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A RANDOMIZED CONTROLLED TRIAL OF ANESTHESIA GUIDED BY BIS VS. STANDARD CARE AND EFFECTS ON COGNITION

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A RANDOMIZED CONTROLLED TRIAL OF ANESTHESIA GUIDED BY BIS VS. STANDARD CARE AND EFFECTS ON COGNITION

DISSERTATION

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the
College of Nursing at the University of Kentucky

By
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ABSTRACT OF DISSERTATION

A RANDOMIZED CONTROLLED TRIAL OF ANESTHESIA GUIDED BY BIS VS. STANDARD CARE AND EFFECTS ON COGNITION

Postoperative cognitive dysfunction (POCD) occurs frequently in individuals undergoing major surgery with general anesthesia. POCD adversely affects morbidity and health-related quality of life. Derived electroencephalographic (EEG) monitoring is utilized to guide the anesthesia provider in titration of volatile anesthetics. POCD has been associated volatile anesthetic neurotoxicity. EEG monitors are known to reduce a patient's total cumulative dose exposure to volatile anesthetics. There is currently little evidence to support utilization of EEG monitors as a guide to reduce the incidence of POCD.

The purpose of this dissertation was to develop and test a technique of general anesthesia, delivered by anesthesia providers and guided by the Bispectral Index™ (BIS) system EEG monitor. This technique was designed to reduce cumulative volatile anesthetic exposure and reduce cognitive decline. Prior to testing the intervention, preliminary work was conducted resulting in a review of evidence for current concepts in the mechanism of volatile anesthetics and their relationship with POCD. Based on information from these manuscripts, a randomized, controlled study was conducted to test the effects of BIS guided anesthetic technique on outcomes of middle aged patients undergoing impatient major surgery.

Eighty-eight patients scheduled for major inpatient surgery were randomized to a BIS guided anesthetic, or to usual care control. Although not in every cognitive domain, BIS guidance resulted in superior and not inferior performance in cognitive testing.

The third manuscript documents predictors of cognitive decline. This was a secondary, planned data analysis of the previous prospective, randomized controlled trial. Consistent predictors of cognitive decline through the study phases were older age, lower income, and lower education. In addition to these, tobacco abuse is a significantly predictive characteristic.

Further research should be focused on at risk cognitive domains, as well as, exploring other anesthetic regimens to avoid cognitive decline.

KEYWORDS: heart failure, anxiety, depression, hostility, trajectories, psychological symptoms

Zohn Centimole

November 28, 2016

A RANDOMIZED CONTROLLED TRIAL OF ANESTHESIA GUIDED BY BIS VS. STANDARD CARE AND EFFECTS ON COGNITION

By

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Dr. Debra K. Moser
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November 29, 2016
Date

Dedication
To my bride, Sarah,
and my boys, Calvin, & Graham,
my love and my joy.

In memory
Stella Centimole
Sue Thread
Vicki Gibson, CRNA
Dr. Wayne M. Mason

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Throughout my life I have been blessed with exceptional mentors who saw in me some worth that inspired them to give. My life, and this dissertation, is the cumulative result of their efforts.

My first and most influential mentors, my parents, provided a core work ethic and sacrificed in ways that continue to influence me every day. I love you both and thank you. My sister, the hardest worker I know, has supported me unendingly. My grandparents found their individual way of love and support. My uncles Steve and Rhea have always been resourceful and demonstrated generosity. Hunter, my nephew, shows ambition and intelligence that inspires me. The future of nurse anesthesia, John-Paul, has heard every concern of mine for the past 15 years. The newest members of my family Faye, Matt, "Bepie" and Ann have inspired me with their grace, welcoming me through their tears.

As a young man I saw in my scoutmasters, Tom Carr and Larry Vaughn, a passion for fastidious attention to their work. Their zeal inspires my approach to nurse anesthesia every day. My high school football coach, Kevin Wallace, afforded grace that I will never forget. In college I had great, formative instructors and professors. Educators like Dr. Wayne Mason and Dr. Susan Jones demonstrated a mastery of their scholarship and set an impressive bar. My college football coach Jack Harbaugh's meritocratic philosophy provided an opportunity to realize my dreams. In graduate school, Dr. Larry Lancaster impacted my education, as he has countless nurse anesthetists and nurse practitioners across the south.

For the past 10 years I have learned anesthesia from the faculty and my CRNA colleagues from the University of Kentucky. My ability is on account of their exceptional skill. Dr. John Eichhorn has been a confidante and support over this entire period. Thank you. Embarrassingly, over the same amount of time, I have been a doctoral student in the college of nursing. The faculty and staff have shown me step by step, through their own work, the manufacture of research. The best of this study is a small reflection of your work. Dr. Frazier's effervescence, Dr. Rayens' easy advice, Dr. Watkins' extension, and Dr. Jicha's grasp of my concept have all been critical for my development as a researcher. My chairwoman, mentor, advisor and the lady I have spent every afternoon with for the last year, Dr. Debra Moser's demonstration of giving of her time and talent is not missed nor will ever be forgotten. Thank you all.

To my boys, Calvin and Graham, you inspire me. I hope in some way, when you are men, you may see this and know that anything is possible with effort. My life's work has been to create a happy childhood for you so that you can be so much more than me. I know you both will, and I love you. She who inspires me greatest is my wife Sarah. The greatest gift I have ever received, my family, was given to me from you. I thank God for you every day. Through the toll this work born on us, I hope that in some way this accomplishment brings you joy. It is truly ours to share.

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CHAPTER ONE

Introduction

Anesthesia is one of the greatest advancements in the health sciences. Anesthesia has not only made invasive procedures tolerable, but also has made countless surgical advancements possible. The last reported statistical summary by the Centers for Disease Control and Prevention indicated that there were over 48 million surgical procedures every year requiring general anesthesia, or the drug induced loss of response and perception of stimulation.[1] The induced state of anesthesia is typically reversible and its consequences predictable and short-lived. Still, some individuals suffer cognitive deficits unexpectedly after surgery. Post-operative cognitive dysfunction, hereafter stated as POCD, is defined as negative changes in cognitive function that continue after appropriate drug half-lives have expired.

Post-operative cognitive dysfunction was the focus of this dissertation because POCD adversely affects learning and memory for discharge and follow-up self-care instructions, short- and long- term recovery, and even mortality risk. In addition, I focused on POCD because the fastest growing segment of the population are the old and elderly, which is the group most likely to undergo surgery and also to begin to manifest mild cognitive impairment (MCI). These old (>60 years of age) and elderly (>75 years of age) individuals are the greatest consumers of health care.[2] Maintaining function and independence are key components to maintaining quality of life, and the old and elderly are at greatest risk for POCD.[3,4]

Many questions important to clinical practice about POCD are yet to be answered. Foremost among them is whether you are more at risk for POCD if you receive volatile

anesthetic agents during surgery. Other unanswered questions include, beyond age, what risk factors result in increased susceptibility for POCD. Are there techniques to reduce the impact of anesthesia on cognitive function? What are the most effective means to evaluate cognitive dysfunction perioperatively? I addressed some of these questions in this dissertation. The purposes of this dissertation were to (1) determine predictors of cognitive function among individuals scheduled for surgery using general anesthesia and volatile anesthetics; (2) determine predictors of cognitive dysfunction after surgery with general anesthesia and volatile anesthetics; and (3) determine if there are anesthetic delivery methods that can reduce the incidence of POCD.

Post-operative Cognitive Dysfunction

The symptomology of POCD is similar to that of delirium, and until the late 1990's was not separated from the diagnosis of delirium. Improved understanding of POCD allowed for differentiation from delerium. Delerium is a vascillating inability to focus and maintain attention compared to POCD, which is a decline in cognitive function (typically in the memory and executive function domains) that lasts from days to months and in some cases, years. POCD, as a syndrome, is widely discussed in the literature, but is not listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V).[5] This is because a cognitive condition cannot have characteristics that could place it into another diagnosis (i.e., delirium, dementia, or amnestic disorder).

Because POCD is not a defined disorder in the DSMMD and because neurocognitive testing is not routine and not available in all hospitals, POCD is largely under-appeciated by most clinicians. The objective finding of POCD requires baseline neurocognitive testing and follow-up testing at intervals after the effective half-lives of

anesthetics have passed. Usually, POCD is simply noted by the patient as "clouded thinking" or by family members as "something just not right".

Symptoms of derangements similar to POCD have been reported for over 60 years.[6,7] Bryson and Wyand describe POCD as a subtle disorder of thought processes that may influence isolated domains of cognition such as verbal memory, visual memory, language comprehension, visuospatial abstraction, attention, or concentration, although the exact areas have not been definitively determined.[8] These deficits in advanced cognitive function and memory continue after surgery and discharge from hospitalization and may last from days to years.[9]

In a seminal study, the incidence of POCD ranged from 10-50% depending on type of surgery.[3] More recently, Monk and colleagues[4] found that 30 to 41% of all adult patients experience POCD at discharge after surgery. This cognitive decline is associated with increased one year mortality, as well as morbidity and family/caregiver stress.[4] The domains that appear to be most affected are attention and cognitive speed but also affected are executive function and memory.[10]

Etiology of POCD

The etiology of POCD is unclear. A widely studied hypothesis for the mechanism underlying POCD alterations is neurotoxic injury. This association between anesthetics and the dementias has been suspected for over twenty years.[11-13] Although there are many different anesthetics, the inhalation anesthetics (isoflurane, sevoflurane, and desflurane) are the basis of anesthesia used today. It is well described that inhalation anesthetics have effects demonstrated in histologic neuropathology similar to those seen in the senile dementias including Alzheimer's disease (AD).

Multiple neuropathogenic mechanisms of inhalation anesthetic have been described and are of increasing concern. The most prevalent of these are increased production and aggregation of amyloid beta (Aβ) peptides, increased caspase activation, and accumulation of hyperphosphorylated tau. Although there are many anesthetics and techniques available to obtain surgical anesthesia, some techniques involve use of high concentrations of volatile anesthetics. These anesthetic techniques lead to higher cumulative doses of the anesthetic and have been demonstrated to produce higher histologic neuropathology from inflammatory changes [14-16] Lately, closer correlates have been drawn between anesthetics, POCD, MCI and AD. This is because the cognitive domains of memory and executive function that are affected by POCD, MCI, and AD are similar.

Alzheimer's disease, the most common form of dementia, is loss of mental ability affecting the cognitive domains of memory (short-term), verbal (expressive), visuospatial, and executive function. Mild cognitive impairment is a state of cognitive ability that falls below norms, but lacks the loss of function seen in the dementias. Mild cognitive dysfunction is considered a prodromal phase of dementia, and is suspected in individuals with memory deficits of the core cognitive domains (recall, language, visuospatial ability, and executive function).

Histological changes associated with AD and MCI are the basis for understanding the genesis of these conditions. The hallmarks for the histological neuropathology are Amyloid precursor protein (APP), Aβ, and hyperphosphorylation of tau. Amyloid precursor protein (APP) is an integral membrane protein believed to be involved in synapse formation. Amyloid precursor protein is present in dendrites, cell bodies and

axons of neurons. Amyloid beta is a peptide enzymatically degraded from the larger APP that are released in neuronal damage. Amyloid beta deposits are neurotoxic, triggering retraction of axon terminals at target cells. Amyloid beta is also thought to trigger a chain-reaction of neuronal destruction in some individuals.[17] Cumulatively, this is described as a senile plaque. Mild cognitive dysfunction is the result of similar neuropathologic changes.

Triggering of the apoptotic pathway and neuronal loss as a precursor to Aβ accumulation have been demonstrated in animal models of anesthetics. Isoflurane was demonstrated by to be an apoptotic neurodegeneration pathway in lower level mammals that were exposed to therapeutic doses of anesthesia in 2, 4, and 6 hour test groups.[18] Xie and colleagues went on to associate isoflurane with caspase-3, a protein activated in the execution-phase of cell apoptosis.[19] This finding was noted in a 2 hour exposure time and at a therapeutic isoflurane concentration of 1.4%.

In addition to Aβ, caspase-3 activation with neuronal apoptosis, and cortical hyperphosphorylated tangles of tau proteins are also noted in the neuropathology of AD. Research in POCD suggests similar neuropathologic changes. Loop and colleagues demonstrated that caspase-3 processing is provoked in a concentration/dose-dependent manner by sevoflurane and isoflurane, resulting in apoptosis.[20] Further, sevoflurane induces caspase activation and apoptosis with subsequent increases of Aβ in human neuroglioma cells.[21] Zhang and colleagues studied the volatile anesthetic desflurane.[22] He found that desflurane alone did not induce caspase or Aβ but may when combined with hypoxia (18% FiO2). Further, exposure to and subsequent inflammatory changes from

volatile anesthetics are postulated to progress AD neuropathogenesis through these pathways.[15,23]

A common criticism of much of the research in POCD is the poor translation of bench science to clinical science with patients. This is a common obstacle with dementias studies, due to the obvious complications trying to translate the results of in-vitro studies to humans. Despite this difficulty, closer correlations are being noted between the dementias and POCD. Liu and colleagues concluded that individuals with amnestic MCI transitioned to progressive MCI in larger numbers in a group exposed to the inhalation anesthetic sevoflurane than those who had no exposure.[24] In this study 55 individuals with MCI were exposed to an anesthetic with sevoflurane inhalation anesthetic. Of these, 30 individuals were noted to have progressive/amnestic MCI at 2 years ($P<0.01$) and 13 were diagnosed with AD.

Although, there is weighty evidence suggesting the risks of volatile anesthetics, this evidence does not warrant the exclusion of the anesthetics. In 2009 a POCD workshop was conducted with experts from anesthesia, neuroscience, and pharmacology. This group recognized the evidence linking inhalation anesthetics to the dementias is considerable on multiple levels of investigation, but that anesthetics provided an immediate benefit to society that outweigh these risks.[36]

In summary, although the etiology of POCD is unclear, the evidence supporting relationship of volatile anesthetics and neuronal inflammatory response is strong. This inflammatory response is particularly similar to that in MCI and AD. It is hypothesized that reducing the cumulative volatile anesthetic dose will reduce cognitive dysfunction.

Improving POCD Outcomes

Classically, volatile anesthetic depth was titrated to Guedel's classification, the presence or absence of various reflexes observed as anesthesia concentrations increased. Newer drugs, such as the neuromuscular-blocking drugs used today have obscured reflexes and thus the use of this classification system has declined. Electroencephalographic (EEG) activity monitors utilize time-domain, frequency-domain, and dual spectral analysis of raw EEG signals to objectively measure level of consciousness. The application of the Fourier transformation to EEG waveforms and subsequently, the correlation with depth of anesthesia ushered in development and use of bedside monitors to guide anesthesia dosing and optimize the depth of anesthesia used so that it is not too little or too much.

Entropy-guided monitors measure EEG and, through proprietary algorithms, convert the degree of irregularity seen with the awake EEG and the more regular patterns seen with increasing depth of anesthesia to a value that can be used by the clinician to judge depth of anesthesia. Although there are multiple proprietary platforms that are used to perform entropy-guided anesthesia, the one used in my study was the Bispectral Index™ system or (BIS). This platform is used by the majority of the market.

There are multiple benefits to the use of BIS-guided anesthesia. Gan and colleagues established that a secondary benefit of this guided technique was a 13.4% reduction in anesthetic drug consumption.[25] There are many other well-known benefits of entropy-guided titration of anesthesia, such as shortened anesthesia emergence time and faster recovery.[26] Investigators have further demonstrated that avoidance of deep anesthesia is associated with improved survival, reduced morbidity[27] and improved 2-year mortality.[28]

Sessler and colleagues described the concept of "triple low" threat, consisting of hypotension, cumulative deep hypnotic time, and presence of co-morbidities, which leads to increased odds of one-year mortality.[29] Cumulative deep hypnotic time (per hour) increased one-year mortality by 1.244% ($P<0.0121$).

In an important study in the field conducted in China, the Cognitive Dysfunction after Anesthesia (CODA) trial investigators demonstrated increased cognitive dysfunction after deep anesthesia.[30] The investigators utilized BIS-guided anesthesia and titrated depth of anesthesia to a score of 40-60 (considered good general anesthesia with a low probability of explicit recall) in 462 individuals and another 459 were randomized to a blinded control group in which anesthesia was delivered without BIS-guidance. The outcome of the study was cognitive function measured by a basic cognitive failure questionnaire including the verbal fluency test, Chinese auditory verbal learning test, and color trail making test. The CODA trial investigators concluded that controlling anesthetic depth to a BIS guided range of 40-60 resulted in 83 patients for every 1000 being protected from delirium during hospitalization and 23 avoiding POCD at 3 months after surgery[31].

In another important study, investigators used the BIS to titrate depth of anesthesia. In this trial, Radtke and colleagues randomized 1277 individuals into two groups, one that received BIS titrated anesthesia (n=593) and one blinded to BIS values (n=600).[32] They found that there was a significant increase in delirium ($p=0.015$) in the patients cared for in the blinded group, but no significant differences in POCD were seen ($p=0.062$) between the two groups. An interesting limitation of the study was the fact that the providers in the two groups did not produce differing anesthetic depths, likely

because the protocol allowed for unblinding of the provider who was allowed to use data from the BIS as deemed appropriated.

In summary, entropy guidance monitors have improved the anesthesia provider's understanding of depth of anesthesia in real time. Over the past decade the availability and acceptance of these devises has become widespread. Previous studies have demonstrated the ability of entropy guidance monitors to positively change the neurocognitive outcomes for patients. These studies can be improved upon by elimination of confounding groups and more rigorous cognitive testing.

Measurement of POCD Outcomes

There is no gold standard instrument for the study of POCD. A literature review of POCD studies by Newman and colleagues reported that at least 70 different measures were used alone and in combinations.[33] There was little similarity in the domains of cognitive function studied (and in most cases, the investigators failed to report which domains they studied), in most cases arbitrary definitions of POCD were used and the definitions were poorly described making replication difficult. All of these problems create a barrier for POCD researchers in that the findings are difficult to compare amongst the studies and it is difficult to determine which instruments to use. To date there is not a neurocognitive battery developed specifically for the study of POCD, nor a definitive study to indicate the optimum neurocognitive battery.

The Uniform Data Set (UDS) from the Alzheimer's disease Centers program of the National Institute on Aging is currently utilized by 32 centers in the United States.[34] The battery is administered by trained neuropsychologist in a clinical office setting. This battery is exhaustive, diagnostic, and used as part of a 918 variable data collection of

research participants, making its use in surgery patients quite difficult and not practical. Lewis noted that, in regard to studies of POCD, increasing the number of tests in a battery increases the sensitivity, but resulted in increasing false positive classifications and error.[35] The landmark study of POCD is the International Study of Postoperative Cognitive Dysfunction study. This study utilized seven different test focusing different cognitive domains to complete the battery. These test and their domains included the visual verbal learning test (executive function), concept shifting test (executive function), Stroop color word interference test (executive function), paper and pencil memory scanning test (visual memory), letter-digit coding test (processing speed), and four boxes test (reaction time).

Although, other investigators have utilized the Cambridge Neuropsychological Test Automated Battery (CANTAB®) system to measure cognitive function, this dissertation includes the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment (CANTAB-MCI®) battery for the first time in the anesthetic population and for the first time, we identified the specific domains of cognitive function being measured. The CANTAB® is very sensitive for detecting mild cognitive impairment, the pre-dementia state most similar to postoperative cognitive dysfunction. Wide use of such a neurocognitive screening tool in clinical practice may alert providers in the future to individuals who need an augmented anesthetic, or will need progressive care postoperatively. This could lead to reduced morbidity, mortality, as well as, patient and caregiver stress.

Overview of the Dissertation

An obstacle in understanding POCD is that the exact mechanism whereby volatile anesthetics produce their effects is not currently known. Chapter Two of this dissertation is a review of the state of the science on the mechanism of inhalational anesthetics and how POCD might occur in that context. This chapter presents an integrative review of the literature that presents mechanisms that are plausible and their associations with neuropathogenic effects.

Chapter Three of this dissertation is a report of a randomized controlled trial of an anesthesia technique guided by the BIS monitor compared with standard care. In a sample of 86 individuals, 45 surgical patients randomized to the intervention of a balanced anesthetic technique with BIS guidance, and 43 to standard treatment. Individuals cognitive performance was evaluated with the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment (CANTAB-MCI®) at three intervals (preoperatively, 3-5 days post-operatively, and 3-5 months post-operatively). An additional 37 age- and sex-matched individuals not undergoing surgery nor anesthesia were evaluated at the same intervals to represent a normative population. The purpose of the study was to determine if an anesthetic technique with cumulative deep hypnotic time result in a greater degree of POCD. A two-way mixed repeated measures ANOVA was utilized to address this specific aim.

Chapter Four of this dissertation is a review of the predictors of cognitive dysfunction as defined from the CANTAB-MCI battery. These were determined by statistical analysis of the randomized controlled trial described in Chapter 3. Predictors of

cognitive dysfunction are described for baseline, at early postoperative testing time, and late testing time. Parameter estimates were obtained and described in this chapter.

Chapter Five is an integrated summary and conclusions from the findings of the manuscript. Recommendations for contemporary clinical practice, as well as, future research are discussed in this chapter. The findings of the study are targeted as practical interventions that nurse anesthetists may use in any practice in the United States. Implications of this research are limiting the effect of anesthetics, in particular volatile anesthetics, on susceptible surgical populations.

CHAPTER TWO

Anesthesia Mechanisms and the Aging Brain

Introduction

The use of anesthetics in the care of individuals undergoing surgery is one of the greatest accomplishments in the health sciences. Since Joseph Priestley's work with nitrous oxide in 1772 and William Morton's 1846 demonstration of ether anesthesia, anesthesia has become an increasingly important component of health care. The last reported statistical summary by the Centers for Disease Control and Prevention[1] indicated that there were over 48 million surgical procedures requiring anesthesia performed in 2009.

Though widely used and accepted as safe, neither the molecular pharmacological site of action, nor the mechanisms of volatile anesthetic action are currently fully understood[2]. There have been no receptors directly identified that account for the activity of inhalational anesthetic activity. Nonetheless, the practice of anesthesia has evolved and allowed many of the great surgical advancements of modern medicine.

Improvements in safety of anesthesia over the past five decades are largely attributed to improved patient monitoring and to optimal training of anesthesia providers. In the 1950's anesthesia-related mortality rates were reported as 1 per 1560.[3] More recent studies suggest that anesthesia-related mortality is 1.1 per million per year.[4] The practice, however, seeks to realize a completely benign anesthetic experience.

Growing interest in defining the risk associated with anesthesia is essential in quality improvement within the practice. Increasing age is an important risk factor for post-operative morbidity and mortality. By 2030, 20% of Americans will be older than 65

and 21% of those over 60 will receive anesthesia with surgery (compared with 12% of those 45-60) A better understanding of anesthesia risks in the elderly can improve outcomes.

Post-operative cognitive dysfunction (POCD) is one such risk. There is controversy about the existence of an association between anesthesia and POCD[5], yet there is a sound theoretical and physiologic basis for such an association particularly among older individuals. Of note, there are similarities in protein abnormalities seen in Alzheimer's disease (AD), mild cognitive impairment (MCI) and POCD, which suggest a foundation for understanding the potential for POCD in older patients.[6] The purpose of this paper is to integrate current concepts of the mechanisms of action of inhalational anesthetics, the pathology of AD and MCI, and the effects of anesthesia on the aging brain. The major concept underlying the relationship among these is protein inhibition. Protein inhibition results in anesthesia. Protein inhibition is associated with multiple deleterious processes, many of which are seen in AD, MCI and POCD and will be discussed below.

Linking Protein Mechanisms to Postoperative Cognitive Dysfunction and Mild Cognitive Impairment

Alzheimer's disease and the prodromal state, MCI are two of the many types of dementia. Abnormalities in neuronal proteins have been studied in AD and other dementias for over three decades.[7] Amyloid proteins are components of cell membrane. Normally, these proteins are dissolved in body fluids and utilized in new cell creation. Occasionally, these proteins become misfolded leading to clumping or aggregates. The misfolding or transformation of the peptides into aggregate proteins are toxic to other local, healthy cells The aggregation of amyloid proteins as a result of misfolding is a

leading theoretical mechanism in the AD pathway. Injury to neuronal cells can create a destructive cascade of injury to healthy cells that is ultimately manifested by dementia.

Mild cognitive impairment is described as a transitional zone or prodromal state to frank dementia. Typically, the dementias effect multiple cognitive domains, whereas, MCI effects a single cognitive domain. MCI is a condition in which an individual displays memory problems disproportionate to their age.[8] This prodromal state bridges normal cognitive function and the more severe dementias including clinical AD.[9] The typical time period for MCI transition to a more severe dementia is 18 months.[10] Volatile anesthetics have been associated with similar deficits in cognitive domains which have led researchers to study if there is an association or causal relationship.

Postoperative cognitive dysfunction is a subtle disorder of thought process that influences isolated domains of cognition such as verbal memory, visual memory, language comprehension, visuospatial abstraction, attention, or concentration[11] after exposure to an anesthetic and that remains after drug half-lives have past. The cognitive domains affected in POCD are very similar to those affected in MCI. Symptoms of poor cognition after surgery have been reported for over 50 years,[12] long before POCD was recognized and named. Postoperative cognitive dysfunction occurs in 27% and 10% of individuals over 60 years old, at 1 week and 3 months after non-cardiac surgery respectively,[13] and has become a focus of anesthesia research among older and at-risk populations. Although there is no data to suggest that surgery aggravates existing AD, inflammation is a critical common pathology of both volatile anesthetic induced POCD and what is understood from the AD pathway.

Protein Abnormalities and Anesthesia

The neuronal abnormalities and protein derangements seen in AD are similar to those seen with use of inhalation anesthetics. Amyloid beta protein (Aβ) aggregates or plaques are a hallmark of AD pathology. Aβ are a specific type of protein fragments left from neuronal destruction and are thought to be highly neurotoxic to healthy cells. The next few paragraphs will highlight significant findings related to POCD pathology.

Anesthetics can induce neurotoxicity via apoptotic neurodegeneration. Apoptotic neurodegeneration is also known as programmed cell death. This is a process where a trigger induces the cell to dramatically alter the nucleus or other component leading to the cell death. Nikizad, Yon, Carter, and Jevtovic-Todorovic[14] induced thalamic and cerebral cortex apoptosis, with clinically appropriate concentrations of volatile anesthetic in rat pups. The resulting buildup of cellular components creates an imbalance of protein clearance leading to Aβ and oligomerization.

After neuronal destruction, cellular components are left behind and are further broken down and cleared in healthy individuals. As mentioned before, in AD a toxic aggregation of Aβ has been noted to appear in susceptible individuals without a clear cause. Oligomerization is the bonding of small peptides that will then form larger aggregates. Eckenhoff et al.[15] demonstrated that volatile anesthetics effect oligomerization or the collection of Aβ, with *in vitro* rat models. These neurotoxic bodies are thought to cause further cell destruction and overwhelm the body's ability to clear Aβ. Eckenhoff et al.[15] enhanced Aβ oligomerization rates and subsequent neuro-cytotoxicity with exposure to the common volatile anesthetics isoflurane and halothane.

Caspases, protease enzymes, are the principle executors of apoptotic pathways. Lu et al.[16] showed increased caspase activation in rat pups after a sevoflurane anesthetic. Lu et al.[16] observed increased apoptosis, altered precursor protein processing, and altered β-amyloid protein levels. Xie et al.[17] demonstrated dose-dependent activation of caspase-3 and apoptosis in human neuroglioma cells with isoflurane. Six hour exposures to isoflurane at 1% showed no change in caspase-3 activation, although at 2% there was substantial activation and apoptosis.

The state of the science in POCD research implicates important pathological outcomes from therapeutic concentrations of volatile anesthetics. Examination of mechanisms thought to explain the action of volatile anesthetics reveals how these anesthetics might produce POCD.

The Classic Theory of Anesthetic Mechanisms

Classical theories of anesthetic action have evolved over the last century. The Meyer-Overton Theory is the oldest concept of inhalational anesthetic action. This theory suggests that lipophilic molecules of anesthetics penetrate axons and inhibit neural transmission.[18] This theory is supported by the concept of partition coefficient, the ratio of the unionized/ionized compound in a solution, which leads to a correlation between anesthesia concentration and potency.[19] As newer medications have been evaluated with the Meyer-Overton Theory, inconsistencies in anesthetic reactions when considered under the tenets of the theory have limited acceptance of the theory today. In particular newer halogenated anesthetics (not commonly used in the United States) violate the proposition of the theory in that immobility or amnesia is not achieved at the predicted coefficient. Nonetheless, the Meyer-Overton Theory is still relevant today given that it is

the theory still used to consider issues of anesthetic potency of volatile anesthetics used currently. This is relevant to POCD because, a careful titration of the volatile anesthetic can reduce the dose needed, which reduces neuronal saturation resulting in lower risk for POCD.

Protein Theory of Anesthetic Mechanisms

Protein theories of anesthesia have been described for many years, and with the use of new investigative instruments, are a major focus of the current study of anesthesia mechanisms. During the induction phase of an anesthetic, tissues are saturated with micromolar anesthetic compounds. Due to the lipophilic nature of volatile anesthetics, there are many hydrophobic protein binding sites available for adherence of anesthetics beyond the neuronal bilayer. Bilayer, or neuronal cell wall proteins control nerve action potentials. Many of these proteins have hydrophobic pockets with water soluble amino acids cores. These hydrophobic pockets, which are typically binding sites for endogenous fatty acids, could be a site of competitive antagonism for micromolar anesthetic compounds.

There are also α-helices in cell membrane proteins that may interact with anesthetics and inhibit protein function. Therefore, there are multiple sites where anesthetic interaction with neuronal proteins could produce wide-spread changes in lipid cell wall relationships, implicating anesthetic action in more sites than just the neuronal bi-layer. The following are just a few of the more convincing areas of volatile anesthetic binding and influence.

A range of technologies, from crude to advanced, have been used to predict and visualize volatile anesthetic interaction with proteins. The principle demonstration of

anesthetic binding with proteins was found using firefly luciferase (the bioluminescent substance from the insect) by Franks and Lieb[20] 30 years ago. More recently, Streiff et al.[21] expanded the firefly study by demonstrating that volatile anesthetics bind to the following other proteins: albumin, apoferritin, and the calcium-calmodulin complex. Of note, the calcium-calmodulin complex is a component of the signaling cascade of G-proteins, integral to autonomic responses throughout the body. Blunting of the autonomic nervous system is a critical component of an anesthetic that can adversely affect cognitive function.

Infrared spectroscopy was utilized by Zou, Liu, and Blasie[22] in 2009 to isolate a binding site for the volatile anesthetic, halothane, in a model of apo-hemoglobin protein. The model demonstrated that halothane has a weak interaction with the backbone peptide core but exerts an impact on the electrostatic environment of the protein. This is another demonstration of binding of volatile anesthetics within membrane protein, but further illustrates the mechanism of action of halothane by demonstrating that the protein charge is changed.

Central Cholinergic Nervous System Proteins

There are several protein type ligand-gated ion channels associated with anesthetic mechanisms. The nicotinic acetylcholine receptors (nAChR) are a broad class of integral excitatory ligand-gated ion channel proteins. Nicotinic receptors are found in various physiologic systems, including the central nervous system. These receptors are responsible for modulation of catecholamine, as well as serotonin, acetylcholine, GABA, and glutamate neurotransmitters. The nicotinic receptor pathophysiological function

implicated in anesthetic mechanism, as well as, the links to neuronal injury are listed below.

GABA, is a subclass of nicotinic wall protein receptor. It is known as the major inhibitory neuroreceptor. GABA receptors respond to neurotransmitters and diminish cell action potentials. Normally GABA activation is a gradual process in which negative membrane potential is maintained to prevent over-excitation. This process involves influx of chloride ions that hyperpolarize cell membranes thus inhibiting function. Induction of GABA the effect, is a widely accepted anesthesia mechanism.

There are multiple subclasses of GABA receptor (Figure 1), but the ligand-gated chloride (Cl) ion channel, $GABA_A$ is closely associated with volatile anesthetics. The GABA receptor has a typical pentameric structure with a central pore. $GABA_A$ receptors contain volatile anesthetic/solvent-accessible space or intrahelical pockets as binding locations within these pores. Volatile anesthetics are believed to modulate the $GABA_A$ receptor by acting directly or indirectly through a second messenger system. Ernst, Bruckner, Boresch, and Sieghart[24] described these intrahelical pockets as binding pockets that can exist in numerous drug-induced conformational states. Volatile anesthetics enhance γ-Aminobutyric acid (GABA) and glutamate inhibition of the central nervous system, establishing a hyperpolarized neuron[23] that produces sedative effects.

Another technology used to improve understanding of the mechanism of anesthesia at the molecular-receptor level is photolabeling. Li et al.[25] utilized photolabeling of a general anesthetic analog of etomidate ([3H] azietomidate), an intravenous anesthesia induction agent, at $GABA_A$ subunits. Photolabeling supported the early theory of GABA action by demonstrating the affinity of an anesthetic compound's for specific amino acids

in a GABA component protein. The photolabeling technique allows for observation of the specific anesthetic binding sites on the GABA methionines amino acids. The binding sites demonstrated were, αM1 transmembrane helix at α1Met-236 and βM3 transmembrane helix at βMet-286 locations.

Providers rarely use etomidate, and halothane is no longer marketed in the US. The more relevant anesthetics, sevoflurane and desflurane, also have GABA binding sites. Specifically, these two volatile anesthetics share the position of the GABA receptor Ser270 of the α1 and α2 subunits, but not the transmembrane 2 of the β2 subunit.[26] In addition to binding at the GABA receptor and influencing neuronal membrane potential, inhibition of exocytosis of neurotransmitter production occurs.[27] Suppression of neurotransmitter release is another mechanism of volatile anesthetic action at the $GABA_A$ subunits. Amyloid β is thought to weaken GABAA receptors and produces similar synaptic inhibition in the AD pathway.[28] Downregulation and weakened synaptic inhibition are plausible pathways in the mechanism of anesthesia and POCD.

$5\text{-}HT_3$, or serotonin receptors, are another type of ligand-gated ion channel that belong to the same family as nAChR. These receptors are found in the peripheral and central nervous systems. Binding of serotonin opens the channel allowing flux of sodium, potassium, and calcium ions, typically producing excitatory effects. Interestingly, the electrostatic mechanism of anesthetic binding to receptor sites determines if there is an excitatory or inhibitory response, demonstrating a mechanism of anesthetic manipulation of a receptor[18]. Acrolein, a lipid peroxidation product that is elevated in the AD brain and is toxic to neurons. The volatile anesthetic sevoflurane has been shown to sequester

a substance acrolein. Thin sequestration may lead to further production of toxic species that led to neuronal vulnerability[40].

Additional Protein Types

Another type of protein channel is the *N*-methyl *D*-asparate (NMDA) receptor. NMDA receptors are ligand-gated, voltage-dependent integral proteins. In contrast to GABA receptors, NMDA receptors produce excitatory actions and potentate depolarization. Dickinson et al.[19] utilized molecular modeling to demonstrate that the volatile anesthetic, isoflurane, competitively inhibits glycine at the NMDA glycine receptor. Manipulation of NMDA through drugs like memantine, have long been utilized in an attempt to slow the progression of AD. The association between NMDA and volatile anesthetics and POCD is still unclear here.

Another, lesser known, possible mechanism of anesthetic action is binding to the potassium channel subfamily of K member 2 proteins (2PK). 2PK channels, including the TREK1 and TASK subfamily of channels, are dual-pores that are present in every part of the central nervous system. These channels remain open to "leak" potassium passively, in order to maintain membrane potentials. These channels can be intrinsically dilated by arachidonic acid, lysophospholipids, and polyunsaturated fatty acids. Greater potassium leak stabilizes cells at hyperpolarized voltages, inhibiting neuronal firing.

Patel et al.[20] studied the anesthetic influence of the volatile anesthetics halothane and isoflurane, as well as, other volatile anesthetics on the neuronal tissue of the *Lymnea stagnalis* mollusk. The study reflected increased channel permeability by halothane and isoflurane via TREK-1 and TASK channel widening. The significance of volatile anesthetic action at these channels was supported by experiments by Heurteaux et al.[21].

Heurteaux[21] utilized mice with a "knock-out", or genetically eliminated, TREK-1 receptors. The mice demonstrated resistance to the volatile anesthetics chloroform, halothane, sevoflurane, isoflurane, and desflurane as evidenced by longer induction times and higher concentrations required to inhibit the righting reflex. TREK-1 receptors are highly expressed in the hippocampal region of the brain, a region known to be associated with memory impairment after exposure to volatile anesthetics.[41]

Discussion

The volume and significance of research provides many mechanisms that may be responsible for the effects of volatile anesthetics. The mechanisms described above are not a comprehensive list, but rather those with the most plausible physiology. Each of the different mechanisms of action listed above is individually or collectively relevant. The classic theories of anesthetic mechanism, including Meyer-Overton and Critical Volume Hypothesis, are also still relevant due to their practical application within clinical practice. With this improved understanding of current concepts in anesthesia mechanism, the relationships between volatile anesthetics and POCD have been elucidated.

The old and elderly, those >60 years and >75, are the greatest consumers of health care[34]. Individuals over age 65 account for 12% of the population, but undergo 40% of surgical procedures[35]. The old and the elderly, are more sensitive to anesthetics. The differences in pharmacokinetic and pharmacodynamic response are largely attributed to the aging of multiple organ systems. Physiologic changes result in a net reduction in anesthetic requirement, as well as increased duration of clinical effects. Minimum alveolar concentration (MAC) is the concentration of an anesthetic where 50% of patients do not respond to a painful stimulus. This concentration is used as a means to compare

volatile anesthetic potency by age. With each increase in decade of life, the MAC of an anesthetic decreases 6.7%. The old and elderly are also more likely to express, through neurocognitive deterioration, neuronal damage from volatile anesthetics. Moller et al.[28] determined advanced age was associated with long term POCD.

In 2008, 16 researchers published a consensus statement regarding anesthesia and Alzheimer's disease[36]. An eight-point summary included evidence from landmark and recent studies suggested an ominous relationship between anesthesia and Alzheimer's disease. These points reviewed the links between volatile anesthetics and the neuropathologic sequelae. Finally, the group concluded with the importance of anesthetics outweighing the potential toxic effects and the critical need to continue studies into this relationship.

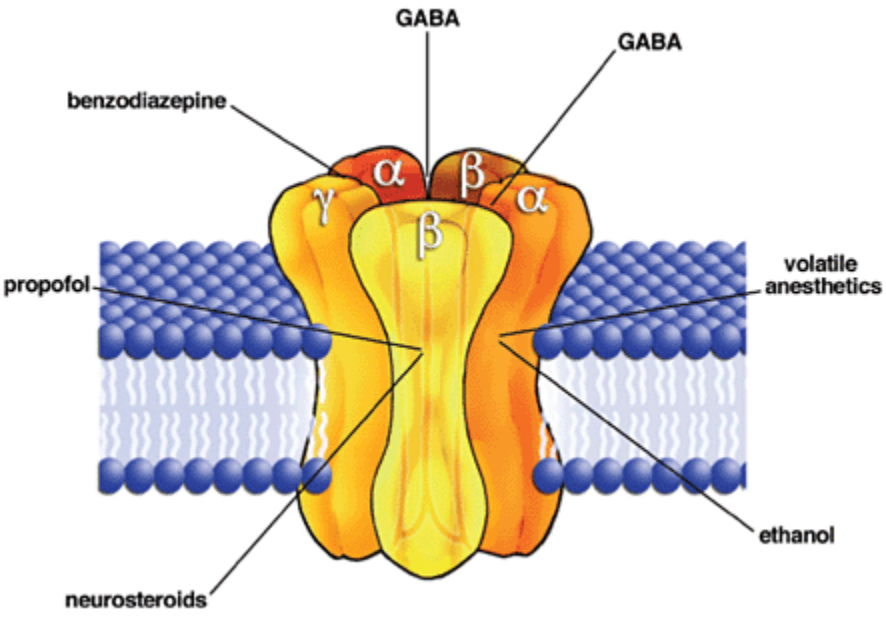
There is concern regarding inconsistencies in reliability and validity in this subject. The anesthetic models and MCI-AD studies have occurred mostly *in vitro* or in rat models at best. Studies in humans have been limited to protein biomarkers (cerebrospinal fluid), imaging, and neurocognitive testing[37]. The associated evidence of anesthesia neurological protein changes have occurred in tests tailored after similar AD studies, not those specifically developed for POCD. Also, there are questions regarding the relevance of neuronal damage and the degree of neurocognitive decline.

Understanding the mechanism of volatile anesthetics is not essential to the practice of anesthesia. This has been demonstrated over the past 100 years. Evolving understanding of mild cognitive impairment-Alzheimer's disease and postoperative cognitive dysfunction makes anesthetic practice by *ex juvantibus* tenuous. Questions of

best practice, anesthetic selection, and even surgical modality all are increasingly relevant as POCD is better understood.

Still, there anesthetics induce apoptosis and/or β-amyloid aggregation, neuronal derangements. Anesthesia is definitely not benign. As more definitive models of anesthetic mechanism and MCI-AD pathways are studied, techniques to limit or avoid neurotoxic anesthetic exposure can be tested and evaluated in hopes of reducing negative anesthetic outcomes.

Figure 2.1.GABAA Receptor



Source: http://neurocycletherapeutics.com/science/gabaa-receptor/

CHAPTER THREE

A Randomized Controlled Trial of Anesthesia Guided By BIS vs. Standard Care and Effects on Cognition

Introduction

Postoperative cognitive dysfunction (POCD) is a subtle deterioration of cognitive function observed after exposure to inhalation anesthetics. In POCD, deficits in advanced cognitive functions and memory continue after appropriate anesthetic drug half-lives have expired, and may last from days to years.[9] The incidence of POCD ranges from 10-50% depending on definitions, study designs, sample sizes, and neurocognitive measured used.[36] This cognitive decline is associated with increased one-year mortality, as well as morbidity and family/caregiver stress.[37] Socially, these deficits also lead to earlier retirement, and greater reliance on social financial support systems.[38] The cognitive domains thought to be most affected are attention, cognitive speed, executive function and memory.[39] It is estimated that over 51 million individuals will undergo a procedure necessitating anesthesia annually, thus exposing a large segment of the population to potential POCD.[1]

Inhalation anesthetics have neuropathogenic effects similar to the changes seen in senile dementias, including Alzheimer's disease. Based on these known properties of inhalation anesthetics, our overall hypothesis is that anesthetic techniques with greater cumulative deep hypnotic time result in a greater degree of POCD. It is possible to decrease cumulative deep hypnotic time by using derived electroencephalographic (EEG) monitoring to titrate volatile anesthetics. One of the major modalities for delivering EEG-guided anesthesia is the Bispectral index™ system (BIS) (Covidien®). Using this system, cumulative deep hypnotic time can be reduced or eliminated without negatively affecting

patient physiologic stress or the surgical conditions. Derived EEG guided anesthesia has been demonstrated to improve recovery,[40] reduce anesthetic consumption,[41] and reduced delirium and confusion post-operatively.[31]

Despite the apparent benefits of BIS-guided anesthesia this technique is rarely used in practice. Reasons that this approach has not been adopted widely include misconceptions that BIS-guided anesthesia is used only to prevent surgical awareness of patients, beliefs that enhanced vigilance is required, lack of awareness by anesthesia providers about the effectiveness of such techniques, and the limited research testing this technique in randomized, controlled trials.

In order to provide rigorous data on the neurocognitive outcomes associated with BIS-guided anesthesia, we conducted a randomized controlled trial of BIS-guided anesthesia versus standard anesthesia using concentration-guided techniques. We used BIS in a tight reference range to avoid deep anesthesia (i.e., BIS <40) by maintaining a BIS range of 45-60. In addition, we used a state-of-the-art, highly sensitive neurocognitive testing system that is easy for patients of all ages to use in order to obtain valid and reproducible outcomes.

The specific aims of this study were:

Specific Aim 1. To compare neurocognitive scores 3-5 days and 3-5 months post-operatively between individuals undergoing anesthetic for surgery lasting greater than 2 hours who were randomized to BIS guided anesthesia (group 1) or standard anesthesia care (group 2),

Specific Aim 2. To compare neurocognitive scores among group 1 (BIS guided depth), group 2 (standard anesthesia care) and a third, non-randomized, normative group

(group 3) of individuals who did not have surgery or anesthesia, and who were age- and sex-matched to the surgical groups.

Methods

Design. This study was a prospective, randomized controlled trial. Parallel study groups underwent anesthesia for select surgeries and completed the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment (CANTAB-MCI®) at three intervals. The standard treatment group underwent anesthesia with inhalation anesthetics titrated around minimum alveolar concentration (MAC) values. Patients in the intervention group were titrated to BIS values 45-60, but not less than 0.5 age adjusted MAC as measured by the Drager Apollo version 4.1. The CANTAB-MCI® was used to measure cognitive function and was done preoperatively, at 3-5 days postoperatively, and at 3-5 months post-operatively. The sample included 86 individuals, 45 surgical patients randomized to intervention and 43 to standard treatment. An additional 37 age- and sex-matched individuals not undergoing surgery nor anesthesia were followed with neurocognitive testing at similar intervals to serve as a normative group.

Sample and Setting. Patients aged 45-70 years undergoing general anesthesia for an elective surgical procedures scheduled to last approximately 2 hours at an academic medical center, who met selection criteria and agreed to participate were eligible for enrollment. After baseline data collection, patients were randomized to receive general anesthesia with either BIS guided titration or standard clinical practice. Computer randomization was utilized for randomization. The normative group was recruited from the community and a large group of them were the spouses of the participants.

Inclusion criteria. Inclusion criteria for patient participants was assessment as American Society of Anesthesiologist (ASA) class I-IV patients. These patients were selected from scheduled surgeries requiring general endotracheal anesthesia with neuromuscular paralytic. Individuals for the normative group were included if they were age 45-70, had not undergone surgery in the past 6 months, and had no surgery planned. Only participants (patients and non-patients) successfully completing the Motor Screening (MOT) test from the CANTAB-MCI® were invited to participate in the study.

Exclusion criteria. We excluded individuals with significant cardiorespiratory or other end-organ disease (i.e., unstable angina, uncontrolled diabetes, severe peripheral vascular disease), inadequate English language skills, and/or substance abuse. We also excluded individuals with pre-existing neurological conditions (i.e., stroke, pre-existing cognitive dysfunction, and neuro-motor disabilities) and neurosurgical candidates.

Recruitment. Patients were referred to the study by physicians and/or nurse practitioners working in the Preoperative Clinic and surgeons in the medical center. Study staff recruited individuals fitting inclusion/exclusion criteria after completing preoperative interview screening.

Intervention. Anesthetic technique for both surgical groups included standard induction with available agents, neuromuscular paralysis guided by nerve stimulator, inhalation anesthetic, and intraoperative monitoring in accordance with the Department of Anesthesiology and ASA guidelines. Invasive monitoring, including arterial pressure, and central venous pressure was performed at the discretion of the anesthesia provider.

BIS monitors were applied to both groups. The anesthesia provider in the standard practice group was blinded to the BIS value via study blind. Titration and administration

were performed according to standard clinical practice judgment and optimal patient recovery in the standard treatment group. In the BIS group, the anesthesia provider titrated the volatile anesthetic to maintain a BIS index range 45-60, but not less than 0.5 age adjusted MAC.

Select physicians and nurse anesthetists performed anesthesia, grouped by treatment and control. These individuals volunteered and underwent a well-defined training period and used well-defined anesthetic plans. Data were collected from the anesthetic record after each case. Intra-operatively, anesthesia clinicians aborted the study protocol as they deemed necessary for participant stability and safety.

Measures

Demographic data. Information including the following variables were collected by patient interview questionnaire: Age, sex, race/ethnicity, marital status and whether patient lives alone, education level, and annual income.

Clinical data. American Society of Anesthesia physical status classification, previous anesthetics, current prescriptive medication regimen, physical exam, and comorbidities were obtained from the anesthetic record. All drugs utilized during the procedure were recorded on the anesthesia record and then transferred to a database for analysis. In particular, inhalation anesthetic type as well as mean, median, and mode inspired and expired concentrations were recorded. Mean, median, and mode BIS scores were also collected from the anesthesia record. Total intraoperative anesthetic time was recorded. Perioperative narcotic exposure was discriminated by narcotic type and dose.

Neurocognitive testing. Neurocognitive testing is an evaluation of a patient's cognitive status by specific domain. Cognitive domains include attention/vigilance,

reasoning and problem solving, verbal learning and memory, visual learning and memory, language and verbal comprehension, working memory, speed of processing, general intellectual functioning, automaticity and procedural learning, psychomotricity, and perceptual processing. The CANTAB-MCI® system was used to measure cognitive function, and is a computerized, touch screen based group of 5 tests.

The CANTAB-MCI® battery includes the Motor Control Task (MOT), Delayed Matching to Sample (DMS), Rapid Visual Information Processing (RVP), Paired Associates Learning (PAL), and Reaction Time (RTI). Tests are scored by number of correct responses and/or time to complete task as appropriate. Test/re-test reliability of versions of CANTAB-MCI® test have been reviewed favorably in previous studies of postoperative cognitive dysfunction and validity of the method has been established.[42]

The MOT (2 minutes) is a simple introduction to the touch screen for the participant. This task also functions as a screening test for visual, movement and comprehension difficulties. Each participant successfully completed this task prior to enrollment in the study, and again successfully completed the task before each subsequent testing session.

The DMS (10 minutes) assesses cognition in the memory domain for non-verbalizable patterns, testing both simultaneous and short term visual memory domains. These non-verbalizable patterns are shown, and after a brief delay, one of four patterns are matched to the original. This test assesses latency or the participant's speed of response/speed of processing domains. We used the outcome measure, 'DMS percent correct'. This outcome measure reports the total number (as a percentage), of correct selections made on the participant's first response (higher score is better).

The RVP (7 minutes) tests sustained attention by assessing the participant's ability to recall a sequence of digits when given different combinations of digits. The RVP is sensitive for the visual sustained attention domain. We used two outcome measures to reflect this domain, 'RVP A' ' and 'RVP median latency'. The RVP A' (this denotes RVP A prime) measures the sensitivity to the target, regardless of response tendency (scored 0.00 to 1.0; bad to good), or how good the participant is at detecting target sequences. The RVP median latency is measured in milliseconds, and shorter is better.

The PAL (10 minutes) assesses the short term/visual memory domain. The PAL is useful for assessing individuals with questionable dementia, MCI, Alzheimer's disease, and age-related memory loss. Patients are asked to associate visual patterns that cannot be verbalized with spatial locations on the computer screen. We used two outcome measures to reflect this domain, 'PAL total errors 6 shapes adjusted' and 'PAL total errors adjusted'. The 'PAL total errors adjusted' measures the total number of errors across all assessed problems and all stages with adjustment for each stage not attempted due to previous stage failures. The lower the score the better. The 'PAL total errors 6 shapes adjusted' is a measure in an advanced stage of the test and can discriminate subtle decrements in cognition in high functioning individuals. The lower the score the better.

The final domain test is the RTI (5 minutes). The RTI test is a speed of processing/latency domain task with a comparative history (the five choice task) and uses a procedure to separate response latency from movement time. This allows for control for participants with tremor. This test involves the use of a press pad controlled by the participant's dominate index finger

The ‘RTI mean simple reaction time’ measures the speed at which the participant releases the press pad button in response to a stimulus from a single location. This test is the mean of the measure reflecting cognitive recognition, lower scores reflecting better performance. ‘RTI median simple reaction time’ measures the same speed of press pad button response. The test reflects the median of the measure of cognitive recognition and is sensitive for slowing, with lower scores reflecting better performance. ‘RTI median simple movement time’ is the median time, measured in milliseconds, taken to touch the stimulus after the press pad has been released in response to a single stimuli. This is a measurement of the motor speed and is sensitive for slowing. The lower the score, the better. ‘RTI median five choice movement’ is the median of the measurement of speed with which the press pad button is released in response to a stimulus in any of five locations. Lower score is better.

Protocol. The study proceeded after approval from the appropriate university Institutional Review Board, and after informed consent was received. Informed consent was obtained by Collaborative Institutional Training Initiative (CITI) trained study staff from all patients and non-surgical participants fitting inclusion criteria who agreed to participate. All research records were secured on computers with university encryption systems. After successful completion of the screening Motor Control Task (MOT), a full consent was completed when the patient agreed to participate.

The CANTAB-MCI® battery was administered upon attaining consent (baseline, test time 1). A version of the battery was administered on post-anesthetic day 3-5 (test time 2), in the patients’ hospital room, service’s clinic, or location convenient to the patient. Three to five days is an appropriate time period that would ensure drug half-lives

have expired. The battery was again re-administered at 3-5 months (test time 3) at a location convenient to the patient.

Data Analysis. Data analysis included a descriptive summary, including means and standard deviations or frequency distributions, as appropriate. Comparisons of the groups at baseline was done using two-sample t-tests, chi-square tests of association or ANOVA.

To address each of the two Specific Aims, two-way mixed (i.e., one within subjects variable [time] and one between subjects variable [group]) repeated measures analysis of variance (ANOVA) was used. Each of the assumptions of repeated measures ANOVA (no significant outliers, the dependent variable is approximately normally distributed for each level of the independent variable, homogeneity of variances and covariances, and sphericity) were tested. The only violations across the various dependent measures were violations of the sphericity or homogeneity of variances assumptions. Both violations were managed using the appropriate p value correction. For example, when the sphericity assumption was violated, the p value was determined using the Greenhouse-Geiser correction.

When a significant group by time interaction was found, appropriate post-hoc pair-wise and group-wise testing was done. Data analysis was conducted using SPSS, version 22; an alpha level of < 0.05 used throughout.

Power considerations. With an alpha level of 0.05 and 34 individuals in each groups by the final assessment, the power of the repeated measures ANOVA F test to detect a significant main effect or interaction was at least 80%, assuming that the ratio of group means to the standard deviation of the observations within the populations was at least 0.25. Cohen[43] considers this a medium effect size. This power analysis was

conservative because the methodology used to estimate the repeated measures models is robust with respect to missing data, as long as they are missing at random. The power estimates are expected to slightly underestimate the actual power, because we increased the sample size to allow for attrition with the goal of having at least 34 per group complete the study. Power analysis was conducted using nQuery Advisor, v. 6.02.

Results

Flow of participants through the study. We screened patients from October 2014 through June 2015 with the last follow-up completed in September 2015. Of the 329 patients eligible for enrollment, 143 did not meet eligibility criteria and 98 chose not to participate (Figure 1). Of the 88 patients scheduled for surgery who were enrolled, 45 were randomized to the intervention limb of the protocol and 43 were randomized to the control protocol. Of the 45 patients allocated to the intervention limb, 2 (4.46%) were lost to follow-up prior to the anesthetic. In the control limb, 1 (2.3%) was lost prior to the anesthetic. Two patients from the intervention (4.46%) and control (4.6%) protocol limbs were lost to follow up prior to their cognitive testing session 2. Two (4.46%) more patients were lost to follow up prior to testing session 3 in the intervention limb of the protocol. There was no difference in rate of withdrawal from the two surgical groups ($p=0.33$). Patients who withdrew from the study were not significantly different than patients who remained in the study on any of the demographic or clinical characteristics measured at baseline including testing time 1 CANTAB-MCI® scores.

In addition we used purposive sampling to enroll an age matched healthy control sample. Seventy-two individuals were approached, with 10 not meeting inclusion criteria and 25 refusing participation. Thirty-seven individuals were enrolled with one lost to

follow up prior to testing time 2. This 36 participant group was age- and gender-matched to the surgical patient groups.

Sample Characteristics. Of the 79 surgical patients available for analysis of cognitive outcomes at the last follow-up point (90% of the enrolled sample), the mean age was 59.1 ± 6.7 years of age, the majority were female (64.3%) and married/cohabitating 83 (72.2%). Seventy-seven percent had combined household incomes of less than $75,000 per year. The most common ASA classification was ASA II (46.8%), while 36.5% were classified as ASA III, and the remainder ASA I. The highest level of education attained was high school graduation/equivalent in 68.7%. Demographic and clinical characteristics of patients by total sample and group assignment are summarized in Table 1. There were no significant differences among the groups on any demographic or clinical characteristic.

Anesthetic Vapor. Demonstrating the expected difference between the intervention group and the control, standard anesthesia techniques group, there were significant differences in mean concentration of inspired and expired anesthesia vapors between the groups summarized in Table 2. Specifically, the mean inspired and expired concentrations of anesthesia vapor were lower in the EEG guided group. Also demonstrating the expected difference between the groups, the BIS value was significantly higher in the treatment versus the control group (48.0 ± 4.6 vs 41.5 ± 6.9, $p < 0.001$).

With regard to safety of the intervention, there were no adverse effects seen in either group intra-operatively. Satisfactory anesthesia was provided for every patient in both groups. There were no instances of operative recall in either group at 3-5 days or 3-5

months post-operatively, even in the intervention group with age-adjusted MAC levels as low as 0.5.

Effect of EEG guided Therapy vs. Standard Anesthesia

Specific Aim 1.

The impact of the intervention on cognitive function was measured in four cognitive domains: memory (DMS percent correct), attention (RVP A' and RVP median latency), visual memory (PAL total errors 6 shapes adjusted and PAL total errors adjusted), and speed of processing (RTI mean and median simple reaction times, RTI median simple movement time, and RTI median 5 choice movement).

Memory (non-verbalizable/patterns). Using repeated measures ANOVA, there was neither a group by time interaction or a time main effect for the outcome 'DMS Percent Correct' (Table 3, Figure 2).

Attention (visual sustained). Using repeated measures ANOVA, for both indicators of this domain 'RVP A' ' ($p=0.58$) and 'RVP median latency' ($p=0.55$) there was no group by time interaction (Table 3, Figures 3 and 4). There was however, a main effect of time for both indictors ($p=<0.001$ and $p=0.003$ respectively).

Short term/visual memory domain. Using repeated measures ANOVA, we demonstrated significant group by time interactions in the multivariate overall test for both indicators, 'PAL total errors 6 shapes adjusted' ($p=0.02$) and 'PAL total errors adjusted' ($p=0.02$), of this domain (Table 3, Figures 5 and 6).

Post-hoc testing to determine at which time points the groups differed revealed that with regard to the 'PAL total errors 6 shapes adjusted' (Figure 5), the scores between the two groups were similar at baseline ($p=0.75$), but the trajectory across time diverged at

time two (p=0.019) in that the intervention group had better scores (lower) than the standard care/control group. At time three, there were again no differences between groups (p=0.32).

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, there was a significant improvement in scores between time 1 to 2 (p=0.016), and time 1 to 3 (p=0.001), but not between time 2 and 3 (p=0.517). In the control/standard care group there was not a difference between time 1 and 2 (p=0.196), but there was a significant improvement between time 2 to 3 (p=0.01) and 1 to 3 (p=0.035).

In regard to 'PAL total errors adjusted' (Figure 6), the trajectories seen mirror those for 'PAL total errors 6 shapes adjusted'. Post-hoc testing to determine at which time points the groups differed revealed that in regard to the 'PAL total errors adjusted' (Figure 2), the scores between the two groups were similar at baseline (p=0.76), and at time 2 (p=0.21). At time 3 the groups diverged (p=0.01) with the intervention group having better scores (lower) than the standard care/control group.

Post-hoc testing to determine where changes lie across time in each group revealed that in the intervention group, there was a significant improvement in scores between time 1 to 2 (p=0.01), and time 2 to 3 (p=0.07), but not between time 1 and 3 (p=0.38). In the control/standard care group there was a worsening of scores between time 1 and 2 (p=0.02), and an improvement from time 2 to 3 (<0.001), and from time 1 to 3 (p=0.01).

*Speed of processing/latency***.** The indicator 'RTI mean simple reaction time' demonstrated a significant group by time interaction (p=0.03). None of the other indicators were found to have significant group by time interactions (Table 3, Figure 7).

Regarding these three, ‘RTI median simple reaction time’ (p=0.07), ‘RTI median simple movement time’ (p=0.15), and ‘RTI median five choice movement time’ (p=0.06), there was no group by time interactions (Table 3, Figures 8, 9, and 10). There was a main effect of time for all (p=<0.001, p<0.001, p=0.001, and p=<0.001, respectively). Specifically, for both groups cognitive function worsened at time point two and returned to baseline by time three.

Post-hoc testing to determine at which time points the groups differed revealed that in regard to the ‘RTI mean simple reaction time’ (Figure 7), the scores between the two groups were similar at baseline (p=0.92), but the trajectory across time diverged at time two (p=0.04) in that the intervention group had better scores (lower) than the standard care/control group. At time three, there were again no differences between groups (p=0.4).

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, there was a significant slowing of cognition in scores between time 1 to 2 (p=0.02), but not between time 2 and 3 (p=0.11), or time 1 to 3 (p=0.56). In the control/standard care group there was a similar slowing between time 1 and 2 (p=<0.001), and also from time 2 to 3 (p=<0.001), but there was no difference between time 1 to 3 (p=0.7).

Comparison of neurocognitive scores among group 1 (EEG guided), group 2 (standard anesthesia care) and group 3 (no anesthesia/surgery).

Specific Aim 2.

Memory (non-verbalizable/patterns). Using repeated measures ANOVA, there was neither a group by time interaction nor a main effect for the outcome 'DMS Percent Correct' (P=0.3 and 0.5 respectively). (Table 4, Figure 11).

*Attention (visual sustained).*Using repeated measures ANOVA, for the indicator of this domain 'RVP A' ' (p=0.03) (Table 4, Figure 12) there was a group by time interaction, but not for 'RVP median latency' (p=0.1) (Table 4, Figure 13). There was however, a main effect of time for both indictors (p=<0.001 and p=0.007 respectively).

Post-hoc testing to determine at which time points the groups differed revealed that in regard to the 'RVP A' ' (Figure 12) there were group differences in the scores at baseline between intervention and normative (p=0.03), control/standard care and normative (p=0.004), but no difference between intervention and control (p=0.46), but at time three, there were no differences between groups (p=0.21). Time two group differences were similar in that intervention to normative groups (p=0.001) and control/standard care to normative (p=<0.001). Again, there was no significant differences between intervention to control/standard care at time two (0.4). Finally, there were no significant group differences at time three. Intervention to normative (p=0.2), control/standard care to normative (p=0.1), and intervention to control/standard care (p=1) all did not find significance.

Post-hoc testing to determine where changes lie across time within each group, revealed that in the intervention group, there was significance between time 2 to 3

(p=<0.001), but not time 1 to 2 (p=0.13), or between time 1 and 3 (p=0.07). In the control/standard care group there was not a difference between time 1 and 2 (p=0.15), but there was a significant improvement between time 2 to 3 (p=0.001) and 1 to 3 (p=0.007). In the normative group, there was not a significant difference over time (p=0.342)

Short term/visual memory domain. Using repeated measures ANOVA, we demonstrated significant group by time interactions in the multivariate overall test in both indicators 'PAL total errors 6 shapes adjusted' (p=<0.001) and 'PAL total errors adjusted' (p=0.005), of this domain (Table 4, Figure 14 and 15). There were also main effect of time for both 'PAL total errors 6 shapes adjusted' (p=<0.001) and 'PAL total errors adjusted' (p=0.005) (Table 4).

Post-hoc testing to determine at which time points the groups differed revealed that in regard to the 'PAL total errors 6 shapes adjusted' (Figure 14), there was not a significant difference amongst groups at base line. These values were intervention to normative (p=0.4), control/standard care to normative (p=0.6), and intervention to control/standard care (p=0.7). At time two the trajectory of the control/standard care group diverged from both the intervention group (p=0.01) and the normative group (p=<0.001). At time three there were no differences between groups, intervention to normative (p=0.3), control to normative (p=0.9), and intervention to control (p=0.4).

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, between time 1 to 2 (p=0.016), and time 1 to 3 (p=0.001), but not between time 2 and 3 (p=0.5). In the control/standard care group there was not a difference between time 1 and 2 (p=0.2), but there was a significant improvement between time 2 to 3 (p=0.01) and 1 to 3 (p=0.04). The normative group demonstrated

significant differences between time 1 and 2 (p=<0.001) and time 1 and 2 (p=0.001), but not time 1 and 3 (p=0.2).

In regard to 'PAL total errors adjusted' (Figure 15), the trajectories seen mirror those seen for 'PAL total errors 6 shapes adjusted'. Post-hoc testing to determine at which time points the groups differed revealed that in regard to the 'PAL total errors adjusted' there was no difference among the groups at time one. Intervention compared to control (p=0.7), intervention to normative (p=0.5) and control to normative (p=0.3) all were not significant. The scores at time two demonstrated difference between the intervention to control (p=0.004) and control to normative (p=<0.001), but not between the Intervention to normative (p=0.3). At time three the groups again were not significant with the Intervention group to control (p=0.2), the Intervention to normative (p=0.7) and control group to normative (p=0.4).

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, there was a significant improvement in scores between time 1 to 2 (p=0.01), but not time 2 to 3 (p=0.07), or between time 1 and 3 (p=0.4). In the control/standard care group there was a worsening of scores between time 1 and 2 (p=0.02), and an improvement from time 2 to 3 (<0.001), and from time 1 to 3 (p=0.01).

*Speed of processing/latency***.** Two indicators were found to have significant group by time interactions. 'RTI median simple reaction time' (p=0.005), and 'RTI median five choice movement time' (p=0.005) both had group by time interactions (Table 4, Figures 16 and 17). Two indicators, 'RTI mean simple reaction time' (p=0.1) and 'RTI median simple movement time' (p=0.1), did not have a significant group by time interaction

(Table 4, Figures 18 and 19). There was a significant main effect of time for all of these outcome measures (Table 4).

Post-hoc testing to determine at which time points the groups differed revealed that in regard to the 'RTI median simple reaction time' (Figure 16), the scores between the three groups were similar at baseline in that Intervention to control (p=0.6), Intervention to normative (p=0.7) and control to normative (p=0.4). Time two trajectory of the control group diverged with Intervention to control (p=0.02) and the control to normative (p=<0.001). The Intervention group mirrored the normative scores (0.1). At time three, there were again no differences between groups. The Intervention to control (p=0.6), Intervention to normative (p=0.9), and control to normative (p=0.5) did not demonstrate significance.

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, there was a significant slowing of cognition in scores between time 1 to 2 (p=<0.001), and between time 2 and 3 (p=<0.001), but not between time 1 to 3 (p=0.8). In the control/standard care group similarly slowing between time 1 and 2 (p=<0.001), and also from time 2 to 3 (p=<0.001), but there was no difference between time 1 to 3 (p=0.7). The normative group performed similarly, with scores from time 1 to 2 (p=0.2) and 2 to 3 (p=0.05) significant. Scores at time 1 to 3 were not significant (p=0.8).

In regard to the outcome measure 'RTI median five choice movement time', post-hoc testing to determine at which time points the groups differed revealed (Figure 17), the scores between the three groups were similar at baseline in that Intervention to control (p=0.3), Intervention to normative (p=0.1) and control to normative (p=0.6). Time two

trajectory of the control group diverged with control to normative (p=0.002). The Intervention to normative (0.2), and Intervention to control (p=0.9) were not significant. At time three, there were again no differences between groups. The Intervention to control (p=0.5), Intervention to normative (p=0.4), and control to normative (p=0.1) did not demonstrate significance.

Post-hoc testing to determine where changes lie across time in each group, revealed that in the intervention group, there was not a significant difference in scores between time 1 to 2 (p=0.5), nor between time 1 and 3 (p=0.07), but there was a significant difference between time 2 to 3 (p=0.001). In the control/standard care group significance between time 1 and 2 (p=0.004), and also from time 2 to 3 (p=<0.001), but there was no difference between time 1 to 3 (p=0.1). There was not a significant change in normative group with scores from time 1 to 2 (p=0.6) and 2 to 3 (p=0.8), and 1 to 3 (p=0.6).

Discussion

Cognitive decline seen in the dementias is associated with increased mortality.[44] Similarly, POCD is associated with higher morbidity and mortality.[4] It is not clear if cognitive decline directly causes this increased mortality or is a peripheral contributor. In concert with these data, our data suggests that early POCD, even when transient, may identify patients who are vulnerable to later morbidity and mortality. If future studies support this association then those individuals with early POCD could be targeted for intervention to reduce later morbidity and mortality. Interventions to reduce the impact of POCD should focus on support, and referral to multidisciplinary providers where defects are found.

We examined the impact of BIS-guided anesthesia on cognitive outcomes using a state-of-the art neurocognitive testing computerized platform and unlike others, we tested specific cognitive domains. We demonstrated significantly lower volatile anesthesia exposure in the intervention (BIS-guided anesthesia) compared to the control group ($p=<0.001$). We demonstrated the safety of the intervention in that there were no adverse events associated with its use. We also demonstrated cognitive decline in the visual memory domain in the control versus BIS-guided anesthesia group in the 3 – 5 day post-surgery period compared to baseline, but not at the 3-5 month period. This reflects that POCD occurs in specific domains but may be time limited, reflecting the findings of some previous studies.[3,4]

Reflecting the main effect of time seen in the regression analyses with both the two surgical groups alone, and the three group analyses, both surgical groups demonstrated postoperative depression in cognitive function in every outcome measure (with the exception of DMS), but in every instance, the standard care group's was more pronounced. These findings indicate there is a higher cognitive obstacle in the memory domains encountered by patients exposed to a higher cumulative dose of volatile anesthetic. The outcome measures 'PAL total errors adjusted' and 'PAL total errors 6 shapes adjusted' were both sensitive to the treatment technique. The PAL component of the CANTAB-MCI battery reflects the greatest impairment, and severity of dysfunction, in MCI and AD[45]. The finding of 'PAL total errors adjusted' is of greatest concern due to a close relationship with amnestic MCI (aMCI)[46]. Hippocampal atrophy and loss of function is a known pattern beginning in MCI and advancing in AD. The recall of objects in space is a process involving the hippocampus directly tested in the PAL.[47] Junkkila

and colleagues found the 'PAL total errors adjusted' variable accounted for the largest difference between aMCI and mild AD.[48] This outcome measure reflects a significant cognitive decline in the visual memory domain. The association of these findings and the known neuropathologic inflammatory sequel of these anesthetics suggest these volatile anesthetics are not benign.

The memory impairments noted in our study with the use of standard anesthesia not guided by EEG have the potential to adversely influence patient discharge. If patients have memory impairments, they will be unable to adequately process and remember important discharge instructions. Even when instructions are written, they are very commonly standard instructions that lack the specificity and detail needed for each individual patient. Patients and family members have substantial difficulty remembering instructions even under ideal situations,[49] and our results suggest that most post-operative patients have enough POCD to impair their ability to retain the information needed for successful discharge and recovery.

Our findings differ from two of the most recent studies investigating use of derived EEG guidance as a means to reduce the incidence of POCD. A large German study led by Radtke failed to find significant difference POCD between derived EEG guidance and standard care at day 7 ($p=0.372$) nor day 90 ($p=0.062$).[32] Our study differs in that we utilized volatile anesthetics exclusively for maintenance, rather than introducing macro-molar anesthetics (propofol), which could be considered a confounder. Other differentiation between the studies was that we utilized the complete CANTAB-MCI battery and examined differences in specific domains that we explicated a priori. Previous investigators who used the CANTAB-MCI reported cognitive function as a

global phenomenon (despite the fact that the CANTAB-MCI has no such measures) failing to take advantage of the precision offered by assessing cognitive function in domains. The CANTAB-MCI battery was designed for sensitivity in MCI, which shares effected domains with POCD. Radtke and colleagues utilized three CANTAB pre-tests of pattern recognition memory (PRM), spatial recognition memory (SRM), and choice reaction time. The PRM and SRM are designed to help prepare for the more robust PAL test. The remainder of their battery consisted of tests administered orally (visual verbal learning test and Stroop color word test). While the number of patients in their study was respectable (n=1155), the differences in methodology could easily account for the different findings.

The CODA trial was the second of the derived EEG guidance studies that have similarities with this study.[30] This study found higher POCD at 3 months (p=0.02) rather than one week (p=0.06), opposite to the findings of our study, and much of the previous literature. Although the findings are similar in that BIS-monitored care demonstrates less POCD, the dramatic difference in early versus late findings could be related to the neurocognitive battery utilized in the CODA trail. In addition, similar to the Radtke study, there were a significant number of patients (n=99, 11%) who received macro-molar anesthetic maintenance (propofol) along with the majority volatile anesthetic group.

As mentioned, this is the first utilization of the complete CANTAB-MCI battery in the study of POCD. The CANTAB-MCI was developed and tested in populations with mild cognitive impairment. Our study demonstrates that the CANTAB-MCI is sensitive enough to detect cognitive changes in the surgical anesthetic population. The study has

demonstrated ease-of-use and no burden for users in the perioperative environment. The BIS-monitor allowed for anesthetic titration to low levels without experiencing an episode of recall.

Limitations

Although this study had the strength of being a randomized, controlled study, it has limitations. The primary limitation was the smaller sample size, which limited our ability to determine any heterogeneity of treatment effect because we could not perform subgroup analyses.

Conclusion

This study is important because it provides important data on patient neurocognitive outcomes that will assist all anesthesia providers to make evidence-based decisions about the optimal anesthetic techniques to promote best patient outcomes. Careful titration, as guided by the BIS-monitor, by experienced anesthetic providers can lead to a measurable improvement in patient outcomes. Taken in concert with previous findings, our results suggest that BIS-guided anesthesia is safe, results in lower total overall volatile anesthetic exposure and fewer disturbances in cognitive function and thus should be considered by more providers as the standard of care.

Table 3.1. Comparison of baseline characteristics among the three study arms (N=115)

Characteristics	Total, N=115	Anesthesia Intervention, n=39	Anesthesia Control, n=40	Healthy Control, n=36	P
	Mean ± SD or n (%)				
Sociodemographics					
Age, years	59.1 ± 6.7	59.6 ± 6.8	58.5 ± 6.4	59.1 ± 6.9	0.76
Female Gender	74 (64.3)	24 (61.5)	26 (65)	24 (67.6)	0.893
Caucasian African-American Other	105 (91.3) 7 (6.1) 3 (2.6)	35 (89.7) 2 (5.1) 2 (5.1)	38 (95) 2 (5) 0	32 (88.9) 3 (8.3) 1 (2.8)	0.640
Education High school or some college College graduate and greater	 79 (68.7) 36 (31.3)	 13 (33.3) 26 (66.7)	 15 (37.5) 25 (62.5)	 9 (25) 27 (75)	0.498
Annual household income <$25,000 $25,001-$75,000 >$75,001	 24 (20.9) 53 (46) 38 (33)	 8 (20.5) 21 (53.8) 10 (25.6)	 13 (32.5) 14 (35) 13 (32.5)	 3 (8.3) 18 (50) 15 (41.7)	0.076
Currently married	83 (72.2)	28 (71.8)	26 (65)	29 (80.6)	0.319
Surgical Characteristics					
Body Mass Index, kg/m^2	32 ± 8.1	31.4 ± 7.6	32.7 ± 8.6		0.489
Premedication None Midazolam Opioid	 29 (36.7) 13 (16.5) 37 (46.9)	 12 (30.8) 4 (10.3) 23 (59)	 17 (42.5) 9 (22.5) 14 (35)		0.084
Anesthesia Time	3:30 ± 0:58	3:27 ± 0:57	3:32 ± 0:59		0.71
ASA physical Status Physical status 2 Physical status 3	 37 (46.8) 42 (36.5)	 19 (48.7) 20 (51.3)	 18 (45) 22 (55)		0.823
Baseline systolic blood pressure	134 ± 15.8	133 ± 17.1	136 ± 14.5		0.387
Surgical procedure					0.394
Open Abdominal	20 (25.3)	9 (23.1)	11 (27.5)		
Laparoscopic/Other	13 (16.5)	9 (23.1)	4 (10)		
Posterior Lateral Interbody Fusion	31 (39.2)	13 (33.3)	18 (45)		
Minimally Invasive Back	15 (19.2)	8 (20.5)	7 (17.5)		

Table 3.2: Mean concentration of inspired and expired vapor, %

	Intervention		Anesthesia-Control		
Anesthetic Vapor	Mean ± SD inspired concentration	Mean ± SD expired concentration	Mean ± SD inspired concentration	Mean ± SD expired concentration	
Sevoflurane[a]	1.78 ± 0.12 €	1.5 ± 0.17 ¥	2.45 ± 0.35 €	2.01 ± 0.19 ¥	
Desflurane[b]	4.54 ± 1.13 €	3.83 ± 0.64 ¥	6.13 ± 0.97 €	5.56 ± 1.93 ¥	
Isoflurane[c]	1.46 ± 0.9 €	1.1 ± 0.81 ¥	1.37 ± 0.35 €	0.9 ± 0.17 ¥	

€ = p value of 0.002 for the interaction of group by inspired vapor; in post-hoc testing using Bonferroni correction, a vs b p value is < 0.001; a vs c p value is 0.491; b vs c p value is < 0.001.

¥ = p value of 0.006 for the interaction of group by expired vapor; in post-hoc testing using Bonferroni correction, a vs b p value is < 0.001; a vs c p value is 0.713; b vs c p value is < 0.001.

Table 3.3: Neurocognitive function between 2 groups across time.

Neurocognitive test and domain		Treatment/BIS Mean ± SD	Anesthesia-Control Mean ± SD	Overall p-value Time main effect Interaction
Memory (non-verbalizable/patterns)				
DMS Percent Correct	Baseline	85.6±10	81.7±11.5	0.17 0.74
	Time 2	83.1±12.6	78.3±16.7	
	Time 3	82.7±12	80.3±13.1	
Memory (short term/visual)				
PAL Total Errors Adjusted	Baseline	39.4±34.4	41.6±32.1	<0.001 0.02¥
	Time 2	34.7±29.6	57.4±43.7	
	Time 3	25.7±21.8	33.2±30.5	
PAL Total Errors 6 Shapes Adjusted	Baseline	12±10.1	11.3±9.6	0.002 0.02¥
	Time 2	7.5±9.9	13.6±12.5	
	Time 3	6.6±5.9	8.3±9.3	
Attention (visual sustained)				
RVP A prime	Baseline	0.88±0.05	0.87±0.06	<0.001 0.58
	Time 2	0.87±0.06	0.85±0.07	
	Time 3	0.89±0.05	0.89±0.06	
RVP Median Latency	Baseline	444.1±114.6	451.8±150.1	0.003 0.55
	Time 2	498.3±179	518.8±218.3	
	Time 3	457.4±150.8	439.5±137.7	
Processing speed/ latency				
RTI Mean Simple Reaction Time	Baseline	347.4±103.7	349.6±92.7	<0.001 0.03¥
	Time 2	390±88.4	438.6±117.7	
	Time 3	362±121.5	343.5±67.5	
RTI Median Simple Reaction Time	Baseline	309.3±54.7	316.4±59.1	<0.001 0.07
	Time 2	355.7±61.6	394±84.4	
	Time 3	312.6±56.1	319±51.4	
RTI Median Simple Movement Time	Baseline	590.9±332.4	522.3±130.8	0.001 0.15
	Time 2	576.3±145.2	615.7±216.4	
	Time 3	494.9±86.9	485.7±97.4	
RTI Median Five Choice Movement	Baseline	545.4±202.9	507.6±118.4	<0.001 0.06
	Time 2	567.7±144.6	640.4±266.5	
	Time 3	486.1±84.7	474.1±94	
Legend. DMS=Delayed Matching to Sample; PAL= Paired Associates Learning; RTI= Reaction Time; RVP=Rapid Visual Information Processing; ¥ = Treatment different from control ($p<0.05$).				

Table 3.4: Neurocognitive function among 3 groups across time

Neurocognitive test and domain		Treatment/BIS Mean ± SD	Anesthesia-Control Mean ± SD	Healthy Control Mean ± SD	Overall p-value Main effect Interaction
Memory (non-verbalizable/patterns)					
DMS Percent Correct	Baseline	85.6±10	81.7±11.5	84.7±10.8	0.5 0.3
	Time 2	83.1±12.6	78.3±16.7	86.5±10.8	
	Time 3	82.7±12	80.3±13.1	87.5±10	
Memory (short term/visual)					
PAL Total Errors Adjusted	Baseline	39.4±34.4	41.6±32.1	34.1±30	<0.001 <0.001£
	Time 2	34.7±29.6	57.4±43.7	25.6±27.1	
	Time 3	25.7±21.8	33.2±30.5	28±32.6	
PAL Total Errors 6 Shapes Adjusted	Baseline	12±10.1	11.3±9.6	10.1±9.2	<0.001 0.001
	Time 2	7.5±9.9	13.6±12.5	4.6±7.6	
	Time 3	6.6±5.9	8.3±9.3	8.4±9.6	
Attention (visual sustained)					
RVP A prime	Baseline	0.88±0.05	0.87±0.06	0.91±0.04	<0.001 0.03€£
	Time 2	0.87±0.06	0.85±0.07	0.91±0.04	
	Time 3	0.89±0.05	0.89±0.06	0.91±0.06	
RVP Median Latency	Baseline	444.1±114.6	451.8±150.1	412.9±84.7	0.007 0.1
	Time 2	498.3±179	518.8±218.3	406.8±69	
	Time 3	457.4±150.8	439.5±137.7	405.1±70.8	
Processing speed/ latency					
RTI Mean Simple Reaction Time	Baseline	347.4±103.7	347±92.5	327.9±71.3	<0.001 0.1£
	Time 2	390±88.4	435.9±118	369.3±118.8	
	Time 3	362±121.5	343.1±68.3	332.1±56.2	
RTI Median Simple Reaction Time	Baseline	309.3±54.7	316.6±59.8	304±60	<0.001 0.005£
	Time 2	355.7±61.6	391.5±84	331.1±56.2	
	Time 3	312.6±56.1	319.3±51.8	310.3±44.6	
RTI Median Simple Movement Time	Baseline	590.9±332.4	523.5±132.3	519±220.3	0.003 0.1
	Time 2	576.3±145.2	617.5±218.9	510.8±105.6	
	Time 3	494.9±86.9	486.4±98.5	494.9±76.8	
RTI Median Five Choice Movement	Baseline	546.8±205.4	508.3±120	488±180.7	<0.001 0.005
	Time 2	569.5±146.1	642.7±269.6	507.4±94.8	
	Time 3	487.1±84.7	474±95.2	503.3±77.4	

Legend. DMS=Delayed Matching to Sample; PAL= Paired Associates Learning; RTI= Reaction Time; RVP=Rapid Visual Information Processing; ¥ = Treatment different from control ($p<0.05$); £ = Control different from normative ($p<0.05$); €=Treatment different from normative (p,0.05).

Figure 3.1: CONSORT Diagram Patient Flow Through Study.

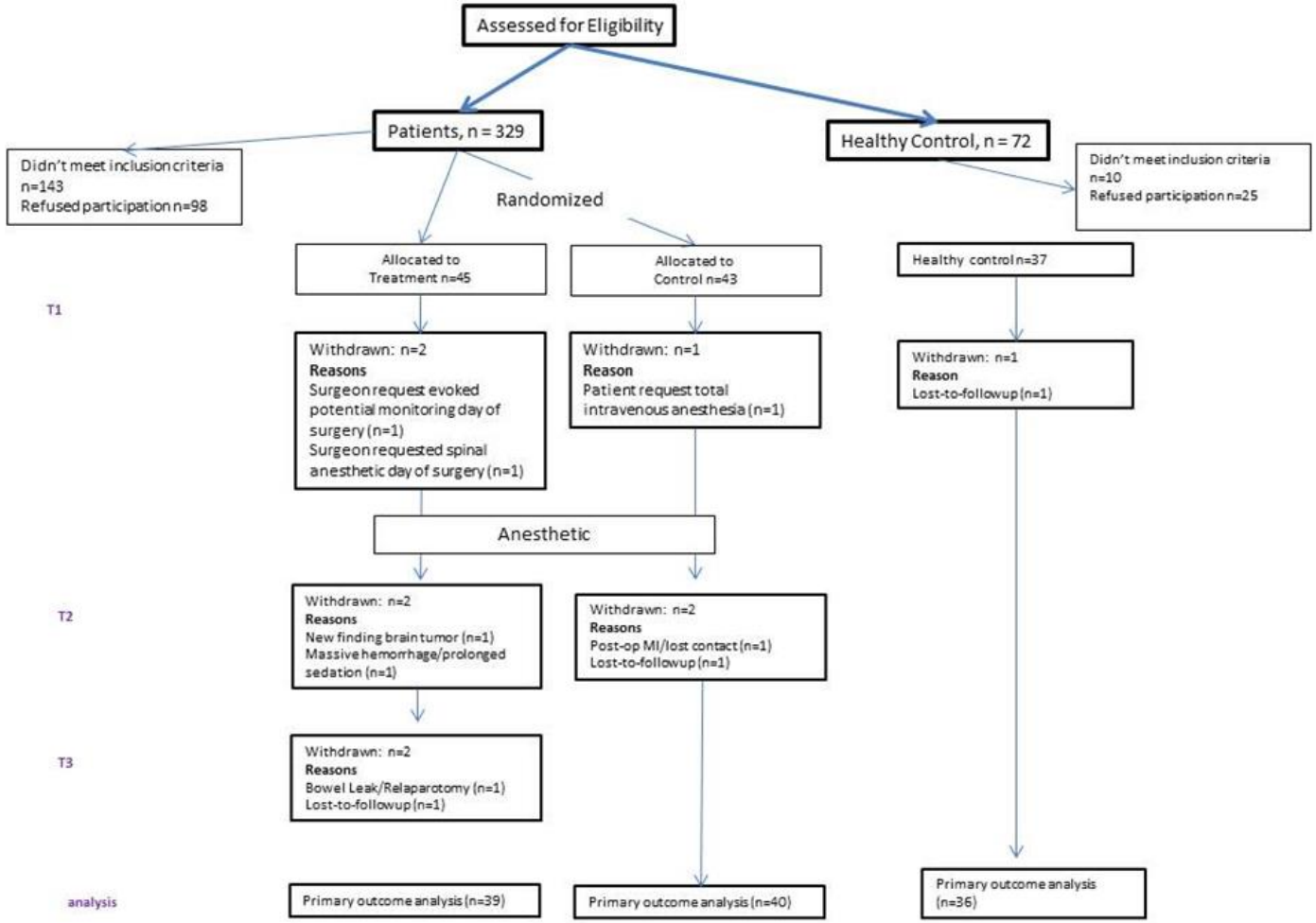
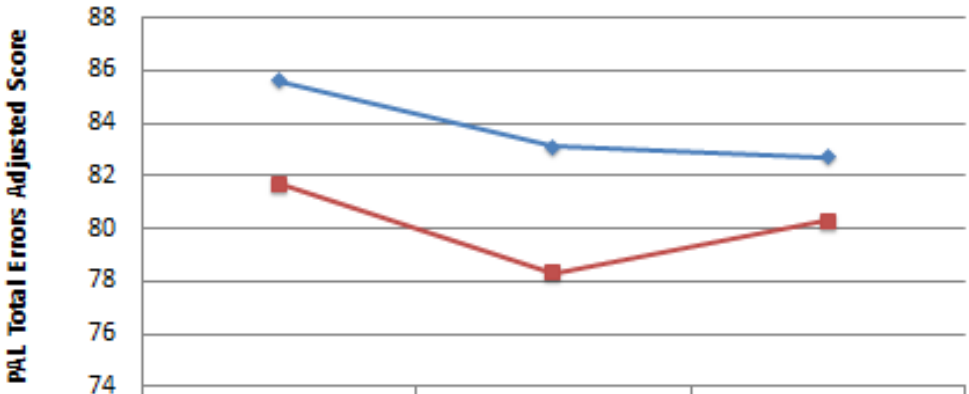


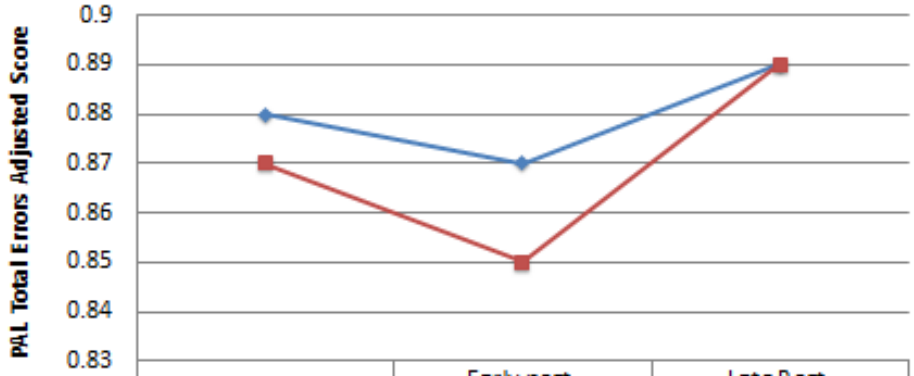
Figure 3.2: Delayed Matching to Sample (DMS) Percent Correct Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	85.6	83.1	82.7
Standard care	81.7	78.3	80.3

Repeated measures ANOVA p value = 0.74 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia. Lower scores indicate better cognitive performance.

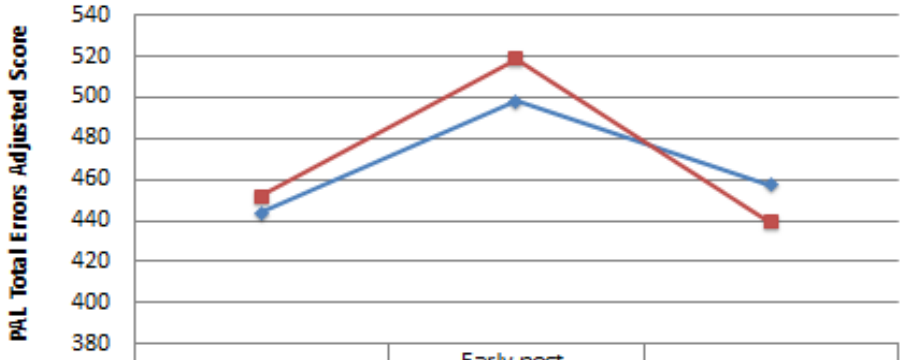
Figure 3.3: Rapid Visual Information Processing (RVP) A' prime Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	0.88	0.87	0.89
Standard care	0.87	0.85	0.89

Repeated measures ANOVA p value = 0.58 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

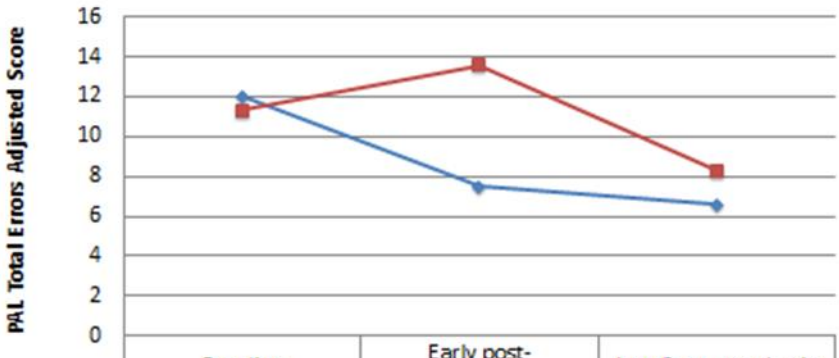
Figure 3.4: Rapid Visual Information Processing (RVP) Median Latency Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	444.1	498.3	457.4
Standard care	451.8	518.8	439.5

Repeated measures ANOVA p value = 0.55 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia. Lower scores indicate better cognitive performance.

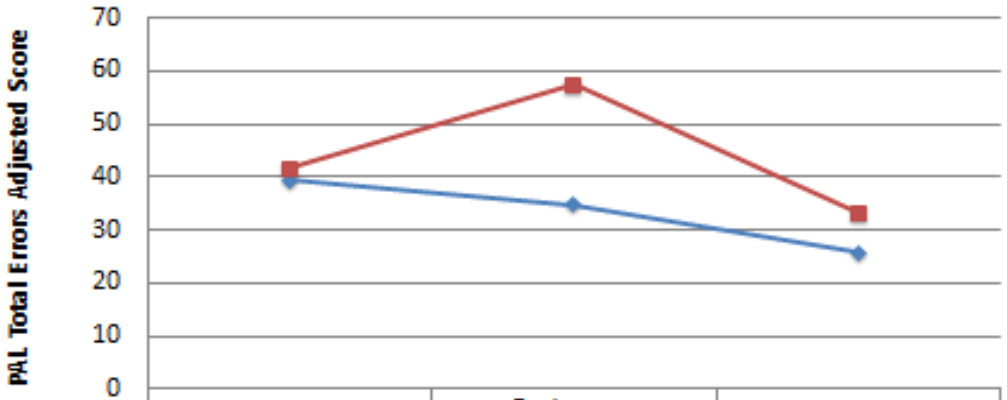
Figure 3.5: Paired Associates Learning (PAL) Total Errors 6 Shapes Adjusted Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	12	7.5	6.6
Standard care	11.3	13.6	8.3

Repeated measures ANOVA p value = 0.02 for group X time interaction; in post hoc tests, groups differ only at time 2 p = 0.019. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia. Lower scores indicate better cognitive performance.

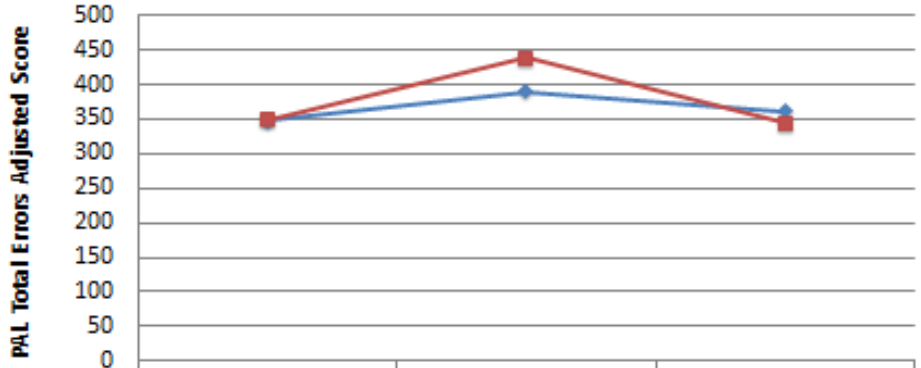
Figure 3.6: Paired Associates Learning (PAL) Total Errors Adjusted Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	39.4	34.7	25.7
Standard care	41.6	57.4	33.2

Repeated measures ANOVA p value = 0.02 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

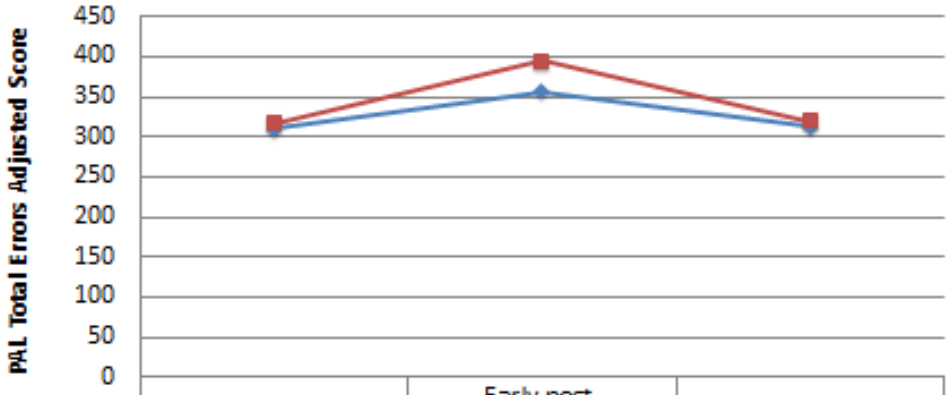
Figure 3.7: Reaction Time (RTI) Mean Simple Reaction Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	347.4	390	362
Standard care	349.6	438.6	343.5

Repeated measures ANOVA p value = 0.03 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

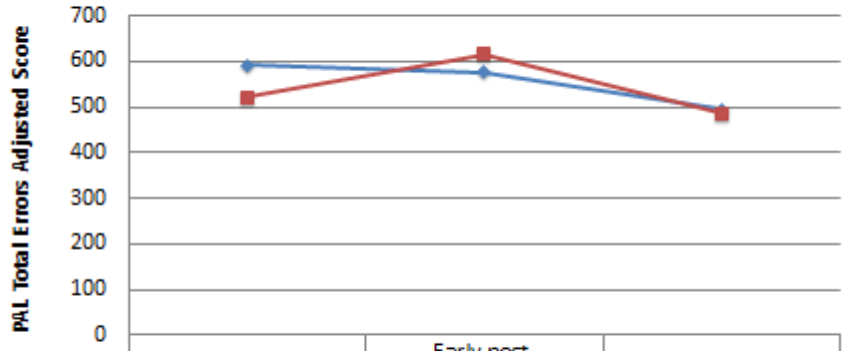
Figure 3.8: Reaction Time (RTI)Median Simple Reaction Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	309.3	355.7	312.6
Standard care	316.4	394	319

Repeated measures ANOVA p value = 0.07 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

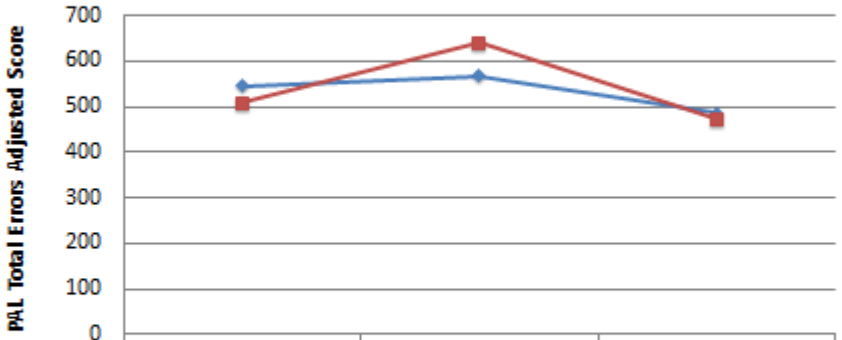
Figure 3.9: Reaction Time (RTI)Median Simple Movement Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	590.9	576.3	494.9
Standard care	522.3	615.7	485.7

Repeated measures ANOVA p value = 0.15 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

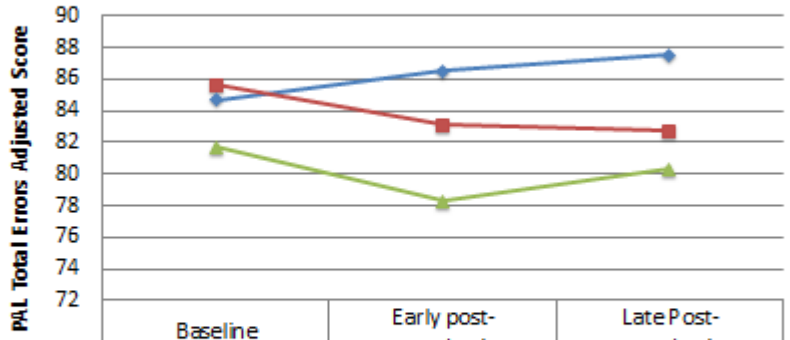
Figure 3.10: Reaction Time (RTI)Median Five Choice Movement Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
BIS	545.4	567.7	486.1
Standard care	507.6	640.4	474.1

Repeated measures ANOVA p value = 0.06 for group X time interaction. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

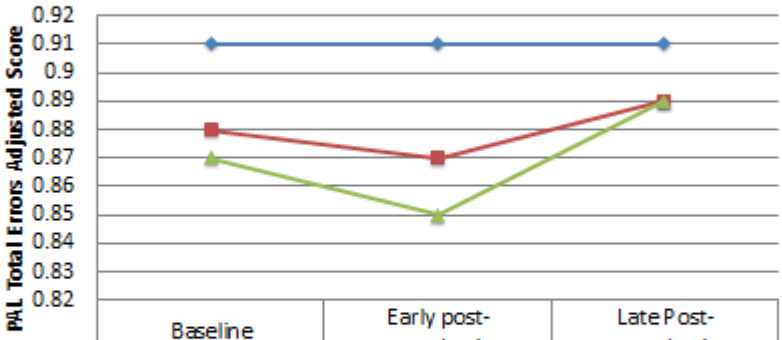
Figure 3.11: Delayed Matching to Sample (DMS) Percent Correct Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	84.7	86.5	87.5
BIS	85.6	83.1	82.7
Standard care	81.7	78.3	80.3

Repeated measures ANOVA p value = 0.3 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

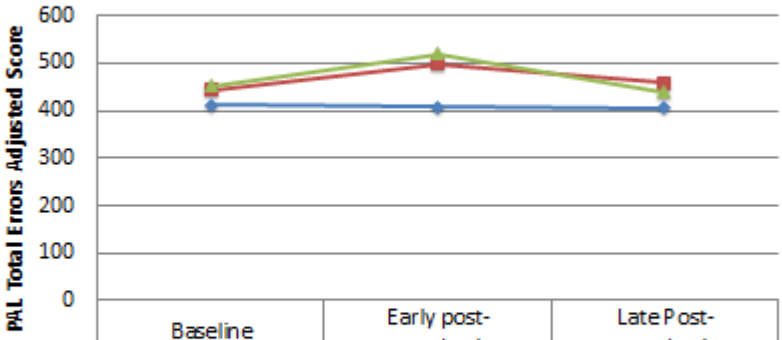
Figure 3.12: Rapid Visual Information Processing (PAL) A' prime Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	0.91	0.91	0.91
BIS	0.88	0.87	0.89
Standard care	0.87	0.85	0.89

Repeated measures ANOVA p value = 0.03 for group X time interaction; no differences between BIS and standard care at any time point. BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

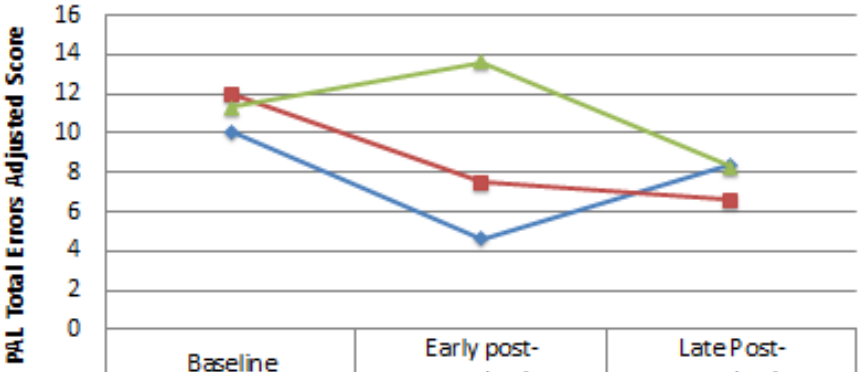
Figure 3.13: Rapid Visual Information Processing (RVP) Median Latency Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	412.9	406.8	405.1
BIS	444.1	498.3	457.4
Standard care	451.8	518.8	439.5

Repeated measures ANOVA p value = 0.1 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

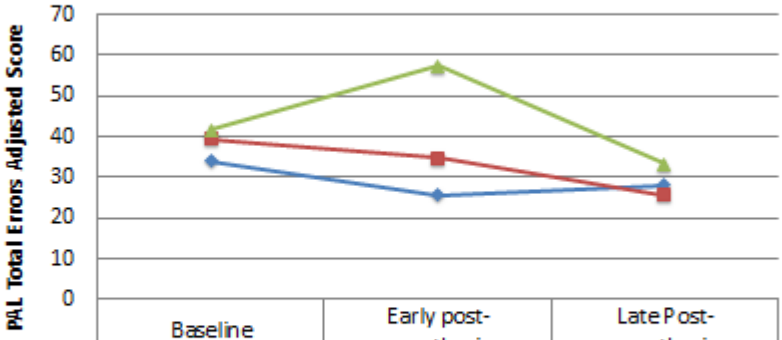
Figure 3.14: Paired Associates Learning (PAL) Total Errors 6 Shapes Adjusted Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	10.1	4.6	8.4
BIS	12	7.5	6.6
Standard care	11.3	13.6	8.3

Repeated measures ANOVA p value = 0.001 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

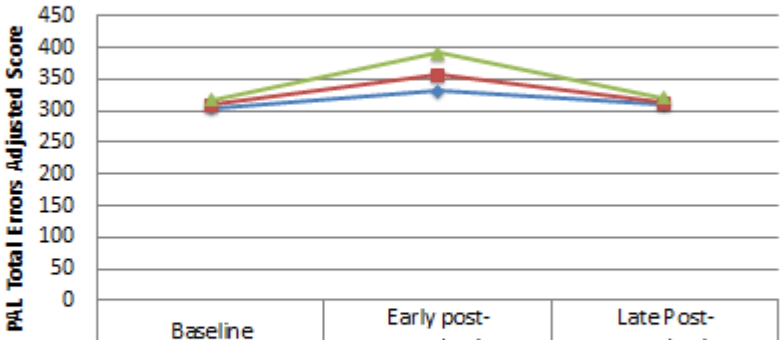
Figure 3.15: Paired Associates Learning (PAL) Total Errors Adjusted Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	34.1	25.6	28
BIS	39.4	34.7	25.7
Standard care	41.6	57.4	33.2

Repeated measures ANOVA p value = < 0.001 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

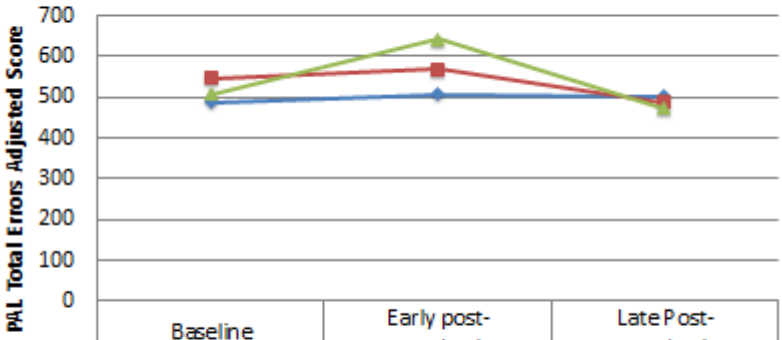
Figure 3.16: Reaction Time (RTI) Median Simple Reaction Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	304	331.1	310.3
BIS	309.3	355.7	312.6
Standard care	316.6	391.5	319.3

Repeated measures ANOVA p value = 0.005 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

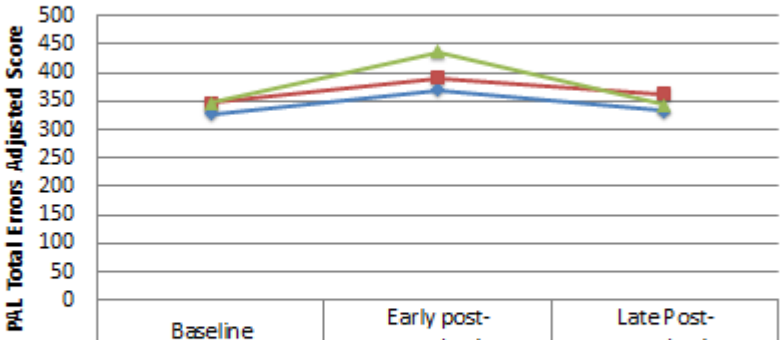
Figure 3.17: Reaction Time (RTI) Median Five Choice Movement Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	488	507.4	503.3
BIS	546.8	569.5	487.1
Standard care	508.3	642.7	474

Repeated measures ANOVA p value = 0.005 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

Figure 3.18: Reaction Time (RTI) Mean Simple Reaction Time Across Time by Group



	Baseline	Early post-anesthesia	Late Post-anesthesia
Normative group	327.9	369.3	332.1
BIS	347.4	390	362
Standard care	347	435.9	343.1

Repeated measures ANOVA p value = 0.1 for group X time interaction: BIS = bispectral index system; early post-anesthesia = 3-5 days after anesthesia; late post-anesthesia = 3-5 months after anesthesia

CHAPTER FOUR

Predictors of cognitive dysfunction from a randomized controlled trial of EEG-guided anesthesia compared to standard care

Introduction

Anesthetics are a critical component of health care. It is estimated by the Centers for Disease Control and Prevention that over 51 million surgical procedures requiring anesthesia were performed in 2010.[1] Anesthetics have become a common occurrence in society with risk perceived low by consumers. Improvements in safety have been attributed to technology and standardization of monitoring.[50] Recent studies suggest that anesthesia-related mortality is 1.1 per million population per year.[51] Still, the practice of anesthesia seeks to evolve and improve patient outcomes.

Deficits in cognition have been reported for over fifty years.[7] Post-operative cognitive dysfunction (POCD) has been identified as a risk for individuals undergoing surgery with volatile anesthetics.[52] Post-operative cognitive dysfunction is defined as negative changes in cognitive function that continue after appropriate drug half-lives have expired. [53] Prediction of those patients likely to experience postoperative cognitive dysfunction (POCD) after surgery could provide clinicians with information on important risk factors for cognitive impairment.

Several large randomized controlled trials have described risk factors for POCD. Most prominently, advanced age is described by many investigators as a principle preexisting risk factor.[3,54] The seminal study of POCD is the International Study of Post-Operative Cognitive Dysfunction (ISPOCD 1).[3] Lower education attainment, anesthesia of extended duration, repeated operations, infections, and respiratory complications were risk factors for POCD. History of substance abuse is also a preoperative risk factor for

POCD.[55] Predisposition to dementias (apoEε4 allele carriers) has been found to be a risk factor in some studies,[56] but not in others.[57,58]

We sought to evaluate a sample of patients who underwent surgery in a randomized controlled trial of EEG-augmented anesthesia to determine if there are baseline predictors of cognitive impairment at baseline and cognitive impairment after surgery. The patients in this study are evaluated by the cognitive battery, Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment® (CANTAB-MCI). This study represents the first time the complete battery was utilized to evaluate patient outcomes after surgery with volatile anesthetics. Although many studies have evaluated risk factors for POCD, the neurocognitive batteries employed in these studies have required highly trained neuropsychologist.[3,30,59] This study represents a practical application of a cost effective neurocognitive battery.

Specific Aim 1: determine sociodemographic and clinical predictors of cognitive function in patients planned for surgery utilizing volatile anesthetics and in a normative group not undergoing surgery.

Specific Aim 2: determine sociodemographic and clinical predictors of cognitive function in patients who have undergone surgery with a general anesthetic involving volatile anesthetics

Methods

Design. This is a secondary, planned data analysis of the prospective, randomized controlled trial, previously described in this dissertation. Parallel study groups underwent anesthesia for select surgeries and completed the CANTAB-MCI pre-operatively and at 3-4 days after surgery and 3-5 months after surgery. The standard treatment group were

anesthetized with volatile anesthetic and titrated with minimum alveolar concentration (MAC) values. The patients in the treatment group were titrated utilizing the Bispectral index™ system (BIS), an EEG-guided method of delivering anesthesia.

Sample and Setting. The sample consisted of 88 individuals, 45 individuals randomized to the intervention and 43 individuals randomized to standard treatment. Additionally, 37 age-and sex-matched individuals not undergoing surgery nor anesthesia were followed with versions of the CANTAB-MCI at the same interval. We included patient assessed as American Society of Anesthesiologist (ASA) class I-IV. These patients were undergoing scheduled surgeries requiring general endotracheal anesthesia with neuromuscular paralytic. Individuals for the normative group were included if they were age 45-70, had not undergone surgery in the past 6 months, and had no surgery planned. Only participants (patients and non-patients) who successfully completed the Motor Screening (MOT) test, which demonstrates muscular and cognitive ability to complete cognitive screening using the CANTAB-MCI, were invited to participate in the study. Patients were excluded who had significant cardiorespiratory or other end-organ disease, inadequate English language skills, and/or substance abuse. We also excluded patients with known neurological conditions (i.e., stroke, pre-existing cognitive dysfunction, and neuro-motor disabilities) and neurosurgical patients. We received patient referrals from physicians and/or nurse practitioners working in the Preoperative Clinic and surgeons in the medical center. Intervention. The intervention has been previously described, but in brief, anesthetic technique in both groups included standard induction with available agents, neuromuscular paralysis guided by nerve stimulator, inhalation anesthetic, and intraoperative monitoring..

BIS monitors were applied to both groups. The anesthesia provider in the standard practice group was blinded to the BIS value. Titration and administration were performed according to standard clinical practice judgment in both groups, but in the BIS group, volatile anesthetic was titrated to maintain a BIS index range 45-60, but not less than 0.5 age adjusted MAC.

Measures

Demographic and clinical data. The following data were collected using a standard questionnaire: Age, sex, race/ethnicity, education level, and annual income. The patients' current prescriptive medication regimen, comorbidities were obtained from the preoperative anesthetic record. All drugs utilized during the procedure were recorded on the anesthesia record and then transferred to a database for analysis.

Neurocognitive testing. The CANTAB-MCI system was used to measure cognitive function in multiple domains, and is a computerized, touch screen based group of 5 tests.

The CANTAB-MCI battery includes the Motor Control Task (MOT), Delayed Matching to Sample (DMS), Rapid Visual Information Processing (RVP), Paired Associates Learning (PAL), and Reaction Time (RTI). Reliability and validity of the method has been established.[42]The MOT (2 minutes) is a simple introduction to the touch screen for the participant. This task also functions as a screening test for visual, movement and comprehension difficulties.

The DMS (DMS percent correct was used in this study) assesses cognition in the memory domain for non-verbalizable patterns, testing both simultaneous and short term

visual memory domains. DMS percent correct counts correct selections made on the participant's first response and higher scores are better.

The RVP (two outcome measures were used to reflect this domain, 'RVP A' ' and 'RVP median latency') tests cognition in the visual sustained attention domain by assessing the participant's ability to recall a sequence of digits when given different combinations of digits. The RVP A' measures how good the participant is at detecting target sequences and is scored (0.00 to 1.0; bad to good). The RVP median latency is measured in milliseconds, and shorter is better.

The PAL (two measures were used to reflect this domain, 'PAL total errors 6 shapes adjusted' and 'PAL total errors adjusted') assesses cognition in the short term/visual memory domain. For 'PAL total errors adjusted' lower scores are better, as they are for the 'PAL total errors 6 shapes adjusted'.

The RTI (RTI median simple reaction time was used to assess this domain) test is a speed of processing/latency domain task. 'RTI median simple reaction time' is sensitive for cognitive slowing, with lower scores reflecting better performance.

Protocol. The study proceeded after approval from the appropriate university Institutional Review Board, and after informed consent was received. After successful completion of the screening Motor Control Task (MOT), a full consent was completed when the patient agreed to participate.

The CANTAB-MCI battery was administered in the patients' hospital room, service's clinic, or location convenient to the patient before surgery (time 1), at 3-5 days after surgery (time 2), and to ensure drug half-lives have expired. The battery was again re-administered at 3-5 months (time 3) at a location convenient to the patient.

Data Analysis

We determined sociodemographic predictors (i.e., group, age, gender, education, income, and race) of cognitive function at baseline assessed in each of the four domains studied using separate nonlinear regression models and a continuous level, gamma with log link, response model. We initially attempted multiple linear regression modeling, but the major assumption of a linear relationship between the independent variables and the outcome variable was violated. Transformation of the outcome variable or appropriate independent variables did not resolve this violation, thus, nonlinear modeling with SPSS version 22 was done.

Because only the two surgical groups had pre-surgical clinical information available, for time 2 (3-5 days after surgery) and time 3 (3-5 months after surgery), only surgical patients were included in the nonlinear regression models for time 2 and time 3. In order to optimize the model and avoid overfitting, we used only the sociodemographic variables that were consistently significant (i.e., age, income) from the baseline models, in the time 2 and time 3 models. Other predictor variables used in these time 2 and time 3 models were group, ASA status, procedure, tobacco use, and psychotropic drug prescription. We tested a small number of other reasonable candidate predictors (i.e., diagnosis of diabetes, length of anesthesia, on beta-blockers preoperatively, body mass index, and baseline blood pressure) for inclusion in the models, and compared the Akaike Information Criterion (AIC) values to determine to best set of predictor variables that resulted in the lowest AICs across the models.

Results

Flow of participants through the study. We screened patients from October 2014 through June 2015 with the last follow-up completed in September 2015. Of the 329 patients screened for enrollment, 143 did not meet eligibility criteria and 98 chose not to participate (Figure 1). Of the 88 patients scheduled for surgery who were enrolled, 45 were randomized to the intervention limb of the protocol and 43 were randomized to the control protocol. Of the 45 patients allocated to the intervention limb, 2 (4.46%) were lost to follow-up prior to the anesthetic. In the control limb, 1 (2.3%) was lost prior to the anesthetic. Two patients from the intervention (4.46%) and control (4.6%) protocol limbs were lost to follow up prior to their cognitive testing session 2. Two (4.46%) more patients were lost to follow up prior to testing session 3 in the intervention limb of the protocol. There was no difference in rate of withdrawal from the two surgical groups ($p=0.33$). Patients who withdrew from the study were not significantly different than patients who remained in the study on any of the demographic or clinical characteristics measured at baseline including testing time 1 CANTAB-MCI® scores.

In addition we used purposive sampling to enroll an age- and gender-matched healthy control sample. Seventy-two individuals were approached, with 10 not meeting inclusion criteria and 25 refusing participation. Thirty-seven individuals were enrolled with one lost to follow up prior to testing time 2.

Sample Characteristics. Of the 125 surgical patients and normative participants available for analysis of cognitive outcomes at the last follow-up point (93% of the enrolled sample), the mean age was 58.9 ± 6.7 years of age, the majority were female (62.4%), and ethnicity coded as Caucasian 114 (91.2%). Sixty-eight percent had

combined household incomes of less than $75,000 per year. The highest level of education attained was at least some college in 69.5%. Demographic and clinical characteristics of patients by total sample and group assignment are summarized in Table 1. There were no significant differences among the groups on any demographic or clinical characteristic.

Specific Aim 1

We evaluated baseline sociodemographic (i.e., gender, age, education, income, and race) predictors of POCD in a population of patients from a randomized controlled trial utilizing BIS guidance versus standard care, and from a normative group who did not undergo surgery. Controlling for group assignment, we demonstrated that older age was predictive of poorer functional status at baseline in all of the dimensions measured except RTI (Table 2). Lower income (less than $25,000 per year compared to greater than $75,000) was predictive of worse cognitive function at baseline for the two cognitive domains reflected by the 'DMS Percent Correct' and 'RVP A'' . Education level lower than a completed college education was predictive of worse cognitive function in the domain represented by the PAL. Caucasian race was associated with poorer cognitive function compared to other races on the DMS. Gender was not associated with cognitive function in any dimension tested, and neither was group assignment.

Specific Aim 2

In addition to group, in the analyses for Specific Aim 2 (post-operative cognitive function), we used age and income as the sociodemographic predictors because (1) they were the most consistent predictors in the previous analysis, (2) education and income were highly correlated and thus, we thought it best to use only one of these predictors,

and (3) given our relatively smaller sample size we were limited in the number of variables that could be used as predictors. We used ASA status, surgical procedure planned, tobacco use, and prescription for psychotropic drugs as clinical predictors, after careful assessment of AIC values from different models.

With regard to predictors of cognitive performance on CANTAB-MCI testing at time 2, (3-5 days after surgery) we found that, just as we found at baseline, older age and lower income were predictive of worse cognitive function (Table 3). Assignment to the EEG-guided anesthesia was associated with better cognitive function compared to the control group. Patients in the EEG-guided group were 60% less likely to demonstrate poor cognitive function than those in the control group. Other predictors of worse outcomes were planned neurological or spinal surgery and tobacco use, prescription of psychotropic drugs was not associated with cognitive outcomes.

Table 4 summarizes characteristics predictive at CANTAB-MCI testing three (3-5 months postoperatively). Assignment to the EEG guided group was associated with better outcomes in the PAL measure at 3-5 months postoperatively. Again, older age and lower incomes were predictive of worse cognitive function at 3-5 months after surgery. . Older age was predictive of worse cognitive function as reflected by three outcome measures 'DMS percent correct',, 'PAL Total Errors Adjusted', and 'RVP A'' ($p=0.001$). The only other predictor of poor outcomes at time three was lower income.

Discussion

In this study, we confirmed the results of our randomized controlled trial in that patients in the EEG-guided anesthesia experienced better outcomes compared to those in the control group. We demonstrated that a few variables that can be assessed prior to

surgery are important predictors of cognitive impairment before and after surgery. . Through each phase of assessment in this study, older age and lower income are consistent predictors of poorer cognitive function. Our findings of advancing age and low education/income reflect the findings of previous studies.[4] Older age is thought to be related to worse cognitive function due to decrements in cognitive function associated with physiologic changes associated with the development of chronic illnesses (e.g., small vascular infarcts or ischemia) and the accumulation of effects of lifestyle choices (e.g., smoking, hypertension, poor diet, sedentary lifestyle). Another possible contributor is a cohort effect associated with lower education levels in current elders. In our study, however, age was independently associated with cognition even when controlling for education level.

An intriguing finding from our study was the effect of tobacco abuse on postoperative performance on all four cognitive outcome measures, where we demonstrated that tobacco abuse was associated with poorer cognitive outcomes at both post-operative testing times. Although hypoxemia has been postulated as a causative factor of POCD,[60] the seminal randomized controlled trial of POCD (International Study of Post-Operative Cognitive Dysfunction: ISPOCD1) found that hypoxemia was not significant risk factors at any time.[3] There were no significant episodes of hypoxemia noted among smokers or nonsmokers in our study, nor reported postoperatively. It is well known, however, that among nicotine-addicted smokers who attempt smoking cessation, cognition and attention are impaired.[61] In addition, smoking is associated with intensive vasoconstriction, which may over time affect blood flow in the brain to produce subtle yet progressive changes in cognition.

The concern of the effect of tobacco abuse is amplified in this study. Beyond the known cardiovascular and wound healing determents, this study finds that there are cognitive effects at the time interval of 3-5 days postoperatively. These individuals have a greater obstacle to overcome and have may have greater needs to be discharged. Their ability to be included in new fast-track regimens such as the Enhanced recovery after surgery (ERAS) protocol may be compromised.[62] Nicotine effects continue to occur 3-4 days after individuals last partake of tobacco products. While it is recommended that patients abstain from tobacco products six weeks prior to surgery, it is commonplace to find patients who have smoked heavily immediately prior to admission for surgery.

Previous studies have suggested that mood stabilizing medication have effects on cognitive performance.[63,64] The use of psychotropic mood stabilizing medications did not prove to be significantly predictive of post-operative function in this study. This may be because other factors that were stronger risk factors for worse cognitive function overshadowed the potential impact of mood stabilizing medications. Moreover, we did not have dosage information or know the length of time patients were on these medications.

Limitations

While the major strength is being a randomized controlled study, there are limitations to the study. The major limitation is a smaller sample size. This limits our ability to determine any heterogeneity of treatment effect because we could not perform subgroup analyses.

Conclusions

Older age, lower income and tobacco abuse are predictive of worse cognitive outcomes, even in the company of specific procedural and clinical variables. All of these factors are easily identifiable to even the busiest clinicians. Use of these characteristics in the risk stratification of surgical candidates prior to surgery can assist healthcare providers to target at-risk patients for early intervention to prevent cognitive morbidity.

Table 4.1: Comparisons of baseline characteristics among the three study groups (N=115)

	Treatment/BIS n=45	Anesthesia-Control n=43	Normative Group n=37	P
Age	60 ± 7	58 ± 6	59 ± 7	0.601
Gender: male	19 (42%)	16 (37%)	12 (32%)	0.659
Caucasian compared minority	41 (91%)	40 (93%)	33 (89%)	0.833
Annual household income				0.075
<$25,000	8 (20%)	13 (32.5%)	3 (8%)	
$25,001-$50,000	12 (29%)	4 (10%)	10 (28%)	
$50,000-$75,000	11 (27%)	10 (25%)	8 (22%)	
>$75,001	10 (24%)	13 (32.5%)	15 (42%)	
Education				0.279
High school or Less	15 (36%)	15 (37.5%)	9 (25%)	
Some college or training	18 (43%)	10 (25%)	15 (42%	
College graduate or more	9 (21%)	15 (37.5%)	12 (33%)	
Legend: BIS = Bispectral™ index system				

Table 4.2: Baseline sociodemographic predictors of baseline cognitive function in four domains from the CANTAB-MCI.

	DMS percent correct		**PAL Total Errors Adjusted**		**RTI Median Simple Reaction Time**		**RVP A'**	
	Odds Ratio [95% CI]	**P value**	**Odds Ratio [95% CI]**	**P value**	**Odds Ratio [95% CI]**	**P value**	**Odds Ratio [95% CI]**	**P value**
Variable								
Group†								
Treatment/BIS	1.025 [0.97-.08]	0.384	0.967 [0.684-1.362]	0.848	1.006 [0.93-1.087]	0.885	0.979 [0.954-1.004]	0.095
Control/standard care	0.987 [0.931-1.045]	0.642	1.153 [0.817-1.625]	0.413	1.035 [0.955-1.123]	0.396	0.997 [0.94-0.992]	0.01
Gender: Male	0.973 [0.927-1.021]	0.26	1.109 [0.82-1.51]	0.505	1.014 [0.947-1.086]	0.686	1.003 [0.98-1.025]	0.8
Age	0.994 [0.99-0.997]	0.001	1.035 [1.015-1.056]	0.001	1 [0.995-1.004]	0.873	0.997 [0.995-0.999]	<0.001
Education ‡								
High school or less	0.983 [0.919-1.05]	0.602	1.699 [1.132-2.552]	0.01	0.993 [0.904-1.09]	0.881	0.99 [0.962-1.02]	0.584
Some college or training	1.009[0.949-1.072]	0.776	1.579 [1.078-2.307]	0.018	1.061 [0.973-1.156]	0.178	0.995 [0.967-1.02]	0.703
Income$								
<$25,000	0.925 [0.857-0.997]	0.04	1.351 [0.851-2.154]	0.2	1.07 [0.964-1.192]	0.198	0.995 [0.922-0.988]	0.008
$25,001-$50,000	0.987 [0.921-1.058]	0.711	1.312 [0.845-2.042]	0.224	1.005 [0.911-1.108]	0.926	0.982 [0.951-1.014]	0.255
$50,000-$75,000	0.998 [0.937-1.062]	0.937	1.172 [0.791-1.746]	0.427	0.974 [0.892-1.063]	0.547	0.98 [0.952-1.008]	0.154
Caucasian £ (compared to all others)	0.912 [0.838-0.99]	0.028	1.27 [0.73-2.101]	0.37	1.003 [0.891-1.126]	0.955	0.992 [0.956-1.03]	0.693

Legend: BSI = Bispectral™ index system, DMS=Delayed Matching to Sample, PAL=Paired Associates Learning, RTI=Reaction Time, RVP A'=Rapid Visual Information Processing A prime

Omnibus test: DMS p= 0.01; PAL p= 0.001; RTI p= 0.775; RVP p= <0.001.

Variable compared to: †= normative group; ‡=finished college or greater; $ = >$75,000; £= all others

Table 4.3: Baseline sociodemographic and procedural predictors of cognitive function within 3-5 days after surgery in four domains measured from the CANTAB-MCI battery.

	DMS percent correct		**PAL Total Errors Adjusted**		**RTI Median Simple Reaction Time**		**RVP A'**	
	Odds Ratio [95% CI]	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**
Variable								
Group†								
BIS	1.058 [0.98-1.15]	0.18	0.595 [0.41-0.87]	0.008	0.91 [0.84-0.98]	0.018	1.01 [0.98-1.05]	0.38
ASA score‡								
ASA 2	0.989 [0.91-1.1]	0.84	0.800 [0.54-1.19]	<0.001	1.03 [0.95-1.12]	0.42	1.01 [0.98-1.04]	0.466
Procedure?								
Neuro/spin	0.876 [0.78-0.98]	0.026	1.695 [0.99-2.89]	0.053	1.18 [1.06-1.33]	0.003	0.95 [0.91-0.993]	0.024
Colorectal	0.928 [0.8-1.07]	0.32	1.642 [0.84-3.22]	0.148	1.16 [1.01-1.34]	0.036	0.95 [0.894-0.998]	0.043
General surgery	0.923 [0.8-1.07]	0.29	1.483 [0.75-2.93]	0.258	1.24 [1.08-1.43]	0.003	0.95 [0.894-0.999]	0.044
Age	0.992 [0.985-0.999]	0.02	1.06 [1.03-1.1]	<0.001	1.01 [1.001-1.014]	0.027	0.99 [0.99-1]	0.107
Tobacco use ₮								
No Tobacco use	1.202 [1.11-1.3]	<0.001	0.618 [0.43-0.89]	0.003	0.89 [0.82-0.96]	0.004	1.03 [1.005-1.07]	0.023
Income $ K								
<$25-25	0.983 [0.88-1.1]	0.78	2.152 [1.25-3.69]	0.006	0.993 [0.89-1.11]	0.90	0.96 [0.92-1.001]	0.053
$25-$50	1.028 [0.91-1.16]	0.66	2.086 [1.15-3.79]	0.016	1.037 [0.92-1.17]	0.54	0.95 [0.91-0.996]	0.033
$50-$75	0.986 [0.89-1.1]	0.799	1.874 [1.15-3.06]	0.012	0.967 [0.87-1.07]	0.53	0.96 [0.92-0.995]	0.027

Table 4.3 Continued

	DMS percent correct		PAL Total Errors Adjusted		RTI Median Simple Reaction Time		RVP A'	
	Odds Ratio [95% CI]	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**
Psychotropics £								
None	1.078 [0.99-1.17]	0.08	0.974 [0.67-1.43]	0.89	0.999 [0.92-1.09]	0.99	1.03 [1-1.07]	0.051

Legend: CI=Confidence interval, DMS=Delayed Matching to Sample, PAL=Paired Associates Learning, RTI=Reaction Time, RVP A'=Rapid Visual Information Processing A prime.

Omnibus test: DMS p=0.001; PAL p= <0.001; RTI p=0.007; RVP p=0.002.

Variable compared to: †= control/standard care group; ‡=ASA3&4; ⁇ Laparoscopic;₸=smoker; $ = >$75,000; £= Psychotropic use

Table 4.4: Baseline sociodemographic and procedural predictors of cognitive function within 3-5 months after surgery in four domains measured from the CANTAB-MCI battery.

	DMS percent correct		**PAL Total Errors Adjusted**		**RTI Median Simple Reaction Time**		**RVP A'**	
	Odds Ratio [95% CI]	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**
Variable								
Group∂								
BIS	0.032 [-0.028-0.99]	0.268	0.16 [-0.73—0.063]	0.02	0.037[-0.079-0.6]	0.833	0.0119 [-0.02-0.26]	0.795
ASA score‡								
ASA 2	0.0334 [-0.067-0.06]	0.961	0.1703 [-0.33-0.34]	0.993	0.038 [-0.06-0.8]	0.816	0.001 [-0.005-0.001]	0.001
Procedure⁋								
Neuro/spine	0.0461 [-0.034-0.15]	0.222	0.241 [-0.642-0.3]	0.477	0.05 [-0.03-1.17]	0.187	0.017 [-0.06-0.005]	=0.091
Colorectal	0.0594 [-0.065-0.17]	0.385	0.3128 [-0.67-0.56]	0.859	0.068 [-0.9-1.17]	0.602	0.022 [-0.08-0.005]	0.08
General surgery	0.0608 [-0.172-0.07]	0.383	0.317 [-0.53-0.717]	0.761	0.068 [-0.056 -0.2]	0.256	0.022 [-0.09-0.01]	0.019
Age	0.003 [-0.014--.003]	0.001	0.0135 [0.05-0.104]	<0.001	0.003 [-0.004-0.008]	0.593	0.001 [-0.01-0.001]	0.001
Tobacco use ₮								
No Tobacco use	0.0325 [-0.018-0.11]	0.164	0.1723 [-0.44-0.24]	0.569	0.037 [-0.14-0.007]	0.079	0.0119 [-0.01-0.042]	0.119

Table 4.4 Continued

	DMS percent correct		**PAL Total Errors Adjusted**		**RTI Median Simple Reaction Time**		**RVP A'**	
	Odds Ratio [95% CI]	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**	**Odds Ratio [95% CI]**	**P**
Income $								
<$25,000	0.044 [-0.24--0.063]	0.001	0.2412 [0.002-0.95]	0.049	0.049 [-0.87-1.108]	0.833	0.016 [-0.095-0.03]	<0.001
$25,001-$50,000	0.048 [-0.156-0.031]	0.19	0.2602 [0.29-1.31]	0.002	0.979 [-1.127-0.084]	0.691	0.018 [-0.09-0.019]	0.002
$50,000-$75,000	0.0425 [-0.103-0.63]	0.637	0.2236 [-0.13-0.75]	0.168	1.043 [-0.059-0.129]	0.466	0.016 [-0.046-0.02]	0.33

Legend: CI=Confidence interval, BIS = Bispectral index system. DMS=Delayed Matching to Sample, PAL=Paired Associates Learning, RTI=Reaction Time, RVP A'=Rapid Visual Information Processing A prime.

Omnibus test: DMS p=0.004; PAL p= <0.001; RTI p=0.83 ; RVP p=0.001.

Variable compared to: ∂=Diabetic ; ‡=ASA3; ⸮ Laparoscopic;₸=smoker; $ = >$75,000.

CHAPTER FIVE
Background and Purpose

Over 51 million Americans underwent surgery in the last reported year.[1] The fastest growing proportion of individuals are the elderly, and are the largest consumers of surgery.[2] The development of postoperative cognitive dysfunction (POCD) after surgery is an important complication of surgery for many patients, likely more than appreciated by clinicians. Volatile anesthetics (e.g., isoflurane, sevoflurane, and desflurane) have been implicated in the development of POCD by triggeringneuroinflammation.[14,20,21] This cognitive decline is associated with increased one-year mortality, as well as morbidity and family/caregiver stress.[4]

The overall purpose of this dissertation was to determine whether an anesthetic technique, with less cumulative deep hypnotic time, results in fewer individuals with POCD. A large obstacle in the better understanding of POCD is that the exact mechanism of volatile anesthetics is still not known. To better understand this void, the manuscript in chapter 2 was developed and is a review of the current concepts of anesthesia mechanisms and the neuropathogenic effects on the aging brain was done.

Based on findings from this manuscript, a randomized controlled trial of anesthesia guided by BIS vs. standard care and effects on cognition was undertaken, and was reported in Chapter 3. This randomized control trial of 115 individuals undergoing anesthesia (39 patients whose anesthesia delivery was guided by Bispectral Index® system [BIS-Covidien-Medtronic™] and 40 who received standard care) was conducted from August 2014-September of 2015. The group whose anesthesia was guided by the BIS system was predicted to have a lower overall cumulative dose of volatile anesthetic than their standard care counterparts. After this trial, we conducted a secondary,

preplanned, data analysis (reported in Chapter 4) to determine risk factors for POCD among the surgery patients enrolled in the clinical trial.

EEG derived systems have been developed to measure depth of consciousness and enable the anesthesia provider to tailor anesthetics to the individual patient. Recent findings from studies utilizing the BIS system have demonstrated this titration is associated with positive outcomes in reduction of postoperative deficits.[30,32] However, these studies have some limitations with regard to the measurement and reporting of cognitive function. This dissertation was innovative and resolved some gaps in the literature because we used the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment (CANTAB-MCI®), an instrument with known reliability and validity in a wide variety conditions, including the measured of pre- and post-operative cognitive function. This battery is delivered on a state of the art touch screen system and is highly regarded as one of the most rigorous methods of measuring cognitive function because it provides measurement of all relevant domains, and is objective and not open to investigator bias in interpretation.

Summary of Findings

Chapter Two was a focused review of the state of the science in the understanding of the mechanism of volatile anesthetic function. Beyond the Meyer-Overton theory, the protein theory of volatile anesthetic mechanism seems most plausible. The manipulation of gamma-aminobutyric acid (GABA) receptor proteins and the known inhibitory effect of chloride ion channels seem to be the machinery of anesthetic function. Still, bench scientists have produced additional examples of volatile anesthetic effect on proteins,

such as, N-methyl-D-aspartate receptors,[65] and potassium channel subfamilies TREK1 and TASK[66].

Studies to elucidate POCD have largely followed the affected cognitive domains. The association of POCD with mild cognitive impairment (MCI) has led researchers to compare the sequela of volatile anesthesia with the neuropathogenesis of the dementias.[67] Pathways including apoptosis,[68] oligomerization,[14] and caspase activation[15] have all been demonstrated with appropriate doses of volatile anesthetics, mimicking dementia neuropathogenesis. These close relationships between the dementias and the current concepts of anesthesia mechanism pose grave concern. Still, there is not a consensus on types of drugs, techniques, nor ways to monitor in mitigation of POCD.[69]

Chapter Three is a report documenting a randomized controlled trial evaluating the effect of EEG guided anesthesia via the BIS monitor on cognitive function in surgical patients. In a sample of 86 individuals, 45 surgical patients randomized to the intervention of a balanced anesthetic technique with BIS guidance, and 43 to standard treatment. Cognitive performance was evaluated with the Cambridge Neuropsychological Test Automated Battery-Mild Cognitive Impairment (CANTAB-MCI®) at three intervals (preoperatively, 3-5 days post-operatively, and 3-5 months post-operatively).

Our findings demonstrate statistically significant differences in two outcome measures of the Cambridge Cognition Paired Associates Learning (PAL) test. The PAL is a test of the short term/visual memory domain. The outcome measures 'PAL total errors adjusted' ($p=0.02$) and 'PAL total errors 6 shapes adjusted ($p=0.02$) were both significantly different in the time by group comparison at 3-5 days, but not at 3-5 months. A two-way mixed repeated measures ANOVA was utilized to address this specific aim.

The BIS group had significantly better cognitive outcomes at 3-5 days than did the treatment group who has a deficit in cognitive function in this domain after surgery. Cognitive function returned to baseline in both groups by the 3-5 month assessment. An additional 37 age- and sex-matched individuals not undergoing surgery nor anesthesia were evaluated at the same intervals to represent a normative population. This study demonstrated that EEG guided anesthesia can reduce cumulative deep hypnotic time without negatively affecting patient physiologic stress or surgical conditions, while at the same time preventing cognitive dysfunction in some domains.

Chapter Four is a dissemination of a analysis of predictors of cognitive function from the randomized controlled trial, Chapter 3. Baseline predictors of poorer CANTAB-MCI test performance to include older age and lower income regardless of group. At the second time period, the BIS guided treatment proved protective (p=0.008) for cognitive impairment, while older age and lower income remained predictive of worse cognitive function. At the long-term measurement period, older age, lower income, and assignment to the control group were associated with poorer outcomes. These findings are reflect larger studies, but were obtained with the cost-effective CANTAB-MCI system.[4]

Impact of Dissertation on the State of the Science

Health care, and its extraordinary cost, is a constant conundrum facing the United States and the world. Over the last 50 years, healthcare costs in the United States has escalated from 5 percent of GDP in 1960 to 17.4 percent in 2013.[70] Many initiatives have been utilized to impact this escalation while seeking to preserve and improve patient outcomes. Recently, the Centers for Medicare & Medicaid Services (CMS) and America's Health Insurance Plans (AHIP) released their first set of clinical quality

measures as part of their Core Quality Measures Collaborative also known as "pay for performance." This initiative seeks to replace diagnosis-related groups (DRG) and International Statistical Classification of Diseases and Related Health Problems (ICD) as the central component for healthcare reimbursement. In the Core Quality Measures Collaborative, along with length of stay, factors such as controlling hypertension, timely screening, and appropriate medication regimens increase reimbursement.[71] Over the last decade, a surgical practice model has evolved to address the same issues of balancing cost with quality. Enhanced Recovery After Surgery (ERAS®) is a set of multimodal care guidelines that include all facets of a surgical patients' perioperative experience.[62]

The ERAS® initiative drastically alters standard tenants of surgical care including reducing preoperative fasting, encouraging minimally invasive surgical approaches, and multimodal approaches to anesthesia care. The goal of ERAS® is prevention of physical and metabolic decline thereby allowing patients to recover more quickly. The ERAS® begins preoperatively with patient preparation and teaching, extends through the surgical/anesthetic phase, and includes critical components postoperatively through discharge/follow-up. Initial evaluations of the guidelines resulted in significantly improved morbidity and mortality (28.4% and 1.6% respectively) from previously reported studies (35% and 2%) ($p=<0.0001$ and $p=0.156$).[72] In the past five years, the surgical approach has been extended successfully to other surgical practices.[73-75] Patient participation, motivation, and communication are critical to the ERAS® approach. Patients unable to fully participate due to cognitive dysfunction postoperatively limit the ultimate effectiveness of the total approach.

This dissertation represents an important contribution to the literature as it is the first study to show that the CANTAB-MCI battery is effective in discriminating the fine difference in cognitive burden between two groups who underwent the stress of surgery. The CANTAB touch screen based system did not produce an undue burden on the patients, staff, nor require an unreasonable expenditure of time. The finding of significant differences in group performance on the Paired Associates Learning (PAL) test suggest that the BIS guided anesthesia technique may present some sparing effect on the integrity of the temporal lobe, especially the entorhinal cortex, as this area is critical for performance in the PAL.[76]

Prior investigators have demonstrated that POCD is associated with higher morbidity and mortality.[4] It is well established that cognitive decline, such as that seen in MCI, is associated with increased mortality.[44] The causative relationship of cognitive decline to mortality is not clear. Bassuk and collegues[44] clearly state that cognitive decline may, "interfere with the ability to recognize signs and symptoms of disease, to seek timely medical assistance, to adhere to a medication regimen, to prepare adequate meals, and to engage in other preventive health care behaviors." While there is no clear relationship between POCD and MCI, the similarity of domains affected and neuropathology is telling. In concert with these data, our data suggests that early POCD, even when transient, may identify patients who are vulnerable to later morbidity and mortality. If future studies support this association then those individuals with early POCD could be targeted for intervention to reduce later morbidity and mortality. Patients identified should have a multidisciplinary team who evaluates and forms a patient specific treatment plan targeted at optimal survivability.

Recommendations for Nursing Practice and Research

The outcome of this dissertation suggests utilization of a BIS-guided, balanced anesthetic technique is effective in reducing effects of volatile anesthetics on postoperative cognition. Although many groups including the young and healthy may not present as at risk for POCD, the old, elderly, and frail should call for increased discrimination in the preoperative setting. Still, it is critical, that salient effects of anesthetics may still be occurring sub-clinically. Individuals with parents diagnosed with Alzheimer's disease, known predisposition to dementias (apoEε4 allele carriers), and cerebral vascular disease should be counseled and anesthetic approach weighed against these risk. Utilization of cognitive batteries, such as, the CANTAB-MCI® can be utilized in these at risk populations when there is no other option for general anesthesia as a means to ascertain domains which may be affected.

This study found susceptibility for deficits in visual memory/learning in individuals undergoing anesthesia with high cumulative hypnotic time. This was found at the 3-5 day time, but not in the late 3-5 month time. This finding is similar to that of larger studies of POCD.[59] This presents a concern with patients undergoing healthcare teaching/discharge planning in this same time interval. Situations where patients receive complicated instructions or procedures they must understand to care for themselves at home may be lost due to cognitive deficits.

The results of this and other studies suggest that special attention needs to be given to discharge education and that follow-up by phone or early return visits to the surgeon or primary care provider are warranted. All discharge instruction should be explained to a family member or friend as well as to the patient. In addition, specific,

clear instructions should be written out. It is common for written discharge instructions to be "generic" or not specifically tailored to the patient. Given the potential for cognitive impairment after surgery, this practice should be avoided.

Additional studies are planned to expand upon this study. For example, integrating a more complete understand of the neurocognitive effects of volatile anesthetics into the ERAS® approach and testing the outcomes of such integration should lead to interesting findings. The old and the elderly, are at highest risk for poor outcomes in regard to POCD[4] and surgical morbidity,[77,78] therefore, it is prudent to approach these populations with great care.[72] Further study, integrating the EEG guided anesthesia technique described in this dissertation, that is focused on improving outcomes in elders is warranted.

Given the previous studies which have shown an association between POCD and higher morbidity and mortality in the long-term, it is interesting to speculate whether interventions could be specifically targeted to patients who experience POCD early after anesthesia. Our finding of early POCD in a specific domain suggests that even with apparent recovery of POCD, patients who experience early POCD may represent a vulnerable subset of patients who may experience worse outcomes in the long term. Further research is suggested to test this possibility and further refine interventions to improve outcomes after surgery.

Conclusions

We were able to demonstrate a practical anesthesia technique can have an important impact on patient outcomes. While volatile anesthetics are a very important component of current anesthetic practice, evidence is substantial that they are not benign.

The Bispectral Index system is one of several EEG guidance systems that are prevalent throughout the United States. Their utilization in individuals identified to be at risk for cognitive decline after anesthesia (advanced age, low education/socioeconomic status, and tobacco abuse) is warranted, but all patients ultimately deserve the best care delivered in the optimal manner and thus, we recommend use of EEG guided anesthesia for all patients. The CANTAB-MCI system demonstrated rugged reliability, sensitivity, and ease of use. Utilization of this cognitive battery as a screening to, especially for at risk groups, could allow providers to follow these patients and personalize their care for their best outcomes.

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Curriculum Vitae
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Education

Institution	Degree	Date Conferred	Field(s) of Study
Western Kentucky University	BSN	2000, May	Nursing
Middle Tennessee School of Anesthesia	MS	2005, December	Nurse Anesthesia

Certifications and Licensure

Certified Registered Nurse Anesthetist #073919
Kentucky Board of Nursing APRN 3004851
Kentucky Registered Nurse 1095264

Professional Experience

Dates	Institution and Location	Academic Position
January 2006-present	University of Kentucky Department of Anesthesiology, Lexington, KY	Staff Anesthetist

Dates	Institution and Location	Clinical Position
January 2003-May 2005	St. Thomas Hospital, Nashville, TN	Staff Nurse Emergency/Chest Pain Ctr.
July 2000-July 2003	Vanderbilt University Medical Center Trauma Unit, Nashville, TN	Staff Nurse Charge Nurse

Awards and Honors

Rosamond Gabrielson Staff Nurses of the Year
Vanderbilt University Medical Center, 2003

Research Activities and Research Funding

March, 2003-May, 2005	Post Discharge Nausea and Vomiting Study, Research Assistant. University of Kentucky IRB #07-0940
June, 2010-Present	Reviewer-***Journal of PeriAnesthesia Nursing***
June, 2014-Present	"A randomized controlled trial of anesthesia guided by BIS vs. standard care and effects on cognition". Centimole ZN, American Association of Nurse Anesthetists Foundation Grant, $26,700.

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