105
IF @age_in_years >= 40    AND @age_in_years <= 59
   SELECT  @sevo_mac = 1.7 ,
         @iso_mac = 1.1 ,
         @halo_mac = 0.75 ,
         @des_mac = 6.0 ,
         @nitrous_mac = 105
IF @age_in_years >= 60    AND @age_in_years <= 79
   SELECT  @sevo_mac = 1.5 ,
         @iso_mac = 1.0 ,
         @halo_mac = 0.7 ,
         @des_mac = 5.2 ,
         @nitrous_mac = 105
IF @age_in_years >= 80
   SELECT  @sevo_mac = 1.2 ,
         @iso_mac = 0.8 ,
         @halo_mac = 0.65 ,
         @des_mac = 4.5 ,
         @nitrous_mac = 105


SELECT  @total_mac = ( ( @sevo_conc / @sevo_mac ) + ( @iso_conc / @iso_mac )
                  + ( @des_conc / @des_mac ) + ( @nitrous_conc
                                    / @nitrous_mac ) )


IF @total_mac <= @mac_threshold
   BEGIN

                  --GET THE CURRENT DEX Rate

      IF @dex_rate >= 0.2
```

```
        AND @dex_rate IS NOT NULL
        BEGIN

           SELECT  @total_mac = ( ( ( @sevo_conc / @sevo_mac ) * 2 )
                        + ( ( @iso_conc / @iso_mac ) * 2 )
                        + ( ( @des_conc / @des_mac ) * 2 )
                        + ( ( @nitrous_conc / @nitrous_mac )
                           * 2 ) )

        END
   END

IF @Total_mac <= @mac_threshold
   BEGIN
      IF @et_co2 < 5
         BEGIN
                        -- looks like mon cap is dead or that there is no sampling going on.
                        -- no need to alert
           SELECT  @no_etco2 = 1
         END
      ELSE
         SELECT  @no_etco2 = 0

   END

IF @total_mac <= @mac_threshold AND @no_etco2 = 0
   BEGIN

          --GET THE CURRENT Propofol Infusion Rate


      IF @propofol_rate <> 0
         AND @propofol_rate IS NOT NULL
         SELECT  @total_mac = @total_mac + ( @propofol_rate / 150 )

--                              print 'in propofol'
--                              select @propofol_rate, @patient_sys, @visit_sys, @op_sys,
@op_date, @time_end
   END

if @total_mac <= @mac_threshold and @no_etco2=0
  begin
                -- check to see if there is a recent propofol, midaz, etomidate, thiopental bolus


                --if exists recent propofol, midaz, etomidate, thiopental bolus
```

```
                SELECT @hypnotic_bolus_yn=1
        --else
                select @hypnotic_bolus_yn =0
    end


if @room_number_int % 2 = 0  --Even Rooms
        begin

                select @bis_room_yn =1
                select @mac_room_yn = 0

        end
        else    --Odd Rooms
        begin

                select @bis_room_yn =0
                select @mac_room_yn =1

        END


if @total_mac <= @mac_threshold   and @no_etco2=0
        select @mac_alert_yn=1

IF @mac_room_yn = 1 AND @mac_alert_yn = 1
BEGIN

    --If user has NOT choosen to "suspend" alerts for 15 minutes:

    --Page user of a MAC alert
END
```

BIS Alert Algorithm

```
if @bis_value > @bis_threshold
        select @bis_alert_yn=1

IF @bis_room_yn = 1 AND @bis_alert_yn = 1
BEGIN
    --If user has NOT choosen to "suspend" alerts for 15 minutes:

    --Page user of a BIS alert
END


--Insert alert into log table of all alerts.
```

Appendix II: Actual SPSS outputs for Chapter 4 MACS Trial

BIS_MAC_org * Definite_Awareness

Crosstab

			Definite_Awareness		
			No	Definite Awareness	Total
BIS_MAC_org	BIS	Count	9452	8	9460
		% within BIS_MAC_org	99.9%	.1%	100.0%
		% within Definite_Awareness	50.2%	42.1%	50.2%
		% of Total	50.2%	.0%	50.2%
	MAC	Count	9365	11	9376
		% within BIS_MAC_org	99.9%	.1%	100.0%
		% within Definite_Awareness	49.8%	57.9%	49.8%
		% of Total	49.7%	.1%	49.8%
Total		Count	18817	19	18836
		% within BIS_MAC_org	99.9%	.1%	100.0%
		% within Definite_Awareness	100.0%	100.0%	100.0%
		% of Total	99.9%	.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.501[a]	1	.479		
Continuity Correction[b]	.229	1	.632		
Likelihood Ratio	.503	1	.478		
Fisher's Exact Test				.501	.317
Linear-by-Linear Association	.501	1	.479		
N of Valid Cases	18836				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 9.46.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for BIS_MAC_org (BIS / MAC)	1.388	.558	3.452
For cohort Definite_Awareness = No	1.000	.999	1.001
For cohort Definite_Awareness = Definite Awareness	.721	.290	1.791
N of Valid Cases	18836		

BIS_MAC_org * Awareness

Crosstab

			Awareness			
			No	Definite	Possible	Total
BIS_MAC_org	BIS	Count	9442	8	10	9460
		% within BIS_MAC_org	99.8%	.1%	.1%	100.0%
		% within Awareness	50.2%	42.1%	55.6%	50.2%
		% of Total	50.1%	.0%	.1%	50.2%
	MAC	Count	9357	11	8	9376
		% within BIS_MAC_org	99.8%	.1%	.1%	100.0%
		% within Awareness	49.8%	57.9%	44.4%	49.8%
		% of Total	49.7%	.1%	.0%	49.8%
Total		Count	18799	19	18	18836
		% within BIS_MAC_org	99.8%	.1%	.1%	100.0%
		% within Awareness	100.0%	100.0%	100.0%	100.0%
		% of Total	99.8%	.1%	.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.706[a]	2	.703
Likelihood Ratio	.708	2	.702
Linear-by-Linear Association	.006	1	.937
N of Valid Cases	18836		

a. 0 cells (.0%) have expected count less than 5. The minimum expected

BIS_MAC_org * Definite_or_Possible_Awareness

Crosstab

			Definite_or_Possible_Awareness		
			No	Definite or Possible Awareness	Total
BIS_MAC_org	BIS	Count	9442	18	9460
		% within BIS_MAC_org	99.8%	.2%	100.0%
		% within Definite_or_Possible_Awareness	50.2%	48.6%	50.2%
		% of Total	50.1%	.1%	50.2%
	MAC	Count	9357	19	9376
		% within BIS_MAC_org	99.8%	.2%	100.0%
		% within Definite_or_Possible_Awareness	49.8%	51.4%	49.8%

	% of Total	49.7%	.1%	49.8%
Total	Count	18799	37	18836
	% within BIS_MAC_org	99.8%	.2%	100.0%
	% within Definite_or_Possible_Awareness	100.0%	100.0%	100.0%
	% of Total	99.8%	.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.037[a]	1	.848		
Continuity Correction[b]	.001	1	.978		
Likelihood Ratio	.037	1	.848		
Fisher's Exact Test				.871	.489
Linear-by-Linear Association	.037	1	.848		
N of Valid Cases	18836				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 18.42.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for BIS_MAC_org (BIS / MAC)	1.065	.559	2.031
For cohort Definite_or_Possible_Awareness = No	1.000	.999	1.001
For cohort Definite_or_Possible_Awareness = Definite or Possible Awareness	.939	.493	1.788
N of Valid Cases	18836		

New_groups * Definite_Awareness

Crosstab

			Definite_Awareness		
			No	Definite Awareness	Total
New_groups	MAC	Count	9365	11	9376
		% within New_groups	99.9%	.1%	100.0%
		% within Definite_Awareness	49.8%	57.9%	49.8%
		% of Total	49.7%	.1%	49.8%
	BIS with BIS	Count	6073	3	6076
		% within New_groups	100.0%	.0%	100.0%
		% within Definite_Awareness	32.3%	15.8%	32.3%

		% of Total	32.2%	.0%	32.3%
	BIS no BIS	Count	3379	5	3384
		% within New_groups	99.9%	.1%	100.0%
		% within Definite_Awareness	18.0%	26.3%	18.0%
		% of Total	17.9%	.0%	18.0%
Total		Count	18817	19	18836
		% within New_groups	99.9%	.1%	100.0%
		% within Definite_Awareness	100.0%	100.0%	100.0%
		% of Total	99.9%	.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	2.589[a]	2	.274
Likelihood Ratio	2.857	2	.240
Linear-by-Linear Association	.000	1	.989
N of Valid Cases	18836		

a. 1 cells (16.7%) have expected count less than 5. The minimum expected count is 3.41.

New_groups * Awareness

Crosstab

			Awareness			
			No	Definite	Possible	Total
New_groups	MAC	Count	9357	11	8	9376
		% within New_groups	99.8%	.1%	.1%	100.0%
		% within Awareness	49.8%	57.9%	44.4%	49.8%
		% of Total	49.7%	.1%	.0%	49.8%
	BIS with BIS	Count	6071	3	2	6076
		% within New_groups	99.9%	.0%	.0%	100.0%
		% within Awareness	32.3%	15.8%	11.1%	32.3%
		% of Total	32.2%	.0%	.0%	32.3%
	BIS no BIS	Count	3371	5	8	3384
		% within New_groups	99.6%	.1%	.2%	100.0%
		% within Awareness	17.9%	26.3%	44.4%	18.0%
		% of Total	17.9%	.0%	.0%	18.0%
Total		Count	18799	19	18	18836
		% within New_groups	99.8%	.1%	.1%	100.0%
		% within Awareness	100.0%	100.0%	100.0%	100.0%
		% of Total	99.8%	.1%	.1%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.229[a]	4	.016
Likelihood Ratio	11.290	4	.023
Linear-by-Linear Association	2.525	1	.112
N of Valid Cases	18836		

a. 2 cells (22.2%) have expected count less than 5. The minimum expected count is 3.23.

New_groups * Definite_or_Possible_Awareness

Crosstab

			Definite_or_Possible_Awareness		
			No	Definite or Possible Awareness	Total
New_groups	MAC	Count	9357	19	9376
		% within New_groups	99.8%	.2%	100.0%
		% within Definite_or_Possible_Awareness	49.8%	51.4%	49.8%
		% of Total	49.7%	.1%	49.8%
	BIS with BIS	Count	6071	5	6076
		% within New_groups	99.9%	.1%	100.0%
		% within	32.3%	13.5%	32.3%

		Definite_or_Possible_Awareness			
		% of Total	32.2%	.0%	32.3%
	BIS no BIS	Count	3371	13	3384
		% within New_groups	99.6%	.4%	100.0%
		% within Definite_or_Possible_Awareness	17.9%	35.1%	18.0%
		% of Total	17.9%	.1%	18.0%
Total		Count	18799	37	18836
		% within New_groups	99.8%	.2%	100.0%
		% within Definite_or_Possible_Awareness	100.0%	100.0%	100.0%
		% of Total	99.8%	.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	10.139[a]	2	.006
Likelihood Ratio	9.942	2	.007
Linear-by-Linear Association	1.565	1	.211
N of Valid Cases	18836		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.65.

Definite_Awareness

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	No	18817	99.9	99.9	99.9
	Definite Awareness	19	.1	.1	100.0
	Total	18836	100.0	100.0	

```
USE ALL.
COMPUTE filter_$=(Definite_or_Possible_Awareness = 1).
VARIABLE LABEL filter_$ 'Definite_or_Possible_Awareness = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMAT filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

CROSSTABS
  /TABLES=New_groups BY Distress_Awareness_Class
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT ROW COLUMN TOTAL
  /COUNT ROUND CELL.
```

New_groups * Distress_Awareness_Class Crosstabulation

			Distress_Awareness_Class		
			0	1	Total
New_groups	MAC	Count	16	3	19
		% within New_groups	84.2%	15.8%	100.0%
		% within Distress_Awareness_Class	57.1%	33.3%	51.4%
		% of Total	43.2%	8.1%	51.4%
	BIS with BIS	Count	2	3	5
		% within New_groups	40.0%	60.0%	100.0%
		% within Distress_Awareness_Class	7.1%	33.3%	13.5%
		% of Total	5.4%	8.1%	13.5%
	BIS no BIS	Count	10	3	13
		% within New_groups	76.9%	23.1%	100.0%
		% within Distress_Awareness_Class	35.7%	33.3%	35.1%
		% of Total	27.0%	8.1%	35.1%
Total		Count	28	9	37
		% within New_groups	75.7%	24.3%	100.0%
		% within Distress_Awareness_Class	100.0%	100.0%	100.0%
		% of Total	75.7%	24.3%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	4.220[a]	2	.121
Likelihood Ratio	3.705	2	.157
Linear-by-Linear Association	.363	1	.547
N of Valid Cases	37		

a. 4 cells (66.7%) have expected count less than 5. The minimum expected count is 1.22.

FILTER OFF.

USE ALL.

EXECUTE.

FREQUENCIES VARIABLES=Class_Awareness

/ORDER=ANALYSIS.

Frequencies

Class_Awareness

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid		18799	99.8	99.8	99.8
	1	16	.1	.1	99.9
	2	8	.0	.0	99.9
	2D	4	.0	.0	100.0
	3	3	.0	.0	100.0
	3D	2	.0	.0	100.0
	4	1	.0	.0	100.0

	4D	2	.0	.0	100.0
	5D	1	.0	.0	100.0
	Total	18836	100.0	100.0	

```
COMPUTE filter_$=(gas_analyzer_problem = 0).
VARIABLE LABELS filter_$ 'gas_analyzer_problem = 0 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
* Custom Tables.
CTABLES
  /VLABELS VARIABLES=New_groups medianMAC DISPLAY=LABEL
  /TABLE New_groups BY medianMAC [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN F40.0]
  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		medianMAC					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	.9391	.2648	.9400	.7905	1.1110	9083
	BIS with BIS	.9372	.2599	.9400	.8105	1.1110	5956
	BIS no BIS	.9108	.2771	.9400	.7690	1.0760	3272

```
*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (medianMAC) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of medianMAC is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Induction_propofol DISPLAY=LABEL

  /TABLE New_groups [C] BY Induction_propofol [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN

    F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Induction_propofol					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	156	67	160	120	200	9225
	BIS with BIS	158	66	160	120	200	6021
	BIS no BIS	153	68	150	120	200	3319

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Induction_propofol) GROUP (New_groups)

/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

/CRITERIA ALPHA=0.05 CILEVEL=95.

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Induction_propofol is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Intraop_propofol DISPLAY=LABEL

  /TABLE New_groups [C] BY Intraop_propofol [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN
F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Intraop_propofol					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	167	78	170	130	200	9225
	BIS with BIS	171	77	180	130	200	6021
	BIS no BIS	164	79	170	120	200	3319

```
*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (Intraop_propofol) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Intraop_propofol is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Total_Midaz_use DISPLAY=LABEL

  /TABLE New_groups [C] BY Total_Midaz_use [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN
F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Total_Midaz_use					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	2.99	3.09	2.00	2.00	4.00	9225
	BIS with BIS	3.12	3.35	2.00	2.00	4.00	6021
	BIS no BIS	2.97	2.98	2.00	2.00	4.00	3319

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Total_Midaz_use) GROUP (New_groups)

/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

/CRITERIA ALPHA=0.05 CILEVEL=95.

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Total_Midaz_use is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.940	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

* Custom Tables.

CTABLES

/VLABELS VARIABLES=New_groups Intraop_Fentanyl DISPLAY=LABEL

/TABLE New_groups [C] BY Intraop_Fentanyl [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN F40.0]

/CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.

Custom Tables

		Intraop_Fentanyl					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	203.0	193.2	175.0	100.0	250.0	9225
	BIS with BIS	216.3	214.9	200.0	100.0	250.0	6021
	BIS no BIS	188.7	196.0	150.0	100.0	250.0	3319

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Intraop_Fentanyl) GROUP (New_groups)

/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

/CRITERIA ALPHA=0.05 CILEVEL=95.

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Intraop_Fentanyl is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Intraop_Morphine DISPLAY=LABEL

  /TABLE New_groups [C] BY Intraop_Morphine [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN
F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Intraop_Morphine					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	2.7	4.4	.0	.0	5.0	9223
	BIS with BIS	3.0	4.7	.0	.0	5.0	6019
	BIS no BIS	2.1	4.1	.0	.0	3.0	3318

```
*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (Intraop_Morphine) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Intraop_Morphine is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups PACU_time DISPLAY=LABEL

  /TABLE New_groups [C] BY PACU_time [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75, VALIDN F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		PACU_time					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	112.64	69.13	98.00	66.00	140.00	8401
	BIS with BIS	109.48	65.84	95.00	64.00	138.00	5473
	BIS no BIS	107.27	63.37	94.00	64.00	133.00	2990

```
*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (PACU_time) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of PACU_time is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
CROSSTABS

  /TABLES=New_groups BY PACU_Nausea_yn PACU_Vomit_yn

  /FORMAT=AVALUE TABLES

  /STATISTICS=CHISQ RISK

  /CELLS=COUNT ROW COLUMN TOTAL

  /COUNT ROUND CELL.
```

Crosstabs

New_groups * PACU_Nausea_yn

Crosstab

			PACU_Nausea_yn		
			None	Yes	Total
New_groups	MAC	Count	6184	511	6695
		% within New_groups	92.4%	7.6%	100.0%
		% within PACU_Nausea_yn	49.4%	50.5%	49.5%
		% of Total	45.7%	3.8%	49.5%
	BIS with BIS	Count	4042	324	4366
		% within New_groups	92.6%	7.4%	100.0%
		% within PACU_Nausea_yn	32.3%	32.0%	32.3%
		% of Total	29.9%	2.4%	32.3%
	BIS no BIS	Count	2286	177	2463
		% within New_groups	92.8%	7.2%	100.0%
		% within PACU_Nausea_yn	18.3%	17.5%	18.2%
		% of Total	16.9%	1.3%	18.2%
Total		Count	12512	1012	13524
		% within New_groups	92.5%	7.5%	100.0%
		% within PACU_Nausea_yn	100.0%	100.0%	100.0%
		% of Total	92.5%	7.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.554[a]	2	.758
Likelihood Ratio	.556	2	.757
Linear-by-Linear Association	.553	1	.457
N of Valid Cases	13524		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 184.31.

New_groups * PACU_Vomit_yn

Crosstab

			PACU_Vomit_yn		
			None	Yes	Total
New_groups	MAC	Count	7149	83	7232
		% within New_groups	98.9%	1.1%	100.0%
		% within PACU_Vomit_yn	49.7%	49.4%	49.7%
		% of Total	49.2%	.6%	49.7%
	BIS with BIS	Count	4617	52	4669
		% within New_groups	98.9%	1.1%	100.0%
		% within PACU_Vomit_yn	32.1%	31.0%	32.1%
		% of Total	31.7%	.4%	32.1%
	BIS no BIS	Count	2608	33	2641
		% within New_groups	98.8%	1.2%	100.0%

	% within PACU_Vomit_yn	18.1%	19.6%	18.2%
	% of Total	17.9%	.2%	18.2%
Total	Count	14374	168	14542
	% within New_groups	98.8%	1.2%	100.0%
	% within PACU_Vomit_yn	100.0%	100.0%	100.0%
	% of Total	98.8%	1.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	.280[a]	2	.869
Likelihood Ratio	.275	2	.871
Linear-by-Linear Association	.096	1	.757
N of Valid Cases	14542		

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 30.51.

FILTER OFF.

USE ALL.

EXECUTE.

		Median_BIS					
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N
New_groups	MAC	41.2	10.5	40.0	34.0	46.0	3816
	BIS with BIS	40.4	8.7	40.0	35.0	44.5	6021
	BIS no BIS	.	.	.	.	.	0

```
USE ALL.

COMPUTE filter_$=(TIVA = 1).

VARIABLE LABELS filter_$ 'TIVA = 1 (FILTER)'.

VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.


* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Intraop_propofol_infusionCC DISPLAY=LABEL

  /TABLE New_groups [C] BY Intraop_propofol_infusionCC [MEAN, STDDEV, MEDIAN, PTILE 25, PTILE 75]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Intraop_propofol_infusionCC				
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75
New_groups	MAC	107.1053	72.7028	94.2820	51.3970	144.8070
	BIS with BIS	120.4140	107.4353	84.8270	50.5570	157.3660
	BIS no BIS	69.2697	43.6690	57.9475	37.1250	100.3430

*Nonparametric Tests: Independent Samples.

NPTESTS

/INDEPENDENT TEST (Intraop_propofol_infusionCC) GROUP (New_groups)

/MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

/CRITERIA ALPHA=0.05 CILEVEL=95.

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Intraop_propofol_infusionCC is the same across categories of New_groups.	Independent-Samples Kruskal-Wallis Test	.009	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
USE ALL.

COMPUTE filter_$=(TIVA = 1).

VARIABLE LABELS filter_$ 'TIVA = 1 (FILTER)'.

VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.

* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups Intraop_propofol_infusionCC DISPLAY=LABEL

  /TABLE New_groups [C] BY Intraop_propofol_infusionCC [S][MEAN, STDDEV, MEDIAN, PTILE 25, PTILE
75, VALIDN F40.0, TOTALN F40.0]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE.
```

Custom Tables

		Intraop_propofol_infusionCC						
		Mean	Standard Deviation	Median	Percentile 25	Percentile 75	Valid N	Total N
New_groups	MAC	107.1053	72.7028	94.2820	51.3970	144.8070	129	131
	BIS with BIS	120.4140	107.4353	84.8270	50.5570	157.3660	58	58
	BIS no BIS	69.2697	43.6690	57.9475	37.1250	100.3430	42	42

APPENDIX III: Actual SPSS outputs for Chapter 5

New_groups * Definite_or_Possible_Awareness Crosstabulation

			Definite_or_Possible_Awareness		Total
			No	Definite or Possible Awareness	
New_groups	MAC	Count	8021	15	8036
		% within New_groups	99.8%	0.2%	100.0%
		% within Definite_or_Possible_Awareness	50.0%	46.9%	50.0%
		% of Total	49.9%	0.1%	50.0%
	BIS with BIS	Count	5169	5	5174
		% within New_groups	99.9%	0.1%	100.0%
		% within Definite_or_Possible_Awareness	32.2%	15.6%	32.2%
		% of Total	32.2%	0.0%	32.2%
	BIS no BIS	Count	2846	12	2858
		% within New_groups	99.6%	0.4%	100.0%
		% within Definite_or_Possible_Awareness	17.7%	37.5%	17.8%
		% of Total	17.7%	0.1%	17.8%
Total		Count	16036	32	16068
		% within New_groups	99.8%	0.2%	100.0%
		% within Definite_or_Possible_Awareness	100.0%	100.0%	100.0%
		% of Total	99.8%	0.2%	100.0%

Crosstabs

Definite_Awareness * BIS_60_alert_triggered_yn

Crosstab

			BIS_60_alert_triggered_yn		Total
			No BIS >60	BIS >60 at least once	
Definite_Awareness	No	Count	3750	1401	5151
		% within Definite_Awareness	72.8%	27.2%	100.0%
		% within BIS_60_alert_triggered_yn	99.9%	99.9%	99.9%
		% of Total	72.8%	27.2%	99.9%
	Definite Awareness	Count	2	1	3
		% within Definite_Awareness	66.7%	33.3%	100.0%
		% within BIS_60_alert_triggered_yn	0.1%	0.1%	0.1%
		% of Total	0.0%	0.0%	0.1%
Total		Count	3752	1402	5154
		% within Definite_Awareness	72.8%	27.2%	100.0%
		% within BIS_60_alert_triggered_yn	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.057[a]	1	.811		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.055	1	.815		
Fisher's Exact Test				1.000	.614
Linear-by-Linear Association	.057	1	.811		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .82.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Definite_Awareness (No / Definite Awareness)	1.338	.121	14.771
For cohort BIS_60_alert_triggered_yn = No BIS >60	1.092	.491	2.431
For cohort BIS_60_alert_triggered_yn = BIS >60 at least once	.816	.165	4.045
N of Valid Cases	5154		

Definite_Awareness * BIS_70_yn

Crosstab

			BIS_70_yn		Total
			.00	1.00	
Definite_Awareness	No	Count	4744	407	5151
		% within Definite_Awareness	92.1%	7.9%	100.0%
		% within BIS_70_yn	99.9%	100.0%	99.9%
		% of Total	92.0%	7.9%	99.9%
	Definite Awareness	Count	3	0	3
		% within Definite_Awareness	100.0%	0.0%	100.0%
		% within BIS_70_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	4747	407	5154
		% within Definite_Awareness	92.1%	7.9%	100.0%
		% within BIS_70_yn	100.0%	100.0%	100.0%
		% of Total	92.1%	7.9%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.257[a]	1	.612		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.494	1	.482		
Fisher's Exact Test				1.000	.781
Linear-by-Linear Association	.257	1	.612		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .24.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_70_yn = .00	.921	.914	.928
N of Valid Cases	5154		

Definite_Awareness * BIS_80_yn

Crosstab

			BIS_80_yn		Total
			.00	1.00	
Definite_Awareness	No	Count	5017	134	5151
		% within Definite_Awareness	97.4%	2.6%	100.0%
		% within BIS_80_yn	99.9%	100.0%	99.9%
		% of Total	97.3%	2.6%	99.9%
	Definite Awareness	Count	3	0	3
		% within Definite_Awareness	100.0%	0.0%	100.0%
		% within BIS_80_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	5020	134	5154
		% within Definite_Awareness	97.4%	2.6%	100.0%
		% within BIS_80_yn	100.0%	100.0%	100.0%
		% of Total	97.4%	2.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.080[a]	1	.777		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.158	1	.691		
Fisher's Exact Test				1.000	.924
Linear-by-Linear Association	.080	1	.777		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .08.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_80_yn = .00	.974	.970	.978
N of Valid Cases	5154		

Definite_Awareness * BIS_90_yn

Crosstab

			BIS_90_yn		Total
			.00	1.00	
Definite_Awareness	No	Count	5113	38	5151
		% within Definite_Awareness	99.3%	0.7%	100.0%
		% within BIS_90_yn	99.9%	100.0%	99.9%
		% of Total	99.2%	0.7%	99.9%
	Definite Awareness	Count	3	0	3
		% within Definite_Awareness	100.0%	0.0%	100.0%
		% within BIS_90_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	5116	38	5154
		% within Definite_Awareness	99.3%	0.7%	100.0%
		% within BIS_90_yn	100.0%	100.0%	100.0%
		% of Total	99.3%	0.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.022[a]	1	.881		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.044	1	.833		
Fisher's Exact Test				1.000	.978
Linear-by-Linear Association	.022	1	.881		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .02.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_90_yn = .00	.993	.990	.995
N of Valid Cases	5154		

Definite_Awareness * BIS_50_yn

Crosstab

			BIS_50_yn		Total
			.00	1.00	
Definite_Awareness	No	Count	2489	2662	5151
		% within Definite_Awareness	48.3%	51.7%	100.0%
		% within BIS_50_yn	100.0%	99.9%	99.9%
		% of Total	48.3%	51.6%	99.9%
	Definite Awareness	Count	1	2	3
		% within Definite_Awareness	33.3%	66.7%	100.0%
		% within BIS_50_yn	0.0%	0.1%	0.1%
		% of Total	0.0%	0.0%	0.1%
Total		Count	2490	2664	5154
		% within Definite_Awareness	48.3%	51.7%	100.0%
		% within BIS_50_yn	100.0%	100.0%	100.0%
		% of Total	48.3%	51.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.270[a]	1	.604		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.276	1	.599		
Fisher's Exact Test				1.000	.525
Linear-by-Linear Association	.270	1	.604		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.45.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Definite_Awareness (No / Definite Awareness)	1.870	.169	20.636
For cohort BIS_50_yn = .00	1.450	.293	7.184
For cohort BIS_50_yn = 1.00	.775	.348	1.726
N of Valid Cases	5154		

Definite_or_Possible_Awareness * BIS_60_alert_triggered_yn

Crosstab

			BIS_60_alert_triggered_yn		Total
			No BIS >60	BIS >60 at least once	
Definite_or_Possible_Awareness	No	Count	3748	1401	5149
		% within Definite_or_Possible_Awareness	72.8%	27.2%	100.0%
		% within BIS_60_alert_triggered_yn	99.9%	99.9%	99.9%
		% of Total	72.7%	27.2%	99.9%
	Definite or Possible Awareness	Count	4	1	5
		% within Definite_or_Possible_Awareness	80.0%	20.0%	100.0%
		% within BIS_60_alert_triggered_yn	0.1%	0.1%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	3752	1402	5154
		% within Definite_or_Possible_Awareness	72.8%	27.2%	100.0%
		% within BIS_60_alert_triggered_yn	100.0%	100.0%	100.0%
		% of Total	72.8%	27.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.131[a]	1	.717		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.140	1	.709		
Fisher's Exact Test				1.000	.586
Linear-by-Linear Association	.131	1	.717		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.36.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Definite_or_Possible_Awareness (No / Definite or Possible Awareness)	.669	.075	5.989
For cohort BIS_60_alert_triggered_yn = No BIS >60	.910	.587	1.411
For cohort BIS_60_alert_triggered_yn = BIS >60 at least once	1.360	.236	7.857
N of Valid Cases	5154		

Definite_or_Possible_Awareness * BIS_70_yn

Crosstab

			BIS_70_yn		Total
			.00	1.00	
Definite_or_Possible_Awareness	No	Count	4742	407	5149
		% within Definite_or_Possible_Awareness	92.1%	7.9%	100.0%
		% within BIS_70_yn	99.9%	100.0%	99.9%
		% of Total	92.0%	7.9%	99.9%
	Definite or Possible Awareness	Count	5	0	5
		% within Definite_or_Possible_Awareness	100.0%	0.0%	100.0%
		% within BIS_70_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	4747	407	5154
		% within Definite_or_Possible_Awareness	92.1%	7.9%	100.0%
		% within BIS_70_yn	100.0%	100.0%	100.0%
		% of Total	92.1%	7.9%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.429[a]	1	.512		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.823	1	.364		
Fisher's Exact Test				1.000	.663
Linear-by-Linear Association	.429	1	.512		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .39.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_70_yn = .00	.921	.914	.928
N of Valid Cases	5154		

Definite_or_Possible_Awareness * BIS_80_yn

Crosstab

			BIS_80_yn		Total
			.00	1.00	
Definite_or_Possible_Awareness	No	Count	5015	134	5149
		% within Definite_or_Possible_Awareness	97.4%	2.6%	100.0%
		% within BIS_80_yn	99.9%	100.0%	99.9%
		% of Total	97.3%	2.6%	99.9%
	Definite or Possible Awareness	Count	5	0	5
		% within Definite_or_Possible_Awareness	100.0%	0.0%	100.0%
		% within BIS_80_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	5020	134	5154
		% within Definite_or_Possible_Awareness	97.4%	2.6%	100.0%
		% within BIS_80_yn	100.0%	100.0%	100.0%
		% of Total	97.4%	2.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.134[a]	1	.715		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.264	1	.608		
Fisher's Exact Test				1.000	.877
Linear-by-Linear Association	.134	1	.715		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .13.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_80_yn = .00	.974	.970	.978
N of Valid Cases	5154		

Definite_or_Possible_Awareness * BIS_90_yn

Crosstab

			BIS_90_yn		Total
			.00	1.00	
Definite_or_Possible_Awareness	No	Count	5111	38	5149
		% within Definite_or_Possible_Awareness	99.3%	0.7%	100.0%
		% within BIS_90_yn	99.9%	100.0%	99.9%
		% of Total	99.2%	0.7%	99.9%
	Definite or Possible Awareness	Count	5	0	5
		% within Definite_or_Possible_Awareness	100.0%	0.0%	100.0%
		% within BIS_90_yn	0.1%	0.0%	0.1%
		% of Total	0.1%	0.0%	0.1%
Total		Count	5116	38	5154
		% within Definite_or_Possible_Awareness	99.3%	0.7%	100.0%
		% within BIS_90_yn	100.0%	100.0%	100.0%
		% of Total	99.3%	0.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.037[a]	1	.847		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.074	1	.786		
Fisher's Exact Test				1.000	.964
Linear-by-Linear Association	.037	1	.847		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .04.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort BIS_90_yn = .00	.993	.990	.995
N of Valid Cases	5154		

Definite_or_Possible_Awareness * BIS_50_yn

Crosstab

			BIS_50_yn		Total
			.00	1.00	
Definite_or_Possible_Awareness	No	Count	2488	2661	5149
		% within Definite_or_Possible_Awareness	48.3%	51.7%	100.0%
		% within BIS_50_yn	99.9%	99.9%	99.9%
		% of Total	48.3%	51.6%	99.9%
	Definite or Possible Awareness	Count	2	3	5
		% within Definite_or_Possible_Awareness	40.0%	60.0%	100.0%
		% within BIS_50_yn	0.1%	0.1%	0.1%
		% of Total	0.0%	0.1%	0.1%
Total		Count	2490	2664	5154
		% within Definite_or_Possible_Awareness	48.3%	51.7%	100.0%
		% within BIS_50_yn	100.0%	100.0%	100.0%
		% of Total	48.3%	51.7%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.138[a]	1	.710		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.140	1	.709		
Fisher's Exact Test				1.000	.532
Linear-by-Linear Association	.138	1	.710		
N of Valid Cases	5154				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.42.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Definite_or_Possible_Awareness (No / Definite or Possible Awareness)	1.402	.234	8.400
For cohort BIS_50_yn = .00	1.208	.413	3.536
For cohort BIS_50_yn = 1.00	.861	.421	1.763
N of Valid Cases	5154		

New_groups * AAMAC_0.4_yn

Crosstab

			AAMAC_0.4_yn		Total
			No AAMAC<0.4 alerts	1+ AAMAC <0.4 alerts	
New_groups	MAC	Count	6397	1639	8036
		% within New_groups	79.6%	20.4%	100.0%
		% within AAMAC_0.4_yn	74.3%	71.6%	73.8%
		% of Total	58.7%	15.0%	73.8%
	BIS no BIS	Count	2209	649	2858
		% within New_groups	77.3%	22.7%	100.0%
		% within AAMAC_0.4_yn	25.7%	28.4%	26.2%
		% of Total	20.3%	6.0%	26.2%
Total		Count	8606	2288	10894
		% within New_groups	79.0%	21.0%	100.0%
		% within AAMAC_0.4_yn	100.0%	100.0%	100.0%
		% of Total	79.0%	21.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	6.795[a]	1	.009		
Continuity Correction[b]	6.656	1	.010		
Likelihood Ratio	6.712	1	.010		
Fisher's Exact Test				.009	.005
Linear-by-Linear Association	6.794	1	.009		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 600.25.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.147	1.034	1.271
For cohort AAMAC_0.4_yn = No AAMAC<0.4 alerts	1.030	1.007	1.054
For cohort AAMAC_0.4_yn = 1+ AAMAC <0.4 alerts	.898	.829	.973
N of Valid Cases	10894		

New_groups * AAMAC_0.5_yn

Crosstab

			AAMAC_0.5_yn		Total
			No AAMAC<0.5 alerts	1+ AAMAC <0.5 alerts	
New_groups	MAC	Count	5673	2363	8036
		% within New_groups	70.6%	29.4%	100.0%
		% within AAMAC_0.5_yn	74.2%	72.7%	73.8%
		% of Total	52.1%	21.7%	73.8%
	BIS no BIS	Count	1969	889	2858
		% within New_groups	68.9%	31.1%	100.0%
		% within AAMAC_0.5_yn	25.8%	27.3%	26.2%
		% of Total	18.1%	8.2%	26.2%
Total		Count	7642	3252	10894
		% within New_groups	70.1%	29.9%	100.0%
		% within AAMAC_0.5_yn	100.0%	100.0%	100.0%
		% of Total	70.1%	29.9%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	2.911[a]	1	.088		
Continuity Correction[b]	2.831	1	.092		
Likelihood Ratio	2.897	1	.089		
Fisher's Exact Test				.091	.046
Linear-by-Linear Association	2.911	1	.088		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 853.15.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.084	.988	1.189
For cohort AAMAC_0.5_yn = No AAMAC<0.5 alerts	1.025	.996	1.054
For cohort AAMAC_0.5_yn = 1+ AAMAC <0.5 alerts	.945	.887	1.008
N of Valid Cases	10894		

New_groups * AAMAC_0.6_yn

Crosstab

			AAMAC_0.6_yn		Total
			No AAMAC<0.6 alerts	1+ AAMAC <0.6 alerts	
New_groups	MAC	Count	4759	3277	8036
		% within New_groups	59.2%	40.8%	100.0%
		% within AAMAC_0.6_yn	74.0%	73.4%	73.8%
		% of Total	43.7%	30.1%	73.8%
	BIS no BIS	Count	1672	1186	2858
		% within New_groups	58.5%	41.5%	100.0%
		% within AAMAC_0.6_yn	26.0%	26.6%	26.2%
		% of Total	15.3%	10.9%	26.2%
Total		Count	6431	4463	10894
		% within New_groups	59.0%	41.0%	100.0%
		% within AAMAC_0.6_yn	100.0%	100.0%	100.0%
		% of Total	59.0%	41.0%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.450[a]	1	.502		
Continuity Correction[b]	.421	1	.517		
Likelihood Ratio	.450	1	.502		
Fisher's Exact Test				.507	.258
Linear-by-Linear Association	.450	1	.502		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1170.85.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.030	.945	1.123
For cohort AAMAC_0.6_yn = No AAMAC<0.6 alerts	1.012	.977	1.049
For cohort AAMAC_0.6_yn = 1+ AAMAC <0.6 alerts	.983	.934	1.034
N of Valid Cases	10894		

New_groups * AAMAC_0.7_yn

Crosstab

			AAMAC_0.7_yn		Total
			No AAMAC<0.7 alerts	1+ AAMAC <0.7 alerts	
New_groups	MAC	Count	3653	4383	8036
		% within New_groups	45.5%	54.5%	100.0%
		% within AAMAC_0.7_yn	73.9%	73.7%	73.8%
		% of Total	33.5%	40.2%	73.8%
	BIS no BIS	Count	1293	1565	2858
		% within New_groups	45.2%	54.8%	100.0%
		% within AAMAC_0.7_yn	26.1%	26.3%	26.2%
		% of Total	11.9%	14.4%	26.2%
Total		Count	4946	5948	10894
		% within New_groups	45.4%	54.6%	100.0%
		% within AAMAC_0.7_yn	100.0%	100.0%	100.0%
		% of Total	45.4%	54.6%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.040[a]	1	.842		
Continuity Correction[b]	.032	1	.859		
Likelihood Ratio	.040	1	.842		
Fisher's Exact Test				.844	.429
Linear-by-Linear Association	.040	1	.842		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 1297.56.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.009	.926	1.099
For cohort AAMAC_0.7_yn = No AAMAC<0.7 alerts	1.005	.959	1.053
For cohort AAMAC_0.7_yn = 1+ AAMAC <0.7 alerts	.996	.958	1.035
N of Valid Cases	10894		

New_groups * AAMAC_0.8_yn

Crosstab

			AAMAC_0.8_yn		Total
			No AAMAC<0.8 alerts	1+ AAMAC <0.8 alerts	
New_groups	MAC	Count	2460	5576	8036
		% within New_groups	30.6%	69.4%	100.0%
		% within AAMAC_0.8_yn	74.1%	73.6%	73.8%
		% of Total	22.6%	51.2%	73.8%
	BIS no BIS	Count	859	1999	2858
		% within New_groups	30.1%	69.9%	100.0%
		% within AAMAC_0.8_yn	25.9%	26.4%	26.2%
		% of Total	7.9%	18.3%	26.2%
Total		Count	3319	7575	10894
		% within New_groups	30.5%	69.5%	100.0%
		% within AAMAC_0.8_yn	100.0%	100.0%	100.0%
		% of Total	30.5%	69.5%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.308[a]	1	.579		
Continuity Correction[b]	.282	1	.595		
Likelihood Ratio	.308	1	.579		
Fisher's Exact Test				.586	.298
Linear-by-Linear Association	.308	1	.579		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 870.73.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.027	.936	1.127
For cohort AAMAC_0.8_yn = No AAMAC<0.8 alerts	1.019	.955	1.087
For cohort AAMAC_0.8_yn = 1+ AAMAC <0.8 alerts	.992	.965	1.020
N of Valid Cases	10894		

New_groups * AAMAC_0.9_yn

Crosstab

			AAMAC_0.9_yn		Total
			No AAMAC<0.9 alerts	1+ AAMAC <0.9 alerts	
New_groups	MAC	Count	1433	6603	8036
		% within New_groups	17.8%	82.2%	100.0%
		% within AAMAC_0.9_yn	73.8%	73.8%	73.8%
		% of Total	13.2%	60.6%	73.8%
	BIS no BIS	Count	509	2349	2858
		% within New_groups	17.8%	82.2%	100.0%
		% within AAMAC_0.9_yn	26.2%	26.2%	26.2%
		% of Total	4.7%	21.6%	26.2%
Total		Count	1942	8952	10894
		% within New_groups	17.8%	82.2%	100.0%
		% within AAMAC_0.9_yn	100.0%	100.0%	100.0%
		% of Total	17.8%	82.2%	100.0%

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.001[a]	1	.978		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.001	1	.978		
Fisher's Exact Test				.999	.501
Linear-by-Linear Association	.001	1	.978		
N of Valid Cases	10894				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 509.48.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for New_groups (MAC / BIS no BIS)	1.002	.896	1.120
For cohort AAMAC_0.9_yn = No AAMAC<0.9 alerts	1.001	.914	1.097
For cohort AAMAC_0.9_yn = 1+ AAMAC <0.9 alerts	1.000	.980	1.020
N of Valid Cases	10894		

```
USE ALL.
COMPUTE filter_$=(New_groups = 1).
VARIABLE LABELS filter_$ 'New_groups = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.
* Custom Tables.
CTABLES
  /VLABELS VARIABLES=quarter_org Percent_case_actual_alerted DISPLAY=LABEL
  /TABLE quarter_org BY Percent_case_actual_alerted [MEAN, SEMEAN]
  /CATEGORIES VARIABLES=quarter_org ORDER=A KEY=VALUE EMPTY=EXCLUDE.
```

Table 1

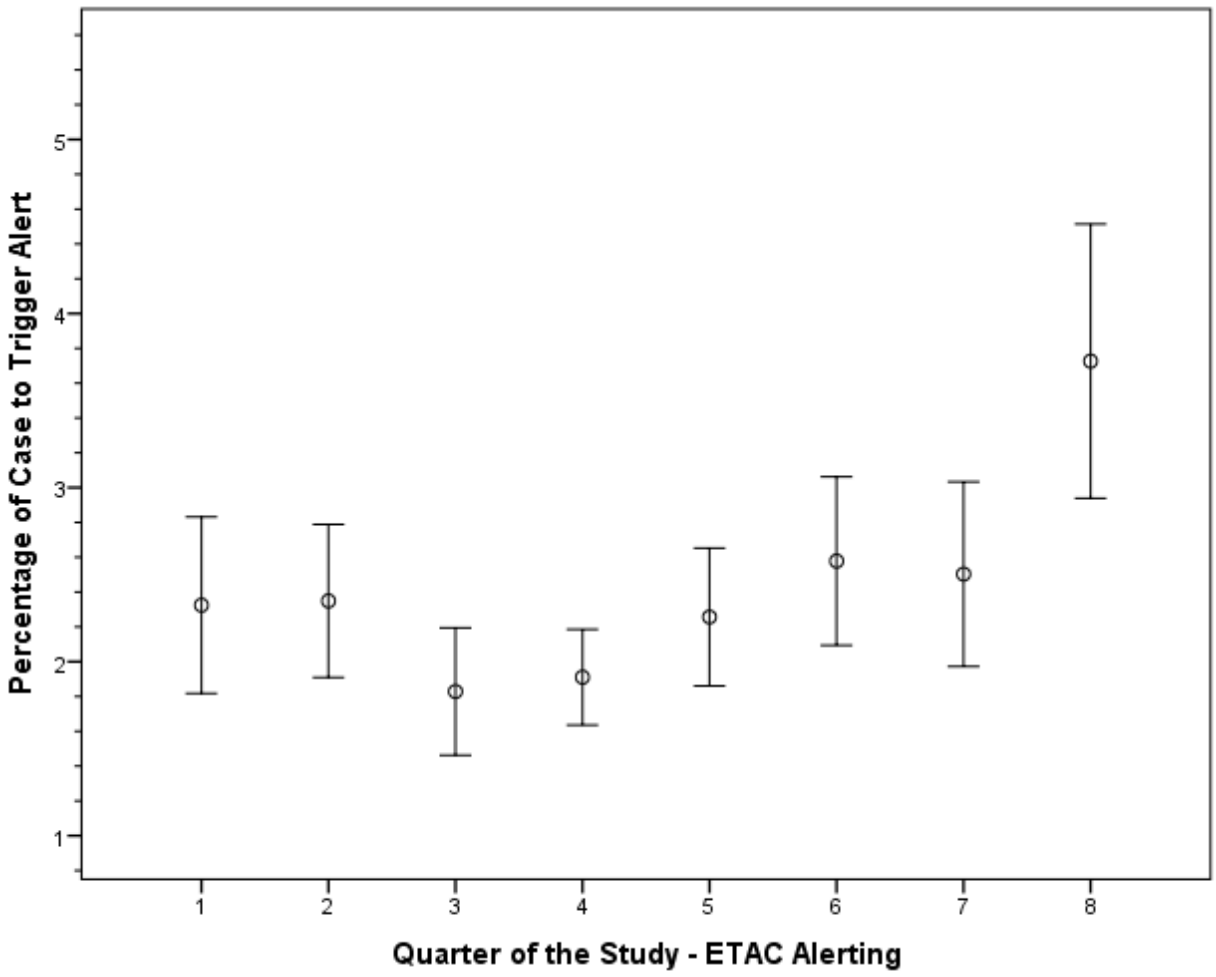
		Percent_case_actual_alerted	
		Mean	Standard Error of Mean
quarter_org	1	2.3247	.2532
	2	2.3491	.2201
	3	1.8286	.1830
	4	1.9109	.1375
	5	2.2568	.1981
	6	2.5781	.2420

7	2.5031	.2652
8	3.7266	.3937

GRAPH

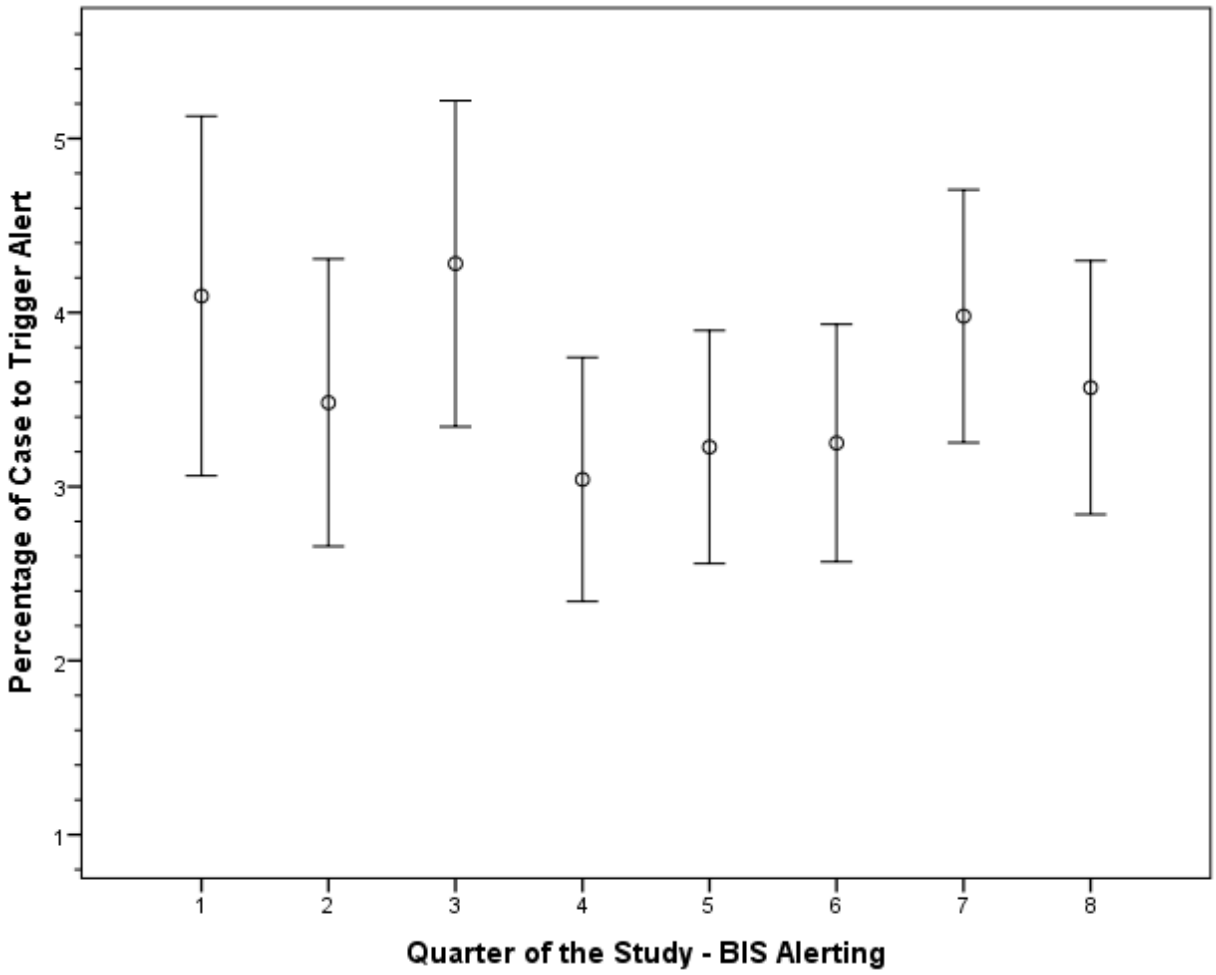
/ERRORBAR(STERROR 2)=Percent_case_actual_alerted BY quarter_org.

MAC only actual alerting



```
GRAPH
  /ERRORBAR(STERROR 2)=Percent_BIS_60 BY quarter_org.
```

BIS alerting




```
* Custom Tables.
```

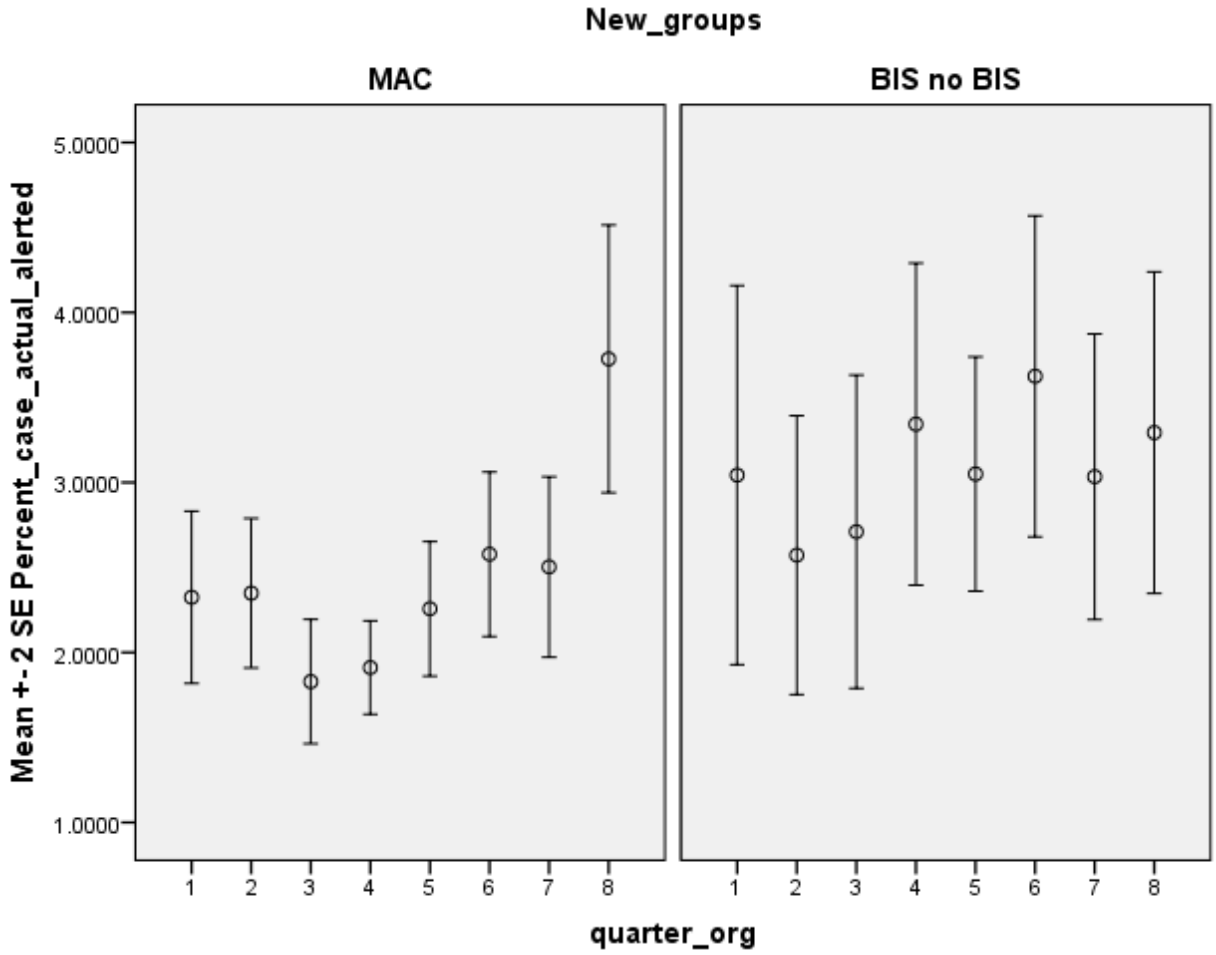
```
CTABLES
  /VLABELS VARIABLES=quarter_org Percent_BIS_60 DISPLAY=LABEL
  /TABLE quarter_org [C] BY Percent_BIS_60 [MEAN, SEMEAN]
  /CATEGORIES VARIABLES=quarter_org ORDER=A KEY=VALUE EMPTY=EXCLUDE.
```

Table 1

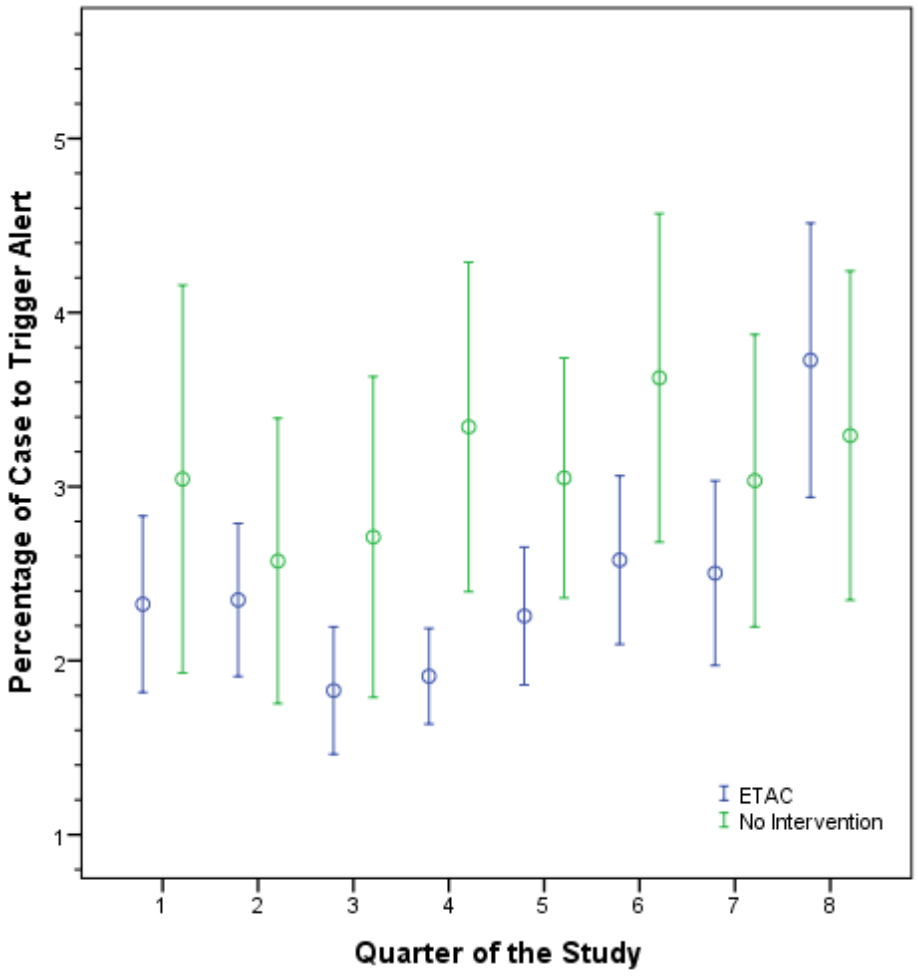
		Percent_BIS_60	
		Mean	Standard Error of Mean
quarter_org	1	4.10	.52
	2	3.48	.41
	3	4.28	.47
	4	3.04	.35
	5	3.23	.33
	6	3.25	.34
	7	3.98	.36
	8	3.57	.36

```
FILTER OFF.
USE ALL.
EXECUTE.
USE ALL.
COMPUTE filter_$=(New_groups = 1 OR New_groups = 3).
VARIABLE LABELS filter_$ 'New_groups = 1 OR New_groups = 3 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
```

```
FILTER BY filter_$.

EXECUTE.

GRAPH

  /ERRORBAR(STERROR 2)=Percent_case_actual_alerted BY quarter_org

  /PANEL COLVAR=New_groups COLOP=CROSS.
```



```
GRAPH
  /ERRORBAR(STERROR 2)=Percent_case_actual_alerted BY quarter_org BY New_groups.
```




```
FILTER OFF.
USE ALL.
EXECUTE.
DATASET ACTIVATE DataSet1.
SAVE OUTFILE='D:\amysha\Desktop\MACS '+
    'alerting\BIS_dissertation_merged_with_deletions_NO_PROPOFOL_INFUSIONS_21Aug12.sav'
  /COMPRESSED.
```

```
USE ALL.

COMPUTE filter_$=(New_groups = 1 OR  New_groups = 3).

VARIABLE LABELS filter_$ 'New_groups = 1 OR  New_groups = 3 (FILTER)'.

VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.


*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (Percent_case_actual_alerted) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.009	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

```
USE ALL.

COMPUTE filter_$=(New_groups = 1 OR  New_groups = 3).

VARIABLE LABELS filter_$ 'New_groups = 1 OR  New_groups = 3 (FILTER)'.
```

```
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.

* Custom Tables.

CTABLES

  /VLABELS VARIABLES=New_groups quarter_org Percent_case_actual_alerted DISPLAY=LABEL

  /TABLE New_groups > quarter_org BY Percent_case_actual_alerted [MEAN]

  /CATEGORIES VARIABLES=New_groups ORDER=A KEY=VALUE EMPTY=INCLUDE

  /CATEGORIES VARIABLES=quarter_org ORDER=A KEY=VALUE EMPTY=EXCLUDE.
```

Custom Tables

Table 1

			Percent_case_actual_alerted
			Mean
New_groups	MAC	quarter_org 1	2.3247
		2	2.3491
		3	1.8286
		4	1.9109
		5	2.2568
		6	2.5781
		7	2.5031
		8	3.7266

BIS with BIS	quarter_org	1	.
		2	.
		3	.
		4	.
		5	.
		6	.
		7	.
		8	.
BIS no BIS	quarter_org	1	3.0432
		2	2.5724
		3	2.7104
		4	3.3431
		5	3.0498
		6	3.6249
		7	3.0340
		8	3.2933

FILTER OFF.

USE ALL.

EXECUTE.

SORT CASES BY quarter_org.

SPLIT FILE LAYERED BY quarter_org.

USE ALL.

COMPUTE filter_$=(New_groups = 1 OR New_groups = 3).

```
VARIABLE LABELS filter_$ 'New_groups = 1 OR  New_groups = 3 (FILTER)'.

VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_$ (f1.0).

FILTER BY filter_$.

EXECUTE.


*Nonparametric Tests: Independent Samples.

NPTESTS

  /INDEPENDENT TEST (Percent_case_actual_alerted) GROUP (New_groups)

  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE

  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

quarter_org = 1

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.550	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 2

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.007	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 3

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.460	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 4

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.007	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 5

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.001	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 6

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.021	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 7

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.105	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

quarter_org = 8

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Percent_case_actual_alerted is the same across categories of New_groups.	Independent-Samples Mann-Whitney U Test	.729	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

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ABSTRACT

NOVEL INCORPORATION OF BIOMEDICAL ENGINEERING ALGORITHMS (BISPECTRAL INDEX GUIDED OR ANESTHETIC CONCENTRATION GUIDED) IN REAL-TIME DECISION SUPPORT TO PREVENT INTRAOPERATIVE AWARENESS USING AN ELECTRONIC ANESTHESIA INFORMATION MANAGEMENT SYSTEM

by

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Background: Intraoperative awareness with explicit recall (AWR) is a feared complication of surgery that can lead to significant psychological distress. Several large prospective trials have been completed comparing two methods of monitoring anesthetic depth [minimum alveolar concentration (MAC) or electroencephalography (EEG) monitoring using the bispectral index (BIS)] for the prevention of AWR. However, these trials were conducted in high risk populations, limiting generalizability.

Research Hypothesis: Real-time decision support with Anesthesia Information Management System alerts based on a novel anesthetic concentration algorithm (incorporating the use of intravenous anesthetics) or an EEG-guided algorithm will reduce the known incidence of AWR.

Methods: First, a MAC-equivalent alerting algorithm that incorporates the use of intravenous anesthetics was developed and retrospectively applied to previously collected data. A threshold was calculated that demonstrated optimal sensitivity and specificity for detecting AWR. Next, a large prospective randomized controlled trial was performed in an unselected surgical population to compare the MAC-equivalent or a BIS alerting algorithm for the prevention of AWR. Finally, discrete intraoperative data collected during that trial were analyzed to determine which specific threshold for MAC or BIS demonstrated optimal sensitivity and specificity in the eradication of AWR.

Results: Retrospective analysis revealed that a MAC-equivalent of <0.5 was associated with the highest positive likelihood ratio; this was used as the threshold in the prospective trial. No difference was detected between BIS or MAC-equivalent alerting algorithms in the reduction of AWR. Post hoc analysis revealed that BIS, when compared to routine clinical care without alerts, demonstrated a 4.7 fold reduction in definite or possible AWR. By secondary analysis, neither MAC nor BIS demonstrated a discrete population-based threshold with optimal sensitivity and specificity in the prevention of AWR.

Conclusion: No difference was detected in the reduction of AWR between BIS or MAC alerting. However, BIS alerting when compared to standard of care reduced the incidence of AWR. There were no discriminating thresholds of MAC or BIS values at the population level associated with the eradication of AWR. In conclusion, real-time decision support reduces the incidence of AWR but individualized patient-based alerting algorithms will be required for its eradication. .

AUTOBIOGRAPHICAL STATEMENT

Amy received her Bachelors of Science in Physiology from Michigan State University in May 1999. Several months later, her professional career started at the University of Michigan Health System (UMHS) in the Department of Anesthesiology as a clinical research assistant. During her pursuit of her doctorate degree, Amy has continuously worked full-time at UMHS. She completed her Master's Degree in Biomedical Engineering at Wayne State University from 2001-2003. Amy started her doctoral work in the Fall of 2004 in Biomedical Engineering at Wayne State University and has actively pursued completion while continuing to grow her career at UMHS.

During her tenure at UMHS, Amy has transitioned from clinical research assistant, to clinical research manager, before moving onto becoming an integral team member that developed and executed the clinical outcomes research infrastructure using UMHS' Anesthesia Information System (AIMS). The Department of Anesthesiology is recognized globally for their perioperative outcomes research using AIMS data and over the past several years has developed the Multicenter Perioperative Outcomes Group (MPOG). Amy currently serves as the Research Director of MPOG under the direction of Drs. Sachin Kheterpal and Kevin K. Tremper. She also serves as the lead of the Statistics Core in the Department of Anesthesiology and has been an author on 53 peer-reviewed articles.