

AN EVALUATION OF SEDATION LEVEL USING BISPECTRAL INDEX (BIS)
AND CORRELATED ADVERSE EVENTS IN PATIENTS UNDERGOING
COLONOSCOPIES

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LIST OF ABBREVIATIONS/SYMBOLS

ASA: American Society of Anesthesiologists

ASGE: American Society for Gastrointestinal Endoscopy

BiPAP: Bi-level Positive Airway Pressure

BIS: Bispectral Index

BP: Blood Pressure

BMI: Body Mass Index

BSR: Burst Suppression Ratio

CMS: Centers for Medicare & Medicaid Services

CSI: Cerebral State Index

CVA: Cerebrovascular Accident

CRNA: Certified Registered Nurse Anesthetist

CPAP: Continuous Positive Airway Pressure

DBP: Diastolic Blood Pressure

ECG: Electrocardiogram

EEG: Electroencephalogram

EMG: Electromyography

ETCO₂: End Tidal Carbon Dioxide

ERCP: Endoscopic Retrograde Cholangiopancreatography

EUS: Endoscopic Ultrasonography

EGD: Esophagogastroduodenoscopy

FDA: Food and Drug Administration

GI: Gastrointestinal

GA: General Anesthesia

HR: Heart Rate

IRB: Institutional Review Board

IV: Intravenous

LMA: Laryngeal Mask Airway

MAP: Mean Arterial Pressure

MOAA/S: Modified Observer's Assessment of Alertness/Sedation

MAC: Monitored Anesthesia Care

NC: Nasal Cannula

N₂O: Nitrous Oxide

NROS: Non-randomized, Observational Studies

OAA/S: Observer's Assessment of Alertness/Sedation

p value: Level of significance

PS: Physical Status

PACU: Post Anesthesia Care Unit

r value: Correlation Coefficient

*r*² value: Coefficient of determination

RSS: Ramsay Sedation Score

RR: Respiratory Rate

SpO₂: Saturation of Peripheral Oxygen

SQI: Signal Quality Index

SBP: Systolic Blood Pressure

ABSTRACT

AN EVALUATION OF SEDATION LEVEL USING BISPECTRAL INDEX (BIS)
AND CORRELATED ADVERSE EVENTS IN PATIENTS UNDERGOING
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The purpose of this prospective, observational study was to provide data for anesthesia providers on current sedation practices during elective colonoscopies. This included determining the incidence of general anesthesia (GA) and the presence or absence of correlated adverse events. Additionally, this research considered if patients who are commonly consented for a MAC anesthetic should be more appropriately consented for GA.

Participants ($N = 39$) consisted of a convenience sampling of physical status (PS) I, II, and III patients scheduled for elective colonoscopies and undergoing sedation with propofol. Data was collected by researchers over a four-week period at a non-teaching rural hospital in Western North Carolina. A bispectral index (BIS) monitor was used to monitor the depth of sedation and values were utilized to determine possible correlated adverse events.

Statistical analysis showed that 100% (39/39) of patients reached levels of GA (i.e., $BIS \leq 60$) at some point during their procedure. Variables that showed a significant

correlation with the occurrence of GA were smaller body mass index (BMI) ($r = -.42$, $r^2 = .17$, $p = .008$), longer length of procedure ($r = .85$, $r^2 = .72$, $p < .001$), and the number of minutes patients experienced an absent end tidal carbon dioxide (ETCO₂) (i.e., apnea) waveform ($r = .49$, $r^2 = .24$, $p = .002$). Additionally, greater BMI correlated with a greater nadir BIS value obtained throughout the entire procedure ($r = .54$, $r^2 = .29$, $p < .001$), and was found to correlate with less time at BIS values ≤ 40 ($r = -.51$, $r^2 = .26$, $p < .001$). Longer procedures correlated with more minutes spent with BIS values ≤ 40 ($r = .43$, $r^2 = .18$, $p = .007$), and more minutes with absent ETCO₂ waveform ($r = .52$, $r^2 = .27$, $p = .001$); however, these findings were *clinically* insignificant since only one absent ETCO₂ waveform actually resulted in a decrease in saturation of peripheral oxygen (SpO₂) to $\leq 90\%$ (i.e., hypoxia), which quickly resolved with a chin lift. Additionally, the number of minutes with SpO₂ $\leq 90\%$ was not significantly correlated with the minutes of GA ($r = -.17$, $r^2 = .03$, $p = .299$).

The results of this study indicate, in patients scheduled for colonoscopies who are consented for IV GA, it is common for anesthesia providers to consistently deliver a level of sedation concordant with GA. The significance of this finding relates to the pre-study clinical observation, that endoscopic patients being consented for anesthesia designated as MAC with IV sedation, actually demonstrate intraoperative signs of GA similar to what were observed in this study. Future studies are warranted to determine the frequency of the various forms of anesthesia consent obtained for elective colonoscopies, along with research that assesses anesthetic depth with BIS monitoring in patients consented for MAC with IV sedation. Such research would help to further enhance patient safety and address potential medical legal concerns.

Keywords: Bispectral Index (BIS), colonoscopy, monitored anesthesia care (MAC), propofol sedation, adverse events.

CHAPTER ONE: BACKGROUND AND RATIONALE FOR STUDY

Introduction

Bispectral index (BIS) is frequently used as a monitor in the operating room to measure the depth of anesthesia and to help guide the titration of medications during general anesthesia (GA); however, it is not routinely used to monitor sedation levels and titrate medications during monitored anesthesia care (MAC) with intravenous (IV) sedation during endoscopic procedures. Although there have been some studies in non-anesthesia journals that have looked at the use of BIS as an adjunctive monitor for titrating a patient's sedation level with sedatives and anxiolytics (Bell et al., 2004; Drake, Chen, & Rex, 2006; Hata et al., 2009), there is limited research that has evaluated BIS values in patients undergoing sedation given by anesthesia providers for colonoscopies.

The most extensively researched electroencephalogram (EEG) device currently used to evaluate depth of anesthesia is BIS (Bruhn et al., 2003; Cortínez, Delfino, Fuentes, & Muñoz, 2007; Doufas et al., 2003; Ge, Zhuang, Y. Wang, Z. Wang, & Li, 2002; Kearse et al., 1998); it has also been shown to be useful with measuring sedation levels during endoscopic procedures (Bell et al., 2004; Hata et al., 2009; Leslie, Absalom, Kenny, 2002). Several studies have shown that GA, or deeper levels of sedation than intended, frequently occur during IV sedation (Drake et al., 2006; El Chafic, Eckert, & Rex, 2012; Patel et al., 2005; Sieber, Gottshalk, Zakriya, Mears, & Lee, 2010). One prospective, mixed-design study showed that 87% of elderly patients undergoing propofol-based sedation combined with spinal anesthesia, experienced GA (i.e., a BIS value ≤ 60) (Sieber et al., 2010). In another prospective study with an observational design, it was shown that 76% of participants undergoing endoscopic sedation were

unresponsive to "deep stimuli" (El Chafic et al., 2012). It has also been demonstrated that deeper levels of sedation during endoscopic procedures leads to an increase in complications such as aspiration, apnea, hypoxia, airway obstruction, respiratory distress, hypotension, and bradycardia (Arrowsmith, Gerstman, Fleischer, & Benjamin, 1991; Froehlich et al., 1997; McCloy, 1992; Sharma et al., 2007; Sieber et al., 2010). According to the American Society for Gastrointestinal Endoscopy (ASGE) (2007), colonoscopy remains the most effective screening option for colorectal cancer with approximately 14.2 million colonoscopies performed in the US in 2002 (Seeff et al., 2004). Therefore, the research findings of this thesis could potentially impact a significant number of patients and healthcare providers.

Purpose Statement

The purpose of this prospective, observational study was to evaluate the level of sedation achieved during the delivery of anesthesia services in patients scheduled for elective colonoscopies; this included determining the incidence of GA and correlated adverse events. Additionally, the researchers attempted to assess if this patient population should be consented for GA versus MAC with IV sedation; given the pre-study clinical observation and literature finding of colonoscopy patients being increasingly consented for MAC with IV sedation (Cohen & Benson, 2009; Cohen et al., 2006; Inadomi, Gunnarsson, Rizzo, & Fang, 2010; Rex, 2011; Siddiqui, Shafiq, & Asghar, 2012; Trummel, 2007). Consequently, the outcomes of this study could have patient safety, medical-legal, and potential reimbursement implications.

Dependent variables for this study were recorded in the preoperative holding area, procedure room, and post anesthesia care unit (PACU). They included BIS values,

saturation of peripheral oxygen (SpO₂) via pulse oximetry, oxygen delivery devices (e.g., nasal cannula [NC], non-rebreather mask), any required intraoperative changes in liters of oxygen flow from baseline oxygen flow rates, if measured, the presence or absence of end tidal carbon dioxide (ETCO₂), the number of airway assistance maneuvers (including but not limited to, chin lift, jaw thrust, combination of chin lift and jaw thrust, nasopharyngeal airway insertion, oropharyngeal airway insertion, and laryngeal mask airway [LMA] placement), heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), temperature, and respiratory rate (RR).

Justification of the Study

Only a paucity of data has been found in the anesthesia literature as it relates to BIS monitoring for patients scheduled for colonoscopies. As noted earlier, the significance of this research can potentially impact a substantial number of anesthesia providers and patients, given that over 14 million colonoscopies were estimated to be administered in the US in 2002 (Seeff et al., 2004). Additionally, the use of sedation for endoscopic procedures continues to increase throughout the world (Cohen et al., 2006) and there has been a significant growth in the number of endoscopic procedures being performed by anesthesia providers (Liu, Waxman, Main, & Mattke, 2012).

Furthermore, it is recognized that some anesthesia departments choose to consent patients for MAC with IV sedation instead of GA for elective colonoscopies. The latter form of anesthesia carries with it an increased risk for complications (Bell et al., 2004; Bhanaker et al., 2006; Petrini & Egan, 2004), especially in patients with significant comorbidities (Behrens et al., 2013; Bell et al., 2004; Sharma et al., 2007). Thus, if research reveals a GA state is being achieved with propofol dosages used by some

anesthesia providers during MAC with IV sedation, then a change in the consenting process may very well be indicated; which could potentially enhance patient safety (alter preoperative risk assessment), as well as have medical-legal implications (obtaining informed consent).

Scientific Rationale

Non-randomized, observational studies (NROS) involve viewing unmodified practice conditions and may represent a more realistic or accurate view of outcomes under these real-world conditions (Biddle, 2013). NROS may be the only means for a researcher to study a specific variable of interest or problem in their field of work as well as the only way to validate findings in the literature (Whittemore & Grey, 2006).

Although there have been some studies that have used BIS monitoring to titrate or assess a patient's sedation level during MAC anesthetics or conscious sedation (Bang et al., 2013; Drake et al., 2006; Hata et al., 2009; Sieber et al., 2010; Verma, Paswan, Prakash, S. Gupta, & P. Gupta, 2013), there has been no research that has quantified sedation levels via the BIS monitor in patients undergoing MAC with IV sedation or GA during elective colonoscopies.

Viewing actual practice conditions is important for collecting data that randomized controlled trials may not interpret correctly in certain scenarios (Black, 1996). Observational research is a type of correlational study that has many advantages such as: the ability to collect a vast amount of information in an area of interest, the capacity to examine the existence and strength of relationships between variables, and the potential to use results as a framework for future experimental studies (Whittemore &

Grey, 2006). Furthermore, observation of real-life practices can lead to the identification of previously unrecognized issues and the development of new research questions.

Assumptions

1. Anesthesia providers accurately documented the total doses of propofol given on the anesthetic record.

2. Patient's medication list was accurately recorded to assess whether patients were taking any medications that could have skewed BIS values.

3. Any preoperative sedation medications given were accurately charted by the anesthesia provider and/or nurse.

4. A patient's history of a neurological disorder such as dementia or Alzheimer's disease was accurately recorded on the surgeon's and/or endoscopist's history and physical note or anesthesia provider's pre-anesthetic assessment form.

Research Questions

The research questions this study intended to answer were:

1. What is the frequency of producing a general anesthetic state, as defined by a BIS value ≤ 60 , during elective colonoscopies in physical status (PS) I, II, and III patients?

2. Is there an association between GA (i.e., BIS value ≤ 60) and adverse perioperative and/or postoperative events (e.g., apnea, desaturation) in PS I, II, and III patients who undergo an elective colonoscopy procedure?

3. Does a relationship exist between the anesthesia providers' years or months of experience and depth of sedation achieved (as determined with BIS values) relative to the planned anesthetic?

4. Should patients who undergo an elective colonoscopy be more appropriately consented for GA versus MAC with IV sedation?

Definition of Terms

- GA: a state of loss of consciousness in patients produced by IV sedative medications or inhalational gases where patients are unresponsive to the painful stimulus of surgery. Patients usually require assistance with producing a patent airway by placement of an LMA or endotracheal tube and may also require the use of vasoactive drugs to support the cardiovascular system.
- MAC: when an anesthesia provider is required to monitor the physiological status of patients undergoing a diagnostic or minor procedure such as a colonoscopy or lump excision.
- MAC with IV sedation: When anesthesia providers administer sedation medications during MAC, including but not limited to, IV sedative and anxiolytic drugs. Patients' sedation can range from minimal to deep at the discretion of the anesthesia provider to keep the patient comfortable during the procedure.
- Sedation: a state of decreased consciousness that can range from minimal to deep produced by titration of sedative or anxiolytic medications. Patients may need assistance with breathing, maintaining a patent airway, and cardiovascular function.

- Comorbidities: major disease processes or conditions that are in addition to the patient's primary diagnosis.
- PS I: a healthy patient, also sometimes referred to as American Society of Anesthesiologists (ASA) I.
- PS II: a patient with mild systemic disease and no functional limitations, also sometimes referred to as ASA II.
- PS III: a patient with moderate to severe systemic disease resulting in some functional limitations, also sometimes referred to as ASA III.
- PS IV: a patient with severe systemic disease that is a constant threat to life and results in significant functional limitations, also sometimes referred to as ASA IV.
- PS V: a patient who is not expected to live 24 hours with or without having surgery, also sometimes referred to as ASA V.
- Dependent variables: BIS values, SpO₂, oxygen delivery device (e.g., NC, non-rebreather mask), any required intraoperative changes in liters of oxygen flow from baseline oxygen flow rates, ETCO₂ presence or absence if measured, the number of airway assistance maneuvers (including but not limited to, chin lift, jaw thrust, combination of chin lift and jaw thrust, nasopharyngeal airway insertion, and oropharyngeal airway insertion, LMA placement), HR, SBP, DBP, MAP, temperature and RR in the preoperative holding area and PACU.
- Independent variables: the anesthesia provider, total propofol dose and total dosages of any other medications given preoperatively and intraoperatively.

CHAPTER TWO: REVIEW OF THE LITERATURE

Endoscopy and Sedation

According to the ASGE, colonoscopy remains the most effective screening option for colorectal cancer, and the number of colonoscopies performed each year in the United States has significantly increased. In 2000, 19.1% of all adults aged 50 to 75 years old underwent a colonoscopy for screening; this increased to 54.9% in 2010 (National Center for Health Statistics, 2013). Furthermore, the use of sedation during endoscopy continues to increase throughout the world (Cohen et al., 2006). Sedation during endoscopy is often administered in an office or outpatient setting by nurses under the supervision of an endoscopist (Cohen et al., 2006). However, over the past several years there has been a substantial growth in the number of endoscopic procedures that incorporate procedural sedation performed by anesthesia providers, specifically from 14% in 2003, to more than 30% in 2009, and over 66% of these patients were not high risk (i.e., PS I or II) (Liu et al., 2012). During this time period, Medicare payments for endoscopic procedures doubled and payment from private insurance companies quadrupled, prompting debate about which patients should and should not receive anesthesia services for endoscopic procedures (Liu et al., 2012). Furthermore, by 2015, anesthesia providers are predicted to provide sedation for over 50% of all colonoscopies (Inadomi et al., 2010). Currently, due to the added costs of anesthesia services, it is agreed upon by major insurers (such as Aetna) that anesthesia services for endoscopic procedures is acceptable for high risk patients only (e.g., PS III or greater, age < 18 or \geq 70, “prolonged” or “complex” procedures, pregnancy, intolerance to sedative medications, uncooperativeness, agitation, history of drug or alcohol abuse, epilepsy, anatomic abnormalities that may increase risk

for airway obstruction) (Aetna, 2007). The Centers for Medicare & Medicaid Services (CMS) as well as UnitedHealthcare have also reaffirmed their insurance coverage for propofol use in colonoscopies by anesthesia professionals or gastrointestinal endoscopists (Centers for Medicare & Medicaid Services [CMS], 2011b; UnitedHealthcare, 2008).

With nurse-administered sedation, midazolam and fentanyl are often used. These agents, when titrated appropriately, are typically considered safe for producing a “light” level of sedation and patients are usually still able to respond to painful stimuli and maintain airway reflexes. Sometimes, nurses administer propofol (Diprivan) for sedation under the direction of a gastroenterologist. This is a controversial practice since patients can unintentionally reach deep levels of sedation, including GA. The 2011(b) recommendations from the ASA state that any healthcare provider administering propofol for sedation should be trained in providing GA. In addition, the manufacturer of propofol lists the following on the package insert: “for GA or MAC sedation, Diprivan Injectable Emulsion should be administered only by persons trained in the administration of GA and not involved in the conduct of the surgical/diagnostic procedure” (Hospira, 2009). Nevertheless, one large ($N = 646,080$) retrospective study argued that MAC with IV sedation is more expensive than endoscopist-directed propofol administration and that MAC with IV sedation does not result in any increased safety for routine endoscopic procedures in average-risk patients (Rex et al., 2009). A 2006 nationwide survey also found that endoscopists were more satisfied with sedation from propofol rather than sedation with a benzodiazepine combined with a narcotic. The reasons given for this preference included: better sedation, superior analgesia, reduced recovery time, faster return to usual activity, and improved quality of endoscopic examination (Cohen et al.,

2006). One large ($N = 756$), prospective, multicenter clinical trial suggested utilizing anesthesia personnel for gastrointestinal (GI) endoscopic procedures because patients were found to be significantly more satisfied ($p < .0001$) when anesthesia personnel were employed (Iravani et al., 2012). Additionally, a Cochrane review of propofol sedation during colonoscopies found that the use of propofol for sedation during colonoscopy procedures in healthy patients (unspecified age range) can speed recovery, quicken discharge times, and improve patient satisfaction without producing a greater frequency of adverse events (Singh et al., 2008).

Understanding sedation levels can be an area of confusion since GA can be regarded as a stage of sedation or as a level of anesthesia on a continuum (American Society of Anesthesiologists [ASA], Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002). For this observational study, GA will be considered a *stage of sedation* unless otherwise stated. Sedation will be defined as a drug induced depression in the level of consciousness consisting of four stages: *minimal* sedation (anxiolysis), *moderate* sedation, *deep* sedation, and *GA* (ASA, Task Force on Sedation and Analgesia by Non-Anesthesiologists, 2002). All patients receiving “anesthesia” (stage not specified) should have oxygenation, ventilation, and circulation monitored, and body temperature should be assessed if clinically significant changes are anticipated (ASA, 2011a). The ASA, in a position statement updated in 2009, further clarified these terms. This document defined and categorized levels of sedation as minimal, moderate, deep, and GA.

- *Minimal sedation*: drug induced anxiolysis with no alteration in response to verbal stimuli and no alteration in cardiovascular, respiratory, or ventilatory function

- *Moderate sedation*: is synonymous with conscious sedation and represents a drug-induced depression of consciousness during which patients respond purposefully to verbal command (with or without light tactile stimulation) and are able to maintain a patent airway without intervention, sustain adequate spontaneous ventilation, and usually maintain their cardiovascular function
- *Deep sedation*: a drug-induced depression of consciousness during which patients cannot be easily aroused but can respond purposefully to repeated or painful stimulation; independent ventilatory function may be impaired, airway assistance may be required to maintain airway patency, and spontaneous ventilation may be inadequate; cardiovascular function is usually maintained
- *GA*: a drug-induced loss of consciousness during which patients are not arousable even by painful stimulation, the ability to maintain independent ventilation is usually impaired, assistance is often needed to maintain a patent airway, positive pressure ventilation may be needed, and cardiovascular function may be compromised

The ASA in 2013 defined MAC as including varying levels of sedation (i.e., minimal, moderate, or deep), but also indicated if a patient becomes unconscious and the ability to respond purposefully is lost, GA has consequently occurred regardless of the need for airway instrumentation. For clarification, there remains in the literature inconsistency with the use of the acronym MAC. Some authors reference this abbreviation to be synonymous with MAC with IV sedation; while others view MAC as representing the monitoring of diverse physiologic parameters without the concurrent use of IV sedatives.

Propofol has a rapid onset and fast recovery time, making it the most commonly used agent for producing minimal and moderate sedation during endoscopy procedures (American Society for Gastrointestinal Endoscopy [ASGE], Standards of Practice Committee, 2008; Cohen et al., 2007; Zakko, Seifert, & Gross, 1999). Propofol based sedation in GI endoscopy procedures increased to 26% of the total U.S. volume by 2006 (Cohen et al., 2006) and a recent study projected that propofol will be used in 53% of endoscopy cases by 2015 (Inadomi et al., 2010). Decreased myocardial contractility and respiratory depression are sometimes seen with the use of propofol; however, these effects can usually be reversed by stopping the infusion or by decreasing the dose (Cohen et al., 2007).

The ASGE Standards of Practice Committee (2008) provides updated guidelines for sedation during GI endoscopy. They state that sedation for these procedures is patient specific, ranging from no sedation at all to GA. Moderate sedation, as defined by the ASA, is usually considered adequate for routine, uncomplicated GI endoscopy procedures. The guidelines further indicate that if propofol is being used for sedation during these procedures, then physiologic monitoring should be incorporated and include the use of pulse oximetry, electrocardiogram (ECG), and intermittent blood pressure (BP) measurements. Capnography should also be considered because it may decrease the risks associated with deep sedation (Nelson et al., 2000). Propofol can be titrated to moderate sedation when combined with low doses of opioids and benzodiazepines, but since deep levels of sedation can quickly occur when propofol is used with or without these sedative agents, providers should always be prepared for deep sedation (Cohen, Hightower, Wood, Miller, & Aisenberg, 2004; Rex, 2011; VanNatta & Rex, 2006). This further

confirms the occurrence of deep sedation when propofol is used for sedation. Overall, the ASGE Standards of Practice Committee recommends always focusing on maximizing patient comfort while minimizing risk during GI endoscopy procedures.

Additional sedation recommendations were provided by the American Gastroenterological Association Institute after completing a review of endoscopic sedation in 2007 (Cohen et al., 2007). This article was designed to standardize the practice of endoscopic sedation. Similar to the previous article from the ASGE Standards of Practice Committee, it was suggested that the overall goal of endoscopic sedation is to keep the patient comfortable without producing side effects from drug administration. They emphasized that endoscopy monitoring should not only include physiologic assessment (e.g., BP, HR, SpO₂) but visual assessment (e.g., grimacing, movement) as well because the latter can often identify potential complications sooner than physiologic monitoring.

Comparable Research

Only a few researchers have evaluated the use of BIS monitoring during MAC anesthetics with IV sedation or conscious sedation (Drake et al., 2006; Hata et al., 2009; Sieber et al., 2010). These studies are diverse in their findings and difficult to compare since there is large variability in their designs. Additional research using the BIS monitor during MAC with IV sedation during endoscopic procedures could lead to a clearer understanding of the sedation levels (and perhaps unintended GA) actually achieved.

In an attempt to evaluate the usefulness of BIS monitoring in patients undergoing endoscopic submucosal dissection for removal of neoplasms from the digestive tract, one randomized controlled trial was conducted over a three-year period (Hata et al., 2009). A

total of 366 patients were included in the study. Propofol was titrated to a pre-determined BIS value; 56 to 65 in one group of patients, and 70 to 75 in another group of patients. All patients received 2 L/min of oxygen via NC, and pentazocine (Talwin) 15 mg via continuous IV infusion (unspecified duration) immediately preceding initiation of sedation. A propofol bolus of 40 mg was then administered to all patients, followed by a continuous infusion at 50 mcg/kg/min, and was titrated by an anesthetist or an “endoscopy specialist trained in anesthesia” to maintain desired BIS values. Pulse oximetry, BP and three lead ECG were monitored at unspecified intervals. Data analysis showed that 3.6% of subjects (13/366) in the 56 to 65 BIS range experienced adverse events: six had bradycardia (HR <50 bpm), four had hypotension (SBP < 90 mmHg), two had respiratory depression (patient needing mandatory ventilation), and one experienced delayed awakening (patient did not awaken within 15 minutes after propofol discontinuation). There were no adverse events when propofol was titrated to BIS values between 70 and 75. This study concluded that BIS is useful for the safe performance of endoscopic submucosal dissection when propofol is titrated to a BIS value between 70 and 75.

The methodology of this study had significant limitations. The first of these being there were no baseline BIS values recorded. This limitation made it difficult to determine the actual percent change in BIS values between the non-sedated and sedated states, and how that may have correlated with adverse events. There was also no mention of other airway interventions, such as jaw thrust or chin lift, so it is unclear how many participants in the study experienced obstruction of their airway. Furthermore, there was no predetermined sample size for each group. Instead, when adverse effects started to occur

in the first group of patients (BIS values maintained at 56 to 65), data collection for that group stopped, and the target BIS value was increased. Data collection was then initiated for the second group (BIS values maintained at 70 to 75). Consequently, maintaining BIS values between 56 and 65 could have led to a higher number of recorded adverse events if data were collected on a pre-determined number of patients. Other limitations included the lack of statistical consideration for PS classification, the omission of *p* values, and failure to report the length of the procedure or exclusion criteria. In general, the study suggested a greater number of adverse events may occur in patients undergoing endoscopic submucosal dissection procedures when BIS values are maintained between 56 and 65.

Research has shown that BIS values ≤ 60 are consistent with a state of GA (Bell et al., 2004; Cortínez et al., 2007; Drake et al., 2006; Hata et al., 2009). The BIS pocket guide and other publications have also indicated that BIS values between 40 and 60 correlate with GA (Johansen, 2006; Kelley, 2010). One prospective, mixed design study examined elderly (> 65 years old) patients undergoing spinal anesthesia with sedation using propofol during repair of hip fractures (Sieber et al., 2010). The focus of this research was to determine if sedation in this patient population was equivalent to GA via BIS monitoring (values ≤ 60). Forty elderly patients undergoing repair for hip fractures were enrolled in the study. Additional criteria for participant selection were not provided by the researchers, and specific comorbidities were not discussed. The 40 subjects were divided into a control group ($n = 15$) that had no alteration in standardized practice or the way drugs were administered, and an intervention group ($n = 25$) that had propofol titrated based on an alertness and sedation scale, known as the observer's assessment of

alertness/sedation (OAA/S) (see Appendix A). The OAA/S is an assessment tool used to subjectively gauge the level of sedation on a five point scale; the lowest score on the scale is 0 and indicates no response to noxious stimuli, and the highest score is 5 and indicates the patient responds to their name spoken in a normal tone. The goal with the intervention group was for the anesthesiologist to maintain a minimum level of sedation by keeping the participant at a sedation level of 4 (i.e., lethargic response to name spoken in a normal tone) or 5 on the OAA/S scale. Scores were measured every 5 minutes, and if the OAA/S score was < 4 , the propofol infusion was reduced. Both groups had BIS monitoring throughout the surgical procedure, which was compared between groups to determine how much time was spent in a state of GA, defined as a BIS value ≤ 60 . Results showed that the control group, which had no alteration in propofol administration in response to an OAA/S score, had 86.7% (13/15) of its participants experience sedation levels consistent with GA (BIS values ≤ 60). The control group also spent a mean surgical time of 32.2% at BIS values consistent with GA. In the intervention group, the OAA/S scale was used to maintain minimal sedation. Propofol was the primary sedative and was administered along with fentanyl as needed. With this group, 44% (11/25) of participants experienced GA for at least 1 minute, and spent a mean surgical time of 5% with BIS values consistent with GA ($p < .001$). The number of anesthesiologists participating in the study was not disclosed; however there was not a significant difference ($p = .797$) in the dosing of fentanyl in the control group ($1.3 \text{ mcg/kg} \pm 1.0 \text{ mcg/kg}$) and in the intervention group ($1.5 \text{ mcg/kg} \pm 2.6 \text{ mcg/kg}$). There was also no significance in the distribution of the various PS classifications between groups ($p = .486$), level of spinal anesthesia ($p = .693$), or length of surgery ($p = .067$). A significant

difference was found for the following variables in the intervention group: lower propofol dose ($p = .014$), older patients ($p = .049$) (83 ± 7 in the intervention group vs. 78 ± 8 in the control group), and lower midazolam dose ($p = .002$). Statistical analysis also showed a significant difference ($p < .001$) in the amount of surgical time spent at sedation levels consistent with GA ($BIS \leq 60$) in the control group versus the intervention group. It was concluded that GA occurs frequently in elderly patients undergoing spinal anesthesia combined with propofol sedation, and titrating propofol to a previously determined BIS value range decreases this occurrence.

Unfortunately, the investigators did not report their exclusion criteria, or the technique used for administering propofol (e.g., infusion, bolus, combination of infusion and bolus), which decreased the external validity of this study. Furthermore, internal validity was weakened because there may have been failure to exclude patients with potential alterations in baseline BIS values (e.g., cerebrovascular accident [CVA], dementia). In spite of these limitations, this research seems to offer some evidence that GA commonly occurs in elderly patients undergoing spinal anesthesia with propofol sedation for repair of hip fractures. Furthermore, this study provides an impetus for additional research into the occurrence of unintended GA in other patients scheduled for surgery or diagnostic procedures.

Of interest during the literature review was the discovering of only one study that suggested there is no benefit to using BIS monitoring with propofol sedation for colonoscopies (Drake et al., 2006). This was a randomized control trial that evaluated the usefulness of BIS monitoring as an adjunct to nurse-administered propofol sedation during colonoscopy procedures. Effectiveness was determined by measurements of

reduction in recovery time and total doses of propofol administered to patients. All study participants ($N = 102$) underwent an elective colonoscopy and were over 18 years old with a PS classification of I or II. The two nurses and one endoscopist participating in this study were said to have had “several years” of endoscopy experience. Participants were randomly divided into one of two phases (see Table 1), each consisting of an intervention group and a control group. In phase 1 ($n = 47$) and phase 2 ($n = 55$), the endoscopist teams (i.e., one of the two nurses administering the propofol and the endoscopist) were randomly assigned to either the control group ($n = 24$, phase 1; $n = 26$, phase 2) or the intervention group ($n = 23$, phase 1; $n = 29$, phase 2). For the control group in both phases, the endoscopist teams were blinded to BIS values, and were instructed to titrate sedation as they normally would within their routine practice. This included considerations for physiologic changes (i.e., HR, BP, ventilatory effort) and subjective assessment of patient discomfort, undesired movement, and the modified observer's assessment of alertness and sedation (MOAA/S) scale (see Appendix B). In the intervention group of phase 1 the endoscopy team was not blinded to BIS values. They were instructed to only use BIS values as an “adjunctive tool” and to avoid titration of propofol in response to BIS values. At the end of phase 1, the researchers conducted analysis before proceeding into phase 2. They found no difference in propofol dose ($p = .45$) or recovery times ($p = .34$) with the blinded (control) versus non-blinded (intervention) groups. Just as in phase 1, the endoscopy team was blinded to BIS values in the control group for phase 2 and were instructed to titrate sedation as they normally would within their routine practice. In the intervention group of phase 2, BIS was used as the primary endpoint for sedation with a target value of 60 to 70 (i.e., deep sedation).

The endoscopy team was instructed to refrain from giving propofol boluses when BIS values were < 60 , except when the patient was believed to be experiencing significant discomfort or moving enough to interfere with the procedure. For all patients, in both phase 1 and phase 2, propofol was the only sedative agent administered and all patients received an initial 40 mg bolus, followed by incremental boluses of 10 to 20 mg. BIS values, HR, SpO₂, and 3-lead ECG were recorded continuously on all patients, but it was not stated how often these variables were documented. Additionally, a baseline BP was obtained, followed by BP recordings every 5 minutes, and the total dose of propofol was documented. Vital sign recordings were continued in the PACU for up to 1 hour or until discharge, whichever came first.

Table 1

Study Design Characteristics

Group	Phase 1		Phase 2	
	<i>n</i>	BIS value	<i>n</i>	BIS value
Control ^a	24	Blinded	26	Blinded
Intervention	23	Used as "adjunctive tool" and not used for propofol titration	29	Targeted to 60-70 with propofol

Note. *N* = 102. BIS = bispectral index

^aSedation titrated according to routine practice

Statistical analysis for both phase 1 and phase 2 showed no significant difference between intervention and control groups in average BIS values ($p = .82$, phase I; $p = .57$, phase II), sedation levels (p values not provided) using the MOAA/S scale (see Appendix B), propofol dose ($p = .45$, phase I; $p = .92$, phase II), recovery time ($p = .34$, phase I; $p = .27$, phase II), or complications. There were no significant differences found between phase 1 and phase 2 in regards to patient satisfaction or recall, however, there were no p

values provided to validate the accuracy of this finding. Oxygen desaturation, defined as an $\text{SpO}_2 < 90\%$, occurred in 2.9% (3/102) of patients and resolved with a chin lift maneuver, deep breathing, or cessation of propofol administration. The phase or phases in which these adverse events occurred was not specified by the investigators. Patients were found to “regularly” experience BIS values consistent with GA during “some part” of the procedure, but the investigators did not offer any defining characteristics or exact frequency of this occurrence. Furthermore, the researchers postulated the possibility that there was no apparent benefit from monitoring with BIS because the endoscopy nurses were already very experienced with propofol administration when the study began. This acknowledgement suggests the endoscopist team assigned to the Phase 2 intervention group may have allowed their propofol titration bias to disregard the prescribed 60 to 70 BIS target value. Lastly, the investigators acknowledged that the sample size was not sufficient to rule out a safety benefit of BIS.

Deep Sedation Occurs with Endoscopy

In clinical practice, it is possible that deep sedation occurs during endoscopy procedures. Some studies have specifically identified this occurrence and the potential associated adverse events (El Chafic et al., 2012; Patel et al., 2005; Soto, Fu, Smith, & Miguel, 2005). In 2012, one such study examined the intra-procedural incidence of coughing, hemodynamic changes, and oxygen desaturation and their correlation with clinical factors and sedation (El Chafic et al., 2012). Although BIS was not used to provide objective data, there was subjective validation of deep sedation occurring during endoscopy procedures. This prospective observational study involved a total of 747 consecutive patients undergoing nonemergent endoscopy procedures (El Chafic et al.,

2012). These procedures consisted of esophagogastroduodenoscopy (EGD) ($n = 254$), colonoscopy ($n = 338$), combination of colonoscopy and EGD ($n = 80$), endoscopic ultrasonography (EUS) ($n = 65$), and others, which were comprised of mostly push enteroscopy and deep small bowel enteroscopy ($n = 20$). Patients were sedated with propofol, and/or midazolam, and/or fentanyl by a registered nurse under the supervision of an endoscopist. Specific dosages and method of delivery (e.g., infusion, bolus) of sedative medications and opioids were not provided, but 63% (476/747) received a combination of propofol, midazolam and fentanyl; 26% (197/747) received a combination of fentanyl and midazolam; 9% (66/747) received propofol only; 1% (10/747) received propofol and midazolam; and 1% (5/747) received propofol and fentanyl. Data recording included: BP every 5 minutes, HR and sedation levels every 2 minutes, and SpO₂ every minute. All patients received oxygen via NC at 4 L/min. Sedation level was determined by using a subjective tool known as the MOAA/S scale (see Appendix B). The MOAA/S scale ranges from 0 to 6, with values ≤ 1 being considered deep sedation, however the scale provides no assessment of GA. Seventy eight percent (593/757) of patients were reported by the researchers to have experienced deep sedation (i.e., MOAA/S ≤ 1) or GA (undefined) during their procedure. Twenty four percent (181/757) of patients were smokers with or without COPD, 8% (59/757) had asthma, 5% were smokers and had asthma (37/757), and 63% (480/757) did not have respiratory disease.

Oxygen saturation dropped from baseline (values not provided) more than 4% in 95% of patients, with 4% dropping below 90% saturation and 2% dropping below 85% saturation. No data was provided indicating the existence of a correlation between

decreases in SpO₂ and medication administration times. However, “deeper” sedation was found to be the only significant risk factor for a decline in SpO₂ to below 90% ($p = .02$). Mean SBP dropped an average of 7.3%, and DBP declined an average of 5.6%, with all changes resolving spontaneously, but within an unspecified amount of time. Regardless of dose and type of agents used, there was an 8.53% greater decrease in SBP with colonoscopy procedures than all other procedures combined ($p < .0001$). Thirteen percent of patients experienced cough at least once. Cough occurring one or more times was greater in patients receiving propofol with or without other agents ($p = .0008$), and in non-smokers ($p = .05$).

The investigators speculated that coughing was associated with upper endoscopy procedures, the use of propofol, longer procedures (unspecified length) ($p = .0001$), and with the development of hiccups ($p = .01$). The clinical implication of this being that coughing can lead to microaspiration of gastric contents. Therefore, it is important for healthcare providers to exercise constant vigilance for signs of aspiration, especially in patients experiencing hiccups, during repositioning ($p = .06$), and in those undergoing “longer” procedures, “deeper” sedation (no p value provided), or both. Furthermore, this study supported a possible association between the dependent variables of oxygen desaturation ($p = .02$) and hypotension ($p = .05$) in patients who received a deep level of sedation (i.e., MOAA/S ≤ 1) during endoscopic procedures, as opposed to lighter levels of sedation.

Some limitations to this study do exist. First, the researchers indicate that some patients experienced a level of sedation consistent with GA; however, there were no criteria for GA provided. Additionally, sedation was provided by nurses working in

conjunction with endoscopists, so the results may not be consistent with those that may be obtained from the administration of sedation by certified registered nurse anesthetists (CRNA) or anesthesiologists. Also, a subjective tool (MOAA/S) was used for measuring sedation, allowing the potential for some variability in interpretation, and it did not include criteria for determining the occurrence of GA. Lastly, PS classification was not included in the presented data. In conclusion, this study identified the occurrence of deep sedation during endoscopic procedures along with some potential risks associated with deep sedation during endoscopic procedures.

Another prospective, observational study sought to determine if deep sedation occurred frequently during elective endoscopy procedures with meperidine and midazolam (Patel et al., 2005). A sample size of 80 patients was administered IV midazolam (EGD $3.9 \text{ mg} \pm 1.48 \text{ mg}$, colonoscopy $4.38 \text{ mg} \pm 2.13 \text{ mg}$, endoscopic retrograde cholangiopancreatography [ERCP] $5.5 \text{ mg} \pm 2.72 \text{ mg}$, EUS $5 \text{ mg} \pm 1.56 \text{ mg}$) and meperidine (EGD $77.25 \text{ mg} \pm 22.27 \text{ mg}$, colonoscopy $89.38 \text{ mg} \pm 31.22 \text{ mg}$, ERCP $103.75 \text{ mg} \pm 31.70 \text{ mg}$, EUS $101.25 \text{ mg} \pm 23.61 \text{ mg}$) for sedation. All participants were over 18 years old, and either PS I or II presenting for EGD ($n = 20$), colonoscopy ($n = 20$), ERCP ($n = 20$), or EUS ($n = 20$). Similar to the previously discussed study (El Chafic et al., 2012), the MOAA/S scale was used for measurement of sedation levels. However, the investigators modified the scale by assigning deep sedation a value of 1 or 2 instead of ≤ 1 and eliminating the value of 0. Initial doses of sedation medications (meperidine 50 to 75 mg and midazolam 2 to 3 mg) were at the discretion of the endoscopist and administered by a nurse. Supplementary doses were given in increments of 25 to 50 mg of meperidine or 1 to 2 mg of midazolam based on assessments (i.e., signs

of discomfort, restlessness, or agitation that were not related to hypoxemia) by the endoscopist and nurse. A single independent physician observed all procedures, documented procedural data, and completed MOAA/S assessments. Recordings of BP, HR, SpO₂, and MOAA/S score were started with the initial dose of sedation medication and repeated every 3 minutes. Additionally, the time and dose of boluses of sedation medication, oxygen desaturation (i.e., < 90%), hypotension (i.e., < 90/50mmHg), the need for emergent airway protection or reversal agents, and the lowest intraprocedural MOAA/S score were recorded. Oxygen was administered via NC only when SpO₂ decreased to < 90%, and IV normal saline was given (unspecified dose) for hypotension. The endoscopist and registered nurse were blinded to the independent physician's MOAA/S assessments.

Results indicated that 68% (54/80) of patients experienced deep sedation, with 45% (9/20) occurring in colonoscopies, 60% (12/20) in EGDs, 85% (17/20) in ERCPs, and 80% (16/20) in EUSs. This is consistent with the results described in the previous study in that 78% (593/757) of patients experienced deep sedation (i.e., MOAA/S ≤ 1) or GA (El Chafic et al., 2012). In the current study, it was also found that transient oxygen desaturation (SpO₂ < 90%) occurred in 58% (46/80) of patients; however, the existence of a correlation with medication doses or times was not indicated, and none resulted in severe adverse events, such as those requiring reversal agents, bag-mask ventilation, or intubation. The procedure type was the only predictor of reaching deep sedation, with increased occurrence during more advanced endoscopic procedures (i.e., ERCP and EUS). In conclusion, the investigators found that deep sedation occurs frequently during elective endoscopy when meperidine and midazolam are used in an attempt to produce

moderate sedation. Nevertheless, it appears endoscopic procedures may be safely performed with analgesia and sedation that reaches a level of deep sedation, as long as there is “appropriate monitoring.” Additionally, the authors hypothesized that deep sedation and oxygen desaturation might occur more frequently in patients with a higher PS status and suggested that future studies include these patients.

There were numerous limitations with this study. Similar to the previous study (El Chafic et.al, 2012), the investigators chose to use a subjective tool for measuring sedation levels; therefore objective data could not be presented. This assessment tool did not have a value for GA, so it is possible that some patients actually experienced GA but it could not be measured. Another concern was that the researchers stated the endoscopist and assistant were blinded to sedation assessments; however, this is not possible since they would need to verbally stimulate or physically shake the patients to accurately assess their MOAA/S score. This ultimately could have led to inadequate blinding. In addition, sedation levels and hemodynamic values were only assessed every 3 minutes; this restricts the ability to determine how long deep sedation occurred, a limitation the researchers acknowledged. Lastly, midazolam and meperidine were chosen for sedation. These are not medications commonly used by anesthesia providers in this clinical setting, thus severely impacting the external validity of this research from an anesthesia perspective. Nonetheless, this study validates that deep sedation likely occurs with the administration of midazolam and meperidine during endoscopic procedures.

Endoscopy, Deep Sedation, and Complications

Sedation for GI endoscopy has been shown to produce serious complications (57 out of 388,404 patients), and most are associated with a PS classification of III or greater

and emergency procedures (Behrens et al., 2013). Hypoxia and hypotension are particularly common occurrences at deep levels of sedation. In an assessment of complications in patients undergoing GI interventional procedures ($N = 100$), one study found that BIS values < 50 were associated with hypoxia, hypotension, or agitation (p values not provided) (Bell et al., 2004). However, patients with BIS values > 78 did not experience hypotension, which shows that deeper levels of sedation can correlate with increased adverse events. This research is discussed more thoroughly later on.

In one retrospective study, an “unplanned cardiopulmonary event” was found to occur in 3.5 of 1,000 patients undergoing diagnostic colonoscopy (Silvas, Nebel, Rogers, Sugawa, & Mandelstam, 1976). Similarly, another retrospective study established that when using midazolam and diazepam for conscious sedation during GI endoscopic procedures ($N = 21,011$), serious cardiorespiratory events accounted for 51.3% of complications in 8,919 colonoscopies, and 5.4 out of 1,000 complications overall (Arrowsmith et al., 1991). In both of these studies, serious cardiorespiratory events were not specifically defined, the actual depth of sedation was not evaluated, and the specialty of the providers administering sedation was not indicated.

Additionally, a large national study evaluated the incidence of unplanned cardiopulmonary events after GI endoscopy (Sharma et al., 2007). This was a retrospective review of 324,737 endoscopic procedures: 174,255 colonoscopies, 140,692 EGDs, 6,092 ERCPs, and 3,698 EUSs. All patients underwent GI endoscopy with conscious sedation, but the specialties of the administering persons were not reported. There were no exclusions based on demographic data or PS score, however, all patients that received sedation with propofol were excluded. The goal of this study was to

determine risk factors that may predict the occurrence of unplanned cardiopulmonary events after GI endoscopy. Data was obtained on GI endoscopies from April 1997 to March 2002 and was voluntarily entered in to a database by endoscopists. Results indicate that “unplanned events” were reported in 4,477 (1.4%) of procedures performed with conscious sedation, and 3,011 (0.9%) were unplanned cardiopulmonary events (e.g., hypoxia, respiratory distress, chest pain, pulmonary edema, arrhythmias, hypotension, hypertension). There were a total of 39 (0.01%) deaths, 28 (0.008%) of which were related to cardiopulmonary causes. Patient age was a significant independent predictor of cardiopulmonary unplanned events ($p < .001$), as well as PS classification, with increased incidence associated with higher PS classification: PS I = 0.7%, PS II = 1%, PS III = 1.8%, PS IV = 3.7%, and PS V = 7.6%. Additionally, inpatient setting ($p < .001$), non-university practice sites ($p = .005$), the need for reversal medications ($p < .001$), the use of supplemental oxygen ($p < .001$), and involvement of a trainee ($p < .001$) were significant independent predictors of unplanned cardiopulmonary events as well. It was determined that gender ($p = .5$) and race ($p = .16$) were not significantly correlated with unplanned cardiopulmonary events.

As previously mentioned, endoscopies performed under propofol sedation were excluded. This is a significant limitation to the external validity of the research since propofol is commonly used by anesthesia providers for sedation during GI endoscopy procedures. Additionally, all procedures were documented to have been performed under conscious sedation. There was no data provided for establishing the actual sedation level of the patients. Furthermore, the retrospective design of this study limits the internal validity. Lastly, there was no information included about intra-procedure complications.

Nevertheless, this study provides data suggesting that complications after endoscopy can be related to cardiorespiratory events.

One common cardiopulmonary complication that can occur during MAC with IV sedation is apnea. In one randomized controlled trial ($N = 39$), the incidence was shown to be 26% (Soto, Fu, Vila, & Miguel, 2004), and was more common when deeper levels of sedation were obtained (Soto et al., 2005). In a second prospective observational study, the investigators used BIS and capnography monitoring to determine if BIS values correlated with apnea in 99 patients receiving MAC with IV sedation. Sedative drugs included propofol ($n = 84$) combined with midazolam ($n = 82$) and fentanyl ($n = 35$) which were given during orthopedic, vascular, gastroenterology, or “pain” procedures (Soto et al., 2005). Patients received an unspecified combination and dosage of these drugs at the discretion of the anesthesia provider – either an anesthesia resident (year of residency and total number of providers not reported) or nurse anesthetist under the supervision of an anesthesiologist. The anesthesia provider was blinded to both BIS and capnography values, and all patients were administered supplemental oxygen of at least 2 L/min. Data was collected at “baseline” and every 3 minutes (duration not reported). The investigators notified the anesthesia provider when unnoticed apnea or airway obstruction occurred for 60 seconds, as detected by capnography.

Statistical analysis of the data showed 49.5% (49/99) of patients experienced at least one episode of continuous apnea (i.e., apnea for 60 seconds), none of which were identified by the anesthesia provider. Twenty patients experienced oxygen desaturation below 90% at least once, with the lowest SpO₂ being 88%, and 17 of these 20 patients also experienced apnea. Patients with apnea had a mean BIS value of 71 ± 14 , and those

without apnea had a mean BIS value of 83 ± 12 , thus the incidence of apnea was shown to be greater in patients with lower average BIS values than those with higher average BIS values. Additionally, the mean BIS value in the 3 minutes immediately preceding apnea was 55 ± 18 , which is largely consistent with GA. Regression analysis showed the likelihood of apnea occurring was 50% when BIS values were approximately 57, and specific medication combinations did not predict the occurrence of apnea. There were no significant differences in age (51 ± 13), sex, or comorbidities among all participants. Overall, these results demonstrate that lower BIS values correlate with increased risk for apnea during MAC with IV sedation.

Aspiration can also be a complication of sedation. From January 2000 to November 2009, a population based analysis of all procedural claims for outpatient diagnostic colonoscopies in patients who were Medicare beneficiaries, showed an increased incidence of aspiration when anesthesia providers were used for the administration of sedation (Cooper, Kou, & Rex, 2013). Since this was a retrospective review and Medicare billing codes were used to establish anesthesia involvement, demographic data (e.g., type of anesthesia provider and years of experience) was not reported. A total of 165,527 diagnostic colonoscopies in 100,359 patients were analyzed, of which 35,128 (21.2%) were anesthesia-assisted and 130,299 (78.7%) were non-anesthesia-assisted. A 30-day period of Medicare claims after each diagnostic colonoscopy was reviewed for the occurrence of aspiration pneumonia, colonic perforation, splenic injury/rupture, or splenectomy. The overall 30-day mortality was similar for colonoscopies assisted by anesthesia (0.32%) versus non-anesthesia (0.28%) providers ($p = .29$). Aspiration, however, occurred in 173 patients and with more

frequency in the anesthesia-assisted group ($p = .02$). Splenic perforation occurred in 101 patients and splenic rupture occurred in 12 patients, but statistically the occurrences of these complications (i.e., splenic perforation or rupture) were similar between anesthesia-assisted colonoscopies and non-anesthesia-assisted colonoscopies.

The increased risk of aspiration pneumonia with anesthesia-assisted colonoscopies was thought to be related to the deeper levels of sedation that often occur with the use of propofol, which would cause decreased ability of the patient to protect their airway. However, the authors admit this was a non-randomized study and the rationale for some patients receiving anesthesia assistance and not others was unknown, thus the patients receiving anesthesia-assisted colonoscopies could have had an increased number of comorbidities that would also increase their risk for aspiration pneumonia. Additionally, anesthesia records were not evaluated, so it was assumed that anesthesia providers only used propofol for sedation in the majority of colonoscopy procedures.

BIS as a Tool for Measuring Sedation

The most recent update on the history and current uses of BIS monitoring was published in 2006 (Johansen, 2006). The BIS monitor is essentially a modified EEG that can reflect the decreased cerebral metabolic rate caused by anesthetic agents (Kelley, 2010). It was first introduced in 1996 to help monitor cortical function during hypnotic states and in 2003 it was approved by the Food and Drug Administration (FDA) for reducing the incidence of intraoperative awareness (Johansen, 2006; Kelley, 2010). BIS values are measured on a scale of 0 to 100. A value of 0 indicates complete cortical suppression (i.e., an isoelectric EEG signal) and a value of 100 indicates the patient is awake (Johansen, 2006; Kelley, 2010). In actuality, values of 93 or above indicate a state

of wakefulness (Johansen, 2006). Sedation is said to occur with BIS values between 65 and 85, and GA occurs between values of 45 and 60 (Johansen, 2006).

BIS does have some limitations. Elevated electromyographic (EMG) activity (i.e., high frequency, low amplitude waves), which occurs from increased muscle tone in the forehead or improper electrode placement, may falsely increase BIS values (Johansen, 2006). The signal quality index (SQI) signifies the reliability of the recorded BIS value, and should be considered, along with hemodynamics (e.g., BP, HR, RR) and visual assessment of the patient, when evaluating depth of sedation (Johansen, 2006; Kelley, 2010). In regards to SQI, a number closer to 100 is more reliable than a number closer to 0 (e.g., an SQI value of 97 means that the BIS value is more trustworthy than it would be if the SQI value is 34). Furthermore, BIS values may not be accurate when monitored during administration of ketamine (Hans, Dewandre, Brichant, & Bonhomme, 2005; Roffey, Mikhail, & Thangathurai, 2000) or nitrous oxide (N₂O) (Coste, Guignard, Menigaux & Chauvin, 2000; Ghoneim, 2001). Additionally, baseline and/or continuous values may be altered in patients with dementia (Renna, Handy, & Shah, 2003) and those with neurological dysfunction such as brain injury or postictal states (Covidien, 2011).

Some studies have validated BIS as being “comparable” to other methods of assessing sedation level, such as the cerebral state index (CSI) (Cortínez et al., 2007) and Ramsay Sedation Score (RSS) (see Appendix C) (Bell et al., 2004). An overview of these studies shows BIS is an accurate tool for monitoring level of sedation.

CSI is similar to BIS in that it produces a numerical value that corresponds to hypnotic states during anesthesia by integrating EEG signals; also like BIS, awake patients have values closer to 100 that progressively decrease as sedation becomes deeper

(Anderson & Jakobsson, 2006; Cortínez et al., 2007; Jensen et al., 2006). The mechanisms for producing these values differ; CSI integrates information from EEG signals via ratios (i.e., time to frequency) and fuzzy logic (i.e., statements are true, false, or on a continuum and based on the logic *if X equals Y then Z*), whereas BIS uses several fragments of an EEG in a mathematical model (i.e., precise calculations) to form a numerical value (Cortínez et al., 2007; Jensen et al., 2006). Both have been shown to produce a comparable numerical value for similar corresponding clinical states (Anderson & Jakobsson, 2006; Cortínez et al., 2007; Jensen et al., 2006).

One prospective, observational study performed in 2007 compared EEG recordings with CSI and BIS over a wide range of sedation levels (Cortínez et al., 2007). Patients ($N=15$) were all healthy (i.e., PS I), aged 20 to 40, and all underwent GA for surgery. After entering the operating room, but before any medications were administered, baseline CSI and BIS values were recorded for a period of 2 minutes. Then a propofol infusion was started at 300 ml/hr (specific dose not provided) and CSI and BIS values were recorded until the burst suppression ratio (BSR) was $\geq 60\%$ in both monitors or until MAP was < 50 mmHg. This allowed for the evaluation of the effect of burst suppression activity on both monitors. Of note, burst suppression is an EEG pattern with alternating slow waves of high amplitude (i.e., burst) and flat EEG (i.e., suppression), and BSR is the fraction of EEG spent in suppression (Amzica, 2009). The study protocol assessed every 5 seconds after starting the propofol infusion, three clinical end points to determine the patient's level of consciousness. These included: loss of response to verbal command, loss of eyelash reflex, and drop of a weighted syringe from the patient's hand.

Baseline variability, prediction probability, and agreement analysis between indices were also evaluated.

Statistical analysis showed significance for BIS and CSI correlation with BSR ($p < .01$). Analysis of the effects of burst suppression on CSI and BIS showed that the CSI performance was nearly completely dependent on BSR at all BSR values. However, BIS was not significantly affected until a BSR was $\geq 40\%$ (p values not provided). The overall performance of both monitors were similar, however BIS may have been superior for evaluating intermediate anesthetic levels (i.e., values between 60 to 40), whereas CSI was better for evaluating deeper anesthetic levels (i.e., values between 40 to 20). These results are consistent with other studies comparing BIS and CSI (Anderson & Jakobsson, 2006; Jensen et al., 2006)

Limitations of this study (Cortínez et al., 2007) included not reporting the type of surgery being performed, how GA was maintained (e.g., titration of propofol infusion, volatile anesthetic), and EMG activity. Additionally, there was no correction for possible time delays in index calculations (i.e., lag time from actual cortical suppression to visible CSI and BIS values). This is a limitation to the internal validity of this research, but it increased the external validity because it evaluated what would be seen in actual clinical situations.

Another study compared BIS to the subjective RSS (see Appendix C) for measurement of conscious sedation in GI interventional procedures such as ERCP, percutaneous transhepatic stent insertion, pancreatic pseudocyst drainage, gastrostomy, and oesophageal, duodenal, and colonic stents (Bell et al., 2004). The RSS is a subjective assessment tool used to evaluate a patient's level of sedation. It ranks the patient's

response to either verbal or physical stimuli on a number scale from 1, meaning the patient is anxious and agitated or restless or both, to 6, meaning the patient is unresponsive to a light glabellar tap (i.e., tap on the forehead between the eyebrows) or loud auditory stimulus. One hundred adult patients with a mean age of 69 years were studied. Participants' PS classifications were as follows: 24 PS I, 43 PS II, 25 PS III, 7 PS IV, and 1 PS V. Furthermore, 22 subjects had ischemic heart disease, 10 had diabetes mellitus, eight had chronic obstructive pulmonary disease, two were said to be demented, and one patient was dysarthric (i.e., had imperfect speech articulation).

Patients were divided into two groups with 30 subjects in group A and 70 subjects in group B. Subjects in group A were sedated according to the hospital's existing protocol, which stated that to give safe sedation, the patient must be arousable and able to protect their airway. Consequently, group A patients received baseline sedation consisting of 50 mcg of fentanyl and 2 mg of midazolam; furthermore, if after 2 minutes sedation wasn't deemed adequate via a RSS of 3 to 4, another 2 mg of midazolam was given. Midazolam continued to be administered in 2 mg increments every 2 minutes as required. Furthermore, additional doses of fentanyl were given in patients who were perceived to be in pain, and doses were halved in patients greater than 80 years old or with a PS classification greater than II. The subjects were assigned a RSS every 5 minutes with the goal being a RSS of 3 to 4. BIS values were recorded at 5-minute intervals and were blinded to the nurses administering the sedation and the endoscopist or surgeon performing the procedure.

Group B patients had IV sedation titrated to a predetermined BIS value. This predetermined level was established from the sedation results obtained from group A,

where they found that the optimal BIS range for conscious sedation was 80 to 85 (corresponding to the desired RSS of 3 to 4). Thus, subjects in group B received the same baseline sedative medications as patients in group A. The only difference in regards to the baseline sedation administered was that 2 to 5 minutes were given to allow the BIS to return to a constant reading before giving more sedative medications. If needed, 2 mg increments of midazolam were administered at 2-minute intervals to target the pre-determined BIS value, and an additional 50 mcg of fentanyl was given for perceived pain if it resulted in a sustained increase in BIS for greater than 2 minutes. If giving fentanyl did not return the BIS value to the optimal range desired, more midazolam (2 mg) was given until the desired BIS value was achieved.

The results of this study demonstrated that only 46.8% of RSS values in group A were within the desired RSS of 3 to 4, which in this group correlated to a BIS level of 87.2 and 80.9. Based on those results, an optimal BIS range for conscious sedation was defined as being between 80 and 85. Also, a significant negative correlation (i.e., correlation between -0.8 and -1.0, demonstrating that as one variable increases the second variable decreases to a similar degree) was found when comparing the RSS and BIS values between patients ($r = -.97, p < .001$) and within each patient's values ($r = -.90, p < .001$) in group A. This significant negative correlation suggested that as the RSS increased, BIS values decreased. Statistical significance in this study was determined by $p < .05$. Due to the significant negative correlation found between both RSS and BIS in group A, the authors concluded that BIS monitoring was an accurate measure of patient sedation levels during interventional radiological procedures.

In contrast, Group B's mean BIS value was 83.79 and this was significantly higher ($p = .001$) than group A's mean BIS value of 79.77. Furthermore, 57.5% (227/395) of BIS readings in group B were in the optimal BIS range of 80 to 85, compared to only 26.5% (48/181) in group A. These results suggest that using BIS values to titrate sedation is more accurate and reliable than the RSS to obtain desired sedation levels. Additionally, group B had no BIS value recorded that was < 60 , but this occurred 5.5% (10/181) of the time in group A.

Other benefits in using the BIS monitor to titrate patients' level of sedation in group B included the mean dose of midazolam (4.64 mg) and fentanyl (58.21 mcg) were both significantly lower ($p = .001$ and $p = .011$, respectively) than group A's mean doses of midazolam (6.27 mg) and fentanyl (74.17 mcg). Likewise, the mean length of the procedure and recovery time were found to be significantly reduced with BIS monitoring, from 30.3 minutes and 25.10 minutes respectively, to 23.01 minutes and 19.90 minutes in group B ($p = .018$ and $p = .001$).

Besides the above mentioned benefits, the BIS monitor could be useful for preventing complications since all patients (unspecified number) sedated to a BIS value < 50 experienced an unplanned complication such as agitation, hypotension and/or hypoxia. Hypotension was defined in this study as SBP < 80 mmHg, and it did not occur in any patients with a BIS value > 78 . The only patient who developed hypoxia (i.e., oxygen saturation $< 92\%$ for > 1 minute) did so with a BIS value of 44. These results reveal that the number of correlated adverse events (e.g., agitation, hypotension, and hypoxia) increases with lower BIS values in GI interventional procedures. Another variable that correlated with lower BIS readings was higher patient PS classification (i.e., PS III and

IV). Subjects with a higher PS classification reached deeper levels of sedation, as a significant negative correlation was found between the subjects' PS classification and their lowest recorded BIS value ($r = -.35, p = .01$).

A limitation of the study included the investigators not mentioning the time the BIS value recording started or stopped. The authors did state, however, that vital signs were recorded 5 minutes before the procedure and every 5 minutes during and after the procedure until the patient was assessed to have fully recovered from sedation, which was defined as being conversant and awake. Another limitation of this study was that the researchers did not operationalize what was meant by a "sustained increase" for BIS. Additionally, the study included an inequality in group size with 30 patients being in group A and 70 in group B. There was also noticeable hysteresis between the BIS recordings and the patients' sedation levels. The display of the BIS value was delayed by 7.5 to 15 seconds from real-time data. One way the investigators accounted for this limitation was by allowing time after the baseline sedative medications were administered for a consistent BIS value to appear before giving more sedatives or starting the procedure. By waiting for a consistent value, group B participants had more time for the sedative medications to take effect, possibly accounting for the fact that group B patients received less medication and recovered significantly faster than group A. In addition, a limitation to the RSS was noted in that the researchers did not operationalize "excessive sedation" and whether this could include GA. Finally, a limitation also included that no BIS values < 60 were recorded in group B patients at the 5 minute increments; however, BIS values < 60 still occurred in group B patients as demonstrated by the BIS ranges given for when complications occurred in each group. Despite these

limitations, the researchers recommended the BIS monitor be used as a standard monitoring tool for patients undergoing "routine interventions" since the dosages of midazolam and fentanyl, the mean length of the procedure, and the recovery time were all significantly reduced with BIS monitoring.

Overall, BIS has been shown to be a valid tool for the measurement of depth of GA (Cortínez et al., 2007). In contrast, well-defined BIS values that correlate with specific levels of sedation (light, moderate, and deep) remain to be determined. Less clearly defined BIS values that correlate with sedation levels characterized as "light/moderate" (Kelley, 2010), "acceptable" (Bell et al., 2004), or the OAA/S scale (Liu, Singh, & White, 1997) have been reported in the literature. For example, an OAA/S score of 4 approximates a moderate sedation level and has been shown to correlate with a BIS recording of 93 to 95 (Liu et al., 1997). The use of a BIS monitoring system involves minimal risks to the patient and provides anesthesia providers with an objective way to estimate the depth of sedation they are providing for their patients, especially at deeper sedation levels when it becomes more difficult to clinically assess patients (Bell et al., 2004). However, for multiple reasons BIS monitoring continues not to be accepted as a standard of care for anesthesia providers: it is not cost-effective (Abenstein, 2009; Liu, 2004), and intraoperative awareness is a rare occurrence (Myles, Williams, Hendrata, Anderson & Weeks, 2000; Pollard, Coyle, Gilbert & Beck, 2007; Sebel et al., 2004; Shepherd et al., 2013). Additionally, in one study, authors concluded they did not find a reduction in intraoperative awareness by using the BIS monitor (Avidan et al., 2008). Results from this study demonstrated there was no difference in the occurrence of intraoperative awareness in patients randomly assigned to BIS-guided

anesthesia (i.e., targeting BIS values 40 to 60) and end-tidal anesthetic gas-guided anesthesia (i.e., targeting end-tidal anesthetic gas values 0.7 to 1.3 minimum alveolar concentration [i.e., the minimum alveolar concentration at which 50% of patients do not move in response to skin incision]) (Avidan et al., 2008). Furthermore, one prospective randomized controlled trial used a similar methodology of comparing BIS-guided anesthesia to end-tidal anesthetic agent concentration-guided anesthesia to assess patients at high risk for awareness. Criteria to determine high risk for awareness were based on previous studies, reviews, and guidelines. Results indicated that 0.24% (7/2861) of patients in the BIS-guided group and 0.07% (2/2852) of patients in the end-tidal anesthetic agent concentration-guided group were determined to have definite intraoperative awareness, demonstrating no superior use of BIS compared to end-tidal anesthetic concentration in preventing intraoperative awareness ($p = .98$) (Avidan et al., 2011).

In contrast, however, other studies assessing intraoperative awareness using BIS monitoring found BIS to be useful (Ekman, Lindholm, Lennmarken, & Sandin, 2004; Sebel et al., 2004). One study concluded that all cases found to have an incidence of intraoperative awareness had high BIS values and no cases of awareness were identified when BIS values were < 60 (Sebel et al., 2004). Similarly, another study discovered that intraoperative awareness occurred when BIS values were > 60 (Ekman et al., 2004).

Informed Consent

It has been estimated that medications producing sedation and analgesia account for 50% or more of complications in endoscopic procedures (Petrini & Egan, 2004) and liability may arise from either failure to administer sedation according to the standard of

care or failure to obtain proper informed consent (Petrini & Egan, 2004). In addition, providing deeper sedation/analgesia is said to reduce a patient's fear of the procedure and allows for a greater recruitment of more at-risk patients; because endoscopists can offer "painless" colonoscopy procedures (Petrini & Egan, 2004). Thus, the proceduralist's desire to provide diagnostic care (which includes "deeper sedation/analgesia") that generates high patient satisfaction scores, also promotes the undesirable consequences of increased procedural risks (Bell et al., 2004; Petrini & Egan, 2004).

It is also important to recall that providing deep sedation and/or GA for endoscopy procedures are generally not within the scope of practice for non-anesthesia providers (CMS, 2011b; Petrini & Egan, 2004; Rex, 2011). In contrast, the standards of practice for GI endoscopists working with a highly trained registered nurse recommend sedation levels not exceed a moderate category - which is recognized by the ASGE as being usually adequate for routine, uncomplicated GI endoscopy procedures (ASGE, Standards of Practice Committee, 2008). Going beyond a moderate sedation level could perhaps result in a violation of the proceduralist's hospital privileges. It could also constitute a violation of the patient's previously agreed upon informed sedation consent.

Similarly, anesthesia practitioners are under obligation to deliver anesthesia services both they and the patient have agreed upon during the consenting process. Thus, if GA was not part of the agreed upon plan of care, reaching this depth of sedation during a colonoscopy procedure could likewise represent a breach in contract of the preoperative informed consent (Berg, Appelbaum, Lidz, & Parker, 2001; Bernat & Peterson, 2006).

Understandably, accurately obtaining an informed consent is important due to differences in risk among the various levels of sedation. GA carries with it more serious

risks than MAC with IV sedation, such as loss of protective airway reflexes (Petrini & Egan, 2004), and when looking at all the closed malpractice claims in the ASA's Closed Claims Database from 1990 to 2002, only 6% of claims were associated with MAC with IV sedation, whereas 78% were associated with GA (Bhanaker et al., 2006).

Another issue faced in procedures performed under MAC with IV sedation is patients may be given false reassurance by the primary care provider, surgeon, or anesthesia provider that they will be completely "asleep" during the procedure and feel no discomfort (Feld, 2008). The anesthesia provider needs to dispel this belief of being entirely asleep without the possibility of recall if the procedure is scheduled to be performed under MAC with IV sedation. If the patient is not satisfied with receiving MAC (i.e., minimal, moderate, or deep IV sedation) for his or her procedure, then it is reasonable to discuss the possibility of consenting for GA instead.

Summary

Colonoscopy is a type of endoscopic procedure that is an effective screening option for colorectal cancer (ASGE, 2007). Sedation during colonoscopies is sometimes administered in an office or outpatient setting by nurses under the supervision of an endoscopist (Cohen et al., 2006). However, there has been substantial growth in the number of endoscopic procedures performed by anesthesia providers (Liu et al., 2012). With nurse-administered sedation, midazolam and fentanyl are often used, but sometimes nurses administer propofol (Diprivan) under the direction of a gastroenterologist. This is a controversial practice because patients can unintentionally reach deep levels of sedation when propofol is used, including GA. The 2011(b) recommendations from the ASA indicate that any healthcare provider administering propofol for sedation should be

trained in providing GA. Hospira (2009), the manufacturer of propofol, also states that only providers trained in GA should administer propofol, but additionally, that person should not be involved in the conduction of the procedure. A 2006 nationwide survey found that endoscopists were more satisfied with sedation from propofol rather than sedation with a benzodiazepine combined with a narcotic because propofol allowed for better sedation, superior analgesia, reduced recovery time, faster return to usual activity, and improved quality of endoscopic examination (Cohen et al., 2006).

Levels of sedation can be viewed as a continuum, with minimal sedation (anxiolysis) being the lightest level, and GA (i.e., patient is not arousable, independent ventilation is usually impaired, airway assistance is often needed, positive pressure ventilation may be necessary, and cardiovascular function may be compromised) being the deepest (ASA, 2009). Furthermore, the ASA (2013) identified MAC as including varying levels of sedation, but if the patient becomes unconscious and the ability to respond purposefully is lost, GA has consequently occurred, regardless of the need for airway instrumentation. Moderate sedation (i.e., patients respond purposefully to verbal command, maintain patent airways without intervention, sustain adequate spontaneous ventilation, and usually maintain cardiovascular function) is usually considered adequate for routine, uncomplicated GI endoscopy procedures, but maximizing patient comfort while minimizing risk during GI endoscopy should be the clinical goal (ASGE, Standards of Practice Committee, 2008).

The BIS monitor is a modified EEG that can reflect the decreased cerebral metabolic rate caused by anesthetic agents (Kelley, 2010). BIS has been validated as being comparable to other methods of assessing sedation level, such as the CSI and RSS,

and has been shown to be a useful tool for the measurement of “different” levels of sedation to help guide titration of sedative medications (Bell et al., 2004; Cortínez et al., 2007; Hata et al., 2009). To date, although some studies have used BIS monitoring to titrate or assess a patient's sedation level during “MAC anesthetics with IV sedation” (Bang et al., 2013; Hata et al., 2009) or “conscious sedation” (Drake et al., 2006), there has been no research that has quantified sedation levels (i.e., mild, moderate, deep, and GA) via the BIS monitor in patients undergoing MAC with IV sedation during elective colonoscopies.

BIS values ≤ 60 correlate with a state of GA (Bell et al., 2004; Cortínez et al., 2007; Drake et al., 2006; Hata et al., 2009; Johansen, 2006; Kelley, 2010). A study from 2010 concluded that GA, as measured by BIS monitoring, occurs frequently in elderly patients undergoing spinal anesthesia combined with propofol sedation, and titrating propofol to a pre-determined BIS value range decreases that occurrence (Sieber et al., 2010). Additionally, evidence has suggested that a greater number of adverse events may occur in patients undergoing endoscopic submucosal dissection procedures when BIS values are maintained between 56 and 65 (Hata et al., 2009). These deep levels of sedation during endoscopy can have adverse effects, such as aspiration, hypoxia, hypotension, and agitation (Bell et al., 2004; El Chafic et al., 2012; Soto et al., 2005). One study found that during GI interventional procedures, BIS values < 50 were associated with more adverse events and no patients experienced hypotension with a BIS value > 78 (Bell et al., 2004). Furthermore, apnea is a complication that can occur with MAC with IV sedation. One study showed the incidence to be 26% (Soto et al., 2004).

There has been significant growth in anesthesia providers administering sedation for endoscopic procedures (Liu et al., 2012). Due to this growth and the potential for the occurrence of unintended GA (El Chafic et al., 2012), it is important to assess the current sedation practices administered by anesthesia personnel and non-anesthesia healthcare providers for these procedures. In addition, it is imperative to determine whether a change in practice (e.g., selection of sedation medications, personnel administering sedation, type of consent) would be beneficial. The BIS monitor has been demonstrated as an additional way to help assess whether patients undergoing surgical and/or diagnostic procedures are experiencing GA (Bell et al., 2004; Cortínez et al., 2007; Hata et al., 2009). Being able to assess GA levels of sedation is essential for patient safety, given GA carries more risk for ventilatory and circulatory complications (e.g., aspiration, respiratory arrest) than minimal, moderate, or deep IV sedation (Petrini & Egan, 2004). Therefore, if levels of GA are being reached in endoscopic procedures such as colonoscopies, patients should be accurately informed of this possibility and consented for GA.

CHAPTER THREE: METHODOLOGY

Research Design

This study incorporated a non-experimental prospective observational research design, with a convenience sampling of PS I, II, and III patients undergoing sedation for elective colonoscopies. This research design allowed surveillance of real-world conditions that may actually be encountered in clinical settings, and it enabled the researchers to have limited or no influence on the actions of the anesthesia providers or participants in the study.

Setting

Data was collected by researchers over a four-week period at a non-teaching rural hospital in Western North Carolina. All procedures were carried out in an endoscopy suite, and sedation was provided by either an anesthesiologist ($N = 1$) or a CRNA ($N = 11$). A limitation with using only one facility is the possibility that sedation could be carried out differently at other institutions due to variations in site-specific protocols, skills of gastroenterologists, and expectations of patients.

Population and Sample

There were a total of 41 subjects enrolled in the study with a range of PS classifications between I to III. Two patients were excluded from the study because of documented neurological deficits secondary to residual effects from a CVA. Other exclusion criteria included patients undergoing sedation in which the anesthesia provider used ketamine or N_2O . Because this was a convenience sampling of patients having elective colonoscopies over a four-week period, the sample size could not be pre-determined.

Protection of Human Subjects

Before commencement of data collection, approval for this study was obtained from the institutional review board (IRB) of the participating hospital on March 18, 2013 (see Appendix D). This study was also approved by Western Carolina University's IRB on April 11, 2013, with the IRB approval number 2013-0246 (see Appendix E). To attenuate bias and assure confidentiality of all study participants, identification numbers were assigned to each patient and anesthesia provider. These identification numbers allowed avoidance of using any patient or provider identifiers such as name and/or medical record number. No participation risks were identified for this observational study.

In the preoperative holding area on the day of their scheduled procedure, the researchers met with all patients undergoing elective colonoscopies. The purpose of the study, the participant's role, confidentiality, and right to refuse were explained to each patient. As part of the consenting process, contact information for the primary investigators, Western Carolina University's IRB, and the participating hospital's IRB were provided to all subjects (see Appendix F). At that time, all patients who met the enrollment criteria were invited to participate in the study. Additionally, each anesthesia provider was informed about the purpose of the study, their right to refuse, and confidentiality measures (see Appendix G). Contact information for the primary investigators, Western Carolina University's IRB, and the participating hospital's IRB were also shared with the anesthesia providers.

Instruments

The BIS monitor is a modified EEG. It was first introduced in 1996 to help monitor cortical function during hypnotic states, and in 2003 it was approved by the FDA for reducing the incidence of intraoperative awareness (Johansen, 2006; Kelley, 2010). BIS values are measured on a scale of 0 to 100 (Kelley, 2010). A value of 0 indicates complete cortical suppression, and values of 93 or above indicate a state of wakefulness (Kelley, 2010). Moderate sedation occurs at BIS values between 65 and 85, and GA is said to occur between values of 45 and 60 (Kelley, 2010). Some studies have shown an increased number of adverse events such as hypotension and hypoxia with BIS values < 60 (Arrowsmith et al., 1991; Charlton, 1995). Other studies have shown that a BIS value of 80 correlates with what has been described as an “ideal” level of sedation for colonoscopies (Bell et al., 2004; Bower et al., 2000).

The BIS monitor is the most extensively researched EEG device currently used to evaluate depth of anesthesia during surgical procedures, and it is frequently used as a monitor in the operating room to measure the depth of anesthesia and to help guide the titration of medications during GA (Bruhn et al., 2003; Cortínez et al., 2007; Doufas et al., 2003; Ge et al., 2002; Kearsse et al., 1998). BIS measurements have also been shown to be useful with measuring sedation levels during endoscopic procedures when sedation is administered by anesthesia (e.g., CRNAs, anesthesiologists) and non-anesthesia (e.g., registered nurses) providers (Bell, et al., 2004; Hata et al., 2009; Leslie et al., 2002; Siddiqui et al., 2012). Additionally, there have been some studies that have looked at the use of BIS as an adjunctive monitor in titrating a patient’s sedation level through the use

of various drugs, such as propofol, fentanyl, and midazolam (Bell et al., 2004; Drake et al., 2006; Hata et al., 2009).

The BIS A-2000™ monitor was used to monitor the depth of sedation and possible correlated adverse events during colonoscopies. As part of the study design, interventions were not implemented in response to observed BIS values, and notification to providers was not given when BIS values dropped below 60 (indicating GA had occurred).

Data Collection and Field Procedures

Participation in the study began from the time consent was obtained in the preoperative holding area to the time the patients' first set of vital signs were taken in PACU. In the preoperative area, per instructions presented on the BIS sensor packaging, the forehead was cleaned with an alcohol wipe and then dried with gauze. The strip was then applied in a diagonal direction starting with sensor number 1 about 2 inches above the bridge of the nose, followed by sensor number 4 directly above the eyebrow and ending with sensor number 3 on the temple, between the corner of the eye and the hairline. The edges of each sensor were pressed, and then the center of each sensor was firmly pressed for about 5 seconds. The sensor strip was then connected to the BIS A-2000™ monitoring device and the first BIS value was recorded. At this time, a non-invasive BP cuff was placed on the patient's arm and the first set of vital signs, including HR, SpO₂, RR, SBP, DBP, MAP, temperature, and liters of oxygen flow were documented.

After arriving in the endoscopy suite (procedure room), a second set of BP measurements (SBP, DBP, MAP) were taken, followed immediately with a recording of

HR, SpO₂, RR, and BIS value. A stopwatch was also started just after the BP measurement was taken to help maintain accuracy for data-recording intervals in the endoscopy suite. Recording of the presence or absence of ETCO₂ (measured via the Salter Labs 4707F adult Salter NC) and liters of oxygen flow began as soon as the NC was placed on the patient in the procedure room. BIS values and ETCO₂ values then continued to be recorded every minute throughout the remainder of the procedure. Also during this time, SBP, DBP, MAP, and HR via ECG (lead chosen by provider) were recorded every 5 minutes, and any intraoperative changes in liters of oxygen flow from baseline oxygen flow rates were documented at the actual time they occurred. Additionally, the SpO₂ value was noted every 5 minutes, except when it dropped below 95%. If this occurred, recording of data took place at 1-minute intervals until the SpO₂ returned to 95% or greater, when it was again recorded at 5-minute intervals. Without regard to frequency, the lowest BIS value observed during each procedure was noted. Also, temperature recordings were taken only in the preoperative area and in the PACU.

All data was recorded and documented by one of the investigators until the patient was detached from monitors in the procedure room in preparation for transfer to PACU. Additionally, medications administered and documented by the anesthesia provider during the procedure were recorded retrospectively, and included the dosage of medications and time administered. The form of primary medication delivery (i.e., one time/single bolus followed by infusion, intermittent bolus, infusion, or combination of intermittent bolus and infusion) was also observed and documented by one of the primary investigators.

Likewise, airway assistance maneuvers and oxygen delivery devices used by the anesthesia provider were recorded throughout the procedure. This included, but was not limited to, chin lift, jaw thrust, combination of chin lift and jaw thrust, and placement of nasopharyngeal airway, oropharyngeal airway, NC, face mask, non-rebreather mask, bag mask, LMA and endotracheal tube. Upon arrival to PACU, one set of vital signs including SBP, DBP, MAP, HR, SpO₂, temperature, and RR were recorded. Additionally, the time of arrival in the PACU, oxygen delivery method and liter flow, and one final BIS value were noted.

Chart documents relevant to the anesthesia care received throughout the procedure were collected. This included copies of the anesthesia record, and information from the pre-anesthesia assessment sheet, PACU record, anesthesia and/or surgical consent form, and surgeon's history and physical and/or medication list. Total drug dosages, length of procedure, consented anesthetic plan (e.g., GA, MAC with IV sedation), postoperative diagnosis, and the patient's demographic data (i.e., gender, age, body mass index (BMI), weight, height, and PS) were recorded. Additional information obtained retrospectively from chart review included use of oxygen at home, presence of obstructive sleep apnea and use of a home continuous positive airway pressure (CPAP) or bi-level positive airway pressure (BiPAP) device, history of previous airway surgeries, and major comorbidities. Lastly, the BIS monitor used in the endoscopy suite was placed out of immediate view from the anesthesia providers and the gastroenterologists or surgeons performing the colonoscopy, which facilitated the blinding of healthcare providers to BIS values obtained during the procedure. The healthcare providers were

also reminded of the need to shield their face from the BIS values during the endoscopy procedure.

A survey tool (see Appendix H) was used to collect demographic data on anesthesia providers. This included 1) the year the CRNA or anesthesiologist passed their national certification exam, 2) the number of years or months of experience with providing anesthesia care for patients scheduled for colonoscopies, 3) the opinion of the anesthesia provider of the level of sedation they typically provide during colonoscopies (i.e., MAC, GA or both), and 4) the highest educational degree obtained (i.e., Doctorate, Masters, Bachelors, or Diploma).

Data Analysis

All quantitative and numerically-coded demographic data was entered into an Excel spreadsheet before analysis. A statistician was consulted to assure the accuracy of proposed statistical tests and provide guidance to investigators on the use of additional statistical tests deemed essential for the study. Correlation analysis (r and r^2) was used for continuous data (e.g., length of procedure, age, BMI, years as provider, propofol dose/min). The Mann-Whitney U test compares two groups with ordinal data, and was used for analysis of correlation between SpO₂, ETCO₂, and gender. One-way ANOVA is a parametric test used for comparing the means of three or more groups (e.g., BIS values of ≤ 60 , ≤ 40 , and ≤ 20) and was chosen for analyzing BIS values versus experience of the anesthesia provider with colonoscopies (e.g., 1-2 years, 3-5 years, 6-10 years). The Kruskal-Wallis, which is an extension of the Mann-Whitney U test and incorporates ordinal data for three or more groups, was utilized to determine if a correlation existed between BIS values, PS classification, SpO₂, ETCO₂, education, and length of experience

as an anesthesia provider. An unpaired t-test, which compares two or more independent samples, was used to assess potential relationships between gender and BIS values. Simple quantitative statistics were used to calculate all other data.

Limitations

The BIS monitor was secured on a pole attached to the head of the bed, so inadequate blinding of anesthesia providers to BIS values may have inadvertently occurred. Instructions were provided to anesthesia personnel to avoid titrating sedation medication based on BIS values accidentally observed; however, it was possible that titration did occur and statistical analysis could not account for this possibility. Another limitation of the study was the duration of apnea (i.e., absence of ETCO_2) was only measured at 1-minute intervals. For example, if a patient experienced 1.25 minutes of apnea, it would have been recorded as a duration of 1 minute; in contrast, if a patient experienced 35 seconds of apnea it may not have been recorded at all due to the previously mentioned assessment intervals of 1-minute. Additionally, negative ETCO_2 waveforms obtained via Salter NC's can be the result of situations other than apnea, such as a patient breathing out of their mouth instead of their nose. Furthermore, some providers performed a chin lift in the absence of apnea, most likely as a preventative measure. Since apnea may have occurred in the absence of this prophylactic chin lift, measuring the actual frequency of apnea, along with resulting interventions during colonoscopies, was not possible. This inability to precisely record the frequency and interventions related to apnea was a limitation that likely skewed statistical analysis involving airway maneuvers in correlation with BIS values, and the presence or absence of ETCO_2 .

Two other limitations of the study involved 1) the anesthesia providers' assignment of a PS classification to each patient, and 2) the absence of SQI and EMG values with the BIS A-2000™. The former could have hindered analysis of the lowest BIS value obtained during each colonoscopy procedure relative to recorded PS classification. The reason this represents a limitation is the subjectivity involved with PS assignment; it is possible the recorded PS value was inaccurate for some patients in the study. Regarding the BIS A-2000™ monitor, it allows for visualization of a non-numerical scale (see Figure 1) of real-time SQI and EMG data, but does not provide a numerical value that can be recorded for statistical analysis in correlation with BIS values. One final limitation was that all subjects were consented for IV GA for their elective endoscopy procedure; thus, it would be anticipated that anesthesia providers would only unexpectedly deliver a lighter level of sedation during the colonoscopy procedure.

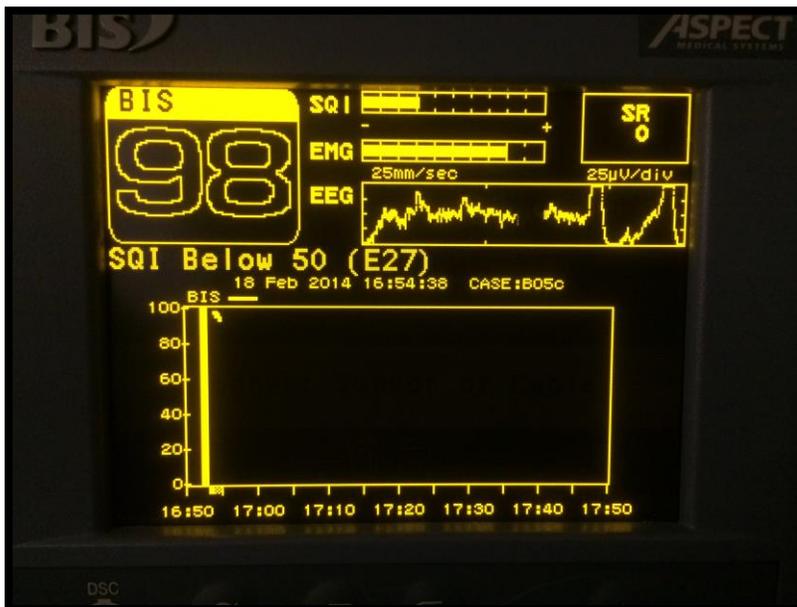


Figure 1. Photograph of BIS A-2000™ monitor displaying SQI and EMG non-numerical data. BIS = bispectral index; SQI = signal quality index; EMG = electromyography; EEG = electroencephalogram.

CHAPTER FOUR: RESULTS

Sample Characteristics

Forty-one adult patients undergoing elective, colonoscopy procedures were observed at one hospital. Two patients were excluded due to a history of a CVA with current neurological deficits ($N = 39$). Descriptive statistics were used to analyze participant demographics, which included clinical characteristics (see Table 2). Twenty-one of the subjects were male (53.8%) and 18 were female (46.2%). Additionally, 5.1% (2/39) of study participants were PS I, 53.8% (21/39) were PS II, and 41.0% (16/39) were PS III. After assessing patient's smoking history, 20.5% (8/39) were found to be current smokers. No patients were documented as using oxygen at home and none had obstructive sleep apnea.

Table 2

Patient and Clinical Characteristics

Variable	Mean	Range
Age (years)	64.8	30-90
BMI (kg/m ²)	27.3	15.1-40.4
Weight (kg)	81.2	38.6-124.7
Propofol dose (mg)	315.0	140.0-650.0
Propofol dose/kg (mg)	4.1	1.9-9.6
Propofol dose/minute (mg)	20.4	9.4-50.0
Length of procedure (minutes)	17.3	8.0-39.0
BIS ^a	47.6	5-98
Lowest BIS	28.6	3-53
Minutes BIS \leq 60	13.1	1-34
Minutes BIS \leq 40	5.8	0-31
Minutes BIS \leq 20	0.5	0-7
Minutes SpO ₂ \leq 90	0.3	0-3

Note. $N = 39$. BMI = body mass index; BIS = bispectral index.

^aBIS mean and range values are derived from BIS recordings taken after sedation was initiated in the endoscopy suite until the end of the procedure.

Preoperatively, all patients had a baseline BIS measurement between 97-98 and every patient experienced a BIS measurement \leq 60 (i.e., GA) at least once during their procedure. The lowest recorded BIS value in one subject was 3 and there were three

separate episodes recorded for this patient of an absent ETCO₂ waveform. The first episode occurred after the initial propofol bolus and was accompanied by a decline in oxygen saturation to 84%, which resolved with a chin lift. The other two episodes resulted in a negligible drop in oxygen saturation to 97% and 98%. Overall, out of a total of 656 minutes of recorded data for 39 patients, 51 minutes of absent ETCO₂ (7.9%) were found (see Figure 2). All patients received oxygen via NC at flows 2-5 L/min and there were a total of seven patients (17.9%) whose oxygen saturation dropped to $\leq 90\%$ for at least 1 minute. One anesthesia provider failed to monitor ETCO₂; therefore, ETCO₂ data on three patients under their care could not be obtained.

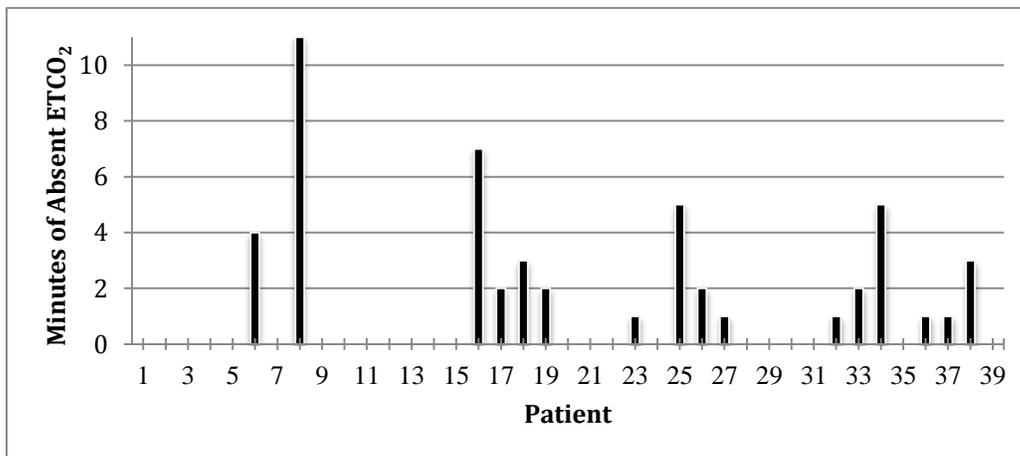


Figure 2. Bar graph demonstrating the number of minutes of absent ETCO₂ each patient experienced. Patients 2, 3, and 10 did not have ETCO₂ monitored by the anesthesia provider. ETCO₂ = end tidal carbon dioxide.

The average propofol dose administered per patient during the entire colonoscopy procedure was 315 mg and 4.1 mg/kg respectively. Propofol was administered via intermittent boluses in 94.9% (37/39) of patients and by bolus followed with infusion in 5.1% (2/39) of patients. In addition, no patient received fentanyl or midazolam. In 89.7% of patients (35/39) MAP decreased at the first BP measurement after the initial propofol bolus, of which 61.5% (24/39) of subjects had a 10.1-42.4% MAP decrease at this time (see Figure 3), and in more than half of these 24 participants (54.2%), the MAP

decreased by 21.5-42.4% (see Figure 4). Overall, the greatest MAP decrease found was 50.8% and this occurred in one patient 7 minutes after the end of the procedure. In contrast, 10.3% of patients (4/39) had an increase in MAP at the first BP measurement after the initial propofol bolus.

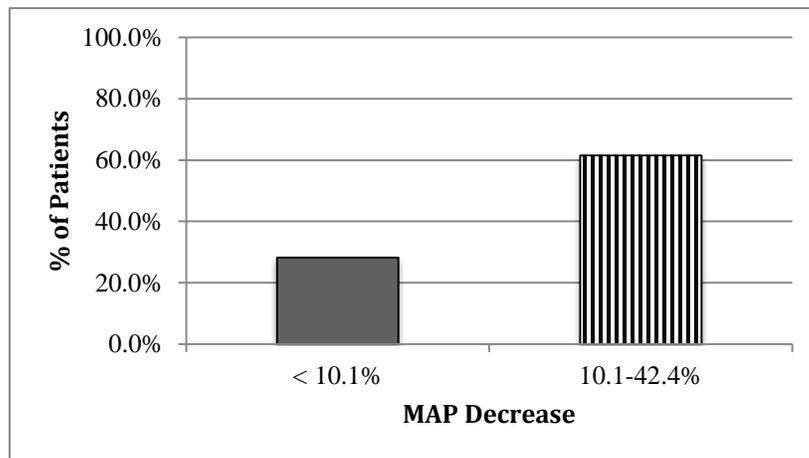


Figure 3. Bar graph demonstrating the percentage of patients with a MAP decrease < 10.1% or 10.1-42.4% at the first BP measurement taken after the initial propofol bolus. There were no patients with a MAP decrease > 42.4% at this measurement time. $N = 39$. MAP = mean arterial pressure; BP = blood pressure.

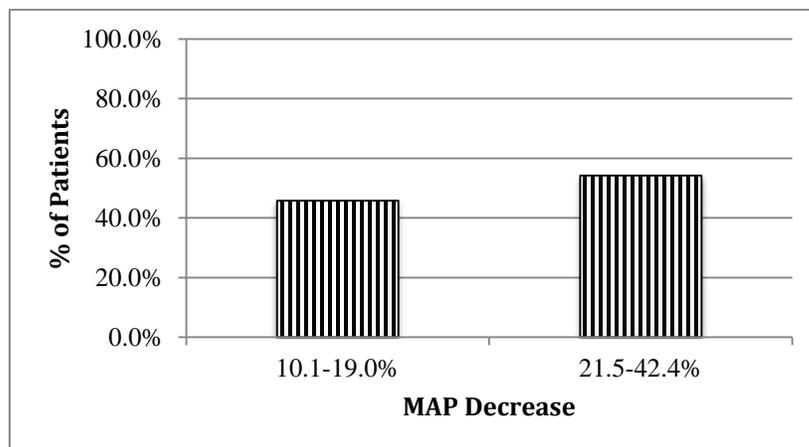


Figure 4. Bar graph exhibiting further breakdown of MAP decrease at the first BP measurement after the initial propofol bolus in the 61.5% of patients (24/39) who had a MAP decrease from 10.1-42.4%. MAP decreases of 10.1-19.0% and 21.5-42.4% shown. $N = 24$. MAP = mean arterial pressure; BP = blood pressure.

A total of 12 anesthesia providers were surveyed with a 100% response rate (see Table 3). The average number of years as an anesthesia provider was 14.3, and 41.7% (5/12) of the respondents had > 10 years of experience with providing anesthesia for

colonoscopies, 33.3% (4/12) had 6-10 years of experience with colonoscopies and 8.3% (1/12) had 3-5 years of experience with colonoscopies. Only 16.7% (2/12) had 0-2 years of experience with colonoscopies. Additionally, 8.3% (1/12) of anesthesia professionals' highest level of education was a doctorate, 66.7% (8/12) a master's degree, 8.3% (1/12) a bachelor's, and 16.7% (2/12) a diploma. When asked what percentage of colonoscopies they believed they were delivering a MAC anesthetic, GA, or a combination of both, 50% (6/12) of the respondents believed they were administering GA 100% of the time, whereas just one anesthesia provider believed they were delivering MAC 100% of the time. The remaining anesthesia professionals (5/12) believed they were administering a combination of a MAC anesthetic and GA (See Figure 5). Survey responses were likely influenced by the fact that all patients undergoing elective colonoscopies at this hospital were consented for IV GA.

Table 3

Anesthesia Provider (AP) Survey Responses

AP	No. of years as an AP	AP's years of experience with colonoscopies	Highest degree held	% of Colonoscopies believe providing MAC	% of Colonoscopies believe providing GA	% of Colonoscopies believe providing combination ^e	No. of patients cared for by AP ^d
1	29	> 10	Diploma	0	100	0	2
2 ^a	4	6-10	Doctorate	3	97	0	4
3	9	6-10	Master's	0	0	100	1
4 ^b	12	> 10	Master's	100	0	0	14
5	8	6-10	Master's	0	100	0	1
6	1	0-2	Master's	0	100	0	1
7	28	> 10	Master's	99	1	0	1
8	29	> 10	Bachelor's	0	100	0	4
9	4	3-5	Master's	0	100	0	2
10	1	0-2	Master's	0	0	100	6
11	8	6-10	Master's	0	100	0	2
12	38	> 10	Diploma	90	10	0	2

Note. AP = anesthesia provider; MAC = monitored anesthesia care; GA = general anesthesia.

^aAnesthesiologist. ^bOnly AP who believed they were administering MAC 100% of the time for colonoscopies. ^cGA and MAC.

^dDemographic data not included as part of the survey.

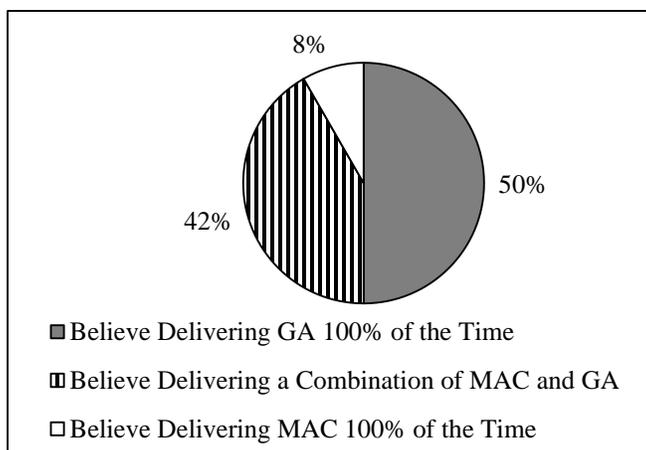


Figure 5. Pie graph with survey results of the percentage of anesthesia providers who believed they were delivering a level of sedation consistent with MAC 100% of the time, GA 100% of the time, or a combination of MAC and GA during colonoscopy procedures. $N = 12$. GA = general anesthesia; MAC = monitored anesthesia care.

Major Findings

The quantitative data were analyzed using Prism 6.0c software. Alpha was two-tailed and set at .05 for all tests, and Pearson product-moment correlation coefficient (Pearson r) test was used to assess whether an *association* existed between each patient's BIS measurements and 1) their respective demographics, 2) clinical characteristics for each subject (e.g., length of procedure, propofol dose given per minute), and 3) each participant's anesthesia provider. Furthermore, r values provide an estimate of how much one variable accurately *predicts* another (Hatcher, 2003). A value of zero means there is no relationship between the two variables. Values ranging from $\pm 0.2-0.4$ represent a mild or weak association between variables, $\pm 0.5-0.7$ a moderate association, and $\pm 0.8-1.0$ a strong association. An r value of 1.0 represents a perfect positive correlation (e.g., the longer the length of the procedure, the more minutes patients spent with BIS values ≤ 60) and -1.0 represents a perfect negative correlation (e.g., the longer the length of the procedure, the less minutes the patients spent with BIS values ≤ 60) (Hatcher, 2003).

In addition, the coefficient of determination (r^2) was computed. These values are a measure of the proportion of variance in one variable that can be explained by its relationship to (or accounted for by) a second variable. The calculated values range from 0 (0%) to 1 (100%). For example, a value of 1.0 means 100% of the deviation in one variable is correlated with the variance in the second variable (Hatcher, 2003). A value of 0.0 means knowing one variable does not help to predict the other. In essence, the higher the number, the better the ability to determine how much divergence of one variable is due to (or can be explained by) another variable's variability (Hatcher, 2003).

Every patient experienced BIS values ≤ 60 for at least 1 minute or more (range of 1-34 minutes or 11.1-100% of their length of procedure); 76.9% of subjects were recorded as having a BIS value ≤ 40 for 1-31 minutes or for 4.5-100% of their procedure, and 15.4% of participants experienced a BIS value ≤ 20 for 1-7 minutes or for 4.0-33.3% of their procedure. A strong positive correlation was found between the length of the procedure and the number of minutes patients had a BIS recording ≤ 60 ($r = .85$, $r^2 = .72$, $p < .001$) (see Table 4). This suggests the longer the length of the procedure, the greater the number of minutes patients experienced BIS values ≤ 60 (See Figure 6).

Additionally, a weaker but still significant correlation was found when comparing the length of the procedure and the number of minutes patients were reported to have BIS values ≤ 40 ($r = .43$, $r^2 = .18$, $p = .007$) (see Figure 7). The significance demonstrated between these two variables is an important finding regardless of the weaker correlation; it suggests there is a low risk that chance alone accounted for the mild positive correlation, which implies as one variable increases, the other also slightly increases. Conversely, the correlation for the length of the procedure and the number of minutes

patients experienced BIS values ≤ 20 was not found to be significant ($r = .31$, $r^2 = .10$, $p = .052$) (see Figure 8).

Table 4

Summary of Length of Procedure Correlations

Correlation	Length of procedure versus lowest BIS	Length of procedure versus minutes BIS ≤ 60	Length of procedure versus minutes BIS ≤ 40	Length of procedure versus minutes BIS ≤ 20	Length of procedure versus minutes SpO ₂ ≤ 90	Length of procedure versus minutes of absent ETCO ₂ ^a
r	-.24	.85	.42	.31	-.14	.52
r^2	.06	.72	.18	.10	.02	.27
p	.137	<.001*	.007*	.052	.409	.001*

Note. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen; ETCO₂ = end tidal carbon dioxide

^aOnly 36 subjects were used to calculate all correlation and p values for absent ETCO₂ due to no ETCO₂ monitoring by one anesthesia provider in three patients.

* $p < .05$

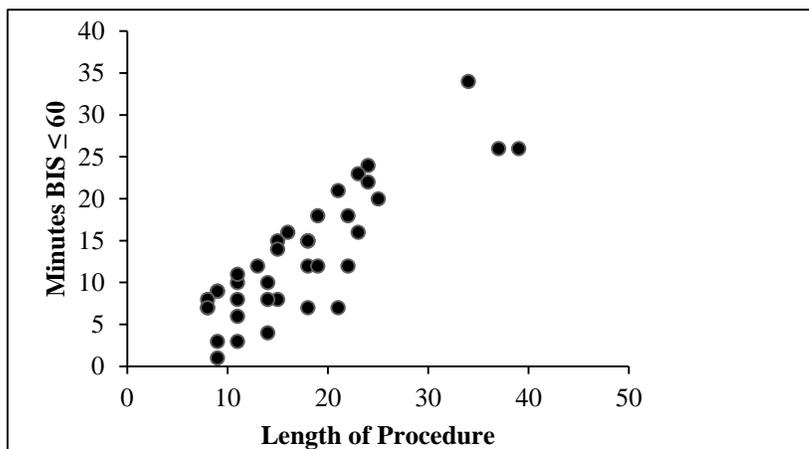


Figure 6. Correlation graph demonstrating the relationship found between the length of the procedure and the number of minutes the patient experienced BIS values ≤ 60 . $r = .85$, $r^2 = .72$, $p < .001$. BIS = bispectral index.

* $p < .05$

A significant, moderate correlation was found when the length of the procedure was compared to the number of minutes patients had an absent ETCO₂ waveform ($r = .52$, $r^2 = .27$, $p = .001$) (see Figure 9). This moderate correlation suggests the longer the procedure, the more minutes patients were likely to experience an absent ETCO₂ waveform. There were no strong or moderate correlations or significance found between

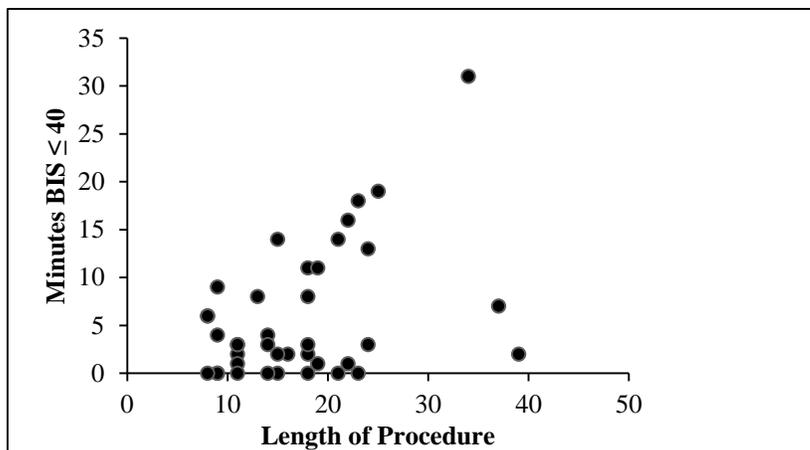


Figure 7. Correlation graph demonstrating the relationship found between the length of the procedure and the number of minutes the patient experienced BIS values ≤ 40 . $r = .43$, $r^2 = .18$, $p = .007$. BIS = bispectral index.
* $p < .05$

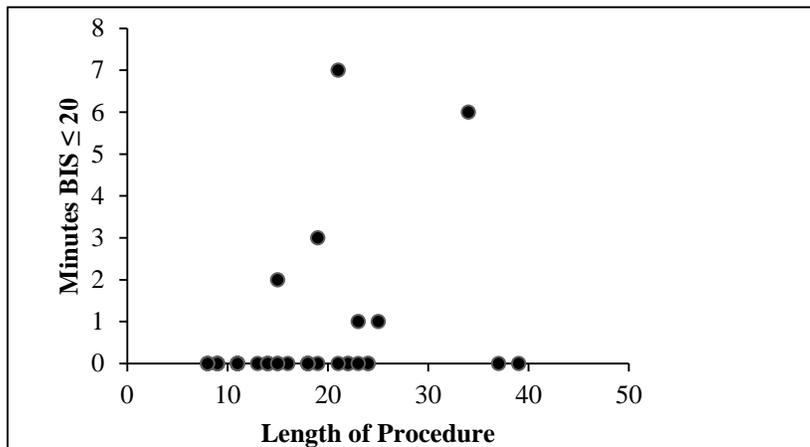


Figure 8. Correlation graph demonstrating the relationship found between the length of the procedure and the number of minutes the patient experienced BIS values ≤ 20 . $r = .31$, $r^2 = .10$, $p = .052$. BIS = bispectral index.
* $p < .05$

the length of the procedure and the number of minutes patients had a $\text{SpO}_2 \leq 90$ or the patient's lowest BIS value obtained during the procedure (see Figures 10 and 11).

Another significant, mild correlation was found when comparing the number of minutes patients had an absent ETCO_2 waveform with the number of minutes patients experienced GA (i.e., BIS values ≤ 60) ($r = .49$, $r^2 = .24$, $p = .002$). This r value suggests the greater number of minutes patients experienced an absent ETCO_2 waveform, the more minutes patients had BIS values ≤ 60 , implying that IV GA has an association with

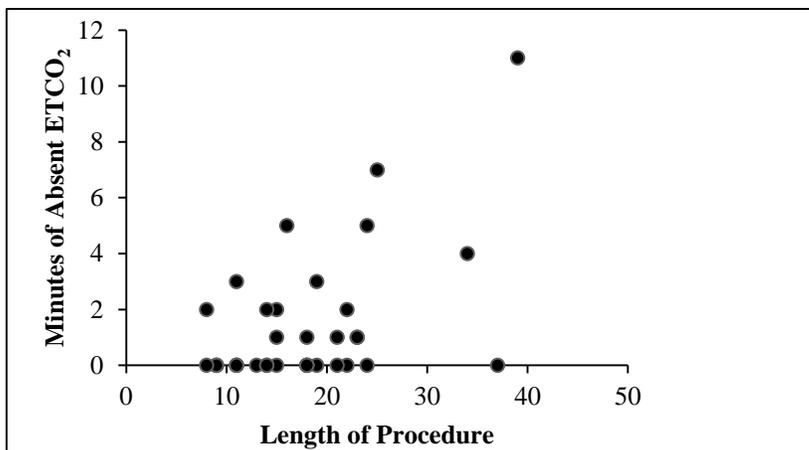


Figure 9. Correlation graph demonstrating the relationship found between the length of the procedure and the number of minutes the patient experienced an absence of ETCO₂. $r = .52$, $r^2 = .27$, $p = .001$. ETCO₂ = end tidal carbon dioxide.
* $p < .05$

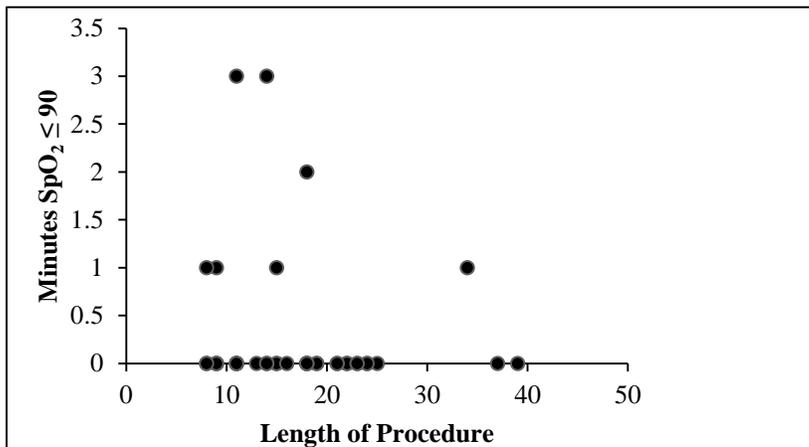


Figure 10. Correlation graph demonstrating the relationship found between the length of the procedure and the number of minutes the patient experienced a SpO₂ ≤ 90. $r = -.14$, $r^2 = .02$, $p = .409$. SpO₂ = saturation of peripheral oxygen.
* $p < .05$

adverse perioperative events in patients who undergo elective colonoscopies (see Figure 12). Also, after comparing the number of minutes patients had a SpO₂ ≤ 90% to the number of minutes patients experienced GA (i.e., BIS values ≤ 60), no significance or mild, moderate, or strong correlations were found ($r = -.17$, $r^2 = .03$, $p = .299$) (see Figure 13). Overall, the adverse event of an absent ETCO₂ waveform (i.e., apnea) was shown to have a significant correlation with IV GA, but there was no significant correlation shown when comparing the number of minutes patients had a SpO₂ ≤ 90% (i.e., desaturation) to

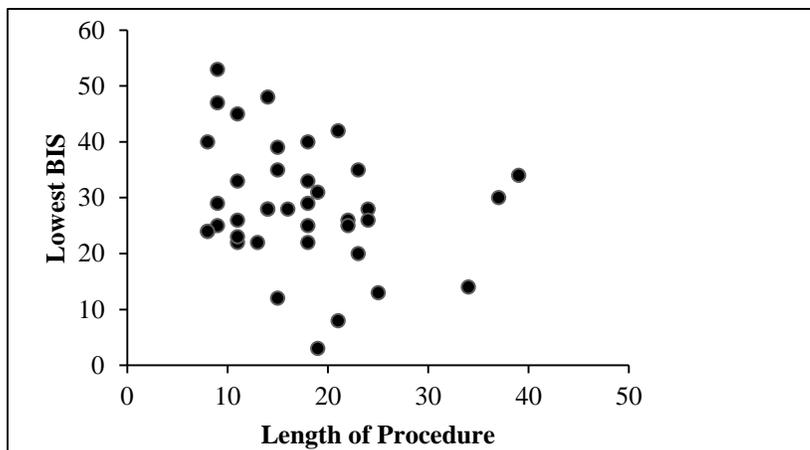


Figure 11. Correlation graph demonstrating the relationship found between the length of the procedure and the patient's lowest BIS value observed throughout the procedure. $r = -.24$. $r^2 = .06$. $p = .137$. BIS = bispectral index.

* $p < .05$

IV GA. In addition, apnea and desaturation did not result in any apparent clinically significant events and no patients required airway interventions, such as placement of a nasopharyngeal airway, oropharyngeal airway, face mask, non-rebreather mask, bag mask, LMA, or endotracheal tube.

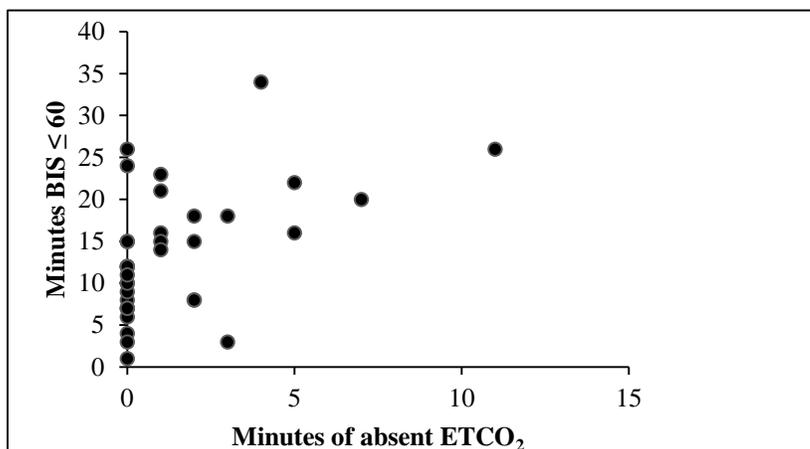


Figure 12. Correlation graph demonstrating the relationship found between the number of minutes the patient experienced an absent ET CO₂ waveform and BIS values ≤ 60. $r = .49$. $r^2 = .24$. $p = .002$. BIS = bispectral index; ET CO₂ = end tidal carbon dioxide.

* $p < .05$

Furthermore, a moderate positive correlation and significance ($r = .54$, $r^2 = .29$, $p < .001$) was demonstrated when comparing BMI with the patients' lowest BIS value

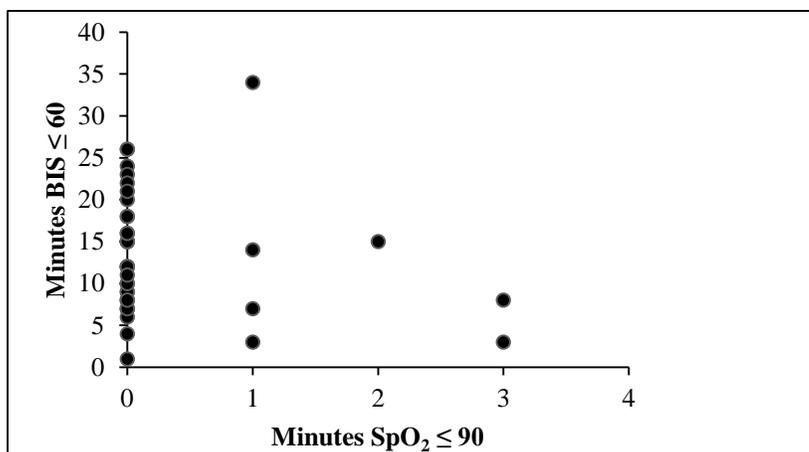


Figure 13. Correlation graph demonstrating the relationship found between the number of minutes the patient experienced a SpO₂ ≤ 90 and BIS values ≤ 60. $r = -.17$. $r^2 = .03$. $p = .299$. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen. * $p < .05$

obtained throughout the entire procedure. This suggested that patients with a larger BMI (compared to patients with lower BMIs) were more likely to have the greatest nadir in recorded BIS value (see Figure 14). Additionally, significance was demonstrated when BMI was compared to the number of minutes patients had a BIS value ≤ 60 ($r = -.42$, $r^2 = .17$, $p = .008$) and ≤ 40 ($r = -.51$, $r^2 = .26$, $p < .001$). The r values suggest the greater the BMI, the fewer number of minutes patients experienced BIS values ≤ 60 and ≤ 40 (see Figures 15 and 16). No significance or strong or moderate correlations were demonstrated when comparing BMI to the number of minutes patients had BIS values ≤ 20, SpO₂ ≤ 90, or an absent ETCO₂ waveform (see Table 5). Similarly, no strong correlations, moderate correlations, or significance were found when the patients' ages and the survey respondents' number of years as an anesthesia provider were compared to BIS values, absent ETCO₂ waveforms, and SpO₂ values (see Tables 6 and 7).

The last data subjected to statistical analysis included the subject's PS classification and the lowest BIS value obtained during the endoscopy procedure. This was accomplished via the Kruskal-Wallis test, a nonparametric test which makes no

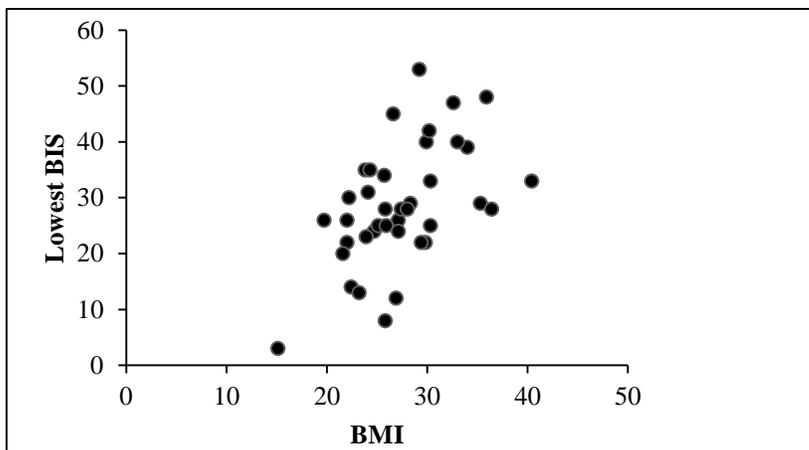


Figure 14. Correlation graph demonstrating the relationship found between the patient's BMI and the patient's lowest BIS value observed throughout the procedure. $r = .54$, $r^2 = .29$, $p < .001$. BIS = bispectral index; BMI = body mass index.
* $p < .05$

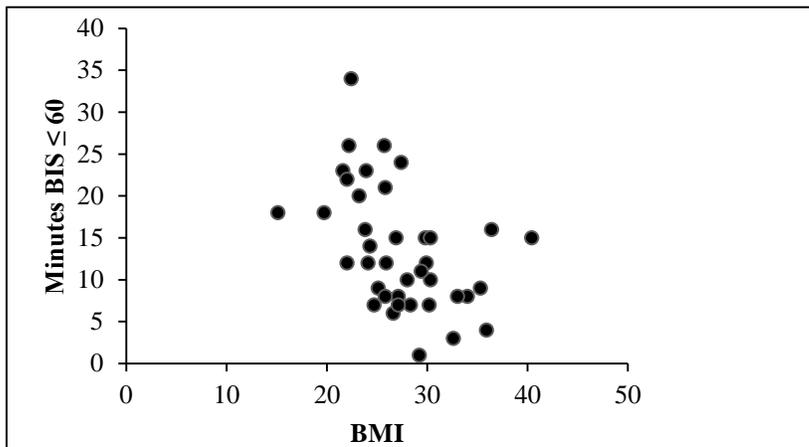


Figure 15. Correlation graph demonstrating the relationship found between the patient's BMI and the number of minutes the patient experienced BIS values ≤ 60 . $r = -.42$, $r^2 = .17$, $p = .008$. BIS = bispectral index; BMI = body mass index.
* $p < .05$

assumptions about the distribution of data within categorical groups. This test is ideal for comparing three or more groups when data is ranked numerically (e.g., patients' lowest BIS value observed throughout procedure) and compared to a categorical data set or group assignment (e.g., PS I, II, III) (Lomax, 1998; Norman, 1999). Consequently, the Kruskal-Wallis test was used to compare PS I, II, and III with the patients' lowest BIS value observed throughout the procedure. This statistical test assigns a rank to all values in each group, sums and averages the rank values for each group, and then calculates a

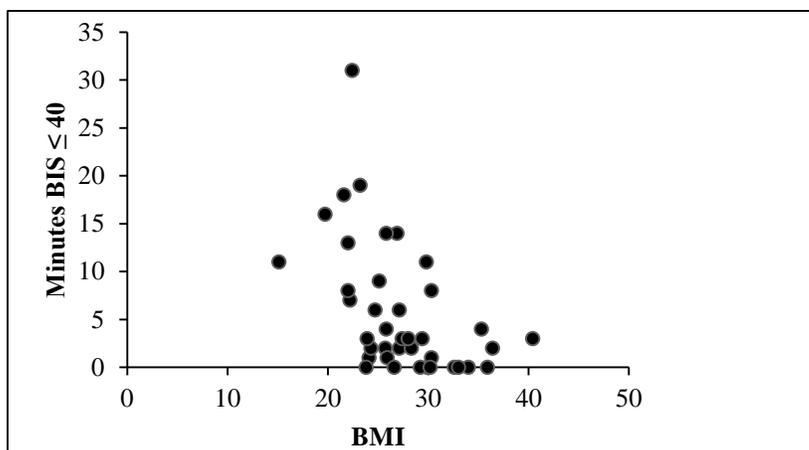


Figure 16. Correlation graph demonstrating the relationship found between the patient's BMI and the number of minutes the patient experienced BIS values ≤ 40 . $r = -.51$. $r^2 = .26$. $p < .001$. BIS = bispectral index; BMI = body mass index.

* $p < .05$

Table 5

Summary of Body Mass Index (BMI) Correlations

Correlation	BMI versus lowest BIS	BMI versus minutes BIS ≤ 60	BMI versus minutes BIS ≤ 40	BMI versus minutes BIS ≤ 20	BMI versus minutes SpO ₂ ≤ 90	BMI versus minutes of absent ETCO ₂ ^a
r	.54	-.42	-.51	-.30	.06	-.25
r^2	.29	.17	.26	.09	.00	.06
p	<.001*	.008*	<.001*	.067	.728	.143

Note. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen; ETCO₂ = end tidal carbon dioxide

^aOnly 36 subjects were used to calculate all correlation and p values for absent ETCO₂ due to no ETCO₂ monitoring by one anesthesia provider in three patients.

* $p < .05$

Table 6

Summary of Age Correlations

Correlation	Age versus lowest BIS	Age versus minutes BIS ≤ 60	Age versus minutes BIS ≤ 40	Age versus minutes BIS ≤ 20	Age versus minutes SpO ₂ ≤ 90	Age versus minutes of absent ETCO ₂ ^a
r	-.06	-.23	-.12	-.21	.15	.12
r^2	.00	.05	.01	.04	.02	.01
p	.720	.156	.474	.197	.378	.500

Note. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen; ETCO₂ = end tidal carbon dioxide

^aOnly 36 subjects were used to calculate all correlation and p values for absent ETCO₂ due to no ETCO₂ monitoring by one anesthesia provider in three patients.

* $p < .05$

Table 7

Summary of Years as an Anesthesia Provider Correlations

Correlation	Years as provider versus lowest BIS	Years as provider versus minutes BIS ≤ 60	Years as provider versus minutes BIS ≤ 40	Years as provider versus minutes BIS ≤ 20	Years as provider versus minutes SpO ₂ ≤ 90	Years as provider versus minutes of absent ETCO ₂ ^a
<i>r</i>	-.26	.31	.13	.08	-.19	.16
<i>r</i> ²	.07	.10	.02	.01	.04	.02
<i>p</i>	.107	.056	.443	.645	.244	.360

Note. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen; ETCO₂ = end tidal carbon dioxide

^aOnly 36 subjects were used to calculate all correlation and *p* values for absent ETCO₂ due to no ETCO₂ monitoring by one anesthesia provider in three patients.

**p* < .05

number representing the difference between the groups' mean ranks to determine if the samples are likely to be from the same group (Lomax, 1998; Norman, 1999). For clarification, the calculated Kruskal-Wallis number is not the value that is cardinal to a researcher's assessment of gross differences in data sets; actually, it is the derived *p* value. If significance is found in the difference between the groups' mean ranks, the null hypothesis (i.e., the mean rank values in each group are the same) can be rejected, suggesting there is a difference between at least two of the groups (Norman, 1999; Petrie & Sabin, 2000). Therefore, significance demonstrated for this test (*p* = .037) implies there is a difference between at least two of the following groups: PS I, II, and III (see Figure 17).

Additionally, the Kruskal-Wallis test was used to compare the survey respondents' years of experience with providing anesthesia for colonoscopies to BIS values, absent ETCO₂ waveforms, and SpO₂ values. Years of experience with colonoscopies was categorized into four intervals (i.e., 0-2, 3-5, 6-10, and > 10 years). No statistical

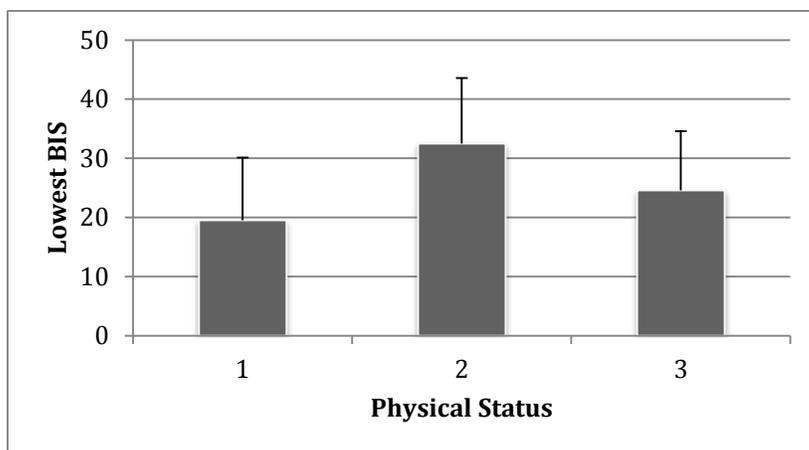


Figure 17. Bar graph demonstrating the mean patients' lowest BIS value observed throughout the procedure for each Physical Status classification. The population standard deviation is represented by the error bars. Kruskal-Wallis statistic = 6.58. $p = .037$. BIS = bispectral index. * $p < .05$

significance, determined by $p < .05$, was demonstrated for any variables when compared to the anesthesia providers' experience with colonoscopies (see Table 8). Thus, the null hypothesis (i.e., the mean rank values in each group are the same) cannot be rejected, in that there is no apparent difference among the various years of experience groups (i.e., 0-2, 3-5, 6-10, and > 10 years) when being compared to each dependent variable (e.g., lowest BIS, minutes of BIS \leq 60). In addition, these tests results should be viewed with caution due to the small sample size of the four categories used (Norman, 1999).

Table 8

Summary of Survey Respondents' Years of Experience Providing Anesthesia for Colonoscopies

Kruskal-Wallis test	Years of experience versus lowest BIS	Years of experience versus minutes BIS \leq 60	Years of experience versus minutes BIS \leq 40	Years of experience versus minutes BIS \leq 20	Years of experience versus minutes SpO ₂ \leq 90	Years of experience versus minutes of absent ETCO ₂ ^a
Statistic	2.76	5.26	1.61	4.76	0.45	0.65
p	.252	.072	.446	.092	.800	.722

Note. BIS = bispectral index; SpO₂ = saturation of peripheral oxygen; ETCO₂ = end tidal carbon dioxide

^aOnly 36 subjects were used to calculate all correlation and p values for absent ETCO₂ due to no ETCO₂ monitoring by one anesthesia provider in three patients.

* $p < .05$

CHAPTER FIVE: DISCUSSION

The purpose of this study was to evaluate sedation levels via BIS monitoring in patients undergoing colonoscopies. Moderate sedation is defined as a drug-induced depression of consciousness during which patients respond purposefully to verbal command (with or without light tactile stimulation) and are able to maintain a patent airway without intervention, sustain adequate spontaneous ventilation, and usually maintain their cardiovascular function (ASA, 2009); and according to the ASGE, this level of sedation is common and considered adequate for colonoscopy procedures (ASGE, Standards of Practice Committee, 2008). In addition, some studies have shown that a BIS value of 80 correlates with what has been described as an “ideal” level of sedation for colonoscopies (Bell et al., 2004; Bower et al., 2000). We hypothesized that levels of sedation in patients receiving anesthesia for colonoscopy procedures are deeper than what is suspected or intended. A convenience sample of 39 patients having colonoscopies performed in a hospital-based outpatient setting and undergoing sedation with propofol, were included in this observational study. Propofol was administered via intermittent boluses in 37 out of 39 (94.9%) patients and by bolus followed with infusion in 2 out of 39 (5.1%) patients; no patient received fentanyl or midazolam. It was found that 100% (39/39) of patients reached levels of GA at some point during their procedure. The amount of time patients spent at this level of anesthesia ranged from 11.1-100% of their procedure. This range was surprising in that during the study all patients were found to be consented for IV GA. The variables that showed a significant correlation with the occurrence of GA (i.e., $BIS \leq 60$) were smaller BMI ($p = 0.008$), length of procedure ($p < 0.001$), with longer procedures correlating with more time spent in GA, and the number

of minutes with absent ETCO₂ (i.e., apnea) waveform ($p = .002$). Additionally, data analysis suggested that patients with a larger BMI (compared to patients with lower BMIs) were more likely to have the greatest nadir in recorded BIS value (see Figure 14). Similarly, the r values suggest the greater the BMI, the fewer number of minutes patients experienced BIS values ≤ 60 and ≤ 40 (see Figures 15 and 16). Thus, overall in our study, patients with larger BMIs tended to exhibit higher BIS values. Studies involving BIS with this endoscopic patient population where anesthesia services are provided have not been previously performed.

Closed claims analysis of anesthesia injuries has shown that 10% of all allegations since 2000 have included “MAC” sedation (Metzner, Posner, Lam, & Domino, 2011). Since 1990, over 40% of all claims involving MAC sedation resulted in death or permanent brain damage. Respiratory complications following “over sedation” with opioids or other sedative drugs was contributory in 21% of these cases, and it was shown that over half could have been prevented with better monitoring, such as continuous ETCO₂ and pulse oximetry (Bhananker et al., 2006). Of note, the ASA in 2011(a) stated that all patients receiving “anesthesia” should have oxygenation, ventilation, and circulation monitored, and that body temperature should also be assessed *if* clinically significant changes are anticipated. Furthermore, deep sedation is defined as a drug-induced depression of consciousness during which patients cannot be easily aroused but can respond purposefully to repeated or painful stimulation; independent ventilatory function may be impaired, airway assistance may be required to maintain airway patency, and spontaneous ventilation may be inadequate, but cardiovascular function is usually maintained. Reaching deep levels of sedation during MAC with IV sedation can lead to

respiratory complications (ASA, 2009; Bell et al., 2004; El Chafic et al., 2012; Hata et al., 2009; Patel et al., 2005; Soto et al., 2005). Noteworthy in our study was that severe respiratory complications (i.e., those requiring advanced airway interventions, such as placement of an LMA or ETT) were not observed, regardless of the sedation level.

However, our sample size was small, and one of the limitations of the study was that it only included patients scheduled for elective colonoscopies. We recommend future studies to include the monitoring of sedation levels in patients consented for MAC with IV sedation for other types of procedures, including those in outpatient centers as well as in hospitals.

Largely, our data indicated that administration of propofol for elective colonoscopies by anesthesia providers results in GA (100% experienced GA for at least 1 minute). In this study, no harmful adverse events were observed (e.g., respiratory or cardiac arrest, unresolved hypotension or hypoxia, aspiration resulting in admission to the hospital). We suspect this was because 50% (6/12) of the anesthesia providers indicated via a survey (see Appendix H) that they believed they would be delivering GA throughout the entire procedure, and all providers (including those that did not believe they would be administering GA) were skilled in the management of GA; this demonstrates that it is probably safe for GA to occur during an elective colonoscopy by an anesthesia provider.

Hypoxia (i.e., SpO₂ < 90%) can be a complication that occurs with deeper levels of sedation (Bell et al., 2004; El Chafic et al., 2012; Hata et al., 2009; Patel et al., 2005; Soto et al., 2005). Several chin lifts were witnessed in response to hypoxia (SpO₂ < 90%) and apnea (absence of ETCO₂ waveform) throughout the data collection period, and

surprisingly some anesthesia providers were observed administering a chin lift without physiological evidence of the need for this action. Therefore, the number of chin lifts that were required to maintain a patent airway could not be accurately determined, and this could explain why an absent ETCO₂ waveform (i.e., apnea) was shown to have a significant correlation with IV GA, but not the number of minutes patients had a SpO₂ ≤ 90% (i.e., desaturation). Furthermore, one patient required a jaw thrust after a chin lift was not effective and another patient was believed to have had a laryngospasm following possible aspiration of secretions. This latter patient had a decrease in SpO₂ to 87% for 1 minute followed by a fall to 84% for a duration of 2 minutes. Simultaneously, this patient was coughing and gagging, and subsequently, required suctioning. Return to baseline SpO₂ occurred within 1 minute after suctioning. No patients required advanced airway interventions, such as placement of a nasopharyngeal airway, oropharyngeal airway, face mask, non-rebreather mask, bag mask, LMA, or endotracheal tube. Of note, 20.5% (8/39) of patients in our study were found to be current smokers. However, no patients were documented as using oxygen at home, and none had a history of previous airway surgery or known serious respiratory comorbidities (e.g., obstructive sleep apnea, emphysema, lung cancer, pulmonary hypertension).

Six patients experienced hypoxia for at least 1 minute and three patients for at least 2 minutes. Of the three patients with at least 2 minutes of hypoxia, two had a decrease in SpO₂ to 84% for at least 1 minute each. All except one of the patients with at least 2 minutes of hypoxia had no ETCO₂ waveform at the time of hypoxia, and each of them required a chin lift or jaw thrust to improve their SpO₂ and achieve an ETCO₂ waveform on the monitor. Out of a total of 656 minutes of data recorded for all 39

patients, a total of 51 minutes of absent ETCO₂ (7.9%) was noted (see Figure 2).

Propofol was the only drug used for sedation during all of the colonoscopies from which this data was obtained. The frequency of hypoxia, absence of an ETCO₂ waveform, or both, that required airway intervention in this study, demonstrates that administering propofol in the absence of an anesthesia provider could be unsafe.

There is a predicted increase, by 2015, in anesthesia professionals delivering sedation for over 50% of all colonoscopies (Inadomi et al., 2010). However, in some endoscopy centers across the United States, nurses administer propofol sedation for endoscopy under the direction of a gastroenterologist. This practice is advocated by some who maintain that MAC with IV sedation does not result in an increased safety for routine endoscopic procedures in average-risk patients (Rex et al., 2009). As mentioned previously, we obtained one preoperative BIS value and then began recording BIS values every minute starting just after the first BP was taken in the endoscopy suite. However, with some cases, several minutes would pass before the endoscopist team was ready for the start of the colonoscopy and before sedation was administered; this delay necessitated the elimination of recorded BIS values during this interval. Therefore, only BIS values documented from the onset of the endoscopic procedure - within 1 to 3 minutes after the initial propofol bolus in most patients - were used for statistical analysis. Out of a total of 674 recorded BIS values, 512 (76%) were ≤ 60 (i.e., GA). This indicates that after the first bolus of propofol (dose not recorded on anesthesia record) most patients reached GA and remained at a GA level of sedation for the majority of their procedure. Therefore, it is possible that nurses who provide sedation with propofol during endoscopy procedures may unknowingly achieve a general anesthetic state, which is not in adherence to current

recommendations from the ASA (2011b) and Hospira (2009). There have been two studies evaluating nurse-administered propofol sedation (Drake et al., 2006; El Chafic et al., 2012). Of note, during the Drake et al. study, all patients were administered an initial 40 mg propofol bolus followed by incremental boluses of 10-20 mg, with a total average rate of 15.8-17.2 mg/min; however, the study from El Chafic et al. did not provide the average doses of propofol administered, and neither study specifically evaluated the level of sedation produced via BIS monitoring. Our study was limited to sedation administered by anesthesia personnel in patients consenting for IV GA. Since patients were consented for GA, it is possible the anesthesia providers did not intend to maintain a lighter level of sedation during any portion of the colonoscopy procedures. We recommend a future study using similar methodology to evaluate nurse-administered propofol sedation.

Since GA occurs frequently with sedation for colonoscopies, and given the pre-study clinical observation and literature finding of colonoscopy patients being increasingly consented for MAC with IV sedation (Cohen & Benson, 2009; Cohen et al., 2006; Inadomi et al., 2010; Rex, 2011; Siddiqui, Shafiq, & Asghar, 2012; Trummel, 2007), a closer look at informed consent practices may be needed. MAC was defined in 2008 by the ASA as including varying levels of sedation, but when consciousness and the ability to respond purposefully is lost, GA is said to have occurred. If patients are receiving GA, but are consenting for MAC with IV sedation or simply “MAC”, then their informed consent would not accurately reflect the level of sedation actually obtained. Anesthesia consent forms presented to patients typically include the type of anesthesia to be administered (e.g., IV GA, MAC with possible GA, MAC with IV sedation, moderate sedation).

Survey responses from our study indicated that only one anesthesia provider believed they were delivering MAC 100% of the time, and 5 providers believed they were administering a combination of a MAC anesthetic and GA. The remaining 50% (6/12) believed they were administering GA throughout 100% of the procedure (see Figure 5); however, responses may have been influenced by the fact that all patients undergoing elective colonoscopies at this one hospital were consented for IV GA. It is likely anesthesia departments that opt to consent patients for IV GA may recognize the potential medical-legal concerns with obtaining consent for a different level of sedation than is actually being provided. The guidelines for obtaining informed consent are clear in that patients must understand the risks and benefits of the prescribed treatment as well as alternative approaches (e.g., GA, MAC with IV sedation) before giving his or her consent (Berg et al., 2001; K. Feld & A. Feld, 2010). Understandably, there is an increased risk for adverse events with deeper levels of sedation, and those risks should be disclosed when obtaining informed consent for any procedure, including colonoscopies. Furthermore, it is generally known that there is a high incidence of litigation in healthcare (U.S. Department of Health and Human Services, 2003), which further emphasizes the necessity of obtaining an appropriate consent by anesthesia providers. In addition, adequate informed consent can assist jurors in deciding the validity of some allegations (Sanford, 2006).

National health care reform is in the process of being implemented and revised. As such, the secondary changes to Medicare that may ensue remains uncertain, including the impact on reimbursement for anesthesia services. The future changes to Medicare reimbursements are important because Medicaid and other large private insurers often

follow Medicare policies (Rohlfesen & Sullivan, 2006). In regards to reimbursement requirements, the CMS (2011a) requires during MAC procedures, close monitoring of the patient, since GA may be required for the treatment of adverse events (e.g., excessive pain, difficulty breathing, adverse reactions), and because of the potential for other unanticipated complications, such as a more extensive procedure with necessary anesthetic interventions. Furthermore, the CMS (2011a) requirements for MAC and GA include the following: performance and documentation of pre and post-anesthetic evaluations, formation of an anesthetic plan, completion of an anesthesia record, and administration of necessary medications. If all of these requirements are met with MAC procedures, reimbursement is stated to be the “same amount as allowed for full GA” (CMS, 2011a). However, this CMS reimbursement policy could understandably change with the recent implementation of the Affordable Care Act.

This study has confirmed that GA occurs frequently during elective colonoscopies in patients who are consented for GA; therefore it is probable that GA also occurs with other endoscopic procedures in patients who are consented for MAC or MAC with IV sedation when similar doses of propofol are used. Thus, this study may help provide noteworthy clinical data during the current implementation of health care reform; for modifying existing billing procedures (that may change) for colonoscopies that are commonly scheduled for a MAC anesthetic but may actually be performed under GA.

As stated earlier, it is important to note that all participants in this study were consented for IV GA, not MAC or MAC with IV sedation. The investigators recognize the limitation this places on the external validity of this study, and recommend that future studies include patients consented for MAC or MAC with IV sedation.

In conclusion, this study evaluated sedation levels via BIS monitoring during elective colonoscopy procedures when propofol sedation was administered by an anesthesia provider. All patients received sedation levels equivalent to GA during their procedure. Factors that correlated with greater time spent in GA were smaller BMI, longer length of the procedure, and minutes with an absent ETCO₂ waveform. Additionally, the lowest BIS value obtained throughout the entire procedure was greater in those patients with a higher BMI. The frequency of apnea correlated with length of procedure, but these findings were clinically insignificant since they did not result in a sustained decrease in SpO₂ for any patient. Serious complications (e.g., unresolved hypoxia, cardiac arrest, CVA, death) did not occur during the conduction of this study, and no relationship was found between the survey respondents' number of years as an anesthesia provider or years of experience with colonoscopies when compared to BIS values, absent ETCO₂ waveforms, or SpO₂ values (see Tables 7 and 8). The results of this study indicate, in patients scheduled for colonoscopies who are consented for IV GA, it is common for anesthesia providers to consistently deliver a level of sedation concordant with GA. The significance of this finding relates to the pre-study clinical observation, that endoscopic patients being consented for anesthesia designated as MAC with IV sedation actually demonstrate intraoperative signs of GA similar to what were observed in this study. Future studies are warranted to determine the frequency of the various forms of anesthesia consent obtained for elective colonoscopies, along with research that assesses anesthetic depth with BIS monitoring in patients consented for MAC with IV sedation. Such research would help to further enhance patient safety and address potential medical legal concerns.

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Appendix A

- Observer's Assessment of Alertness/Sedation (OAA/S)
 - 0 = does not respond to noxious stimuli
 - 1 = does not respond to mild prodding or shaking
 - 2 = responds only after mild prodding or shaking
 - 3 = responds only after name is spoken loudly or repeatedly, or both
 - 4 = lethargic response to name spoken in a normal tone
 - 5 = responds readily to name spoken in a normal tone

Appendix B

- Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)
 - 0=unresponsive to deep stimuli
 - 1=unresponsive to shaking
 - 2=responsive to shaking only
 - 3=responsive to loud verbal command
 - 4=lethargic response to normal verbal command
 - 5=responsive & alert
 - 6=agitated
- Deep Sedation defined as ≤ 1

Appendix C

- Ramsay Sedation Score (RSS)
 - Awake
 - 1. Patient anxious and agitated or restless or both
 - 2. Patient co-operative, orientated and tranquil
 - 3. Patient responds to verbal commands only
 - Asleep; response to a light glabellar tap or loud auditory stimulus
 - 4. Brisk response
 - 5. Sluggish response
 - 6. No response
 - Interpretation
 - 1: Inadequate sedation
 - 2-4: Acceptable sedation
 - 5-6: Excessive sedation

Appendix D



Margaret R. Pardee Memorial Hospital
800 North Justice Street, Hendersonville, NC 28791
www.pardeehospital.org

March 18, 2013

Paula Grey, SRNA
Principal Investigator
15 Kenlan Drive
Swannanoa, NC 28778

Jenna L. Poziombke, SRNA
Principal Investigator
310 Armstrong Avenue
Hendersonville, NC 28739

Dr. Mark A. Kossick, Chairperson
28 Schenck Pkwy
Biltmore Park, Suite 300
Office 310
Asheville, NC 28803

Dear Investigators,

Following OHRP Title 45 CFR Part 46.110 and FDA Title 21 CFR Part 56.110, IRB Procedures for Expedited Review, specifying the IRB Chair, or experienced designee, may review a protocol or amendment to a protocol if such amendments involve only "minimal risk:"

On March 18, 2013, the Margaret R. Pardee Memorial Hospital Institutional Review Board (IRB), using an expedited review process, reviewed and approved the following:

An Evaluation of Sedation Level using Bispectral Index (BIS) in Patients Undergoing Monitored Anesthesia Care (MAC) for Colonoscopies and Correlated Adverse Events

**Protocol Version 3/11/2013
Informed Consent Version 2/26/2013
CRNA Survey**

The approval period will be for a period of one year. You will be required to submit a status report in writing for the annual review by the IRB at the notification of the Chairperson. The report should contain the number of patients, therapeutic outcomes, problems encountered, and any other relative data obtained during the course of the study.

As always, you are required to report immediately to the IRB any adverse drug reactions or events using the FDA MedWatch form, or the appropriate form provided by the study sponsor. Also, the IRB must be notified immediately of any changes to the approved protocol or consent form before those changes are made, as a full IRB review and approval is required unless the changes are minor and can be approved by the Chairperson (or designee) under the FDA Expedited Review procedure. If there is a life-threatening emergency, the change should be implemented and the IRB Chairperson notified immediately after the fact.

Be aware that the IRB and the FDA have the authority to inspect any records of the study at any time in order to ensure the protection of the patients. Failure to comply with the record keeping or reporting requirements of the sponsoring agency, FDA, or the IRB, will result in suspension of the IRB's approval with notification to the FDA and the sponsoring agency. Continuation of the study beyond the one-year approval will depend upon compliance with the above instructions and the information provided to the IRB in the status reports. At the time of each review, the IRB will decide that the study should be amended, terminated, or allowed to continue as originally approved.

Please feel free to contact the IRB Office for additional information at 828-698-7337.

Respectfully,

Marcia Cage, RN, OCN, CIM
IRB Coordinator
marcia.cage@pardeehospital.org

5525-14 (12/11/2012)

Appendix E

Western Carolina University
 Institutional Review Board
 c/o Office of Research Administration
 109 Camp Building
 Cullowhee NC 28723
irb@wcu.edu | 828-227-7212



IRB number: 2013-0246

Date of review decision: 11 April 2013

Investigators: Jenna Poziombke, Paula Grey, and Dr. Mark Kossick

Project Title: An Evaluation of Sedation Level Using Bispectral Index (BIS) in Patients Undergoing Monitored Anesthesia Care (MAC) for Colonoscopies and Correlated Adverse Events

Your IRB protocol has been approved, effective with today's date, under the following category of expedited review, as authorized by 45 CFR 46.110 and 21 CFR 56.110:

- Clinical studies of drugs and medical devices (a) when an investigational new drug application (21 CFR Part 312) is not required or (b) medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling
- Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture
- Prospective collection of biological specimens for research purposes by noninvasive means
- Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves
- Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)
- Collection of data from voice, video, digital, or image recordings made for research purposes
- Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies
- Continuing review of research previously approved by the convened IRB

Your protocol is approved for one year and may be renewed annually. If you wish to make changes to your protocol, including recruitment procedures, sampling, consent, interventions, data collection methods, and investigators, please use the amendment request located on the IRB website (<http://www.wcu.edu/6801.asp>) to submit your request in advance.

This approval does not cover research conducted prior to the approval date. Please remember that you are responsible for reporting adverse events or unanticipated risks to the IRB immediately.

IRB representative: Brian Byrd (bbyrd@wcu.edu; X2607)

A handwritten signature in black ink, appearing to read "Brian Byrd".

Appendix F

IRB APPROVAL

MAY 22 2013

CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

An Evaluation of Sedation Level using Bispectral Index (BIS) in Patients Undergoing Monitored Anesthesia Care (MAC) for Colonoscopies and Correlated Adverse Events

You are being asked to participate in a research study. Our names are Paula Grey and Jenna Poziombke. We are currently graduate nurse anesthesia students at Western Carolina University, and we are the investigators in charge of this study, our faculty advisor is Dr. Mark A. Kossick, Professor, Western Carolina University.

What is the purpose of this study?

We are conducting research to better understand the level of sedation used during colonoscopies and are visiting this hospital to collect data on patients.

What will happen if I take part in this study?

Your involvement in this project involves allowing us to place a sticky sensor on your forehead in the pre-procedure area. It will remain on your forehead throughout your procedure and will be removed after your procedure, in the post anesthesia care unit. The sensor will be connected to a Bispectral Index monitor, which will provide values that allow measurement of sedation level. This monitor is frequently used by nurse anesthetists in the U.S. and in other countries, to help evaluate the depth of anesthesia throughout surgical procedures.

The study investigator will record information from your medical record. The information recorded will include:

- Vital signs (body temperature, heart rate, blood pressure)
- Use of oxygen and O₂ saturation (amount of oxygen in your bloodstream)
- Medications and anesthesia used during the procedure
- Demographic information such as age, weight, gender, physical status, history of prior surgery or sleep apnea, use of oxygen at home

How long will I be in the study?

The sticky sensor will be removed after completion of your procedure. This will complete your participation in the study.

What are the risks and benefits of being in the study?

There are no foreseeable risks or benefits to you for participating in this study. It is hoped that the information obtained will help us understand the level of anesthesia typically achieved throughout colonoscopies.

What if I change my mind about participating in the study?

Your participation is voluntary. You may choose either to take part or not to take part in this research study. You may withdraw at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

What other choices do I have if I do not participate in this study?

You would undergo the colonoscopy without use of the Bispectral Index Monitor and research monitoring.

Will my medical information be kept private?

To protect confidentiality, an identification number will be assigned to you. Your name or any other identifying information will not be used.

What are the costs of participating?

There is no additional cost to you or your insurance company.

Who do I contact if I have questions or concerns?

If you have any questions or concerns about your treatment as a participant in this study, you should contact Paula Grey, Nurse Anesthesia student, Western Carolina University, at 828-337-0584 or Jenna Poziombke, Nurse Anesthesia student, Western Carolina University, 715-225-2274, Dr. Mark A. Kossick, Faculty Advisor, Professor, Western Carolina University at 731.431.8896 or by e-mail at makossick@wcu.edu, or the Chair of the Western Carolina University Institutional Review Board through WCU's Office of Research Administration at 828-227-7212 or by e-mail at irb@wcu.edu

If you have any questions or concerns about your rights as a participant in this study, you may also call the Margaret R Pardee Memorial Hospital Institutional Review Board (IRB). The IRB is a committee that reviews this research for the rights and safety of participants. The IRB is composed of members of the hospital, as well as lay members of the community not connected with the hospital. The IRB has reviewed and approved this study. You can reach the IRB at 828-698-7337.

Please complete the portion of the consent form below:

I give my permission to participate in this study. Yes No

The investigators may use my demographic information and data obtained during my procedure for their research results. Yes No

Participant Name _____ Date _____

Participant Signature _____

Researcher Name _____ Date _____

Researcher Signature _____

Appendix G

CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

An Evaluation of Sedation Level using Bispectral Index (BIS) in Patients Undergoing Monitored Anesthesia Care (MAC) for Colonoscopies and Correlated Adverse Events

You are being asked to participate in a research study. Our names are Paula Grey and Jenna Poziombke. We are currently graduate nurse anesthesia students at Western Carolina University, and we are the investigators in charge of this study, our faculty advisor is Dr. Mark A. Kossick, Professor, Western Carolina University.

What is the purpose of this study?

We are conducting research to better understand the level of sedation used during colonoscopy procedures.

What will happen if I take part in this study?

Your participation in this project involves answering a short questionnaire. The questions you will be asked are: year and month passed national certification exam, number of months of experience with providing anesthesia care for colonoscopy procedures, opinion of type of anesthesia being provided during colonoscopies, and highest educational degree obtained.

What are the risks and benefits of being in the study?

There are no foreseeable risks or benefits to you for participating in this study.

What if I change my mind about participating in the study?

Your participation is voluntary. You may choose either to take part or not to take part in this research study.

Will the information I provide be kept private?

To protect confidentiality and assure anonymity, an identification number will be assigned to you. Your name or any other identifying information will not be used.

Who do I contact if I have questions or concerns?

If you have any questions or concerns about your treatment as a participant in this study, you should contact Paula Grey, Nurse Anesthesia student, Western Carolina University, at 828-337-0584 or Jenna Poziombke, Nurse Anesthesia student, Western Carolina University, 715-225-2274, Dr. Mark A. Kossick, Faculty Advisor, Professor, Western Carolina University at 731.431.8896 or by e-mail at makossick@wcu.edu, or the Chair of the Western Carolina University Institutional Review Board through WCU's Office of Research Administration at 828-227-7212 or by e-mail at irb@wcu.edu

I give my permission to participate in this study. Yes No

Participant Name _____ Date _____

Participant Signature _____

Researcher Signature _____ Date _____

Appendix H

Survey of CRNAs participating in Colonoscopies

Date: __/__/__

CRNA ID: _____

1. What year did you become a Certified Registered Nurse Anesthetist? _____
2. Highest degree obtained? (Check one)
 - Diploma
 - Bachelors
 - Masters
 - Doctoral
3. How many years or months of experience have you had with colonoscopies? (Check one)
 - 0-6 months
 - 7 months – 1 year
 - 1 -2 years
 - 3-5 years
 - 6-10 years
 - More than 10 years
4. What percentage of colonoscopies do you believe you are providing the following levels of sedation? (Numbers must equal 100%)
 - MAC _____
 - General Anesthesia _____
 - Combination of MAC and General Anesthesia _____

Appendix I

DATA COLLECTION SHEET

-Evaluation of Sedation Level Using Bispectral Index Research-

Jenna Poziombke, RN, BSN, SRNA & Paula Grey, RN, BSN, SRNA

Dr. Mark A. Kossick

Hospital ID _____

Patient ID _____

CRNA ID _____

Date ___/___/___

BIS Time _____

CRNA Time _____

	BIS	HR	BP/MAP	O2 Sat/ Flow +/-	RR	Temp	Aldrete Score	Time
Preop							-----	
PACU/Bypass								

Procedure Room

Mins	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
BIS																										
EMG																										
SQI																										
Sat																										
L/m																										
Deliv.																										
CO2																										
A/w																										
Bolus																										
HR																										
SBP																										
DBP																										
MAP																										

*A/w: C=chin lift, J=jaw thrust, B=combo of chin lift & jaw thrust, N=nasopharyngeal a/w insertion, O=oropharyngeal a/w insertion, M=mask ventilation, L=LMA placement, ETT=endotracheal tube placement

*Deliv: (O2 Delivery): NC=nasal cannula, FM=face mask, V=venturi mask, NRB=non-rebreather, M=mask ventilation, L=LMA, ETT=endotracheal tube

*Time 0=when first BP is complete

Mins	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50
BIS																									
EMG																									
SQI																									
Sat																									
L/m																									
Deliv.																									
CO2																									
A/w																									
Bolus																									
HR																									
SBP																									
DBP																									
MAP																									

Technique: One time/single bolus followed by infusion _____ Intermittent bolus _____ Infusion _____ Combination of intermittent & infusion _____

- Postop Diagnosis: _____
- Anesthesia consent: GA _____ MAC _____ Both _____
- Length of Procedure (mins): _____
- Total drug dosages:
 - Propofol: _____
 - Midazolam: _____
 - Fentanyl: _____
 - Other: _____

Gender: _____ Age: _____ BMI: _____ Wt: _____ Ht: _____ PS: _____

1. Previous airway surgeries? _____
2. Home O2? _____
If yes, how many L/m? _____
3. Hx OSA? _____
If yes, home CPAP or BiPAP? _____
4. Major comorbidities _____
5. Extenuating circumstances _____

Check List

- Anesthesia Record
- Pre-anesthesia work up or assessment sheet
- PACU or bypass anesthesia record
- Anesthesia and/or surgical consent form
- Surgeon's history and physical/medication list

*L/m & Deliv: will be recorded at baseline and when any intraoperative changes from baseline occur

*Sat: will be recorded at baseline, every 5 minutes, and every 1 minute when it drops below 95% (until value is back at 95% or greater, then recorded again every 5 minutes)

BIS=bispectral index, **EMG**=electromyography, **SQI**=signal quality index, **Sat**=oxygen saturation, **L/m**=Liters per minute flow of oxygen, **CO2**=carbon dioxide's presence or absence, **A/w**=airway, **Bolus**=presence or absence of propofol bolus, **HR**=heart rate, **SBP**=systolic blood pressure, **DBP**=diastolic blood pressure, **MAP**=mean arterial pressure

