COMBINING OBSERVATIONAL AND PHYSIOLOGIC SEDATION ASSESSMENT TOOLS

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ABSTRACT

Purpose: This study was designed to test the hypothesis that bispectral index (BIS) monitoring, when used as an adjunct to current sedation assessment, reduces the amount of sedation used.

Background/Significance: ICU patients frequently experience episodes of oversedation. A wide array of sedation scales have been proposed and tested with varying results. There is some confusion about BIS monitoring both in literature and practice; BIS is neither adequate, nor designed, to replace observational assessments of the patient's response to sedation. This study is unique in that it explores how a specific outcome variable (the amount of sedation) is impacted by augmenting (not replacing) current methods of sedation assessment.

Methods: This prospective randomized controlled trial blinded nurses to the primary purpose of the study. Following informed consent by the subject's legally authorized representative, for this institutional review board approved study, 51 subjects were randomized to receive sedation assessment with either the standard of care alone (Ramsay-alone group; n = 25), or the standard of care plus BIS (BIS-augmentation group; n = 26). The study period began at 8:00 a.m. on the day of study and lasted 12 hours. Nurses were instructed to adjust sedation to a Ramsay score of 4 (both groups) and a BIS value between 60 and 70 (BIS-augmentation group).

Results: The results represent data from 51 subjects included in the interim analysis of a planned enrollment of 90 subjects. The interim analysis was performed using a significance level of .025 to explore the primary research question. Upon rejecting the null hypothesis for

the primary research question, the remaining research questions were explored using a significance level of .05. Data were analyzed using SAS v9.1 (Cary, NC). The mean infused volumes for the Ramsay-alone group (175.36 ml) and the BIS-augmentation group (97.51 ml) were significantly different ($F=6.00$, $p=.018$, $r^2=.011$). The mean infusion rates for the Ramsay-alone group (30.19 mcg/kg/min) and BIS-augmentation group (15.35 mcg/kg/min) were significantly different ($F=8.63$, $p=.005$, $r^2=.15$). The length of time for subjects in the Ramsay-alone group (9.47 minutes) compared to the BIS-augmentation group (1.44 minutes) to awaken (recovery rate) when the sedation was discontinued was significantly different ($F=24.48$, $p<.0001$). There were no undersedation events reported in either group.

Conclusions: BIS augmentation of current observational assessment resulted in a reduction in the sedation use and a shorter time to recovery from sedation; no increase in undersedation associated with the reduced use of sedation in the BIS augmented group. Physiologic sedation assessment tools with EEG-derived parameters such as BIS provide useful information that may decrease the incidence of oversedation in critically ill patients.

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This dissertation carries one name, but is the work of many.

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LIST OF ABBREVIATIONS

ACNP	Acute Care Nurse Practitioner
ADN	Associate Degree in Nursing
AEP	Auditory Evoked Potential
ANCOVA	Analysis of Covariance
APACHE®IV	Acute Physiology and Chronic Health Evaluation
APN	Advanced Practice Nurse
ARAS	Ascending Reticular Activating System
BIS	Bispectral Index
BSN	Bachelor of Science in Nursing
CBF	Cerebral Blood Flow
CI	Confidence Interval
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
EEG	Electroencephalography
EMG	Electromyographic
ERP	Event Related Potential
GABA	Gamma-Aminobutyric Acid
GCS	Glasgow Coma Score
HTN	Hypertension
ICP	Intracranial Pressure
ICU	Intensive Care Unit

kg	Kilogram
IV	Intravenous
MAAS	Motor Activity Assessment Scale
ml	Milliliter
mcg/kg/min	Micrograms per kilogram per minute
MSN	Master of Science in Nursing
NCC	Neural Correlate of Consciousness
NCCU	Neurocritical Care Unit
NPTC	Neurophysical Theory of Consciousness
RASS	Richmond Agitation-Sedation Scale
RN	Registered Nurse
SAS	Sedation-Agitation Scale

CHAPTER I

INTRODUCTION AND THEORETICAL FRAMEWORK

The major aim of this study was to examine how the addition of a physiologic measure of consciousness to current observational sedation assessment impacts sedative use in neurocritically-ill patients requiring continuous infusion of sedatives. Concurrent aims were to assess the impact of augmenting observational sedation assessment with physiologic data on facilitating a more appropriate level of sedation. In this chapter, the problem of sedation and the significance of this study are discussed. A background and significance section is then presented with emphasis on the implications for practice. Next, the conceptual framework of the study is discussed and the specific aims of the study and research questions are presented.

The Problem

Neurocritically ill patients have an acute injury to their central or peripheral nervous system and often require continuous intravenous (IV) sedation to facilitate mechanical ventilation, decrease intracranial hypertension, protect the patient from further brain injury and prevent the recall of unpleasant events (Jacobi et al., 2002; Murdoch & Cohen, 2000; Young, Knudsen, Hilton, & Reves, 2000). Immediately following an acute brain injury, both nursing care and medical care is directed towards the prevention of secondary brain injury which may occur as a result of the effects (edema, neurotoxin release, or hypo-perfusion ischemia) of the initial injury (Fabregas et al., 2004; Littlejohns, Bader, & March, 2003; Marion, 2002; Reinert & Bullock, 1999; Yanko & Mitcho, 2001).

Often, neurocritically ill patients require oral-tracheal intubation and mechanical ventilation (Greenberg, 2001; Yanko & Mitcho, 2001). Sedation use for these patients may facilitate mechanical ventilation and thus improve the patient's end-organ oxygen perfusion (Olson, Chioffi, Macy, Meek, & Cook, 2003). Control of intracranial pressure (ICP) is a primary method of minimizing secondary brain injury, but often requires sedation during the acute and early subacute phases of brain injury (Dennis & Mayer, 2001; Jacobi et al., 2002; Littlejohns & Bader, 2005; Mirski, Muffelman, Ulatowski, & Hanley, 1995). Patients with brain injuries often become confused and combative during the acute phases. Patients who are combative require sedation to prevent self-extubation, purposeful or accidental removal of invasive monitoring devices, or injury to staff members (Boulain, 1998; Grap, Glass, & Lindamood, 1995; Tung et al., 2001). Sedation may also prevent the recall of unpleasant experiences and procedures.

Monitoring and recording the patient's level of neurologic status are expected functions of the neurocritical care unit (NCCU) nurse (AANN, 2004; Blumenfeld, 2002; Greenberg, 2001). The nurse must vigilantly monitor the neurologic exam for cues that signal changes in intracranial dynamics associated with secondary brain injury (Littlejohns & Bader, 2005). Early recognition of neurologic changes is essential to prevent secondary brain injury (Blumenfeld, 2002; Greenberg, 2001). To accurately track these changes, a sedation-free exam is considered to represent the patient's best level of functioning. In the NCCU, sedation-free neurologic assessments are needed at least once every 2 hours to track changes in patient condition. The neurologic exam tests the patient's current "best possible" level of function, but an artificially depressed level of consciousness inhibits the ability to accurately estimate function. Since sedatives decrease a patient's level of consciousness, they may

decrease the accuracy of the neurologic exam. Therefore, short-acting sedatives are used for this population so that the patient can be periodically awakened for accurate neurologic assessment (Olson, Graffagnino, King, & Lynch, 2005). At the same time, providing an adequate level of sedation between these neurological assessments remains an essential component of the NCCU nurses' role. The need to obtain a sedation-free neurologic assessment while meeting the need for sedation creates a challenge for NCCU nurses and creates opportunities for patients to experience periods of oversedation and/or undersedation (Olson et al., 2005; Park et al., 2001).

Oversedation is the administration of sedatives at a level greater than the amount of drug required by the individual to achieve the desired effect. Oversedation can lead to longer time to wake-up when sedatives are removed for the purpose of obtaining a neurological examination and more drastic changes in physiologic parameters during waking periods, limiting the ability to obtain a representative neurologic examination (Arbour, 2000). Another complication of oversedation is impaired ability to wean a patient from mechanical ventilation (Carrasco, 2000). Sedation decreases ventilatory drive and excess sedation will impair the ventilator weaning process and increase a patient's length of stay (Kollef et al., 1998). Therefore, the amount of sedation used should be appropriate to prevent periods of oversedation that are associated with these negative outcomes (Jacobi et al., 2002).

Undersedation is the administration of sedatives at a level inadequate to meet the sedation goals set by the medical team and may lead to a wide variety of adverse medical events, including unplanned patient self extubation, (Boulain, 1998; Grap, Glass, & Lindamood, 1995; Tung et al., 2001) unpleasant recall of medical events and procedures, increased awareness of pain and discomfort, increased oxygen demand and consumption and

adverse changes in vital signs (Weinert, Chlan, & Gross, 2001). Vital sign changes associated with undersedation include tachycardia, tachypnea and hypertension. However, the bedside nurse cannot rely on these physiological changes as signals for inadequate sedation (Flaishon, Windsor, Sigl, & Sebel, 1997; Weinert, Chlan, & Gross, 2001). For example, a patient who arrives with a history of severe congestive heart disease may not be able to produce hypertension, and mild tachypnea may be normal for that patient. Therefore, assessing for undersedation is difficult and requires that nurses develop skills specific to this task. Nurses monitoring sedation must become aware of the combination of cues including patient behaviors and physiologic parameters that are affected by sedation while placing these cues within the context of the patient's individual state of health.

The goal for sedation is to achieve comfort and safety and allow appropriate medical therapies while preserving the ability to quickly obtain an accurate neurologic exam (Burchardi, 2004; Jacobi et al., 2002; Olson et al., 2005). Short-acting sedatives facilitate this goal because the drug effect can be rapidly adjusted (Jacobi et al., 2002). However, the use of short-acting sedatives can often lead to episodes of hypotension (Jacobi et al., 2002). If the sedative infusion results in episodes of hypotension, the medical team may prescribe treatments to raise blood pressure through fluid administration and vasoconstrictive medications; however, this too carries risks when sedation is decreased to obtain a neurologic exam. As the effects of sedation wear off during awakening periods, the patient's physiologic balance is at risk: practitioners may observe acute changes in heart rate, respiratory rate, blood pressure and intracranial pressure. Therefore, it is important to use only as much drug (sedative) as is required to maintain the patient at an appropriate level of sedation.

The problem addressed in this study is whether physiologic data used as an adjunct to current observational data provides a significant contribution to clinical decision-making about the patient's level of sedation. Oversedation has been found to be common through all critical care settings, and thus, the contribution of physiologic data to clinical decision-making is operationalized as a decrease in oversedation (de Wit & Epstein, 2003). As will be discussed later, oversedation is further operationalized as a decrease in sedative use, and a shortened length of time to arouse from sedation. The use of physiologic data for sedation management has been explored only when physiologic data is used as a replacement for observational data. Prior research in this field has virtually ignored the complexity of bedside care in an active clinical setting wherein it is improbable, if not impossible, for nurses to ignore the contribution of their observations. This study is unique in that the unit of analysis is a complete nursing shift rather than a single moment of time. This, in effect, allows the nurse to acquire knowledge about how the patient responds to sedation, (knowledge that may not be included as elements of a sedation scale), and to use that knowledge when providing care.

Significance of the Study

Clinical decision-making about sedation has been poorly investigated, yet continuous sedation remains a cornerstone of intensive care unit (ICU) care and the bedside nurse is most often the responsible party for deciding to increase or decrease sedation. Bispectral index (BIS) monitoring is a physiologic measure which is hypothesized to provide clinically relevant cues about changes in the level of consciousness (Schneider et al., 2004). BIS monitoring is rapidly growing in popularity in critical care settings as a decision support tool for sedation monitoring. To date, studies have discussed BIS monitoring as though it were a

possible replacement for observational sedation assessment. BIS monitoring should be seen as an adjunct tool that provides additional data the nurse could not otherwise obtain, not as a replacement for nursing observation.

The Coma Cue-Response conceptual framework for the care of neurologically-injured patients highlights the importance of the decisions nurses make when caring for unconscious patients and details the importance of the timing of those decisions (Olson & Graffagnino, 2005). This study addresses a focal component of caring for the neurocritically-ill and sedated patient; the question of whether BIS monitoring will provide useful information that, when incorporated with observational sedation assessment, affects clinical decision-making as evidenced by changes in sedation-related patient outcomes. BIS monitoring was not examined in the absence of observational sedation assessment, but rather in the manner to which it is most likely to be used, namely, as providing nurses with additional information about the sedated patient. This research provides the first prospective randomized control trial of a combination of observational data and physiologic data (sedation assessment with BIS and with the Ramsay scale) versus only observation data (sedation assessment with only the Ramsay scale) for monitoring and adjusting continuous sedative infusions.

The significance of this study is three-fold. Primarily this study builds on the foundation for understanding the impact of adding a physiologic measure of sedation on specific patient outcomes. Second, because BIS is rapidly growing in popularity, the ability to conduct a randomized trial in which BIS use is examined may be severely compromised in the very near future. Some institutions are now writing sedation policies that incorporate the routine use of BIS for sedation monitoring despite the lack of clear evidence to support this

practice. BIS may soon be viewed as a standard component of ICU care; hence, in the future, a study in which one group does not receive BIS may be equated with a study in which one group does not receive the standard of care, and that creates an ethical dilemma. Finally, while there are studies exploring sedation assessment with observational tools and there are studies exploring sedation assessment with physiologic monitors such as BIS, this study provides a vital link in understanding sedation assessment because the study provides a valuable opportunity to learn more about sedation assessment as it occurs in the clinical setting. Specifically, the study explores sedation assessment when both BIS and observational tools are used simultaneously.

Significance of the Study for Nursing

The significance of the study for nursing is supported by the role of the nurse in clinical practice. In the acute setting, nursing care occurs at the bedside. Nurses need clinical support and readily available information to make accurate decisions. The results of this study further the science of nursing both in providing care to the sedated patient and in evaluating the impact of a decision support tool. The bedside nurse will hopefully benefit through a direct increase in the science of determining whether or not the BIS provides information that is useful in impacting patient care outcomes. Finally, nurses involved in writing and revising practice standards for care of the sedated patient will benefit from an evaluation of the BIS as it impacts patient outcomes.

Theoretical Framework for the Study

Coma Cue-Response Conceptual Framework

Optimally timing neurological assessments that are performed during a period of time when sedative dosages must be increased and decreased is dependent upon the decisions

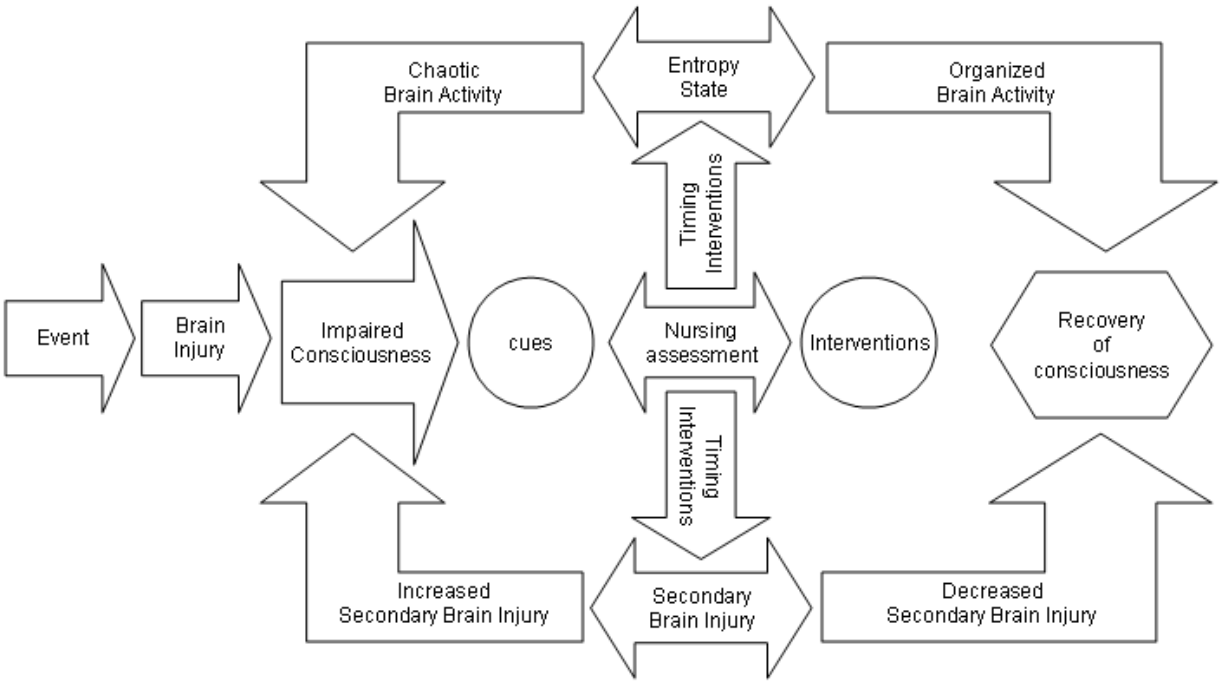
nurses make when caring for sedated patients. Nurses decide when to take an action based on the existing set of available cues they can process. The larger context within which these decisions are couched is best explained through an understanding of the coma cue-response conceptual framework (Olson & Graffagnino, 2005). The coma cue-response conceptual framework provides a fundamental link between ongoing research, current theory on consciousness, and specific bedside nursing interventions (Figure 1). This framework applies solely to the patient who is in a comatose state resulting from neurologic injury and can be explained in a sequential manner. Initially, some event causes an injury to the brain. Some, but not all, brain injuries result in impaired consciousness; this may occur directly, as a result of injury to the cerebral cortex or brainstem, indirectly through the administration of sedative agents, or by a combination of direct and indirect mechanisms.

How a comatose patient responds to therapy is not always readily apparent. However, for the astute practitioner, physical and physiological data become cues that indicate whether a patient's response was good, bad, or neutral. A physical cue is defined as that which can be observed directly and without monitoring (thrashing arms, grimacing, and opening of the eyes are but a few examples); these are observable behaviors from the patient. A physiological cue is that which is a measured patient parameter, such as the heart rate, respiratory tidal volume, or intracranial pressure (ICP). Nursing assessment interprets the meanings of these cues and the implications of planned interventions and determines the optimal timing of nursing interventions. Optimally timed, nursing interventions will promote the setting for recovery. Poorly timed, nursing interventions will lead to increased secondary injury and extended loss of consciousness (Olson & Graffagnino, 2005). Adjusting IV sedation and interrupting sedation to obtain a neurologic exam are examples of nursing

interventions that need to be optimally timed (Olson et al., 2005). Timing affects recovery directly through an impact on secondary brain injury and indirectly through an impact on shifting the state of entropy.

Figure 1.

The Coma Cue-Response Conceptual Framework proposed by Olson & Graffagnino (2005).



An understanding of the concept of entropy will help the reader understand how entropy relates to consciousness. Entropy is a measure of the degree of order in a system. The concept of entropy has been applied to the gestalt of consciousness (John, 2002; Zeman, 2002). In the extremes of consciousness the brain demonstrates a high degree of entropy as measured by electrical signals (John, 2002). The very awake brain is organized towards achieving consciousness; in the opposite direction, brain death displays a very organized

(isoelectric) signal. The timing of nursing interventions impacts the patient's state of entropy within the brain. Over time, if interventions are timed such that they inhibit the ability of the brain to become organized, a continued state of chaotic brain activity (high entropy state) results. However, interventions can be timed to permit the ascending reticular activating system (ARAS) and sleep inhibitory mechanisms to establish a more organized pattern (low entropy state). An increase in organized sleep pattern is associated with an increased likelihood that the patient will recover full consciousness. The change from a high entropy state to a low entropy state (organized brain activity) thereby signals an increased likelihood of the recovery of consciousness.

Additionally, the timing of nursing interventions impacts the degree of secondary brain injury (Wong, 2000). By decreasing secondary brain injury, nursing care acts to promote an environment in which the recovery of consciousness is enabled. Poorly timed, nursing interventions will exacerbate the conditions of secondary brain injury (Greenberg, 2001; Littlejohns & Bader, 2005). For example, suctioning a patient who has an ICP of 30 mm Hg may increase the ICP even further and thereby decrease cerebral perfusion which results in further damage to brain tissues (Littlejohns, Bader, & March, 2003). However, nursing interventions, such as turning, may be performed when patient cues signal that the patient will tolerate these procedures. Turning reduces the risk of pulmonary infection, improves oxygenation and reduces the risk of skin decubiti (Grap & Munro, 2004). This is one example of how optimally timed nursing interventions set the stage for optimizing a patient's chances for recovery by decreasing the risk of secondary brain injury and promoting cerebral perfusion. A more accurate assessment of the patient's response to sedation will provide the nurse with cues about when to initiate, or abort, specific interventions.

Cues, Assessment, and Interventions

Sedation assessment is an attempt by the nurse to acquire cues and attach meaning to these cues through which a decision can be made about the degree of sedation and any needed changes in sedative dosing. The nature of sedation assessment is such that patients exist in various degrees of unconsciousness. Information provided by unconscious patients includes physical cues such as head thrashing, physiological cues such as increased breathing rate, and cues from secondary sources such as monitors, radiographic data and laboratory findings. The unconscious patient, by definition, is unable to consciously communicate and interact with the nurse (Zeman, 2001). Interpreting cues that indicate a patient is receiving too much stimuli is an acquired nursing skill; as nurses gain proficiency they develop the ability to attach meaning to the nuances of these fundamental elements (cues from nursing observations and assessments) of nursing care (Benner, 1984). For example, maxims describing the care of patients with tachycardia take on new meaning to the expert nurse who considers that an increase in respiratory rate may be a signal to assess for hypoxia. The expert then links hypoxia to tachypnea. Further, tachypnea and hypoxia are linked as joint causes of tachycardia; whereas the less experienced novice nurse may see the tachycardia as an isolated finding. Nurses who are alert to the cues will use this information to base decisions regarding sedation and these decisions will ultimately impact the patient's recovery from illness.

A variety of nursing interventions may stimulate the comatose patient and lead to the conditions that cause secondary brain injury (Robertson, 2001). During the early subacute phase of brain injury even small changes in a patient's position, such as increased neck flexion or decreased head elevation, may markedly increase ICP (Greenberg, 2001).

Increases in temperature are associated with an increase in ICP, a decrease in the integrity of the blood brain barrier, and increase in cerebral metabolic demand that leads to increased edema and increased secondary damage (Cairns & Andrews, 2002). Optimal timing of interventions that promote cerebral blood flow may promote recovery of consciousness by permitting blood flow to the ARAS and to specific arousal inhibitory mechanisms. Altering sedation to obtain a neurologic exam or stabilize hemodynamic status are two examples of nursing interventions that are timing dependent. This implies that nurses must time certain interventions, such as the assessment, to occur when patients are awake and not during periods of rest. Such timing may promote the recovery of consciousness by allowing the competing mechanisms of the ARAS and arousal inhibition system to find new set points. Intracranial hypertension, increased oxygen consumption, and decreased cerebral perfusion are linked to increased activity (Wong, 2000). Timing interventions to allow rest periods may decrease the risk of secondary brain injury by reducing incidences of increased ICP and promoting cerebral perfusion (Drummond, 1990).

The timing of nursing interventions is further complicated by the sedation-assessment conundrum (Olson et al., 2005). This occurs when nurses are faced with the dilemma of needing to allow a patient to lighten from sedation so that the neurological examination will reflect the patient's best possible response, yet the very act of lightening sedation creates a state of undersedation and carries the risk of inducing secondary brain injury. Further, there is a negative feedback loop that may be present in which the undersedation event results in secondary brain injury; the secondary brain injury is manifest as a change in the neurologic exam, the change in neurologic exam requires additional assessments and further episodes wherein sedation is decreased for the sake of obtaining the exam. In this manner, it can be

seen that the act of obtaining the neurologic exam may alter the results of the following exam.

The conundrum of balancing the need for a neurologic assessment against the need to maintain adequate sedation is especially pertinent in the early stages of brain injury. Intermittent and frequent exams of neurocritically ill patients are common during the early subacute phase of brain injury when the patient is at greatest risk for secondary brain injury (Greenberg, 2001; Wong, 2000). Sedation is indicated during this period to prevent injury (for example, preventing self extubation), to facilitate medical goals (e.g., maintaining hemodynamic goals), and for humanitarian goals (i.e., preventing unpleasant recall of events) (Murdoch & Cohen, 2000; Young et al., 2000). Established guidelines for the management of brain-injured (BI) patients at risk for intracranial hypertension recommend mild sedation and, in cases refractory to mild sedation, barbiturate coma therapy to control ICP and improve ventilation (Bullock et al., 2000). Sedatives decrease global oxygen consumption, resulting in greater oxygen availability for at-risk tissue (Dennis & Mayer, 2001; Simmons, Riker, Prato, & Fraser, 1999). Sedation is indicated to facilitate ventilation, and indirectly reduce ICP (Wong, 2000). Because both adequate sedation and accurate neurologic exams are a focus of care in the early subacute phase, a great deal of effort is spent on solving the sedation-assessment conundrum by optimally timing nursing interventions based on clinical information.

The administration and monitoring of sedation requires that the nurse recognize a wide variety of patient cues that signal oversedation and undersedation. The bispectral index monitor (BIS) has been suggested as a means of optimizing sedation monitoring practices and may facilitate the timing of patient care interventions in this patient population (Arbour,

2003; Olson, Cheek, & Morgenlander, 2004; Olson et al., 2003). The BIS monitor may be particularly suited to sedation assessment of comatose patients (Jacobi et al., 2002). When used in conjunction with observational nursing assessments of sedation, information from the BIS monitor may provide additional cues that nurses can use to recognize and respond to incidences of oversedation and undersedation (Deogaonkar et al., 2004). For example, the nurse notes that the BIS values are steadily trending upward and interprets that the patient is inadequately sedated. The nurse may decide to perform a complicated and painful dressing change only after increasing sedation and administering analgesics. This action will minimize awareness of unpleasant events and decrease the risk of secondary brain injury that might have occurred if the patient's awareness of pain resulted in increased ICP, hypertension, or increased oxygen consumption. In this example, BIS provided the nurse with essential cues that were used to determine the timing of specific nursing interventions.

Timing Nursing Interventions

A key aspect of the Coma Cue-Response conceptual framework is the timing of nursing interventions to optimize the conditions that promote recovery of normal sleep-wake patterns. In the clinical setting, nursing care has developed untested strategies that support they are making efforts to determine the optimal timing of patient care interventions. A clear example of the history of the concern of nurses for determining when an intervention should occur can be found in the works of Florence Nightingale (Nightingale & Skretkowicz, 1992) who wrote, "The absence of smoke, the quiet, all tend to making night the best time for airing the patients." Nurses have long been the gatekeepers to patients; ensuring that patients are allowed to 'rest' and 'recover' during uninterrupted periods of time. Benner (1984) describes how expert nurses have developed an intuitive sense of knowledge regarding their patients.

This is a knowledge built upon the recursive process of interpreting and responding to cues that comatose patients produce. Sandelowski (1997) echoes this sentiment, stating, "As the primary machine tenders in health care, nurses often acquire an understanding of how to apply, operate, and interpret the products of devices that becomes an integral part of the tacit know-how of clinical practice" (p. 76). There is sufficient empirical evidence to support the inclusion of timing as a key aspect of any conceptual framework for care of the brain injured comatose patient.

Timing Impacts Secondary Injury

Secondary brain injury occurs through a variety of pathways and may result in and from a cascade of events that increases cell death (Yanko & Mitcho, 2001). Key content in the prevention of secondary brain injury includes ICP management, ensuring adequate tissue oxygenation, and optimizing cerebral tissue perfusion (Greenberg, 2001; Yanko & Mitcho, 2001). To achieve these goals, nurses should make efforts to modify the physical environment to promote sleep, and to avoid clumping activities together because this can create a cumulative effect (Arbour, 1998; Littlejohns & Bader, 2005). For example, if a patient responds to turning with an increase in ICP, and mild tachypnea, allowing the patient to rest before performing a dressing change will allow the ICP and respiratory rate to return to baseline; performing these procedures one on top of the other may further elevate ICP, exacerbate tachypnea, and result in decreased cerebral perfusion. The expert nurse consciously makes decisions about which interventions occur when. This deliberate action is based on the interpretation of numerous cues provided by the patient, the monitoring equipment, and the environment. An example of this can be seen in the expert nurse who hears the ventilator alarm (monitor-derived cue), looks at the patient and observes him

pulling at his restraints (patient-derived cue), then, noting that the family had left the T.V. and lights on (environmental cue), the nurse intervenes by decreasing the environmental stimulus (turning off the television and the lights) before reassessing the patient's sedation status. For the expert, these cues are incorporated into interpretation and response schema that have been developed through years of clinical practice (Benner, 1984). Interventions, tools, and education that provide novice and beginner nurses with a means to recognize not only the cues, but the importance of those cues, will improve care of the unconscious brain-injured patient.

Timing Impacts Entropy

Consciousness and sleep are often linked together in the literature as examples of changes in cortical entropy (Zeman, 2001). The neurophysical theory of consciousness is one such example and is specifically relevant for incorporation into nursing practice (John, 2002). This theory holds that consciousness is a neurobiological event that can be studied by exploring electrical and electro-chemical changes in the brain. This theory expands the nurses' understanding of the care of the comatose patient in general and care of the comatose patient within the cue-response framework in specific (Olson & Graffagnino, 2005). The fundamental value of the neurophysical theory of consciousness for nursing is the degree to which the theory incorporates knowledge from multiple disciplines, including biological, medical, and philosophical (John, 2002). The theory can be readily applied to current nursing therapies that focus upon the holism of the patient-family experience. Although the definition of entropy may be foreign to many, the concept of consciousness existing along a continuum can be easily explained to family members. Situation-specific events occur throughout the patient's stay and nurses are often responsible for determining the timing of these events. The

need to promote situations that facilitate a return of full consciousness can be understood as being influenced by a balance between sleep and activity. This theory provides a conceptual link between existing knowledge regarding sleep disruption in neurologically-injured patients, empirically-based nursing practice, and theory-based knowledge (Olson & Graffagnino, 2005).

Current state of practice

The literature supports the need to improve sedation assessment and management (Egerod, 2002; Jacobi et al., 2002). Sedation policies generally endorse an observational assessment tool as the primary indicator for adequacy of sedation (De Jonghe et al., 2000; Jacobi et al., 2002; Watson & Kane-Gill, 2004). Still, the practice of sedation monitoring in the NCCU remains primarily one of nursing judgment as most tools are poorly used and lack adequate psychometric evaluation (Jacobi et al., 2002; Magarey, 1997; Murdoch & Cohen, 2000). The current set of sedation guidelines offer insight and recommendations, but, as yet, no standards (Jacobi et al., 2002). Thus, this study will examine the usefulness of providing an additional cue, a physiologic measure of sedation, to help nurses who care for patients receiving sedation.

Specific Aims of the Study

Continuous IV sedation is a common treatment for patients with acute neurologic injury and sedation is indicated for injury prevention as well as to facilitate medical therapy (Murdoch & Cohen, 2000; Young et al., 2000). However, in caring for these patients, nurses must determine when and how to adjust the sedative to prevent oversedation and undersedation while at the same time facilitating rapid awakening to obtain neurologic assessments (Burchardi, 2004; Olson, Cheek, & Morgenlander, 2004; Olson et al., 2005).

The nurse is challenged to use the minimal amount of sedation required such that the interruption of sedation to obtain a neurologic examination does not result in rebound agitation and dramatic changes in hemodynamic stability (Wittbrodt, 2005). The difficulty in determining sedation needs typically results in patients being oversedated and may lead to longer periods of mechanical ventilation (de Wit & Epstein, 2003; Kollef et al., 1998). Determining the minimal amount of IV sedation that will keep the patient safe and facilitate frequent brief awakenings requires that a nurse be skilled at interpreting observational and physiologic data within the context of the patient's condition.

Patients in the ICU are dependent on technology to maintain life. Sedation increases this dependence. Assessment tools that rely on observations of the patient are widely used for sedation management, and previously, only observational assessment tools have been used by nurses when making decisions regarding sedative adjustment (De Jonghe et al., 2000; Devlin, Fraser, Kanji, & Riker, 2001; Walder, Suter, & Romand, 2001). However, these tools may not be sensitive enough for optimal management. Recent technological advances have made it possible to continuously monitor the patient's level of consciousness and therefore, their response to sedation.

The BIS monitor uses an electroencephalographic (EEG) signal and provides physiologic data (cues). As Sandelowski (1998) points out, technology (in this study, the BIS monitor) becomes a way of knowing the patient. Cues provided by technology may aid practitioners in optimizing sedation (Ely et al., 2004; Fraser & Riker, 2005; Hilbish, 2003; Jacobi et al., 2002; Olson, Cheek, & Morgenlander, 2004; Sebel et al., 1997). Fraser and Riker suggested that the BIS should be routinely used to provide physiologic data about responses to sedation (Fraser & Riker, 2005). Currently, no gold standard for sedation

assessment exists and despite numerous clinical trials, current practice has yet to adopt physiology-based assessment and combine physiologic data with observational assessments (Jacobi et al., 2002).

The purposes of this study were to examine the effect of combining a physiologic measure of consciousness (BIS) with observational sedation assessment (Ramsay) of a group of neurocritically ill patients on infused sedation drug volumes, undersedation events, and the recovery time to arouse from sedation. During a 12-hour data collection period, patients received sedation assessment and management with either the current standard of care (sedation assessment with the Ramsay scale), or the standard of care plus the addition of physiologic data from BIS monitoring. The following research questions explore how BIS monitoring might impact short-term sedation-related outcomes.

Research Questions

1. Is there less sedation drug use for patients when nurses monitor sedation with BIS augmentation of Ramsay than when nurses monitor patients with Ramsay alone?
    A. Does injury severity act as a covariate for sedation drug use in neurocritically ill patients?
    B. Does illness severity act as a covariate for sedation drug use in neurocritically ill patients?
2. Is sedation assessment augmented by BIS use associated with a decreased time to wake-up (recovery time) when nurses are instructed to interrupt sedation and obtain a neurologic examination, compared to use of Ramsay alone?

3. Are there differences in the number of events associated with undersedation (e.g., self-extubation) for patients assigned to BIS augmentation compared to patients assigned to Ramsay alone?

Summary

The results of the present study should contribute to the knowledge of how BIS monitoring, when used to augment current sedation assessment practices, impacts specific outcomes related to sedation management of neurocritically-ill patients. The practice of continuous sedation infusion and monitoring has previously been studied only from the perspective of decision-making based on either observational data or physiologic parameters (Alexander & Duane, 2005). This study provides for the exploration of a more true-to-life model in which sedation management is not separated from the realities of the clinical setting. The nurse does not separate observational cues from physiologic cues when caring for the sedated brain-injured patient. Rather, all cues are fused together to create a more comprehensive reflection of the patient's overall response to sedation therapy. Because patients are typically oversedated, this more comprehensive response should be reflected as a decrease in drug infusion rates without an increase in undersedation events and a shorter time to wake-up when the nurse performs a neurologic exam.

CHAPTER II

REVIEW OF THE LITERATURE

As the purpose of this study was to examine the combination of physiologic and observational assessment data on sedation management in neurocritically ill patients, this chapter will discuss brain injury, sedation and sedation monitoring. The discussion of brain injury will include primary injury, however the focus of this section will be the prevention and management of secondary brain injury. Brain injury and sedation are two processes whereby a loss of consciousness may occur and a thorough discussion of consciousness will build the foundation for understanding how these two processes interact and create a unique conundrum for the nurse who oversees the care of these patients. The discussion of sedation will explore current literature on the science of sedation as it pertains to the critical care setting. Next, sedation monitoring techniques, tools and the various strengths and weakness of these tools will be discussed. Finally a brief discussion of decision-making, as it applies to sedation management of neurocritically ill patients, will provide the reader with an understanding of how these distinct, yet interrelated, concepts are linked within this study.

Brain Injury

The incidence of brain injury in the United States has reached epidemic proportions. Brain injury may result from external trauma, stroke, or purposeful invasion of the cranial vault. Each year nearly 1.4 million Americans will sustain a traumatic brain injury; 235,000 will be hospitalized and 50,000 will die as a result of this injury (CDC.gov, 2005). Stroke from cerebral hemorrhage or infarction occurs in approximately 700,000 Americans each

year; of these, nearly 25 percent will die (Americanheart.org, 2005). Current estimates indicate that there are approximately 5.4 million stroke survivors in the U.S today. The American Cancer Society (2005) estimates that 18,500 Americans will be newly diagnosed with a brain tumor each year, the vast majority of these Americans will experience an elective craniotomy for tumor resection at least once during their battle with cancer. Survival rate estimates for brain tumor patients are widely varying according to diagnostic grade. Whether by unintentional physical injury, vascular lesions or surgical intervention, it is estimated that over 5 million Americans currently live with some form of disability as the result of brain injury (BIAUSA.org, 2005).

The human brain is a delicate organ protected against injury by membranes, tissue, fluid and bone (Greenberg, 2001). Still, brain injuries can and do occur. Brain injury is commonly discussed and treated as being either a primary or secondary brain injury. Brain injury can be defined in a variety of ways using different criteria, but it is an accepted standard that the term brain injury indicates a condition in which there is damage to the brain tissue resulting in or from an insufficient supply of blood or oxygen, or by direct physical trauma. Further, an injury to the tissues and structures comprising the brain can be described in terms of local, regional, or systemic injury to the intracranial vault (BIAUSA.org, 2005). Primary brain injury is that which occurs as the initial event, the clearest example being the point during which a bullet enters the skull and causes damage to the cerebral tissues which results in an insufficient blood supply to those areas.

The primary brain injury period is generally very short in duration. This is due in large part to the restrictions of the brain itself. A large intracranial hemorrhage, for example, will increase the volume inside the skull and thereby increase the intracranial pressure. If

substantial bleeding occurs the pressure will rise rapidly and result in central herniation and death (AANN, 2004). While unfortunate, in this example, the primary brain injury period is limited in time by death. If the bleeding event were shorter in duration and the intracranial pressure does not increase to the point of causing herniation then the primary brain injury period is limited to the time from initial bleeding to the time at which bleeding stops (whether temporary or permanently). Treatment during the early subacute phase, (the first two weeks immediately after the injury), is designed to prevent secondary injury (Marion, 2002; Reinert & Bullock, 1999; Yanko & Mitcho, 2001).

Secondary Injury

The primary therapeutic goal following brain injury is the prevention of secondary brain injury (March, 2000). Treatment of neurologically-injured comatose patients during the early subacute (ESA) phase is not focused on healing the patient (Greenberg, 2001). Rather, treatment during this phase, (the first two weeks immediately after the injury), is designed to prevent secondary injury (Marion, 2002; Reinert & Bullock, 1999; Yanko & Mitcho, 2001). The injured brain can be divided into tissue that has sustained permanent irreversible injury, brain tissue that is at low risk for injury, and brain tissue that is at high risk for injury (Greenberg, 2001). The brain tissue immediately surrounding the site of injury, the penumbra, is the tissue at greatest risk. During the early subacute phase of brain injury an increase in intracranial pressure (ICP), a decrease in cerebral blood flow (CBF), programmed cell death, focal cerebral hypoxia and cerebral edema are the greatest sources of risk for secondary injury to the penumbral tissue (Bullock et al., 2000).

Injury to the brain occurs through a variety of pathways, each resulting in a decrease in the oxygen perfusion to the brain. Secondary injury may result in and from the cascade of

events that follows primary injury and can result in an increase in cell death (Yanko & Mitcho, 2001). Understanding this cascade of events requires a basic intuitive understanding of compensatory mechanisms of the brain.

The brain is housed in and protected by the skull. The skull is a thick portion of the skeletal system which fuses shortly after birth and becomes inflexible. The Monroe-Kellie hypothesis essentially states that because the skull is a rigid compartment, the combined volumes of the matter within the skull must be kept in balance if a stable pressure is to be maintained. Three sources of volume, blood, brain, and cerebral spinal fluid (CSF), exist in a relatively fixed state within the skull. The approximate volumes of each are: brain 80%, blood 10%, and CSF 10% (Bader, Littlejohns, & March, 2003). Any increase in one or more of these volumes without a corresponding decrease in one or more of the other volumes will result in an increase in the ICP (Greenberg, 2001).

Normal ICP is generally considered to be less than 15mmHg. Intracranial hypertension (HTN) is generally classified as a pressure greater than 20mmHg and may result as a direct effect of changes such as an acute intracerebral event, metabolic encephalopathy, or secondary brain injury (Greenberg, 2001). A classic example of a primary event causing increased ICP is rupture of a cerebral aneurysm, which results in blood escaping into the intracranial space resulting in a sudden increase in ICP and absence of perfusion to portions of the brain. Intracranial HTN secondary to metabolic abnormality may occur through changes in cellular permeability and result in increased ICP as the brain swells and takes up more space (Abou-Assi & Vlahcevic, 2001). An example of intracranial HTN as a secondary consequence can be seen following a concussive event in which an increase in

the volume of the brain tissue occurs as damaged cells begin to absorb free water and swell (Kiening, Unterberg, Bardt, Schneider, & Lanksch, 1996).

Incidences of intracranial HTN may also be temporary and resolved through compensatory mechanisms of the brain. The sudden increase in blood volume that occurs with aneurismal rupture, for instance, may be compensated for by a shunting of CSF, or decrease in venous blood. The classic example of changes in volume is seen with space occupying lesions. A brain tumor increases the tissue volume slowly over time. In compensation, CSF and blood flow are gradually reduced. This explains why a fairly large tumor may not manifest intracranial hypertension.

Key content in the prevention of secondary brain injury includes ICP management, ensuring adequate oxygenation and optimizing cerebral tissue perfusion (Bullock et al., 2000; Greenberg, 2001; Yanko & Mitcho, 2001). Procedures that directly reduce ICP include active CSF drainage, osmotic therapy, and positioning (March, 2000; Marik, Varon, & Trask, 2002). Additional efforts to control arterial blood pressure and circulating blood volume within tight parameters should be targeted to secondary measures such as brain oxygenation and preload that more accurately reflect changes in these parameters (Littlejohns, Bader, & March, 2003). Currently, there are no gold standards to define the minimum value at which ICP treatment should be initiated, but a value of 20-25mmHg is reported as the upper limit by which treatment should be initiated (Bullock et al., 2000; Greenberg, 2001).

Outcomes for patients at risk for secondary brain injury are improved if the patient is admitted to a neurocritical care specialty unit (Elf, Nilsson, & Enblad, 2002). Nurses in these units are educated to observe for changes and trends in ICP, blood pressure, oxygenation, and changes in neurologic function that may signal a change in intracranial dynamics (Olson et

al., 2003). Only vigilant monitoring will ensure that the signs of increasing ICP are quickly recognized. Once observed, the nurse must decide upon the most appropriate action available, or to contact the medical team and obtain new orders for treatment (March, 2000). Nurses rely on several tools to help guide these assessments. One such tool, the Glasgow Coma Score (GCS) was published in 1974 (Teasdale & Jennett) and is the most common means of assessing the severity of brain injury.

The GCS a 3-item tool which provides a cumulative score between 3 and 15 (Heron, Davie, Gillies, & Courtney, 2001; Juarez & Lyons, 1995). When free of the effects of sedation, patients were scored on best eye opening response, best motor response and best verbal response (Fischer & Mathieson, 2001; Teasdale & Jennett, 1976). Most authors agree that the GCS was developed to assess severity of injury in brain injury, not response to sedation (Fischer & Mathieson, 2001; Olson, Cheek, & Morgenlander, 2004; Teasdale, Pettigrew, Wilson, Murray, & Jennett, 1998). The severity of illness differs from the injury and the Acute physiology and chronic health evaluation (APACHE) score was developed to assess the severity of illness in critically ill patients (Cho, Wang, & Lee, 1995). The most current version of this scoring system is the APACHE®IV, which is derived from 49 separate items (ICU_Medicus, 2004). The severity of injury and the severity of illness provide important information when exploring secondary brain injury.

At the extremes of injury and illness severity, there is less attention required by the staff with regards to preventing secondary brain injury. If a patient has a very minor injury, or the severity of their illness is very limited, then the likelihood of that patient experiencing a negative effect from secondary brain injury is equally diminished (Littlejohns & Bader, 2005). As the level of injury increases, the risk of secondary brain injury also increases, but

only to a certain point. If an injury is sufficiently severe such that the entire brain is already injured then there is no risk for secondary brain injury, but only because the entire brain has already suffered primary brain injury. It is helpful to explore three exemplars. 1) The 93 year old patient who arrives with a GCS of 3 (no cortical function) after a severe open skull fracture obtained when he fell down the stairs after a severe myocardial infarction. This patient has no brain function, is brain dead, and will die. Nursing care is focused not on preventing secondary injury, but on palliative care. 2) The 83 year old male patient with a history of diabetes and cardiomyopathy who arrives with multiple fractures and is combative, requiring an artificial airway and intracranial pressure management. This patient does have coritical function and is at high risk of secondary brain injury and will require a great amount of care. The healthy-young female patient who arrives awake, alert and oriented following a low-speed motor vehicle crash. This patient does have cortical function, but is not at high risk for secondary brain injury and will thus require fewer resources aimed at preventing secondary brain injury. Thus the relationship between resources aimed at preventing secondary brain injury and the severity of illness or injury is best described as an inverted U-shape where the most effort is required for those patients in the middle.

Consciousness

A comprehensive discussion of consciousness is essential to fully understand care of the acute brain-injured patient receiving sedatives. The changes in consciousness that arise from a reversible infusion of medication are subtly different from those which arise from structural damage to brain tissues. These differences may alter the goals of sedation. Further, although both types of patients have a decrease in their level of consciousness, the cues that can be derived from patients who have suffered a brain injury and require sedation are

fundamentally different from the cues that can be derived from a patient who is simply sedated. The following discussion will provide the reader with a foundational understanding of consciousness that will provide a more comprehensive understanding of the importance of this study and how physiologic cues may provide additional resources for nurses who care for these patients.

The Concept of Consciousness

Consciousness may be viewed from both the cognitive and arousal perspective. The cognitive component of consciousness may be easily exemplified by the statement, "he is conscious of his upcoming dissertation defense." Consciousness as it relates to cognitive function, which is determined in large by attentional, memory and executive function systems, will not be discussed within this paper (Boss, 2002; Zeman, 2002). Rather, this paper will examine consciousness from the arousal perspective and define the concept of consciousness as the degree of internal awareness a being has regarding itself and external awareness that being has of the outside environment. This concept can be exemplified by the statement, "at the start of his dissertation defense he passed out, but now he is conscious." Examining consciousness as a state of arousal allows us to test for each individual patient's greatest level of arousal as their level of consciousness. It is likely that the study of consciousness is now moving into theory development and testing because variations in conscious states are now widely recognized as being controlled entirely by neurological processes in the brain (Edelman, 2003; John, 2002; Searle, 2000; Zeman, 2002).

Consciousness states range from that of deep coma to a fully awake state. A patient who is unable to be aroused to an awake state of consciousness (a state at which the patient is able to interact with the environment) may still respond to stimuli. More succinctly,

essentially every patient responds in some manner. For some patients the response is limited to cranial nerve function (Greenberg, 2001); some have hemodynamic changes; and some may have profound changes in their level of consciousness. For patients to have completely unresponsive brains, they must also meet the criteria of brain death.

The patient with brain injury will likely have a different baseline state of consciousness than will non-brain-injured patients and this baseline will alter the cues each patient can provide as to their changing level of consciousness. The responses that signal consciousness in each patient are dictated in part by the degree of brain damage and in part by the degree of sedation. For example, a patient may become violently agitated while being repositioned. This cue may be interpreted as inadequate sedation, or increase in injury depending on the contextual relevance of the individual situation. Cues such as agitation are frequently much more easily recognized by novice nurses because of the obvious nature of such events. However, nurses caring for comatose patients may develop the skills to recognize even the smallest of patient responses as cues. For example, the experienced nurse may note a change in respiratory depth after a patient has been repositioned. The accumulation of knowledge from cues should help to direct future care. The example of the patient who becomes agitated when repositioned presents the opportunity for the nurse to adjust his or her actions the next time the patient is to be repositioned. The example of a patient whose respirations change when repositioned presents the opportunity to adjust the sedative dose after the patient is repositioned. Patient cues, like the patients themselves, are individualized within various baseline states of consciousness; the nurse's response to those cues must be likewise individualized to the patient.

The Concept of Coma

Coma is defined as a totally unconscious and unarousable brain state that results from physical, biochemical, and metabolic injuries to the brain's arousal mechanisms (Plum & Posner, 1980). Functionally coma is an unarousable state of unresponsiveness to internal or external stimuli. Direct physical trauma due to blunt physical force or compression from an intracerebral hemorrhage are examples of physical causes of coma. Hypoxia, hypoglycemia, and hyponatremia are examples of metabolic changes that produce coma. Finally, pharmaceutical agents, such as pentobarbital, may produce coma. Coma as a result of damage to one or more components of the ascending reticular activating system (ARAS) is commonly associated with injury to the brain stem (Plum & Posner, 1980).

Typically, coma that results from brain injury is defined by the Glasgow Coma Score (GCS) (Sternbach, 2000). The GCS is based upon three major components that can be assessed in all patients; best eye opening, best motor response, and best verbal response. The combination of scores range from a low of 3 to a high of 15 and a score of 8 or less is generally considered to indicate the presence of coma (Sternbach, 2000; Teasdale & Jennett, 1974). Just as the coma score ranges from 3 to 15, consciousness ranges from coma, one extreme of consciousness, to being fully awake, the opposite extreme (Zeman, 2001). Plum and Posner (1980) define coma as a state wherein the unconscious patient continually has closed-eyes and there is an absence of any sleep-wake cycle.

The Anatomical and Physiological Basis of Arousal

Early work by Moruzzi and Magoun (1995) is responsible for our current understanding of the ascending reticular activating system. The key components of the ARAS are a set of interacting anatomical networks and neurotransmitters found in the central pons, midbrain, hypothalamus and thalamus (Zeman, 2001). Current theory supports that

arousal is related to ascending pathways that stimulate the cerebral cortex and are mediated by the thalamus (Zeman, 1997, 2001). Once cortical arousal has been achieved, a positive feedback mechanism between the cerebral cortex and the thalamus maintains a wakeful state (Robinson et al., 2003).

Theories of consciousness

Each of the theories discussed below attempts to explain the neural correlate of consciousness (NCC). Specifically the NCC is the neurobiology of awareness; how one comes to link the factors of awareness, (the state of being fully conscious), with specific regions or activities in the brain (Zeman, 2002). A number of theories have been recently proposed to explain the phenomenon of consciousness and many of these focus on specific areas within the brain or the specified role of neural substrates (Tononi & Edelman, 1998). For the reader this discussion will provide information about the competing theories of consciousness, culminating with John's (2002) Neurophysical Theory of consciousness, which provides keen insight into how consciousness may be examined not only from the observation of patient-specific behaviors but also from physiological data.

Baar's Global Workspace Theory.

Baars' Global Workspace Theory was first fully described in 1988 (Baars) and has since undergone several revisions. Currently, this theory posits that there are competing forms of information processing that are always occurring in the human brain. Certain processes are dependent upon the specialized role for which they are developed (i.e. interpreting the color green). Other processes command a global workspace (the entirety of the brain) and it is these processes that give rise to consciousness (Zeman, 2002). An overwhelming number of tasks that our brains perform are automatic; for instance,

interpreting touch, seeing color, pulling one's hand away from pain (Cho, Baars, & Newman, 1997). Other tasks require the specific determined coordination of interacting parts of the brain. These coordinated events occur in what Baars terms the theatre of consciousness which becomes the global workspace within the brain (Baars, 1997).

Penrose's Quantum Mechanical (QM) Theory.

Penrose's QM Theory of Consciousness indicates that there is a specific biophysical substrate that is responsible for the production of consciousness (Penrose, 1994). Following this, Dayhoff, Hameroff, Lahoz-Beltra, and Swenberg (1994) postulated that this substrate may be located in the microtubules of the cytoskeleton of neurons. Much of the work on this construct has been done by Hameroff and associates in determining the full relationship of neuronal microtubules in the emergence of consciousness (Hagan, Hameroff, & Tuszynski, 2002; Hameroff, 1998; Hameroff, Nip, Porter, & Tuszynski, 2002). This work appears to have impacted the original theory, for in a more recent paper Penrose postulates that the substrate may reside in specified neuronal microtubules critical to activities relevant to the emergence of consciousness (2001). The major limitation of this theory is the self-imposed restriction to discussing only one finite anatomical constituent of a complex neuroanantomical network.

The Glial-Neural Theory of Brain Function.

The Glial-Neural Theory of Brain Function attempts to explain the activation of consciousness as dependent upon the interaction of how the glia divide the brain into specialized compartments and functional units (Mitterauer, 1998; Vernadakis, 1988). This theory may have some support in Zeman's earlier work in which he describes that portions of the thalamus and upper brainstem are integrally involved in the anatomy of awareness

(1997). In a brief article summarizing the role of glial cells, Kettermann (1996) relates that glial cells influence neurons and somehow, in a yet undiscovered way, control their environment.

The Neurophysical Theory of Consciousness.

While each of the theories above describes specific substrates postulated to be associated with consciousness, their limitation is the inability to account for states of altered consciousness such as stupor, coma and persistent vegetative state. This shortcoming limits the practical ability to modify nursing interventions that could lead to a reversal of such states. The Neurophysical Theory of Consciousness (NPTC) postulated by E. Roy John (2002) incorporates both electrophysiologic changes observed in alternating states of consciousness and the previous body of neuroscience literature relating to consciousness. In this theory, consciousness is a neurobiological event that can be studied using standard methods of scientific investigation (Searle, 2000). John discusses consciousness from the perspective of entropy; or a measure of the amount of the potential for change in a system. Maximum entropy refers to maximum disorder and negative entropy refers to an increasing degree of order.

In his NPTC John (2002) posits that electrical transactions within and between neurons, are maintained in a homeostatic state by specified systems at set non-random thresholds, called the *ground state* for normal brain activity. This ground state is a state of maximum entropy (there are no changes in this state), the brain is considered to be without information. The brain is at a maximum disorder (the parts are not communicating) but the laws of entropy, which mimic the second law of thermodynamics, infer that neural connections could be made that would bring about negative entropy (order) and move to

consciousness. If one thinks of entropy as the potential for change (an oversimplification of the concept) then it is easier to see how entropy here is like a U-shape; if the brain is really ordered and organized, it has the greatest potential to move out of that state, equally, if the brain is a ground state it has the greatest potential to move out of that state. Excitation of brain regions leads to negative entropy and activates specific neurons in the cortex. This information is still fragmented, but can be formed into coherence in the thalamus through cortico-thalamic volleys. These volleys are bursts of synchronized neural discharges that converge in the thalamus, linking fragmented bits of information together. Finally, there are re-entrant pathways that send impulses from the thalamus to the cerebral cortex and, when sustained, lead to a critical mass of resonating energy that moves the brain to a state of negative entropy and produces consciousness (John, 2002).

To illustrate this complex theory, it is useful here to give a practical example of a common experience. You smell an apple. The olfactory nerve (Cranial Nerve I) stimulates the entorhinal cortex which relays information to multiple brain regions. Your occipital-parietal association cortex is stimulated and "sees" an apple, your superior temporal lobe may "hear" the crunch you associate with prior experience from eating an apple, and so forth. The integration of this set of stimuli leads to a global state of arousal in which part of your brain becomes conscious of the experience.

Sedation

The discussion heretofore has concluded that the prevention of secondary brain injury is a major concern for the nurse caring for neurocritically ill patients. An essential method of preventing secondary brain injury is the prevention of intracranial hypertension using interventions that often require sedation. Further, the prevention of secondary brain injury

requires the frequent and accurate assessment of patients at risk for such; this assessment is complicated by the very nature of the injury itself, and of the treatments (such as sedation) for that injury. Brain-injured patients have varied baseline levels of consciousness and provide nurses with a variety of cues (both observational and physiologic) that must be interpreted within the context of patient-specific situations. Finally, the discussion of consciousness has provided the background to support a discussion of sedation, a process of purposely impairing consciousness in neurocritically ill patients for the purpose of preventing secondary brain injury.

Sedation, paralysis, and analgesia remain separate, yet often intertwined concerns (Burchardi, 2004). When discussing sedation it is important to recognize that the sedation goal is a two-tiered goal. The primary goal is the 'why' goal, or the reason for sedation. The secondary goal is the 'how much' goal. The individualized patient need for sedation, the 'why' goal, drives the decision to determine the desired degree of sedation, the 'how much' goal. In 2002, the American Society of Health-systems Pharmacists (ASHP) and Society of Critical Care Medicine (SCCM) developed a set of guidelines for sedation assessment and monitoring (Jacobi et al., 2002). A key aspect amongst these guidelines is the need to set and regularly redefine the goal of sedation. In the intensive care setting, there are a variety of reasons why one might choose to chemically sedate a patient. However, three of the primary indications for sedation are: injury prevention, facilitation of medical goals and humanitarian goals (Murdoch & Cohen, 2000; Young et al., 2000).

Reasons for Sedation

The reasons for sedation are individualized to the needs of the patient (Jacobi et al., 2002). The first reason for sedation is that the patient, if left without adequate sedation, may

cause injury to themselves or others. This may include removal of medically necessary monitoring or support devices as well as causing injury to the staff members caring for them while they are in a state of delirium. The brain injured patient may, for instance, be cognitively impaired and incapable of understanding the necessity of the many tubes and purposefully attempt to remove these tubes. Another example of injury to self is the patient who bites down on an endotracheal tube; this results in the risk of eventually biting the tubing in half, and the more immediate threat of injury by occluding the only patent airway available for lung ventilation. Adequate sedation will impair the patient's ability to harm themselves, or others, by decreasing the patient's ability to generate physical actions.

Another major reason for sedating a patient is to facilitate the medical goals set for the patient. This includes goals such as maintaining hemodynamic goals, increasing ventilatory compliance and controlling intracranial pressure (Dennis & Mayer, 2001). Critically ill patients who suffer dangerous neurological instability from minimal stimulation can have lasting harmful effects if exposed to extremely painful noxious stimuli for an extended period. Proper sedation is the only answer in preventing iatrogenic induction of a harmful metabolic crisis in response to the stimulus put upon a critically ill under-sedated patient.

The third reason for sedating a patient is for humanitarian intentions. All patients treated with neuromuscular blocking agents should be concurrently sedated to avoid the mental distress associated with total body paralysis (Alspach & American Association of Critical-Care Nurses., 1998). Adequate sedation of the critically ill patient also becomes paramount when an individual is inflicted with a barrage of noxious stimuli and invasive procedures such as the insertion of ICP monitoring devices or placement of medically

necessary catheters and monitoring devices. Adequate sedation also results in a degree of induced amnesia for the events associated with the intensive care admission thus protecting the patient against the long term emotional stress of the acute illness (McCann et al., 2002). Although each of these three reasons is valid enough to justify sedation often the needs may overlap.

Target sedation

When the medical team has decided that it is in the best interest of the patient to employ chemical sedation the goal depth of sedation can then be determined. This goal should be communicated in a manner that is clear to both the prescribing authority and the nurse adjusting the sedating agent (Burchardi, 2004). There must be some mechanism for the nurse to determine if the patient is at target sedation. Most often this is achieved solely through multiple evaluations of a single patient response against an observation sedation assessment tool (Jacobi et al., 2002). Recently, physiologic data has been explored as a means of providing information about response to sedation (Riess, Graefe, Goeters, Van, & Bone, 2002; Schneider et al., 2004). The use of an observational assessment tool in conjunction with physiologic data may provide more information about the level of sedation than either tool can account for individually (Avramov & White, 1995; Berkenbosch, Fichter, & Tobias, 2002; Olson, Cheek, & Morgenlander, 2004).

The sedation goal must be individualized to the patient's need for sedation (Young et al., 2000). If the indication for sedation is one of injury prevention a lighter state of sedation is likely indicated, such that the patient is cooperative but still able to communicate with the staff (Burchardi, 2004). If the indication for sedation is to facilitate an individual medical goal, the sedation level may need to be somewhat deeper (Young et al., 2000). The most

challenging situation involving sedation is the one in which the indication for sedation is for humanitarian needs. It is here that we see the greatest variability in depth of sedation required in order to provide comfort for a given individual. Sedation for palliative care may range from mild to deep sedation based upon the individual desires of the patient and family (Braun, Hagen, & Clark, 2003; Burchardi, 2004; Muller-Busch, Andres, & Jehser, 2003). For a patient who is chemically paralyzed it is highly undesirable to experience an awakened state, thus most staff prefer to err on the side of a deeper level of sedation.

Achieving and maintaining a specific sedation goal requires nursing vigilance (Olson et al., 2005). Patient response to medication is often unpredictable and varies not only within and between patient populations, but also within a single hospital stay for an individual patient. Drug accumulation, changes in hemodynamic status, changes in renal, endocrine, and liver function, and the effects of drug to drug interaction can increase or decrease the effectiveness of sedating agents (Young et al., 2000). The challenge of maintaining goal sedation without incidences of over-sedation or under-sedation, while allowing the monitoring of a patient's neurological exam requires the nurse to be skilled in the art of incorporating both observational and physiological data. It's all about balance, and the key to sedation is to have neither too much, nor too little sedation on board.

Oversedation

Oversedation is common to many ICU settings and may result from the limitations inherent in many of the tools used to assess the patient's response to sedation (Magarey, 1997). Oversedation may also occur as a result of different modes of providing sedative drugs. Long-term sedation in the critical care setting is most often achieved by the use of a continuous infusion of a sedative agent, often with concurrent administration of analgesic

agents that may have synergistic drug effects often resulting in a decreased level of consciousness. It is critical that the nurse be certain whether an individual patient requires increased analgesia to reduce pain or whether it is sedation that is required thus prompting an increase in the sedative drug. Too often analgesics are used interchangeably as sedatives thus failing to meet the patients need for a balance of pain control and sedation. Increased length of mechanical ventilation, decreased wound healing and decreased gastrointestinal motility have all been attributed to oversedation in the critical care setting (Guin & Freudenberger, 1992; Park et al., 2001; Rodrigues Junior & do Amaral, 2004). Recently, the use of high-dose propofol, a common sedative used in the NCCU, has been linked with an increased incidence of rhabdomyolysis, cardiac failure, metabolic acidosis, and renal failure, although these complications are more common in children than adults (Cannon, Glazier, & Bauman, 2001; Valente et al., 2002; Vasile, Rasulo, Candiani, & Latronico, 2003). Oversedation may impair the reliability of the neurological exam particularly when the evaluating individual is less experienced (Arbour, 2003; Mirski et al., 1995). In contrast to the use of continuous infusions, patients managed with bolus or no sedation have been shown to have significantly higher scores on the Sedation-Agitation Scale (more agitated) and higher BIS scores (more alert) than patients receiving continuous infusions of sedatives/hypnotics (de Wit & Epstein, 2003). This results in higher doses of both sedative and analgesic drugs being used in order to achieve the same sedation goals.

Undersedation

While undersedation is less common to the critical care setting than oversedation, the morbidity associated with undersedation can be quite profound (Magarey, 1997). The three reasons previously cited in this manuscript as indicators for sedation are injury prevention,

facilitation of medical goals, and facilitation of humanitarian goals. Inadequate sedation can lead to decreased patient safety and increased risk of injury. Compromised patient safety as a result of undersedation is most easily manifest in the example of patients removing intravenous/intra-arterial lines, and unplanned self-extubation (Boulain, 1998; Tung et al., 2001). Undersedation may contribute to ventilatory asynchrony, patient movement during procedures, and episodes of hemodynamic and intracranial instability (Olson et al., 2003). Few studies have examined the incidence of recall of unpleasant events within the critical care setting, however Cheng (1996) suggests that improved sedation and sedation monitoring will decrease the incidence of unpleasant recall in the ICU setting (Wagner, Zavotsky, Sweeney, Palmeri, & Hammond, 1998).

The Sedation-Assessment Conundrum

The sedation-assessment conundrum is defined by two diametrically opposed goals; one goal is to maintain an appropriate level of sedation, the competing goal is to obtain a comprehensive neurological examination that most accurately reflects the patient's neurological status (Olson et al., 2005). Planned interruption of continuous IV sedation is a necessary part of the routine nursing practice in the neurocritical care unit and is used to obtain a neurologic examination that represents the patient's best effort and thereby most accurately reflects the patient's neurological status (Arbour, 2003; Blumenfeld, 2002; Greenberg, 2001). As discussed above, sedation is also often indicated in critically ill neurologic patients. Therefore the need arises to alternate between periods of sedation and periods during which sedation is either decreased or eliminated for the purpose of obtaining the neurologic examination. In the neurocritical care unit, this is most often achieved by using optimizing sedation using medications which can be rapidly adjusted to achieve the

desired effect (Jacobi et al., 2002). Some of the difficulty in optimizing sedation may be attributed to the complexity of drug selection and drug combinations available. The determination of what drug to use is not very well defined (Ostermann, Keenan, Seiferling, & Sibbald, 2000; Rhoney & Murry, 2002).

Sedation Monitoring

The art and science of sedation monitoring has evolved very little in the past several decades. Traditional observations of patients have resulted in a number of observationally-based sedation assessment tools. However, despite the plethora of tools available, there is little practical difference between these tools. Newer physiologically-based sedation assessment tools have been developed and are currently being marketed to the critical care environment. The following discussion begins with an exploration of the four most common observational sedation assessment tools and moves to a discussion of various physiological tools that have been examined as sedation assessment tools. Finally, this section concludes with an evaluation of correlations between observational and physiologic tools as they pertain to reliability and validity assessments.

Observationally-based and physiologically-based sedation assessment tools examine different components of consciousness. The concept of consciousness is defined earlier as a matter of degree relating to the state of internal awareness a being has regarding itself and external awareness a being has of the outside environment (Olson & Graffagnino, 2005; Zeman, 2002). Within this concept, observational assessment measures only responsiveness to stimuli whereas physiologic measures can be used to explore the entropy state that is not dependent on stimuli. Observational tools examine similar domains of consciousness and it is reasonable to expect that there may be high correlation between two tools such as the

Ramsay scale and the Sedation-Agitation Scale (SAS) which are both used to examine responsiveness. Physiologic tools such as the bispectral index (BIS) monitor examine a different domain of consciousness (entropy). It is reasonable to expect that the correlation between SAS and Ramsay will be higher than the correlation between Ramsay and BIS for sedation assessment since these two tools use two different methods of assessing two different domains of the single concept of consciousness.

Observational Sedation Assessment

A variety of observational sedation assessment tools that use some form of numerical reference have been developed and tested with varying degrees of validity and reliability (Chernik et al., 1990; de Lemos, Tweeddale, & Chittock, 2000; Devlin et al., 2001; Ramsay, Savege, Simpson, & Goodwin, 1974; Riker, Fraser, Simmons, & Wilkins, 2001; Riker, Picard, & Fraser, 1999; Sessler et al., 2002). Observational sedation scales indicate a patient's status at a single moment in time and are limited by the frequency with which they can be performed. This section will discuss the four most common observational scales.

No gold standard by which to assess sedation currently exists (Carrasco, 2000; De Jonghe et al., 2000). The current practice in critical care relies primarily upon observational methods of sedation assessment to determine when and how to adjust sedative dosages (De Jonghe et al., 2000). Although tools used in observational sedation assessment have been developed by various authors, they are very similar in form and format: (1) the assessor is asked to rate the patient response to sedation by observation of a given set of cues such as patient movement or response to sound and (2) the assessor rates the level of sedation based upon a single direct observation and interaction with the patient. A major drawback of these tools are that the period of observation is limited to a discrete and short period of time and

therefore does not measure the changes in sedation response that may occur between sedation assessments.

Response to sedation exists along a continuum and assessments are complicated by multiple patient domains including agitation, sleep, pain, baseline consciousness, and the ability to respond to stimulus (Jacobi et al., 2002). For example, the patient in deep sleep may have very little sedation effect, but still respond sluggishly to stimuli. Similarly, a patient receiving large doses of sedation may respond briskly to stimuli if the patient is also experiencing pain. Current observational tools assign only one value that expresses one domain of consciousness (the patient's ability to respond to external stimulus). Assigning a single ordinal value that best expresses where along this continuum a patient is at any given one point in time is difficult, if not impractical. Assigning a single ordinal value that expresses the response to sedation in only one domain is potentially misleading. Hence, these scales result in the production of a single categorical response for one domain impacted by the patient. Further, these tools have not had adequate prospective testing to determine whether they reliably detect changes in sedation status.

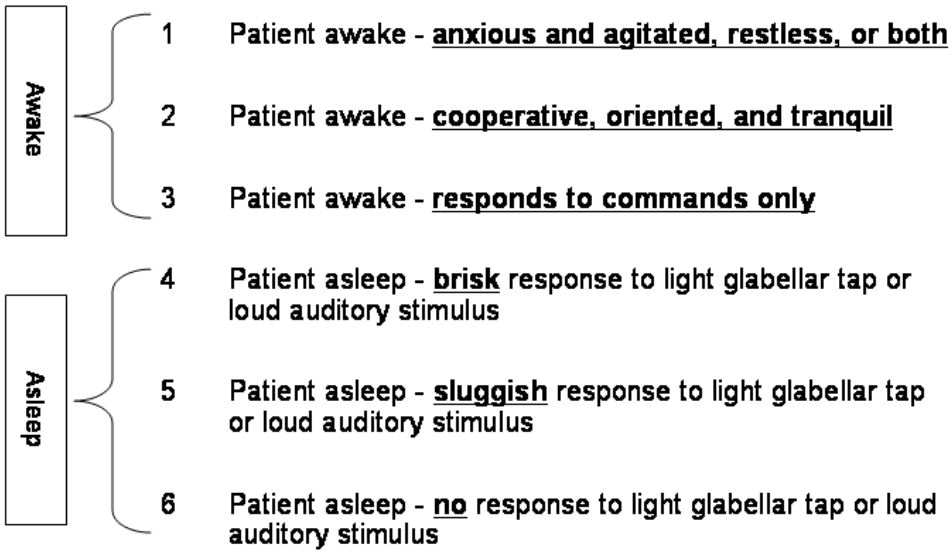
The Ramsay Scale

The Ramsay scale (Figure 2) is a single-item tool that allows for three levels of consciousness scoring in patients who are awake and three levels of consciousness scoring in patients who are judged to be asleep (Ramsay et al., 1974). Therefore to use the Ramsay scale the practitioner must first determine if the patient is awake or asleep. If the patient is deemed to be awake they will be given a score of 1, 2, or 3; patients who are asleep will be given a score of 4, 5, or 6. If an awake score is indicated, the assessor next grades the patient's responsiveness. Awake patients who are responding to stimuli in an agitated manner

are scored 1, awake patients who are oriented and respond in a calm and cooperative manner are scored 2, and awake patients who require verbal stimuli to produce a response are scored a 3. If the patient is deemed to be asleep the assessor administers verbal and tactile stimulation. A loud auditory stimulus, such as calling the patient's name, and a glabellar tap (tapping the forehead), are used as stimulus for sleeping patients. Hence, the score for patients who are asleep is based on a brisk (Ramsay = 4), sluggish (Ramsay = 5) or lack of response (Ramsay = 6) to these stimuli.

Figure 2.

The Ramsay scale developed by Ramsay, Savege, Simpson & Goodwin (1974).



There is a great deal of subjective interpretation when using the Ramsay scale in both the clinical and research setting. Hansen-Flaschen, Cowen and Polomano (1994) argue that the levels of sedation described by Ramsay et al. are neither clearly defined nor mutually exclusive. It is possible, for example, to observe a patient who is responding to commands

only (level 3), yet remains cooperative, oriented, and tranquil (level 2). Also, the definitions for terms such as "brisk response" and "sluggish response" are not evident. Further, there is no indication of how to score a patient whose response is neither brisk nor sluggish. Although there are six levels of sedation identified, most authors using Ramsay scores evaluate those scores on one of three levels: oversedated, undersedated, or adequately sedated (de Wit & Epstein, 2003; Hogarth & Hall, 2004). At first, this appears to devalue the Ramsay scale. However, further evaluation of the original manuscript by Ramsay et al (1974) demonstrates that the original authors use a similar framework for evaluating sedation. In the original article, Ramsay values of 1 indicate an unsatisfactory (inadequate) level of sedation, Ramsay values of 2-5 are satisfactory levels of sedation, and Ramsay values of 6 indicate an unsatisfactory (excessive) level of sedation (1974).

The Ramsay scale is the most widely used observational assessment tool for evaluating sedation. The Ramsay scale was first published in 1974 (Ramsay et al.) as part of a study examining a sample of 30 patients receiving Althesin. Although it is cited by researchers as the default "gold standard" for observational sedation assessment, the Ramsay scale lacks adequate psychometric testing (Barrientos-Vega et al., 1997; Devlin et al., 2001; Gill, Green, & Krauss, 2003; Jacobi et al., 2002; Soliman, Melot, & Vincent, 2001). The Ramsay scale is cited in over 450 journal articles and countless textbooks, however it appears that each author assumes that the Ramsay scale has been tested for reliability and validity. The first reliability study was completed 25 years after the original Ramsay study and published a finding that nurse scores varied less than 10% (Haberthur, Lehmann, & Ritz, 1996). Additional studies have found interrater reliability scores ranging from .71 (Schulte-Tamburen, Scheier, Briegel, Schwender, & Peter, 1999) to a kappa of .94 (Ely et al., 2003).

These reliability scores are similar to the reliability of other observational assessment tools. Ramsay remains the gold standard tool for assessing sedation in critically ill patients due to the ease of use and the inability of any other observational tool to provide newer information, more reliable information or information that assesses a different domain of consciousness. The most comprehensive interrater reliability study of Ramsay assessments of sedation included responses from 237 critical care nurses and found that the Ramsay scale has poor (Kappa = .28) interrater reliability (Olson, lynn, Thoyre, & Graffagnino, in press).

Despite these obvious shortcomings, the Ramsay scale continues to be the most widely used tool for evaluating the effect of sedation in the critical care setting. Scales developed since the Ramsay add little to the understanding of sedation management because they do not address a different domain. Nor have they been demonstrated to be sufficiently more accurate in predicting dose-response changes in sedation for individual patients.

The Sedation-Agitation Scale

The sedation-agitation scale (SAS) is a single-item 7-point scale developed by Riker, Fraser, and Cox (1994). Scores range from a low of 1, indicating the lowest level of responsiveness (deep sedation), to a maximum of 7, representing severe agitation (Figure 3). Each score has a primary category designation and a description. The assessor is expected to read the description and select that category (and corresponding score) that most accurately reflects the patient's current state. In 1999 the SAS was found to have good interrater reliability (Riker, Picard, & Fraser, 1999). Psychometric evaluation of SAS found good interrater agreement of SAS in 114 observations by trained investigators and staff nurses (weighted $k = .87$, $p<.001$) and by two trained investigators (weighted $k = .92$, $p<.001$), (Brandl et al., 2001). Initial construct validity of the SAS was evaluated with the Ramsay

scale and Harris scales, and has since been evaluated with BIS and a visual analogue scale (Brandl et al., 2001; Riker et al., 2001; Riker, Picard, & Fraser, 1999). The primary advantage to the SAS is it's relative ease of use. The disadvantage is the focus on agitation. Three scores (5, 6, and 7) all refer to different states of agitation, while at first this may seem worthwhile, it is clinically limited. Given that one of the three primary goals of sedation is to prevent harm from coming to the patient or the staff any state of agitation would require that the nurse immediately respond.

Figure 3.

The Sedation-Agitation Scale developed by Riker, Picard & Fraser (1999)

Score	Category	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down on verbal instructions
4	Calm, cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

The Motor Activity Assessment Scale

The Motor Activity Assessment Scale (MAAS), a single-item tool with seven response-defined categories of behavior, originated from the SAS and is structurally similar

to the SAS (Clemmer, Wallace, Spuhler, Bailey, & Devlin, 2000; Devlin et al., 1999). The MAAS scores range from 0 to 6 (Figure 4) wherein a score of 0 is given to the unresponsive patient and a score of 6 equates with observations that the patient is dangerously agitated. A score of 1 or 2 is given to the patient who responds only to stimulation; 1 for patients who respond only to noxious stimuli and 2 for patients who respond to voice or light touch. A score of 3 is given if the patient is observed to be calm and cooperative. Patients who are restless or agitated will score a 4, 5 or 6. Patients who are restless, but remain cooperative with are scored 4, patients who are restless and agitated are scored 5, all others are deemed dangerously agitated and scored 6 (Devlin et al., 1999).

Figure 4.

The Motor Activity Assessment Scale developed by Devlin et al. (1999).

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimulus
1	Responsive only to noxious stimulus	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus
2	Responsive to touch or name	Opens eyes or raises eyebrows or turns head toward stimulus when touched or name is loudly spoken
3	Calm and cooperative	No external stimulus is required to elicit movement and patient is adjusting sheets or clothes purposefully and follows commands
4	Restless and cooperative	No external stimulus is required to elicit movement and patient is picking at sheets or tubes or uncovering self and follows commands
5	Agitated	No external stimulus is required to elicit movement and attempting to sit up or moves limbs out of bed and does not consistently follow commands (e.g., will lie down when asked but soon reverts back to attempts to sit up or move limbs out of bed)
6	Dangerously agitated, uncooperative	No external stimulus is required to elicit movement and patient is pulling at tubes or catheters or thrashing side to side or striking at staff or trying to climb out of bed and does not calm down when asked

In the initial prospective psychometric evaluation of the MAAS tool, Devlin et al. (1999) examined MAAS using simple linear regression to explore the relationship of MAAS and a 10-cm visual analogue scale in which the nurse placed a mark along the scale to represent their assessment of the patient's level of sedation (slope = 0.5; $p<.001$), between the MAAS and the percent change in blood pressure (slope = 3.13; $p<.001$), between the MAAS and heart rate (slope = 3.91; $p<.001$), and between the MAAS and the occurrence of agitation events associated with undersedation (slope = 1.02; $p<.001$). The study used a data set composed of 8 paired repeated measures on each of 25 patients and the authors report high interobserver correlations scores ($k = .83$) for the paired observations. In the only other psychometric evaluation of this tool, Hogg et al. (2001) evaluate 155 measures from 5 observers using 31 patients. The authors conclude that the variations in scores for MAAS (Pearson r = .75-.92) are significantly better than the variation in scores for the Luer Sedation scale (Pearson r = .37-.94) and therefore the MAAS is a more reliable tool for assessing sedation than the Luer. Unfortunately, this study has major flaws: (1) the authors fail to recognize the nearly identical interclass correlation scores of MAAS (r = .81) and Luer (r = .79), (2) there is little support for the use of a pharmacist as a primary evaluator of sedation status (a task which is rarely, if ever, performed by a pharmacist), and (3) what the authors refer to as the Luer Sedation scale was not published as a sedation tool, but rather was the author's description of a protocol for adjusting sedation. The original manuscript by Luer (1995) was not a research study, it was an opinion paper that included a single case study. Ultimately, the MAAS, although used in numerous ICU's does not have sufficient psychometric evaluation, nor is it sufficiently different from the SAS to warrant consideration as a method of evaluating sedation.

The Richmond Agitation-Sedation Scale

The Richmond Agitation-Sedation Scale (RASS) has also been tested for reliability, and the authors concluded that the tool has good interrater reliability and correlates well with both the Ramsay (r = -0.78) and SAS (r = 0.78) sedation scales (Ely et al., 2003; Sessler et al., 2002). The RASS is also a single-item scale, but has 10 levels of response which range from -5 to +4. Because the RASS was developed by a multidisciplinary team including nurses, the tool has good clinical utility (Olson, Cheek, & Morgenlander, 2004). The RASS requires the nurse to complete a three-step procedure for assessing sedation. Each step corresponds to specific levels of sedation (Figure 5). This may help to explain why the higher degree of interrater reliability (k = .91 in Ely et al. 2003) and (r = .92-.98 in Sessler et al. 2002) with the RASS compared to the interrater values of scales such as the SAS, which do not clearly limit the steps of the assessment to the levels of sedation.

As with the MAAS, the RASS has only limited evaluation to date. Further, like the MAAS, the RASS assesses responsiveness in a like manner to SAS and Ramsay, only the terms to describe the response, and the number of levels at which the response may be graded are different. Finally, the RASS is limited in the same manner as other measures of observational sedation assessment. These scales all look at the patient's condition as it exists at a single moment in time and require the assumption that any given single observational period is representative of the patient's status over the entire period of time between assessments. As such, the RASS is not yet ready to be considered for a primary method of evaluating sedation in the NCCU. Even as there are numerous new scales being developed, the Ramsay is the most universally used tool for assessing sedation at the bedside.

Figure 5.

Steps to completing the RASS assessment.

Step	Procedure for RASS Assessment	RASS Score
1	Observe patient	
	- Patient is alert, restless or agitated	0 to +4
2	If not alert, state patient's name and say to open eyes and look at speaker	
	- Patient awakens with sustained eye opening and eye contact	-1
	- Patient awakens with eye opening and eye contact, but not sustained	-2
	- Patient has any movement in response to voice but no eye contact	-3
3	When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum	
	- Patient has any movement to physical stimulation	-4
	- Patient has no response to any stimulation	-5

Physiological Sedation Assessment

This section will cover recently advanced measures of physiologic data that may correlate with changes in consciousness that occur as a result of sedation. Physiologic data that change in response to changes in the patient response to sedation offer a unique advantage to current sedation assessment. Observational scales, while essential to assessing the response to sedation, are limited in that they rely heavily on assessing the response to stimulus. Therefore, a stimulus must be applied and said stimulus will alter the level of consciousness. More simply put, the very act of assessing the patient affects the condition of sedation that was being assessed. Physiologic data that does not require stimulus may provide a means of understanding a different component of consciousness that will create a more comprehensive overall picture of the patient's status.

Several forms of physiologic monitoring for the purpose of sedation assessment exist and are discussed below. Although some practitioners discuss heart rate, blood pressure and respiratory rate, these parameters provide no useful information about the response to sedation. Other forms of physiologic monitoring, such as auditory evoked potentials and EEG monitoring provide valuable information about the patient's level of consciousness, but have varying degrees of practical use in the clinical setting due to the complexity of the equipment required to initiate monitoring. The BIS represents a solution to these shortcomings and will be discussed in depth at the end of this section.

Vital Signs as a Physiologic Measure of Sedation

Vital signs are a routine component of the ICU assessment. The term vital signs is generally used to describe the set of physiologic measures that includes heart rate, blood pressure, respiratory rate, temperature, oxygen saturation, and most recently, some assessment of the patient's level of pain. In the ICU setting vital signs are measured and recorded electronically through monitors attached to the patient. A continuous real-time display of the vital signs is located in each patient room.

There is no significant predictable change in vital signs associated with changes in consciousness as a result of sedation (Davies, Mantzaridis, Kenny, & Fisher, 1996; Flaishon et al., 1997). Often discussed in the clinical setting is a presumed relationship between a patient's hemodynamic responses to sedation and their relative level of consciousness. The most common statement appears to be that an increase in blood pressure and heart rate signal emergence from sedation. There are several potential pitfalls with this approach (Olson et al., 2005). Changes in heart rate can be attributed to a variety of factors that are not related to emergence from sedation; therefore it is not a sensitive measure of sedation response.

Hypovolemia, infection, pain, hypotension, hypoxia and activity, can all contribute an increase in heart rate. Likewise, an increase in blood pressure may be related to changes in oxygen demand, intravascular fluid volume status, electrolyte concentration, etc. For example a septic patient may be receiving a vasopressor to treat septic shock; an increase in blood pressure does not signal emergence from sedation, it is a sign that the drug is working. A study done by Flaishon (1997) demonstrated a lack of predictive relationship between vital signs and emergence from sedation.

The use of vital signs as a physiologic indicator of sedation is neither supported nor recommended. The 2002 sedation guidelines (Jacobi et al.) go so far as to state, "Vital signs such as blood pressure and heart rate are not specific or sensitive markers of the level of sedation among critically ill patients." The published report from the consensus conference on sedation assessment (AACN & Abbott Laboratories, 2004) indicates that vital signs are assessed under the heading of hemodynamic stability and that the goal of maintaining hemodynamic stability falls under the more global concept of maintaining physiological stability. Within this consensus statement, a stated goal of sedation is to maintain physiological stability. This implies that although vital signs may be used to define endpoints for hemodynamic stability and should be routinely assessed during periods of sedation the vital signs themselves are not stand-alone indicators of changes in levels of consciousness; rather, they are surrogate markers of physiologic stability.

Auditory Evoked Potentials in Assessing Consciousness

The Auditory evoked potential (AEP) provides a means of determining if a human subject is conscious or not conscious. The AEP is a form of event related potential (ERP) monitoring in which the event is an auditory signal (Gazzaniga, Ivry, & Mangun, 1998). The

ERP signal is measured from EEG electrodes applied to the scalp. Most commonly a series of stimulus-response dyads are observed and averaged. The resulting signal from this averaging process is a series of waves that are embedded in the EEG signal and related to the stimulus event. The waveforms are aligned and the background waveforms (those seen and not related to the stimulus event) are subtracted. Knowledge of when and what stimulus is used allows the ERP to be linked to specific brain responses (Bell, Smith, Allen, & Lutman, 2004; Gazzaniga, Ivry, & Mangun, 1998). Through testing the AEP, it is possible to determine whether a subject is conscious, and using this tool for sedation assessment would therefore provide cues to the practitioner to increase or decrease sedation.

Neurologically, the auditory response enters the brain through cranial nerve VIII, the auditory or vestibulocochlear cranial nerve (Blumenfeld, 2002). The brainstem auditory evoked response is usually seen 1.5 to 15 milliseconds (ms) after stimulus. The middle latency AEP is seen 20-70 ms after stimulus and is marked by the negative waves, Na and Nb, and the positive wave, Pa (S. L. Bell et al., 2004). The presence of this set of waves is associated with cortical awareness. In the setting of evaluating consciousness, the middle latency AEP response is most commonly explored and has been demonstrated to provide a measure of depth of anesthesia (Kurita et al., 2001; Mantzaridis & Kenny, 1997; Schulte-Tamburen et al., 1999). Because the AEP measures only a limited consciousness pathway, only temporal cortical response is evaluated (Blumenfeld, 2002; Davies et al., 1996).

Clinically, the use of AEP struggles from practical application. The resources required for ERP monitoring are extensive and include a full set of EEG electrodes, monitoring and analysis hardware and software, and a stimulus generator linked and timed with the monitoring equipment. The feasibility of applying scalp electrodes, headphones, and

dedicating computer facilities to continuously monitor a critically ill patient makes AEP monitoring an unlikely prospect for the ICU setting. The concern of using a stimulus to evaluate consciousness has also been questioned; essentially, does the introduction of the click used in AEP alter the level of consciousness and thereby decrease the evaluation of the pre-stimulation level of consciousness? The use of an auditory signal in the ICU or operative setting has also been questioned. The AEP waves are typically small, less than 1uV in amplitude, and sufficient waveforms to filter out noise (electrical interference) may not be feasible in a non-controlled setting (S. L. Bell et al., 2004). Still, AEP has been received favorably as a measure of depth of anesthesia in the research setting despite clinical limitations (Gajraj, Doi, Mantzaridis, & Kenny, 1999).

Electroencephalography (EEG)

The EEG signal provides a direct measure of cerebral cortical activity that can be interpreted as consciousness and used to adjust sedation. The EEG signal is an electrical wave signal, and as such, it is amenable to analysis using techniques first introduced by Jean Baptiste Fourier (Haberthur, Lehmann, & Ritz, 1996). All electrical signals can be broken down into a series of sinusoids. In the biological being, electrical activity is generated from the movement of ions across membranes (Martin, 2000). In the brain, this is a relatively unstable state because various parts of the brain are stimulated during different activities (Gazzaniga, Ivry, & Mangun, 1998). Postsynaptic potentials carried along the pyramidal cells in the cerebral cortex give rise to the electrical signal that we read from the scalp as an EEG signal (Rampil, 1998). A full-spectrum EEG requires that scalp electrodes are placed over the frontal, temporal, parietal and occipital lobes of both hemispheres of the brain. The degree of

synchrony, or entropy, of these electrical signals has been associated with the gestalt of consciousness (John, 2002; Rampil, 1998; Zeman, 2001).

Rampil (1998) notes that observable changes in the EEG during anesthesia have been noted in literature since 1939. As greater amounts of anesthetic are infused the EEG signal will lose randomness and move towards entropy (Bruhn, Ropcke, & Hoeft, 2000). Clinically this has been applied to the care of patients in status epilepticus and patients requiring barbiturate coma therapy (Bullock et al., 2000; Jaggi, Schwabe, Gill, & Horowitz, 2003). Indeed, the concept of titrating consciousness to the point of a partially or fully suppressed (isoelectric) EEG is now an accepted method of management for severe intracranial hypertension (Arbour, 2003; Bullock et al., 2000).

Although EEG correlates of consciousness exist, it is difficult to imagine that EEG could be used to monitor and adjust sedation amongst a group of practitioners. Unlike the electrical signal generated by the myocardium, there is not a stable pattern that can be observed (by the human eye) throughout the continuum of consciousness. In both theory and practice, full-spectrum EEG signal provides a concrete method for evaluating changes in consciousness for the specialist trained in reading EEG (Moruzzi & Magoun, 1995; Rampil, 1998; Schneider et al., 2004; Young, 2000). Actually, the pitfalls and limitations to continuous EEG monitoring to assess sedation are based on practical concerns rather than a lack of scientific integrity. The EEG monitor requires that up to 24 separate leads are attached to the patient. The leads are expensive and difficult to keep in place. The resources to have an EEG technician available 24-hours a day are exhaustive. EEG monitoring computers occupy a large amount of space and are expensive to purchase and maintain; purchasing a separate EEG computer for every patient is not economically feasible. Finally,

nurses (and most physicians) are not adequately trained in the interpretation of EEG waveforms and adequate training would require a significant expenditure of time and money. Put simply, continuous full-spectrum EEG monitoring is not a practical solution to sedation monitoring.

Bispectral Index Monitoring

BIS monitoring provides computerized interpretation of the EEG pattern that may provide a viable alternative to full-spectrum EEG monitoring. The BIS monitor is a stand-alone device that reads the electrical signal generated by the frontal lobe of the cerebral cortex and transmitted through the forehead (Figure 6). The signal is carried through a digital signal converter and processed into digital value. The processed signal is displayed in whole numbers ranging from 0 to 100.

Through delegating the task of signal processing to technology, the practitioner is provided with more easily interpretable information. The BIS monitor uses a complex algorithm to digitize and process an electrical signal that is normally seen as a waveform. The bedside practitioner is provided with the opportunity to see both the raw EEG waveform and the digital output. The BIS value, which is displayed in the upper left hand corner of the monitor ranges from 0 to 100. Higher values are indicative of a more awake (conscious) subject. Lower values indicate decreased consciousness and values of zero correlate with isoelectric brain states (no cortical activity). The signal quality index (SQI) and EMG bars assist the practitioner with interpreting the reliability of the displayed BIS values. BIS values associated with low SQI (less than 50%) or with excessive EMG (greater than 50 decibels) are considered unreliable (Nasraway, 2005; Schneider et al., 2004; Tonner et al., 2005). By

default, the manufacturer has designed the monitor such that the BIS value is shadowed when either the SQI is less than 50% or the EMG is greater than 50 decibels.

Figure 6.

Components of the BIS monitoring system.

The BIS monitor (left) is shown here with a cable connecting to the digital signal converter (center front) and BIS sensor (seen here on forehead).
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Although continuous full-spectrum EEG is not a practical solution to physiologic sedation monitoring, it has been theorized that a single lead of the EEG signal obtained from the frontal cerebral cortex, and read by the BIS monitor, may be used to represent global

changes in consciousness that occur with the onset of sedation (Sigl & Chamoun, 1994). Each EEG signal can be examined as a set of sinusoids and each sinusoid has a frequency, a phase angle, and an amplitude (Sigl & Chamoun, 1994). At this point, an analogy is helpful. Imagine measuring the noise level (decibels) in a restaurant. During peak hours, the restaurant is fully awake and in a state of negative entropy. The decibel readings reflect stable, albeit high, levels. The linear pattern is one of constant noise. During normal hours, the noise has little discernable pattern, a breaking plate or lull in the conversation may occur and contribute to the random and chaotic rise and fall of the dB level. As closing time nears there is a shift in the dB, the frequency and amplitude of the measured sound are more stable and patterns begin to re-emerge as the restaurant moves towards negative entropy and becomes more synchronous. Finally, when the restaurant is closed a clear pattern (flat-line) emerges, there is no sound; this is maximal negative entropy and complete synchrony of the dB readings. While crude, this analogy serves as a fair explanation of the signals in the brain. Like the maitre d' of a restaurant, the brainstem and thalamus and reticular activating system are intricately involved, but not solely responsible, in regulating consciousness (Blumenfeld, 2002; Zeman, 2001).

Once a signal has been acquired it must be amplified and filtered (Webster & Clark, 1998). High-pass filters, low-pass filters and notch filters (set at 60 Hz to filter out interference from electrical appliances) further clean the signal, (Rampil, 1998). A major source of noise in the EEG signal comes from electromyographic (EMG) contribution, which is the electrical signal generated by muscles. The algorithm for signal processing begins to search for key features of the sinusoids that can be analyzed (amplitude, phase angle, and frequency), using a fast-Fourier transform. Aliasing occurs when false frequencies are

detected due to the sampling process whereby the sampling rate does not capture the entire signal, or high-pass and low-pass filters cutoff portions of the source signal (Webster & Clark, 1998). Sampling for key features and using a fast-Fourier transmfrom may result in aliasing due to the risk of loss of data from filtering and subtracting EMG artifact may result in aliasing (Rampil, 1998). Aliasing is the creation of false signals secondary to sampling error; typically this occurs when the processor is looking for points along a sinusoid and references artifact or an incomplete (shadow) signal (Webster & Clark, 1998). The exact features and subparameters that comprise the final algorithm used to analyze the signal are based on the selection of key features from a large database of EEGs and is property of Aspect Medical Systems, Inc.

The BIS monitor displays a representation of the current BIS value. The monitor may be programmed to use a 15-second or 30-second smoothing rate depending on the desires of the practitioner. Essentially, the smoothing rate dictates the amount of artifact free EEG that must be acquired to generate a BIS value. A 15-second smoothing rate requires only 15-seconds of "clean" signal and therefore will provide a more rapid response to changes in cortical activity and is more commonly used when BIS is used during anesthesia monitoring and short-acting anesthetics are used (Aspect Medical Systems, 2004). In the ICU setting, patients are on more predictable levels of sedation and changes are less frequent. Typically 30-second smoothing rates are used in the ICU setting and provide the advantage of looking at a larger window of time (Frenzel, Greim, Sommer, Bauerle, & Roewer, 2002). It is important to recognize that the smoothing rate applies to the digital display on the monitor and not to research data obtained directly from the BIS monitor. When data is obtained directly (computer downloading) from the BIS monitor a 10-second sampling window is

used. There is no consensus agreement of the best smoothing rate in the clinical setting. For research purposes the raw signal values should be collected and reported (Frenzel et al., 2002).

Figure 7.

BIS monitor showing live data.

The BIS monitor seen above displays a current BIS value of 42 (upper left), the signal quality index (center, top), EMG (center, second line) and a 1-hour trend (bottom center). Because the subject has zero isoelectric brain activity the suppression ratio (SR) is zero (upper right).

The current BIS value is derived principally from the most recent artifact-free 15 or 30 seconds of EEG, depending upon the smoothing rate selected. Because the brain exists in such a dynamic state, using a smoothing rate, or moving average, to calculate BIS results in a more stable and clinically useful parameter (Olson et al., 2003). However, an abrupt change

in consciousness (occurring within the period of time used to estimate BIS) may not be immediately reflected by a change in the displayed BIS. This may result in a delay in the change in BIS score relative to the current patient condition which could impact on decisions regarding sedation. If, for example, a patient experiences an abrupt arousal and the electrical signal the BIS obtains has a large amount of artifact, then it may take several minutes before the BIS can collect a full 30-seconds of clean EEG signal. Two studies have explored the contributions of EMG to BIS scores in the presence of neuromuscular blocking agents and conclude that this BIS monitoring may result in episodes of undersedation because EMG is subtracted as a component of the BIS algorithm and neuromuscular blockade significantly decreases EMG artifact (Messner, Beese, Romstock, Dinkel, & Tschaikowsky, 2003; Vivien et al., 2003). Other authors have found BIS to be a reliable predictor of consciousness state in patients receiving neuromuscular blockade (Arbour, 2000; Bader, Arbour, & Palmer, 2005; Hilbish, 2003). It is conceivable, therefore, that the patient could be fully conscious with low BIS readings. For this reason, nurses need to retain the skills to interpret subjective parameters associated with sedation.

Studies of Observational and Physiologic Assessment of Sedation

The ability to continuously monitor and record trends in a patient's level of consciousness will benefit the bedside practitioner. However, there are no randomized controlled trials documenting the benefit of incorporating BIS as an adjunct to observational sedation assessment (Ely et al., 2004; Fraser & Riker, 2005). The contributions of physiologic data from BIS monitoring have been heretofore evaluated primarily as a replacement for observational data regarding sedation management; as such the psychometric evaluations of BIS are limited to assessments of validity and no reliability assessments of

BIS scores were found in the literature. The one possible exception to this may come from Venn and Grounds (2001) who examined two drugs used for sedation and found that for deeply sedated patients (Ramsay 4-6) when there are no differences in Ramsay scores ($p=.68$) there are also no differences in BIS scores ($p=.32$). The following discussion will explore the critical components of articles which have examined correlations between BIS and Ramsay, correlations between BIS and SAS, and finally correlations between BIS and other physiologic measures of sedation.

Ramsay and BIS

Research examining correlations between BIS and Ramsay scores, while generally reporting statistically significant values, has resulted in inconsistent, and often confusing, clinical discussions. There are two primary methods of evaluating the relationship between BIS and Ramsay; primarily a correlation is computed that evaluates the combination of Ramsay scores against the combination of BIS scores. A second method is the evaluation of a mean BIS value for each level of Ramsay. Of the 10 articles which examine the correlation in scores for the set of BIS scores and the set of Ramsay scores, all 10 articles find statistically significant correlations (Table 1). Similarly, each of the five articles examining the relationship between individual Ramsay scores and mean BIS values find significant results (Table 2). The confusion appears to arise from an approach to psychometric evaluation by authors such as Nasraway, Wu, Kelleher, Yasuda, and Donnelly (2002) in which each given Ramsay value is expected to correlate with some absolute BIS value; this implies the desire to make a statement such as "a Ramsay of 3 is the same sedation level as a BIS of 67." It bears repeating that Ramsay examines the patient's responsiveness to stimuli using observations that are scored with a pen and paper whereas the BIS examines the degree of

cortical entropy using physiologic data from one of two frontal lobes with a computerized algorithm. Ramsay and BIS are not expected to correlate perfectly, and their lack of perfect correlation does not indicate that either tool has poor validity for use in sedation assessment. The following section will discuss the contributions of these articles in evaluating the validity of BIS monitoring.

Ramsay and BIS are inversely related. A decrease in Ramsay scores is associated with a decrease in sedation effect whereas a decrease in BIS values is associated with an increase in sedation effect. While values of Ramsay are not absolute correlates of BIS, the BIS values for patients who are asleep, as indicated by lower Ramsay scores, are all lower than the BIS values for patients who are awake, as indicated by higher Ramsay scores (J. K. Bell et al., 2004; Mondello et al., 2002; Riess et al., 2002).

Table 1 presents correlation results from authors who have examined the relationship of Ramsay and BIS values. If the assumption that Ramsay is the default gold standard for sedation assessment is accepted, then this data set demonstrates that Ramsay and BIS are adequately correlated to provide additional data to support the validity of BIS as a sedation assessment tool. Gilbert, Wagner, Halukurike, Paz, and Garland (2001) examined 108 observations of Ramsay and BIS values for 31 critically ill patients, finding a stronger correlation ($r = -.63$) for neurocritically ill patients than the correlation ($r = -.51$) for the entire set of patients. Although Ramsay and BIS are inversely correlated, later authors have found it useful to explore the correlations in scores that occur with increasing sedation; to wit, a higher Ramsay score and lower BIS values (Agrawal, Feldman, Krauss, & Waltzman, 2004; Aneja, Heard, Fletcher, & Heard, 2003; J. K. Bell et al., 2004; Gill, Green, & Krauss, 2003).

Table 1.

BIS and Ramsay correlation values.

Publication					
1st Author	Year	*n*	Correlation	*p* value	comments
Gilbert	2001	31	r = - .51	<.001	108 samples on 31 patients
Walder	2001	28	Not Reported	0.0208	Tested difference in group means BIS mean 83 ± 10 when Ramsay = 4 BIS mean 74 ± 10 when Ramsay = 6
Berkenbosch	2002	28	r = .35	<.001	428 samples on 28 patients
Frenzel	2002	19	t > 0.5906	<.001	
Reiss	2002	44	r = -.64	<.01	All BIS versus All Ramsay
		12	r = -.56	ns	Shivering patients only
Reiss	2002	32	r = -.70	<.01	Non-Shivering patients only
		22	r = -.33	Ns	EMG > 42
		22	r = -.55	<.01	EMG < 42
		17	r = -.69	<.01	Medicated with sufentanil
		8	r = -.76	<.05	Medicated with pirinitramide
		19	r = -.41	Ns	Epidural analgesia
Aneja	2003	48	r = .77	<.0001	478 samples on 48 patients
Gill	2003	37	r = .69	<.005	
Agrawal	2004	20	r = .78	<.001	
			r = .67	<.001	
Bell	2004	30	r = -.90	<.001	Within subjects
		30	r = -.97	<.001	Between subjects
Tonner	2005	46	Tau = -.40	<.01	

Methodology of evaluating BIS scores may also account for differences in correlation studies, although this is not clear since few authors address the method by which they determine the BIS value. One study exploring the use of BIS to monitor deeply sedated patients found an initial Spearman's rank correlation (r=.64) for BIS and Ramsay scores in

all subjects to be significant (Riess et al., 2002). When the effects of patient movement were removed by using only BIS scores with EMG values below 42, the newer correlation (r =.70) between BIS and Ramsay represents a marginal improvement in correlation. These findings are consistent with later reports demonstrating that patient movement may cause high EMG activity and decrease the reliability of BIS values (Fabregas et al., 2004; Nasraway et al., 2002).

Table 2 provides data from those authors who have examined how each level of Ramsay may relate to specific ranges of BIS. The discrepancy in absolute values for BIS across these studies can partially be explained by the limitations of Ramsay scores, and partially by the use of the Ramsay scale in each study. Recall that the Ramsay scale, as it was originally created, was not created to measure levels of sedation, it was created to help determine if sedation was inadequate or adequate (Ramsay et al., 1974). Although the authors each cite the original Ramsay scale developed in 1974, they each use a different version of the scale (Mondello et al., 2002). Each of these five studies, however, does result in statistically significant relationships between Ramsay and BIS.

Much of the literature that explores the validity of BIS by evaluating subjects with both BIS and Ramsay is grossly flawed because each author uses and interprets the Ramsay scale differently. The penchant for modifying the Ramsay scale and then reporting values is rampant in literature. The number of variations of the Ramsay scale are overwhelming (Burchardi, 2004; Jacobi et al., 2002). Most frequently, the definitions for the levels of Ramsay are altered or shortened (Berkenbosch, Fichter, & Tobias, 2002; Frenzel et al., 2002; Schulte-Tamburen et al., 1999). Occasionally, the number of levels in the scale are altered (Agrawal et al., 2004; Gill, Green, & Krauss, 2003). However, even seemingly insignificant

changes to the scale impact both the reliability and validity of the scale. Glaring examples can be found in the literature describing BIS and Ramsay. Gill, Green and Krauss (2003) claim to have designed a study to correlate BIS scores and Ramsay scores. They find that BIS only moderately correlates with Ramsay, but describe a modified Ramsay scale which has 8 levels of sedation, and has no reliability or validity testing. There is a higher correlation in scores of Ramsay and BIS when the Ramsay scale has not been altered.

As with Ramsay, the SAS has been explored for correlations with BIS values. The SAS is a more recently developed tool and as such, there are fewer instances where this tool is cited in literature and fewer still where the SAS and the BIS are used jointly for evaluating sedation levels. To date there are five published reports of correlation scores for BIS and SAS (Table 3). Two additional studies report to have completed correlation analyses, but do not include this information in the manuscript (Frenzel et al., 2002; Olofsson, Alling, Lundberg, & Malmros, 2004). Published squared correlation values are noted to range from r^2=.21 ($p<.001$) to r^2=.73 ($p<.0001$) with each of the five studies finding statistically significant correlation scores for SAS and BIS (de Wit & Epstein, 2003; Deogaonkar et al., 2004; Nasraway et al., 2002; Riker et al., 2001; Simmons et al., 1999).

Table 2.

Comparison between absolute values of Ramsay and absolute values of BIS.

1st Author	Year	*n*	Ramsay Value	BIS Value	BIS Range	*p* alue	Comments
Berkenbosch	2002	37	1	54	(44-76)	not	BIS values are
		31	2	65	(61-81)	given	reported as the
		87	3	48	(40-66)		median and
		99	4	42	(34-51)		interquartile
		61	5	42	(34-62)		range
		111	6	36	(24-54)		
							Remifentanil dose
Cavaliere*	2002	10	1 (1-3)	93	(50-98)	ns	No remifentanil
		10	2 (2-5)	88	(40-83)	ns	.02 mcg/kg/min
		10	2 (2-5)	60	(35-60)	<.05	.05 mcg/kg/min
		10	4 (2-5)	54	(36-60)	<.01	.10 mcg/kg/min
		9	3 (1-5)	48	(40-68)	<.01	.15 mcg/kg/min
		8	4 (4-6)	49	(28-60)	<.05	.20 mcg/kg/min
		4	5	50	not given	<.01	.25 mcg/kg/min
Mondello**	2002	980	2	88.0	± 2.8	<.01	Values are
			3	81.4	± 2.8	<.01	reported as
			4	69.7	± 3.6	<.01	a 95%
			5	56.1	± 5.6	<.01	confidence
			6	52.3	± 4.1	<.01	interval
Riess	2002	1	1	98.0	± 0.0	<.001	Values are
		4	2	94.8	± 3.9	<.001	reported as
		7	3	80.6	± 9.4	<.001	plus or minus
		4	4	79.8	± 15.4	<.001	one
		5	5	66.8	± 24.5	<.001	standard
		23	6	51.3	± 20.8	<.001	deviation
Bell**	2004	181	1	96.6	± 0.7	<.001	Values are
			2	96.4	± 0.6	<.001	reported as
			3	87.1	± 0.8	<.001	a 95%
			4	80.9	± 1.2	<.001	confidence
			5	71.6	± 1.1	<.001	interval
			6	54.8	± 5.9	<.001	

* Cavaliere et al. display the median and range for Ramsay and BIS values. Different concentrations of remifentanil were infused.

** No data were reported by Mondello et al, nor by Bell et al. for the number of observations at each level of Ramsay.

SAS and BIS

The first two of the five articles discussing correlation scores of SAS and BIS are attempts to examine the validity of the SAS tool for sedation assessment (Riker et al., 2001; Simmons et al., 1999). This is interesting in that these studies begin with the assumption that BIS is adequate in describing some domain of the patient's response to sedation. The correlation of scores in the article by Simmons et al. (1999) are explored not for their ability to validate one score or the other, rather, this is a descriptive study in which the authors attempt to describe the level of sedation for patients who are mechanically ventilated. BIS values, averaged for 15-minute segments of time, were reviewed by an independent investigator who selected the BIS readings he felt were most stable and representative of the "baseline value" for each patient. The squared correlations were found to be statistically significant for both the baseline BIS values ($r^2 = .14$, $p = .004$) and the average BIS values ($r^2 = .21$, $p < .001$). The study by Riker et al. (2001) is clearly defined as an attempt to validate the SAS tool; the findings of significant correlation, while supporting further validity of both tools, is primarily used to justify the validity of the SAS.

Riker et al. (2001) found that although SAS and BIS were valid measures of wakefulness in post-operative cardiac patients, the correlation score ($r^2=.61$) was diminished by the presence of shivering in patients who were more awake. A separate study examining the clinical utility of BIS concluded that the presence of shivering, as indicated by higher EMG scores (> 42 dB) impacted correlation of BIS and SAS ($r^2 = .36$, $p <.001$), however, correlation significantly improved ($r^2 = .50$, $p <.001$) when EMG was controlled for (Nasraway et al., 2002). This same article concludes that BIS is not valid for monitoring the response to sedation in critically ill patients; however, the authors also conclude that

excessive EMG artifact (which can be observed by the bedside practitioner) is a significant contributing factor to the validity assessment of BIS (Nasraway et al., 2002). It remains unclear why the authors did not simply conclude that the interpretation of BIS requires the practitioner to incorporate an assessment of the EMG values associated with the given BIS values.

Table 3.

Comparisons of SAS and BIS.

1st Author	Year	n	Correlation	p value	Comments
Simmons[a]	1999	64	r = .46	< .001	64 observations on 63 patients
			r = .72	= .018	Trauma patients
			r = .451	= .2	General patients
			r = .50	= .008	Cardiac patients
			r = .32	= .19	Surgical and medical patients
Riker	2001	39	r = .61	< .001	
Nasraway[b]	2002	97	r = .61	= .006	SAS values between 1, 2, and 3
		60	r = .71	< .001	EMG values < 42 decibels
de Wit	2003	64	r = .69	< .001	Before stimulation
		64	r = .66	< .001	After stimulation
Deogaonkar[c]	2004	128	r = .65	< .001	
		64	r = .62	< .001	Using older BIS monitor
		64	r = .85	< .0001	Using BIS X-P monitor

a Simmons et al. report on 64 observations made on 63 patients, the number of observations for each patient classification were not given.
b Nasraway et al. report on 97 and 60 observations made on 19 patients.
c Deogaonkar et al report on 128 observations made on 30 patients

Deogaonakar et al. (2004) examined relationships of BIS, SAS, GCS and the RASS. The authors used the most recent version of BIS software and concluded that BIS associated well with SAS ($r^2 = .725$, $p < .001$). De Wit and Epstein (2003) correlated BIS values with SAS scores before and after stimulation, where stimulation was defined as a neurological

assessment using the SAS. In this manner, two sets of BIS values, averaged over 2-minutes each, were correlated with a single SAS value. The coefficient of determination values for BIS before stimulation ($r^2 = .48$, $p < .001$) were only modestly different from those obtained after stimulation ($r^2 = .44$, $p < .001$). The study included 80 observations of 19 patients, and concluded that physiologic data and observational assessments of sedation assessments are highly associated.

Correlations of SAS and BIS values, as with correlation studies of Ramsay and BIS vary widely. SAS and Ramsay are both response-generated tools. However, it must be repeated that the Ramsay scale is considered by most authors to be the current gold-standard for observational sedation assessment (Barrientos-Vega et al., 1997; Gill, Green, & Krauss, 2003; Soliman, Melot, & Vincent, 2001). Jacobi et al. (2002) more accurately state that no true gold-standard exists for assessing a patient's response to sedation. The SAS having undergone initial psychometric testing with variations in the results may eventually be demonstrated to be more reliable than Ramsay, if only because of the newness of the scale and the push by the authors for additional psychometric testing. Several authors erroneously conclude that there is insufficient correlation between either Ramsay or SAS with BIS to support the use of BIS in the ICU (Gill, Green, & Krauss, 2003; Nasraway et al., 2002; Tonner et al., 2005). Fraser and Riker (2005) recently addressed these apparent inconsistencies, concluding that responses from observational sedation assessment tools may provide different information about the patient's ability to respond than do objective tools such as the BIS monitor.

Conclusion

The ability to continuously monitor the patient's response to sedation is a fundamental necessity. In the neurocritical care unit the focus of care is often aimed at preventing secondary brain injury. The NCCU nurse may be required to adjust sedation both upwards and downwards. Adjusting sedation downwards allows the patient to lighten from sedation such that the nurse may obtain a comprehensive neurologic exam that informs the medical team about the patient's progress. Adjusting the sedation upwards may be required to meet the goals of sedation. The current practice in the NCCU relies heavily upon the ability of the nurse to recognize cues associated with sedation. Although both observational and physiologic tools are available for evaluating an individual patient's response to sedation, these tools assess different domains of consciousness and are therefore expected to provide different and complimentary data that will allow the nurse to have a greater understanding of the patient's response to sedation than would either tool alone.

It is hypothesized that augmenting current observational sedation assessment with BIS monitoring will result in a decrease in sedative use. This decrease in sedative use is important because patients are chronically oversedated which leads to increased length of mechanical ventilation, decreased wound healing and decreased gastrointestinal motility (Guin & Freudenberger, 1992; Park et al., 2001; Rodrigues Junior & do Amaral, 2004). The purpose of this study therefore is to study the change in sedation drug use when BIS monitoring is used to augment sedation assessment.

CHAPTER III

RESEARCH DESIGN AND METHODS

Chapter three includes a comprehensive discussion of the research design and methods used in the study. The research design, setting, sample population, variables, and the procedures used will be discussed as they relate to the study. Following this, the data management and analysis plan is explained.

This randomized clinical trial explores how coupling a physiologic measure of consciousness and traditional observational assessments impacts sedation management. Sedation management was explored for that portion of a single nursing shift for which a single nurse was responsible for the primary adjustment of sedation levels based on physician-prescribed parameters. The sample of 51 neurocritically-ill patients was randomized to two groups. One group received sedation management solely with observational assessments and the other group received sedation management with a combination of observational and physiologic data. This is operationalized as a study wherein the Ramsay scale is the traditionally used observational assessment tool and the bispectral index (BIS) monitoring is a physiologic measure of consciousness that will provide physiologic data. It is assumed that nurses also incorporate other observational data not measured by the Ramsay scale and that these data were used equally by nurses in both groups. To determine the feasibility and appropriateness of the methods, including data collection tools, a pilot study of two patients was first conducted and the proposed data collection tools were modified.

Assumptions

The fundamental assumption behind this study is that ICU patients are chronically oversedated. This assumption is supported by de Wit and Epstein (2003), Devlin, Holbrook, and Fuller (1997), Magarey (1997), and Wittbrodt (2005). Any decrease in sedation use without a corresponding increase in the markers of undersedation will benefit the patient. Though most clinicians believe that patients in the ICU setting are chronically oversedated there is no gold standard by which to assess adequate sedation, oversedation, or undersedation (Jacobi et al., 2002; Magarey, 1997; Rhoney & Murry, 2002). However, certain events such as failure to respond to stimulus or self-extubation have been cited in literature as correlates of oversedation and undersedation. It becomes reasonable, therefore, to use the absence of events associated with oversedation and the absence of events associated with undersedation as the boundaries of adequate sedation. Patients benefit from a more appropriate level of sedation because those who are less ill will be taken off sedation earlier (able to breathe on their own), and those who are extremely ill do not require sedation (if subject is already unconscious they do not need medication to remain so). The assumption that patients are oversedated is supported by literature and therefore a decrease in sedation and a shortened length of time to awaken from sedation without an increase in events related to undersedation will support the assumption that the patient was receiving more sedation than was required.

Undersedation is defined by the needs of sedation. These needs are threefold: injury prevention, facilitation of medical goals, humanitarian goals (Murdoch & Cohen, 2000; Young et al., 2000). Humanitarian goals for sedation are best described as the relief of pain and suffering and the lack of recall of unpleasant events (Cheng, 1996). There are no tools by

which to measure recall in the patient who has recovered from an injury to the brain. Undersedation will therefore be measured by the inability to meet one or both of the remaining needs. Injury may be measured by self removal of tubes or injury to self or others (Boulain, 1998). The facilitation of medical goals is most clearly exemplified by the presence of ventilator asynchrony, measured as asynchronous events and documented on the respiratory care flowsheet by the respiratory therapist.

There is an assumption that nurses monitoring sedation may use tools outside of the BIS and Ramsay. For example, the nurse who obtains a Ramsay score of 4 and then observes the patient to be pulling out his IV catheters may not perform and document a new Ramsay score, nor is that nurse expected to change her prior Ramsay score of 4, rather the nurse will incorporate this new information into her decision. Likewise, a potential limitation of the BIS is the slow rate of change that may occur in BIS scores when rapid changes in consciousness occur. As discussed in the review of literature, this results from the smoothing rate and the need to obtain a sufficient amount of artifact-free recordings for analysis. The assumption herein is that nurses monitoring sedation will react to abrupt changes in patient status (e.g., eyes open) without regard to current BIS values. The process of randomization will control for the effect of different nurses using additional assessment skills with both control and intervention patients (Maxwell & Delaney, 2004).

There is an assumption that the appropriate length of time to examine the response variables is 12 hours. This assumption is based on knowledge of the nursing shift for the NCCU in which the study will occur. Each nursing shift begins at 7:00 (a.m. or p.m.) each day with a shift handover (nursing report) that lasts approximately 30 minutes. The first nursing assessment occurs at approximately 8:00 a.m. and it is at that time when it is most

likely that the on-coming nurse would first make a change in the sedation level. The period of time from 7:00 to 7:30 is jointly managed, but heavily influenced by the nurse who is departing (ending his/her shift). The period of time from 7:30 to 8:00 is often most often occupied by the nurse preparing for the shift (e.g., checking the ICU room to ensure that there is an adequate supply of materials, obtaining medications). Additionally there is an assumption that the nurse-patient interactions of day-shift nursing care are fundamentally different from the nurse-patient interactions during the night shift. Therefore, a study of the 12-hour shift from 7:00 a.m. to 7:00 p.m. would not adequately represent the interactions of one nurse with one patient and this study will explore the 12-hours from 8:00 a.m. to 8:00 p.m.

Setting

The study setting was the neurocritical care unit (NCCU) at Duke University Hospital in Durham, NC. This is a 16-bed unit dedicated to the care of critically ill neurosurgical and neurological patients. The NCCU has 24-hour nursing, respiratory therapy and physician/nurse practitioner coverage. Two part-time nurse research assistants were employed and available to assist with subject enrollment. The nurses in the NCCU work 12-hour shifts that begin at 7 a.m. In the NCCU, the handover is a face-to-face exchange and is not limited in discussion style or content; nurses may fully discuss the patient's sedation requirements in any fashion they see fit. The first nursing assessment was performed at 8 a.m. Nurses were free to express their opinions of the patient or family response to care and needs for the coming shift.

Daily medical team rounds began at 8 a.m. and were coordinated by the attending physician. The rounding team was composed of the attending physician, the off-going and

on-coming house officer (which may be a nurse practitioner or resident physician), a neurocritical care fellow, a clinical pharmacist, the charge nurse and the primary care nurse, the NCCU respiratory therapist, and a clinical dietician. Rounds included a systematic in-depth discussion of the patient's condition and addressed the neurologic, respiratory, cardiovascular, renal, integumentary, and hemodynamic systems as well as a discussion of the patient's infectious status, pharmacologic regimen, nutritional concerns and the patient-family dyad needs for emotional or educational support. While all members of the medical team were encouraged to provide input to the patient's plan of care, the attending physician was responsible for the final decisions. The goals and target for sedation were discussed each morning for all patients in whom sedation therapy was initiated.

Once the decision was made that a patient would benefit from sedation therapy, sedation management was initiated by a physician's order which included the specific medication (drug), infusion rate, and sedation target. Most commonly, the target was a Ramsay score equal to 4. In the past 4 years, NCCU physicians had been writing a BIS sedation target of 60-70 and this target was the standard throughout the 7-months of data collection for this study. Ramsay remained the standard of care. BIS is not a standard of care and the NCCU medical director agreed that BIS monitoring would not be ordered for any patients until the study was completed. Thus, only patients who were in the study and randomized to the intervention arm of the study received BIS monitoring.

Propofol remained a standard-of-care medication for sedation in the NCCU throughout the study and was used at the discretion of the physician or physician-designee as a routine component of medical care for patients in this study. Propofol is a phospholipid-based parentally administered anesthetic that is metabolized in the liver and excreted via the

kidneys (McMurray, Collier, Carson, Lyons, & Elliott, 1990; Ronan, Gallagher, George, & Hamby, 1995). Propofol inhibits the N-methyl-D-aspartate subtype of glutamate receptors by channel gating modulation and has agonistic activity at the GABA receptors (Miller & Reves, 2000). Propofol has a relatively short half-life with sedative effects generally lasting from 4 to 8 minutes when used in doses of 1.5-2.5 mg/kg/hour although the pharmacokinetic effect of propofol has been shown to be dependent in part upon body weight and fat content (Frenkel, Schuttler, Ihmsen, Heye, & Rommelsheim, 1995; McMurray et al., 1990; Schuttler & Ihmsen, 2000). Despite the higher cost of propofol relative to short acting benzodiazepines such as midazolam (Ostermann et al., 2000), its use as a sedative in mechanically ventilated patients has actually been shown to decrease the overall cost of care because of the relatively short half-life of the drug which facilitates a shorter time to extubation (Barrientos-Vega et al., 1997; Ostermann et al., 2000).

At the time of this study, the practice in the NCCU was that all sedation assessments were performed and documented by the care nurse. The NCCU standards of practice remained throughout the study; following these standards patients had vital sign documentation at least hourly, a complete physical assessment at least once every 4 hours and a neurological assessment, including the Glasgow Coma Score (GCS) was performed at least once every 2 hours. Sedation assessments were completed at least once every two hours and documented electronically. The NCCU documentation system (CareVue^{tm}) was used throughout the study.

Subjects

All of the subjects in this study were patients who were admitted to the Neurocritical care unit at Duke University Medical Center. By nature of the subject's admission he/she was

unable to provide self-consent, therefore the subject's legally authorized representative was approached for informed consent. The following section provides details for subject recruitment.

Power

Determining power for the primary research question would ideally have been done with data that reflected changes in sedation drug infusion rates during a single nursing shift when nurses are provided with new information about the patient's response to sedation. Unfortunately, no data exist reflecting this proportion with appropriate sedation. Therefore, this power analysis was based on a previously published study in which changes in drug rates during a single one-hour of BIS monitoring were reported (Olson, Cheek, & Morgenlander, 2004). Sample size calculations were performed using tables from Lipsey (1990). A sample size of 90 patients (45 per group) was determined based on an effect size of .60, a two-tailed alpha level of .05, and a desired power of .80.

These estimates, while conservative, were deemed appropriate given the relative paucity of studies available for interpretation. The effect size and pooled standard deviation were calculated using common formulas (Equation 1). The control group mean (21.164 ml) and standard deviation (14.427), as well as the treatment group mean (12.491 ml) and standard deviation (10.769) were obtained from the prior study with equal sample sizes (Olson, Cheek & Morgenlander, 2004). It could be argued that an effect size of .68 could be used instead of .60 and this would reduce the sample size. Additionally, from the one-direction hypothesis (decrease in mean sedative use) it was reasoned that testing a null hypothesis of no decrease in mean sedative use permits a sample size calculation using a one-tailed alpha, and that could also reduce the sample size. While basing sample size

calculations on these two assumptions would reduce the sample size to 52, the final decisions were based on the desire to use conservative estimates because of the implications from a Type II error. An interim data analysis was performed at 6-months (Chapter IV) and, following the decision to reject the null hypothesis of the primary research question, "no difference between groups" analysis was performed on the remaining research questions.

Equation 1.

Effect size and pooled standard deviation formulas.

Formula for effect size	Formula for pooled standard deviation
$ES = \frac{\mu_t - \mu_c}{\sigma}$	$Sp = \sqrt{\left(\frac{s_t^2 + s_c^2}{2}\right)}$
$ES = \frac{21.164 - 12.491}{12.73}$	$Sp = \sqrt{\left(\frac{14.427^2 + 10.769^2}{2}\right)}$
Effect size = .68	Pooled S = 12.73

Patients as Subjects

The inclusion criteria for this study were that the patient be admitted to the NCCU with a neurological or neurosurgical diagnosis (Table 4). Patients must have been at least 18 years old, orally intubated and on mechanical ventilatory support with a GCS less than 11 and currently receiving propofol sedation via continuous intravenous route. By only including patients in the NCCU and those patients with a neurological or neurosurgical diagnosis, internal validity was stronger. Patients were required to be at least 18 years of age because the adult BIS sensor was used in this study. Patients were required to be orally

intubated and on mechanical ventilatory support because patients who are tracheally intubated are less likely to require sedation for the purpose of preventing harm to self (unplanned self-extubation) and patients who are not on mechanical ventilation are less likely to require sedation for the purpose of maintaining ventilatory synchrony. The cutoff of a GCS of 11 was used because patients with higher GCS values are expected to no longer require endotracheal intubation. The choice was also made that internal validity would be strengthened if the study included only those patients with continuous IV propofol as their primary sedating agent.

Table 4.

Patient inclusion and exclusion criteria.

Inclusion	Exclusion
Patient in the NCCU	Pregnant women
Admitted with a neurological / neurosurgical diagnosis	No available space on the forehead: (example: frontal de-gloving trauma)
Age > 18	Continuous EEG-seizure monitoring
Endotracheally intubated	Bifrontal brain injury
Receiving mechanical ventilatory support	Barbiturate coma therapy
Glasgow Coma Score less than 11	Benzodiazepine administration
Continuous IV sedation with propofol is ordered by the attending physician	

Patients were excluded if they had continuous EEG monitoring for status epilepticus because continuous EEG monitoring required the placement of electrodes on the forehead and temporal regions in the same space where a BIS monitor would have been applied. Thus, the two therapies were incompatible because of the limited space available on the forehead. Patients who were enrolled in the study and then had EEG electrodes placed to rule out seizure activity were not excluded from the study. Patients were also excluded if they had a

bifrontal brain injury because the BIS sensor is applied to the forehead and detects frontal cortical activity; the patient who has bifrontal cortical injury will presumptively have changes in cortical signal not associated with sedation. Patients with frontal injury isolated to only one hemisphere remained eligible for inclusion and the BIS sensor was placed over the contralateral (non-injured) frontal lobe. Patients with frontal de-gloving injuries were excluded from the study because this type of injury destroys the connective tissue between the scalp and the pericranium and this may alter the quality of the EEG signal by increasing the signal impedance. Patients were also excluded if they were receiving benzodiazepine or barbiturate coma therapy because the goal of therapy for patients receiving these medications is a deeper level of sedation than a Ramsay score of 4.

Patients were unable to give consent by virtue of their condition. Therefore, informed consent was obtained from the next of kin. All patients included in the study needed to be over 18 years of age. Because the BIS sensor is made for adults; a pediatric sensor has only recently been developed. Further, EEG characteristics and response to sedation differ for children and adults, and nursing concerns also differ. For example, the pediatric endotracheal tube does not have a cuff, creating an additional risk for self-extubation and nurses may have opted for deeper sedation. Finally, patients less than 18 years of age are not routinely admitted to the adult NCCU; roughly 3% of the patients admitted to the NCCU during the study were between the ages of 18 and 21.

Variables and Their Measurement

The study included variables measured by a combination of physiologic monitors, observations, and chart abstraction. Standard monitoring equipment used in the NCCU was used for the study. This equipment included the Carevue^{tm} bedside documentation system.

The BIS monitor (model BIS-X from Aspect Medical Systems Inc., Newton, MA) was used to monitor BIS values. BIS data was downloaded from the BIS-X monitor onto a single USB disk and transferred to a password-protected laptop computer that housed the data.

Table 5.

Variables.

Concept	Type of Variable	Instrument	Data Collection	Descriptors
Patient Demographics	Independent	Medical Chart	Chart abstraction on admission	Age, Sex, Ethnicity
Undersedation Events	Dependent	Medical Chart	Extubation, ventilator asynchrony, line removal, physical threat	Number of events occurring >10 minutes apart.
Sedative Use	Dependent	Medical Chart	Chart abstraction: total volume (ml)	Total ml/kg for each hour, each 12-hour shift, and total length of stay
Recovery Time	Dependent	Stopwatch	Continuous: nearest second	Time from when sedation is interrupted to the recovery of baseline consciousness
Observational Assessment of Sedation	Independent	Ramsay	Periodic: every 2-hours	Single measure numeric value
Physiological Assessment of Sedation	Independent	BIS	Continuous: nearest tenth	Mean BIS value for each 60-seconds
Potential Covariate		**Instrument**	**Data Collection**	**Descriptors**
Injury Severity	Independent	GCS	Once: On admission	Single numeric value of GCS
Illness Severity	Independent	APACHE®	Once within 24 hours of admission to the NCCU	Single numeric value of APACHE®

Patient Demographics

Following informed consent, the patient's age, weight, gender, and ethnicity were collected from a review of the subject's medical record. Age was measured in years and calculated as the number of completed whole years at the time of admission to the ICU. Age was determined from the subject's date of birth. Weight was the measured weight in kilograms at the time of admission. The beds used in the NCCU have a built in electronic scale and the patient admission weight is obtained for all patients as a routine component of nursing care. The admission weight is documented in the demographics section of the electronic health record. These characteristics were used to describe the sample population.

Undersedation Events

There is no gold standard tool to measure the appropriateness of sedation, or identify undersedation. Undersedation was defined as the number of undersedation events per nursing shift. The following events were included as undersedation events: unplanned self-extubation, self removal of invasive lines and/or monitoring devices, ventilatory asynchrony documented by the respiratory therapist, attempts to exit the bed, and physical threat to self or staff (J. K. Bell et al., 2004). These events were documented in the electronic patient record and recorded on the undersedation event form (Figure 8) by the investigator from chart review. A tally of the total number of undersedation events in each group was maintained. As will be noted in the results and analysis chapter, there were no undersedation events reported.

Figure 8.

Undersedation event form.

Subject	Date	Time	self extubation	Self line removal	Device removal	Ventilatory asynchrony	Bed Exit	Threat to self	Threat to staff

Sedative Use

The most common choice of continuous IV sedation in the NCCU of study was propofol (Diprivan). Propofol is available as a 1% (10 mg/ml) emulsion in 10% soybean oil, 2.25% glycerol and 1.2% purified egg phospholipid with pharmacokinetics similar to those of barbiturates (McMurray et al., 1990). Although the pattern of onset and duration of propofol anesthesia is similar to barbiturates, there is a more rapid rate of recovery from propofol infusion, mostly due to its rapid clearance. Propofol is metabolized primarily in the liver to a less active metabolite that is excreted via the kidneys. Propofol has been used clinically primarily as a parental anesthetic, either via induction or short term maintenance infusion (Ghouri, Ruiz, & White, 1994). In the NCCU, propofol is employed as a sedating agent for mechanically ventilated neurological and neurosurgical patients because it has a relatively short half-life, which allows frequent sedation interruption for neurologic exams (Ghouri, Ruiz, & White, 1994; Grounds, Lalor, Lumley, Royston, & Morgan, 1987; Higgins et al., 1994; Roekaerts, Huygen, & de Lange, 1993; Ronan et al., 1995; Wolfs, Kimbimbi, Colin, Noël, & Neuberg, 1991).

The amount of propofol was measured as the total volume (ml) of drug infused during each nursing shift between 8 a.m. and 8 p.m. Propofol use was adjusted to the patient's

weight and reported as the average number of milligrams infused per kilogram of body weight each minute (mg/kg/min). The patient weight was recorded at the time of admission. The volume of propofol infused was documented in milliliters and in mg/kg/min for each hour and found in the electronic patient record; these values were obtained from chart review. The mean propofol volume for each group and the mean propofol infusion rate (mcg/kg/min) were calculated for each group.

Recovery Time

The recovery time was defined as the period of time from which the sedative infusion was interrupted to the point of time at which the patient had recovered their baseline consciousness state. Because there is no reliable method of determining the recovery of baseline consciousness in brain-injured patients, this variable was determined as the length of time in minutes from when sedation is turned off, until the neurologic exam represents the patients' best level of response. The recovery time examination occurred at the same time each shift and was be performed by an independent investigator. Although recovery times occur once every two hours, only one recovery time, the 4:00 p.m. recovery time was assessed. This was to increase consistency and to provide the nurse with ample time (8:00 a.m to 4:00 p.m.) for which to fine tune the subject's sedation based on either the Ramsay scale or the Ramsay scale and the BIS values. At 4:00 p.m. each day, an independent assessment of the neurologic exam was performed by one of five advanced practice nurses (APN) familiar with the care and assessment of brain-injured patients. No special instructions or training was provided for the APN and they were blinded to the research questions throughout the study.

For this assessment, the primary nurse turned the propofol off and covered the BIS monitor (so that the display was not visible) before the APN entered the room. When the RN turned the propofol off, the investigator started a stopwatch. The APN was informed that the propofol was off, but was not provided with information about what the propofol infusion rate had been prior to interrupting the sedation. The APN informed the research staff when he/she felt that the subject had fully recovered from the effects of sedation and a neurologic exam could be performed that represented the patient's best level of function. When the APN stated that the subject had recovered from the effects of sedation, the investigator stopped the stopwatch and recorded the time in minutes and second. Upon completion of the neurologic exam, the propofol infusion was resumed by the primary care nurse. The mean recovery rates in seconds were calculated for the two groups and used in the analysis of the second research question.

Observational Assessment of Sedation

Sedation assessment in the NCCU is typically done intermittently using the Ramsay scale, a single-item 6-level tool that uses direct observation of the patient (see Figure 2 chapter 2). Ramsay scores, which are documented every 2 hours by the primary care nurse, were collected from review of the medical record. These scores were averaged for comparison with mean BIS scores and used in the analysis of intervention fidelity. The Ramsay scale is a subjective scale based on nursing observations of the patient's response to stimuli and may be inconsistently interpreted by different assessors (Watson & Kane-Gill, 2004). However, despite these shortcomings, at the time of this study, the Ramsay scale was the only sedation scale endorsed by the hospital and the scale the nurses were most familiar with. Therefore, it was used throughout the study.

During their orientation to the NCCU all nurses receive instructions on use of the Ramsay scale. Additional refresher training was provided as part of this study. To ensure that all the nurses in this study were using the scale in a similar manner, each nurse received training in the use of the Ramsay scale. The Ramsay scale is performed while the sedative is infusing and is used to assess the subject's response to sedation. All nurses received identical instructions (Appendix A). Prior to data collection the nurse was given a set of written instructions detailing that sedation assessment with Ramsay begins with an evaluation of whether the patient is awake or asleep and then the nurse must determine the level of sedation based on the criteria described earlier. The nurse was given an opportunity to ask questions and have them answered. Additionally, a laminated copy of the instructions was posted at the bedside of each patient who was enrolled as a subject in the study.

Physiological Assessment of Sedation

Physiological data of sedation assessment were obtained from the BIS monitor and used in the analysis of intervention fidelity. The BIS is composed of three parts: the sensor, the digital signal converter and the display. The sensor is a self-adhesive pad which is placed across the patient's forehead and extends to the space between the outer canthus of the eye and the hairline. The sensor picks up the electrical signal from the cerebral cortex. This signal is then converted to a digital value. The BIS algorithm uses spectral analysis and fast-Fourier transform to analyze the sinusoids, frequency, and amplitude of the electrocortical signal. This value is displayed as a whole number ranging between 0 and 100. The BIS score is continuously updated and is interpreted along a continuum, representing a measure of cerebral cortical activity (De Deyne et al., 1998). The lowest value is zero and corresponds to isoelectric activity (a flat EEG waveform). Scores between 90 and 100 correlate with an

awake state, 70's to 80's with conscious sedation, 60's to 70's with deep sedation, and 40's to 60's with general anesthesia, 1-39 with deep anesthesia (Simmons et al., 1999).

The BIS monitor provides not only the current BIS score but also several additional parameters. A single-channel raw EEG tracing may be continuously displayed on the lower half of the screen, and the Signal Quality Index (SQI) bar, an indication of the reliability of the signal, is displayed near the top of the screen. The electromyographic bar indicates the degree of electromyographic activity, which is increased by poor electrode contact, muscle tone, seizures, tension, and eye movement. The suppression ratio indicates the percentage of isoelectric EEG tracing in the previous 63 second window. Nurses interpret BIS scores within the context of SQI and EMG values. BIS scores are not considered to be reliable when the SQI is less than 50% or there is greater than 50% EMG present. The trend portion of the screen displays the history of various parameters and is useful in monitoring changes in a patient's response to sedation over time. To improve the congruence of interpreting and recording BIS scores, the nurses received identical written instruction on the use of BIS when caring for sedated patients. The instructions informed the nurses to observe the digital display on the BIS monitor and to record the displayed value on the NCCU flowsheet while interpreting both the trend and the displayed value (e.g., the displayed value is 72, and the trend over the past 10 minutes indicates that the values are continuing to decrease, which indicates an increasing depth of sedation). As with the Ramsay scale, laminated copies of the instructions were posted at the bedside of each patient who was enrolled as a subject in the study.

The BIS monitor is capable of spectral analysis for frequencies below 50Hz. Frequencies of 70-110 Hz are used to detect electromyographic activity, which is subtracted

from the bispectral analysis. Values can be measured to the nearest tenth (Sleigh, Andrzejowski, Steyn-Ross, & Steyn-Ross, 1999). The BIS monitor stores average BIS values every 10 seconds. Date and time-linked data (raw BIS score, EMG score, SQI score) were downloaded directly from the BIS monitor using a USB drive and transferred to a laptop computer. The mean BIS value for each 1-minute was used in exploring the intervention fidelity.

Injury Severity (Potential Covariate)

The neurological assessment and the sedation assessment evaluate two different aspects of brain responsiveness. The Glasgow Coma scale (GCS) is a neurologic assessment tool used to assess the maximum possible level of cognitive function (Fischer & Mathieson, 2001; Sternbach, 2000; Teasdale & Jennett, 1974; Teasdale et al., 1998). The GCS was assessed by the RN only when the patient was sufficiently free of sedation to produce the best possible response to commands.

The degree of brain injury was measured by the GCS (Figure 9), a 3-item tool which provides a cumulative score between 3 and 15 (Heron et al., 2001; Juarez & Lyons, 1995). When free of the effects of sedation, patients were scored on best eye opening response, best motor response and best verbal response (Fischer & Mathieson, 2001; Teasdale & Jennett, 1976). The GCS was developed to assess severity of illness in brain injury, not response to sedation (Fischer & Mathieson, 2001; Olson, Cheek, & Morgenlander, 2004; Teasdale et al., 1998). However, sedation requirements were expected to covary with GCS scores. Only the admission GCS (the first GCS score obtained) is used as a prognostic indicator of the severity of injury (Teasdale, 1978; Teasdale & Jennett, 1974).

Figure 9.

The Glasgow Coma Scale.

Points	Category / Description
	Best eye response
4	Opens eyes spontaneously
3	Opens eyes to verbal commands
2	Opens eyes to painful stimulus
1	No eye opening
	Best verbal response
5	Oriented
4	Confused
3	Inappropriate verbal response
2	Incomprehensible verbal response
1	None
	Best motor response
6	Follows commands
5	Localizes to painful stimulus
4	Withdraws to painful stimulus
3	Flexion (decorticate) to painful stimulus
2	Extension (decerebrate) to painful stimulus
1	none

* Points are added to produce a cumulative score ranging from 3 to 15

A GCS of less than nine equates with a brain injury that has resulted in coma (Sternbach, 2000; Teasdale & Jennett, 1976). Patients with very low GCS scores often require little or no sedation because they are not able to move purposefully and therefore have a low risk of causing injury to self or staff. For patients to obtain a score of 12 or higher, they must be able to speak and therefore cannot be endotracheally intubated or require continuous sedation. Good interrater reliability (k = 79 -81) of GCS has been noted in studies of nurses working in both a general care ICU and NCCU (Heron et al., 2001; Weir, Counsell, McDowall, Gunkel, & Dennis, 2003; Wijdicks, Bamlet, Maramattom, Manno, & McClelland, 2005). Percent agreement for the exact total GCS score (32%) and component

score agreements (eye opening = 74% , motor response = 72%, verbal response = 55%) were reported by Gill, Reiley, and Green (2004). Fischer and Mathieson (2001), in a review article, conclude that the GCS provides a universal, standardized measure of injury severity in brain-injured patients. GCS values were collected from review of the medical record. The mean admission GCS was calculated for each group. The admission GCS independently, and as a component of illness severity (measured by the Acute Physiology and Chronic Health Evaluation (APACHE®IV) score) were explored as covariates of sedation use.

Illness Severity (Potential Covariate)

The APACHE® score has been developed and modified over the past several years as an indicator of illness severity in critically ill patients (Zimmerman, Kramer, McNair, & Malila, 2006). The current version APACHE®IV is a registered trademark of Cerner Corporation, Kansas City, Missouri, and is available for use without restrictions. The APACHE®IV score provides prognostic data for predicting the length of stay and mortality rates of critically ill patients (Cho, Wang, & Lee, 1995; Gardner & Sibthorpe, 2002; Zimmerman et al., 2006). APACHE® IV calculators are available as a free download from the World Wide Web (ICU_Medicus, 2004). The APACHE®IV scoring system uses 49 items to calculate a single score ranging from 0 to 71 where in higher numbers indicate greater illness and risk of mortality. The APACHE®IV score, which was derived from observational data collected on 110,558 subjects (66,270 in the training set and 44,288 in the validation set) and was based on the prior model (APACHEIII) with new discriminator variables added into the model (Zimmerman et al., 2006). The predicted mean mortality rate with APACHE®IV (13.55%) was similar to the observed (13.51%) mean (standardized mortality ratio = .997, p=.76; chi-square = .002, p=.92). Data for the 49 items is part of the routine NCCU data set.

Data were abstracted from the subject's electronic health record by the primary investigator and the APACHE®IV score was calculated using the electronic media described above. The mean APACHE®IV score for each group was used to explore illness severity as a potential covariate.

Procedures

Institutional Review Board (IRB) approval was obtained from the University of North Carolina, Chapel Hill, NC and Duke University Hospital, Durham, NC. The family members of patients eligible for inclusion in the study were asked for consent within 24 hours of the patient's admission to the NCCU. The NCCU charge nurse determined whether patients met initial eligibility criteria. For patients who met requirements for participation in the study, the charge nurse or care nurse asked the family for permission to contact the principal investigator, who then spoke with the next of kin to obtain informed consent.

Family members of patients were informed that the BIS monitor is a tool that has been recently developed for use in the ICU and may provide helpful information about the patient's responsiveness to sedation. Family members were informed that this is a randomized trial and the nurses will only be able to observe the BIS values from those patients randomized to the intervention group. Additionally, family members were told that they may continue to visit and interact with the patient as they normally would and that this study does not alter the current NCCU visiting policy. To protect the study from a potential Hawthorne effect, nurses were informed that the study is exploring the relationship of Ramsay and GCS with and without BIS monitoring.

Prior to enrolling the first subject, and throughout the study, nurses were provided with education about sedation assessment with Ramsay and with BIS. Nurses were given an

education sheet (Appendix A) and individual instruction. This sheet was also placed on the door of each subject enrolled in the study and a copy remained at the nursing station. Throughout the study, the investigator continued to meet with nurses who were caring for subjects (these were not scheduled meetings and occurred when it was convenient for both parties). Nurses were provided with the investigator's cell phone number and additional education was provided on request.

Following consent, patients were randomized, using a random number table, to the Ramsay only or Ramsay and BIS group. The study period began at 8:00 a.m. on the morning following informed consent. Patients in both groups received BIS monitoring; however, nurses caring for patients in the control group were blinded to BIS values by blacking-out the LCD display on the monitor. Nurses adjusted sedation using assessment with either BIS and Ramsay (BIS augmentation) or Ramsay alone, as determined by the patient's randomization.

The hospital policy on sedation assessment continued to be applied to all subjects; all subjects continued to receive the standard-of-care. In addition, some subjects received the standard of care and also received BIS monitoring. Following the hospital policy, nurses performed a sedation assessment with Ramsay at least once every 2 hours. Nurses who cared for subjects in the BIS-augmentation group were instructed to observe the BIS trend, which is displayed in 1-hour increments (Figure 7. pg 61). Sedation was adjusted to maintain adequate sedation and avoid oversedation. A Ramsay score of 4 was the sedation goal for all subjects in the study, in addition to the Ramsay, a BIS value of 60-70 was the sedation goal used to provide conscious sedation for subjects randomized to the BIS augmentation group. The investigator downloaded BIS data at the completion of the study.

Except for BIS data, all variables were documented on the electronic patient record and password protected. Chart abstraction of this information was completed within 48-hours of the subject being discharged from the NCCU. Chart abstraction was performed in the nursing workroom, a private area.

The possibility existed that nurses may have changed their practice over the course of the study. That is, nurses may have begun "testing themselves" against the BIS by comparing observational data with BIS scores. While this may serve to hone the skills of the nurse in adjusting medication rates and is a positive effect of incorporating BIS monitoring, it may decrease the measured differences in propofol infusion between the control and intervention groups over time. Data collection was planned to occur over a short time frame to marginalize this potential maturational effect. An interim analysis was performed after 6 months of data collection; the results of this analysis are present in chapter V. Testing for cohort effects included post-hoc testing for a decrease in the overall mean infusion rates over the study.

Nurses develop patterns, routines, and schemas when caring for patients. It was impossible to keep nurses from talking to each other including talking about different techniques to monitor sedation. However, several studies that incorporated BIS had been conducted in this unit and there was no evidence that a Hawthorne effect had been present (Olson, Cheek, & Morgenlander, 2004; Olson et al., 2003). Equipoise is a state of uncertainty as to which treatment is superior (Freedman, 1987). To both preserve clinical equipoise and diminish threat of a Hawthorne effect, nurses were informed that the principal aim of the study was an examination of BIS and Ramsay across differing GCS scores, and they were not informed of the specific research questions.

Intervention Fidelity

Santacroce, Maccarelli and Grey (2004) define intervention fidelity as "the adherent and competent delivery of an intervention by the interventionist as set forth in the research plan." For this study, the research plan indicated that the nurse/interventionist should adjust the sedative medication to achieve the effect of a Ramsay score equal to 4, and a BIS value between 60 and 70. Further, as defined by patient randomization, the nurse should use either only observational data (Ramsay scale and observable patient cues) or a combination of observational data and physiologic data (Ramsay scale, observable patient cues and BIS monitoring) when adjusting the sedative infusion rate. In this study, adherence to the intervention was promoted through education, and researcher availability. An exploratory analysis of Ramsay scores and BIS scores provided information about the degree to which nurses in the study adhered to the intervention.

The difficulty in promoting intervention fidelity in the NCCU and assessing the degree to which an individual nurse, or group of nurses has adhered to the intervention is caused in part by how nurses provide care in the clinical setting. Nurses in the NCCU have a great deal of autonomy. The nurses in the NCCU were provided with written education on the use of the Ramsay scale, and the use of the BIS scale following informed consent. The NCCU has a nursing turnover rate of approximately 60% per year. Throughout the study the investigator was available to provide education to nurses new to the NCCU. Additionally, each RN who participated in the study was provided with an education update on BIS and Ramsay. An information packet on this study included information on the Ramsay scale and the BIS monitor and was kept at the 4200 nursing station to facilitate fidelity (Santacroce, Maccarelli, & Grey, 2004). Members of the research team were available in the NCCU at

least daily, and nurses were encouraged to ask questions of the research team throughout the study.

One method of assessing intervention fidelity is to check for adherence to specific treatment elements (Santacroce, Maccarelli, & Grey, 2004). It is the case in this study that the prescribed Ramsay scores and the prescribed BIS values are treatment elements that may be most easily assessed. Individual patient scores were evaluated for adherence to the prescribed level of sedation. The percent of time during which the patient was documented at the prescribed sedation level was compared in both groups.

Equation 2.

Formula for calculating the percent of time at goal sedation.

$$\%time = \left(\frac{prescribedtime}{total\,\min utes} \right) x100$$

Where: % time at sedation = ((minutes at prescribed) / (total minutes)) x 100

Data Management and Analysis

Data Preparation

Three types of data were analyzed: physiologic data (BIS scores), chart abstraction data (patient demographic data), and observational data (Ramsay Scores, GCS, sedative use, and undersedation events).

The physiologic data from BIS was extracted from the BIS-X monitor (Aspect Medical, Newton, MA) and imported into a single Excel data file for cleaning. The Data were stored as delimited text files that were translated to Microsoft Excel[tm] as a single database using MySQL v5.0 software (Sweden). The single Excel spreadsheet was converted

to SAS v9.1 (Cary, NC) using DBSMCOPY® software. Data cleaning involved removing fields not required for this analysis and deleting scores with excessive EMG artifact (values associated with EMG >40 dB), poor signal quality (values with a SQI < 50), and fields associated with missing data (for example, when the BIS sensor was not connected to the patient). All physiologic data were exported into a statistical program (SAS version 9.1, SAS Institute, Cary, NC). Each 1-minute average of BIS was scored and coded as either less than sedation target (1), at sedation target (2), or greater than sedation target (3). This data was used in examining intervention fidelity as described above.

Descriptive data collected from patients was entered by the primary investigator or research assistant and then verified by the research assistant/primary investigator. Additional consultation for data preparation was obtained from the statistician. All descriptive data was entered into a single msExcel spreadsheet and converted to SAS v9.1 using the DBMSCOPY software. Nominal data were coded numerically to facilitate analysis (e.g. male = 0, female = 1, Caucasian = 0, etc.). Age, recovery time, and APACHE®IV data, which were already numerical, required no further preparation. The admission GCS included 3 components (eye, motor, and verbal), each with a corresponding score. Each of these scores was entered separately into msExcel spreadsheet and the admission GCS was calculated by adding these three scores together; only the combined score (admission GCS) was converted to SAS for data analysis.

Observational data included Ramsay scores, sedative use, and undersedation events and each of these variables were treated separately during data preparation. All of the observational data, including Ramsay, sedative use, and undersedation events, were entered into a separate Excel spreadsheet for each subject. Individual spreadsheets were then copied

and pasted into a single Excel spreadsheet which was converted to a SAS dataset using DBMSCOPY software. The mean Ramsay score for each subject was calculated as the sum of all Ramsay observations divided by the number of observations (hence if only one observation was recorded for the subject, that observation would represent the entire data for the subject). The total volume of sedation infused was calculated by adding the total volumes for each hour. This method was preferred because there were occasions (rare) when the nurse did not record the total volume for a given hour, rather the next hour represented two-hours worth of volume. An example of this would be the nurse who accompanies a patient to radiology and does not have the opportunity to chart data into the electronic health record until after returning from the transport. There were zero undersedation events during the study.

Data Management

All data collected as part of the study were kept on a personal protected laptop computer dedicated for this research project. Two passwords were required in order to access information. The initial password was used to activate the computer, and a different password was required to open any files containing protected health information.

Data Analysis Plan

Descriptive statistics on patient age, sex and ethnicity were used to describe the sample. Descriptive statistics included testing of the range, mean, and standard deviation for age; the percentage of male to female patients, and a percentage report for each ethnicity. Simple descriptive statistics (mean, standard deviation, and frequency histograms) were reported for sedative use, recovery time, Ramsay scores, BIS values, GCS admission scores, and APAHCE®IV scores.

Each of the research questions were answered separately using SAS version 9.1. The primary independent variable was the method of sedation assessment and was determined by group assignment (Ramsay alone or BIS-augmentation).

Research question 1 asks if there is less sedation drug use for patients in the BIS augmentation group versus the group in which sedation assessment is with Ramsay alone. This question was answered using two-way ANCOVA to explore for a difference in mean drug volume infused in the Ramsay-alone and BIS-augmentation groups. The potential covariates: injury severity, determined by Glasgow Coma Score, and illness severity, determined by APACHE® IV, scores were examined separately.

Research question 2 examines the length of time to recover from sedation in the two groups. To answer this question, ANOVA was used to compare the variance estimates to determine if there were differences in recovery time for the BIS augmentation and Ramsay alone groups.

The third research question explores for a difference in the number of undersedation events that occur in each group during the study period. There were zero occurrences of undersedation in either group. Analysis of research question 3 was not done.

CHAPTER IV

INTERIM ANALYSIS PROPOSAL

The following was the interim analysis plan for the "Combining Observational and Physiologic Sedation Assessment Tools" (COST) study. The original design of the COST study stipulated a sample size of 90 subjects. It was estimated that data collection would last approximately 6 months. At the 6-month mark subject enrollment was over 50% complete. An interim data analysis was performed to explore if the data were sufficient to answer the primary research question. The following interim analysis plan was proposed as a means of assessing the reasonability of continuing to enroll subjects. Included in this proposal were specific justifications for an interim analysis including a growing threat of historical bias, and an understanding that the original power was purposely conservative, which may result in requiring fewer subjects to provide sufficient evidence to reject the null hypothesis.

Purpose of the Study

The primary purpose of the COST study was to examine the effect of combining a physiologic measure of consciousness (BIS) with an observational sedation assessment tool (the Ramsay Scale) on the amount of sedation drug infused. Additional purposes were to explore the impact of this combination on undersedation events, and the recovery time to arouse from sedation, in a group of neurocritically ill patients. The study randomized subjects to one of two groups (Ramsay alone and BIS augmentation) for a 12-hour data collection period. During the study, subjects received sedation assessment and management with either the current standard of care (sedation assessment with the Ramsay Scale), or the standard of

care plus the addition of physiologic data from BIS monitoring (BIS augmentation of the Ramsay Scale).

Justification for an interim data analysis

The interim data analysis was deemed to be reasonable given the conservative estimates used in the original power analysis and the inherent risk of introducing historical bias as data collection continued to progress. The original power analysis was calculated using the most conservative estimates available. There were no data available from which to provide sedation infusion rates during a single nursing shift so the power analysis was performed using data from a study that explored sedation infusion over the course of 1-hour (Olson, Cheek, & Morgenlander, 2004). The sample size of 90 patients (45 per group) was determined based on an effect size of .60, a two-tailed alpha level of .05, and a desired power of .80 where the desire was to decrease the risk of a type II error. The effect size and pooled standard deviation were calculated using the control group mean (21.164 ml) and standard deviation (14.427), as well as the treatment group mean (12.491 ml) and standard deviation (10.769), both were obtained from the prior study (Olson, Cheek and Morgenlander, 2004). This supported an argument that effect size of .68 could be used instead of .60; recalling that the effect size of .60 was selected to err on the side of being conservative. Likewise, the sample size was based on a two-tailed null hypothesis despite the directionality of the primary research question. Altering these two conservative estimators, and keeping a power of .80 reduced the sample size calculation to 52 (Lipsey, 1990).

It is arguable that a historical bias was developing as BIS became more routine. Nurses were working with subjects in both arms of the study, often with patients in the study being in adjoining rooms. Nurse may have begun to recognize that patients do not require the

high rates of sedative infusion that were common prior to introducing BIS into the neurocritical care unit. If this was the case, then the difference in sedation infusion rates would decrease over time because the nurses would have begun to incorporate learned behaviors from BIS when taking care of patients who are not receiving BIS monitoring.

Interim Data Analysis Plan

The interim analysis plan was as follows: Each of the research questions would be answered separately using SAS version 9.1. The primary independent variable was the method of sedation assessment and was determined by group assignment (Ramsay alone or BIS augmentation).

The first research question asks if there is less sedation drug use for patients in the BIS augmentation group versus the group in which sedation assessment is with Ramsay alone. Therefore, the first priority in the interim data analysis was a test of the null hypothesis that there was no difference in sedation infusion rates for the Ramsay alone group versus the BIS augmentation group. This question was answered using two-way ANCOVA to explore for a difference in mean drug volume infused in the Ramsay-alone and BIS-augmentation groups. The proposed alpha level of .05 was partitioned equally for the interim and final analysis. The interim analysis was tested using a significance level of .025 (had the data failed to be sufficient to reject the null hypothesis using this significance level, the final analysis would also have been tested using a significance level of .025). If the results of the interim data analysis had been insufficient to reject the null hypothesis then no further analyses would have been performed prior to completion of enrollment (90 subjects). However, the results of the data analysis supported rejecting the null hypothesis and the remainder of the research questions were explored.

CHAPTER V

RESULTS

Sedation assessment based on combination of information from physiologic and observational tools results in a significant decrease in the amount of propofol infused. For this study the subject's legally authorized representative was approached for informed consent. A total of 55 subjects met inclusion criteria. Informed consent was obtained for 51 subjects, no subjects withdrew from the study. The results are based on data from the 51 subjects who met the inclusion criteria (admitted to the neurocritical care unit, over 18 years of age, endotracheally intubated on mechanical ventilatory support, a Glasgow Coma Score less or equal to 11, and receiving continuous intravenous propofol for sedation). The study was powered to detect a significant difference in mean propofol usage with 90 patients. However, an interim data analysis led to early termination of subject enrollment. The data provided sufficient evidence upon which to draw conclusions about the primary hypothesis, and the planned full enrollment of 90 subjects was not required (see Chapter IV).

Descriptive Statistics for Key Variables

There were 51 patient-subjects enrolled in the study (Table 6). There were 25 subjects randomized to the Ramsay-alone group. There were 26 subjects randomized to the BIS-Augmentation group. The following section will describe data on the key variables (Chapter III, Table 5). Each variable is discussed individually.

Subject Demographics

Although the average subject could be described as 53 year old male Caucasian who weighs roughly 80 Kg, the subjects in this study were reasonably heterogeneous (Table 6). Gender, ethnicity and weight were evenly distributed amongst the two groups. An exploration of the baseline characteristics provides reasonable support these subjects are representative of patients admitted to the NCCU.

Table 6.

Admission demographics for subjects

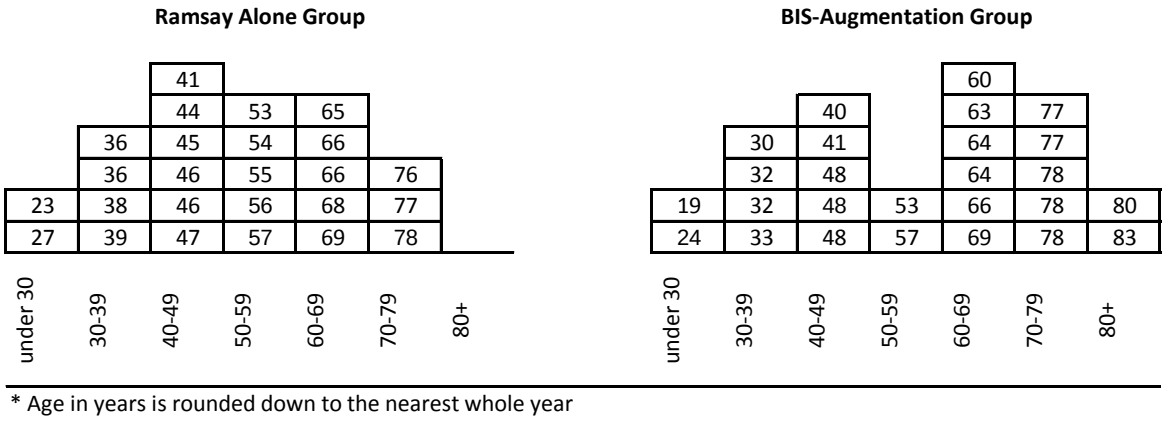
Variable	measure	Ramsay-alone Group N = 25	BIS-Augmentation Group N = 26	t-test of Difference
Age	Mean (SD)	52.32 (15.42)	55.46 (19.52)	n.s.
Weight	Mean (SD)	78.40 (20.42)	82.23 (19.87)	n.s.
Gender	*% female*	40.00%	58.69 %	n.s.
Caucasian	Percent	48 %	50 %	n.s.
African American	Percent	40 %	42.31 %	n.s.
Native American	Percent	8 %	3.85%	n.s.
Pacific Asian	Percent	4 %	-	n.s.
Hispanic	Percent	-	3.85 %	n.s.

n.s. = no significant difference

Age was determined by date of birth and rounded down to the most recent whole year. The distribution of ages was similar for both groups (Figure 10). The mean age and standard deviation for the Ramsay-Alone group (μ=52.32, SD=15.42) was similar to that of the BIS-augmentation group (μ=55.46, SD= 19.52).

Figure 10.

Frequency histograms for age by group assignment.



* Age in years is rounded down to the nearest whole year

The subjects' weights were taken on admission to the NCCU by the admitting nurse. Weights were actual (not stated) weights obtained from the built-in weight scale on the Hillrom SPORT^{tm} beds. The distribution of weights was similar for both groups (Figure 11). The mean age and standard deviation for the Ramsay-alone group (μ=78.40, SD=20.42) was similar to that of the BIS-augmentation group (μ=82.23, SD=19.87).

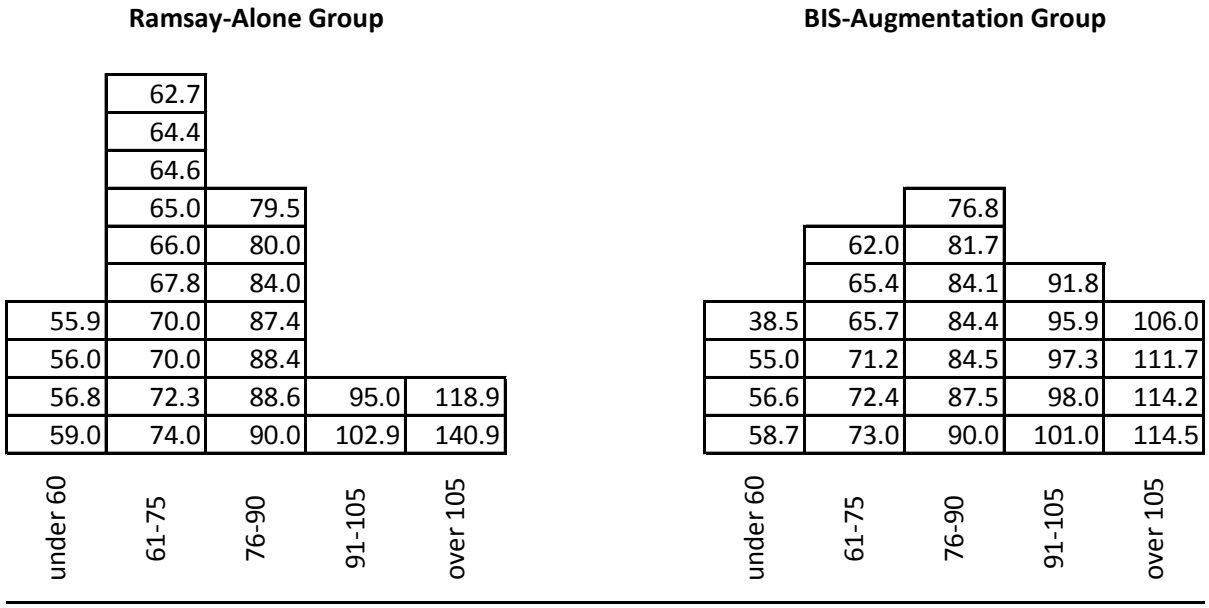
The subjects were fairly evenly distributed by gender and race. The percent of female subjects in the Ramsay alone group (40%) was lower than that of the BIS-augmentation group (58.69%). The two groups also compared favorably by race. The Ramsay-alone group was 48% Caucasian, 40% African-American, 8% Native American, and 4% Pacific Asian. There were no subjects who described themselves as Hispanic or Latino in the Ramsay-alone group. The BIS-augmentation group was 50% Caucasian, 42 % African-American, 4 % Native American, and 4 % Hispanic or Latino. There were no Pacific Asian subjects in the BIS-augmentation group.

The diversity of race represented by this data set is only slightly different than 2006 population statistics for Durham, North Carolina (The U.S. Census Bureau, 2006). The most

recent population statistics for Durham County estimate that 56.2% of the population is Caucasian, 38% is African-American, 11% is Hispanic or Latino, and less than 1% Pacific Asian. Each subjects' legally authorized representative was required to be able to read and understand English in order to provide informed consent and it is likely that this limited the number of Hispanic or Latino subjects. It is also important to note that although the study was conducted in Durham, NC, subjects were recruited from Duke University and it is not uncommon for patients who are not residents of Durham County to be transferred to Duke for in-patient care.

Figure 11.

Frequency histograms for weight by group assignment



Ramsay-Alone Group				
	62.7			
	64.4			
	64.6			
	65.0	79.5		
	66.0	80.0		
	67.8	84.0		
55.9	70.0	87.4		
56.0	70.0	88.4		
56.8	72.3	88.6	95.0	118.9
59.0	74.0	90.0	102.9	140.9
under 60	61-75	76-90	91-105	over 105

BIS-Augmentation Group				
		76.8		
	62.0	81.7		
	65.4	84.1	91.8	
38.5	65.7	84.4	95.9	106.0
55.0	71.2	84.5	97.3	111.7
56.6	72.4	87.5	98.0	114.2
58.7	73.0	90.0	101.0	114.5
under 60	61-75	76-90	91-105	over 105

* All weights are measured in kilograms and rounded to the nearest tenth.

Undersedation Events

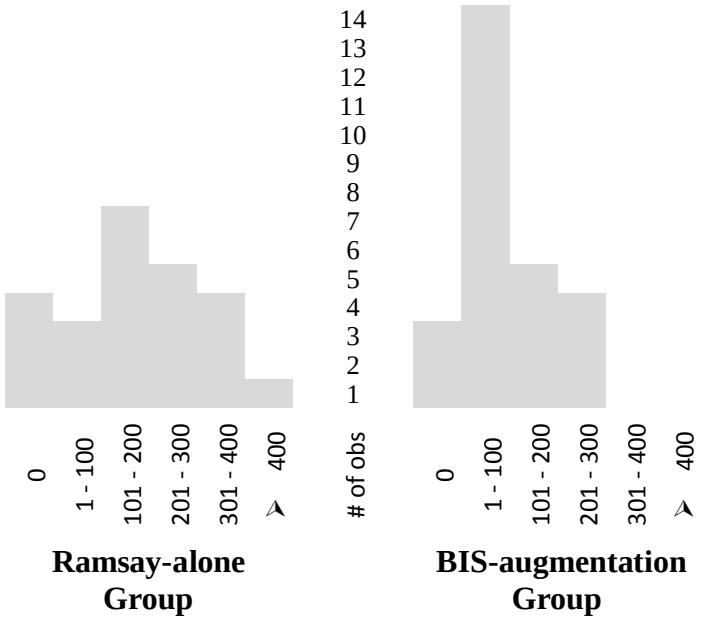
There were no undersedation events recorded on any of the 51 subjects during the study period.

Sedative use

The use of propofol as a sedation agent in the neurocritical care population was explored in both the Ramsay-alone group and in the BIS-augmentation group. Propofol volumes in the Ramsay-alone group followed an approximately normal distribution (Figure 12). The distribution of propofol in the BIS-augmentation is shifted slightly to the left and has a decreased variance. This is not unexpected given the hypothesis that BIS-augmentation of sedation assessment will decrease propofol use.

Figure 12.

Frequency histogram of propofol volumes by group assignment.



The histogram above shows the number of subjects in each group with an observed propofol volume within the range described (measured in milliliters).

Standard descriptive statistics were computed using the proc means function in SAS v9.1 (Table 7). The mean infusion rate for propofol in the Ramsay-alone group was 30.19 mcg/kg/min with a standard deviation of 22.23. The mean infusion rate for propofol in the BIS-augmentation group was 15.35 mcg/kg/min with a standard deviation of 12.80. The 95%

upper and lower confidence intervals were computed for each group and found to be mutually exclusive.

Recovery time

The mean recovery time was measured using a stopwatch. This measurement was recorded at 4:00 p.m. during the study day. To obtain this measure, the care nurse would turn the propofol off and an advanced practice nurse, one of the acute care nurse practitioners (ACNP) who was blinded the BIS and Ramsay scores would determine when the patient was sufficiently awake (recovered from the effects of sedation) that a comprehensive neurologic exam would best represent the patients current non-sedated level of neurologic function. Descriptive statistics on the recovery time are reported in minutes where 1.5 minutes equals 1-minute and 30-seconds (Table 8). Overall, the mean recovery time (4.9 minutes) was noted to have a wide range (28.3 minutes) and a slightly positive skew. There was a significant difference in the Ramsay-alone group recovery time (mean = 9.47 minutes) compared to the BIS-augmentation group recovery time (mean = 1.45 minutes) recovery time ($F = 24.48$, $p < .0001$).

Table 7.

Descriptive statistics for propofol infusion rate (mcg/kg/min) by group assignment.

Group	n	Mean	Median	Standard Deviation	Lower 95% C.I.	Upper 95% C.I.
Ramsay-alone	25	30.1946	27.4741	22.2270	21.0198	39.3694
BIS-augmentation	26	15.3490	13.8892	12.7964	10.1805	20.5177

Table 8.

Descriptive statistics for recovery times.

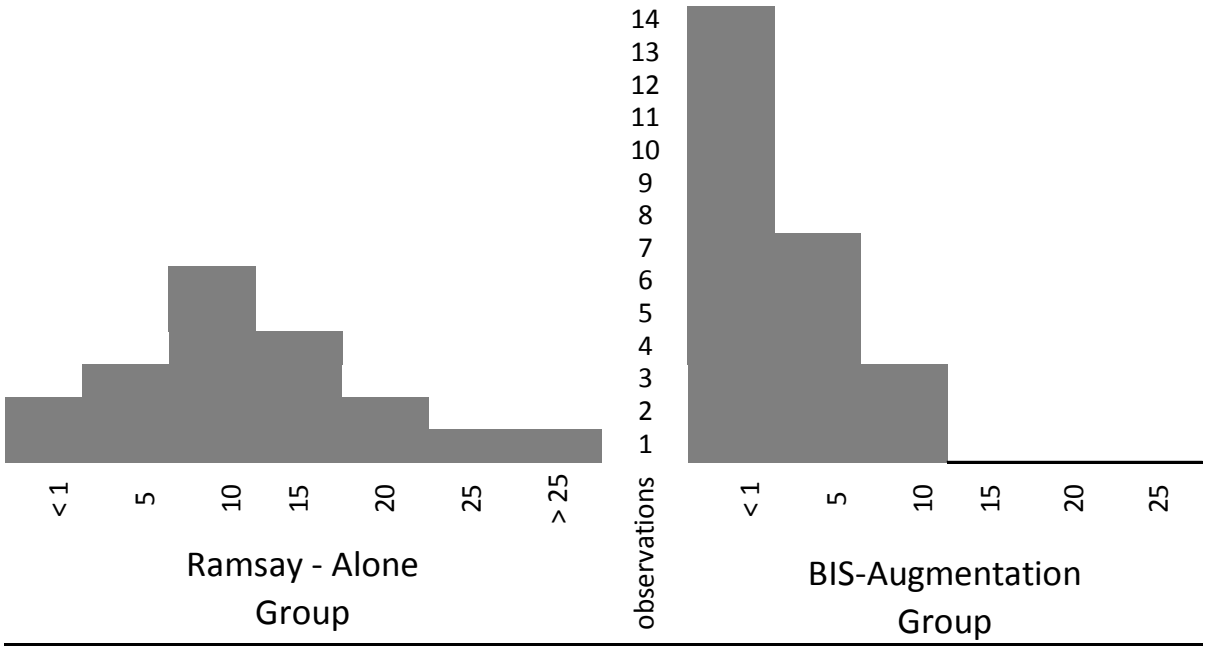
Group	N	Mean	Standard Deviation	Skewness	min / max
Both Groups Combined	43	4.9902	6.5903	1.8276	.01 / 28.3
Ramsay-alone	19	9.4663	7.5742	1.0380	.01 / 28.3
BIS-augmentation	24	1.4467	2.1815	1.5777	.01 / 7.35

* means are reported as minutes and fractions thereof

The recovery times for subjects in the Ramsay-alone group is normally distributed, as would be expected (Figure 13). The left shift and decrease in variance of recovery times in the BIS-augmentation group is not unexpected given the hypothesis that BIS-augmentation will allow nurses to keep subjects at lighter levels of sedation that will allow for more rapid recovery times.

Figure 13.

Frequency histogram of Recovery times by group assignment.



Observational Assessment of Sedation (Ramsay)

The observational assessment of sedation used in the study was the Ramsay scale. Ramsay scale scores were entered by the nurse caring for the patient and abstracted by medical record review. Any assessments of the effect of sedation using the Ramsay scale were made when the sedative was infusing (GCS scores were obtained when the sedative was off). Nurses were instructed to record Ramsay scales according to the hospital policy (at least once every two hours). There were a total of 265 observations of Ramsay that were recorded by the nurses caring for subjects. Ramsay scores were not significantly different for both groups (

Table **9**). The mean for all subjects combined was 4.16. The difference in the Ramsay-alone group mean (4.28) compared to the BIS-augmentation group mean (4.05) was neither statistically significant (p=.2183) nor clinically significant.

Table 9.

Descriptive statistics for Ramsay scores.

Group	N	Mean	Standard Deviation	Skewness	min / max
Both Groups Combined	265	4.1585	1.4660	-.2772	1 / 6
Ramsay-alone	122	4.2787	1.4216	-.5589	1 / 6
BIS-augmentation	143	4.0559	1.5001	-.0585	1 / 6

Physiologic assessment of Sedation (BIS)

The physiologic measure of sedation was the bispectral index (BIS). BIS values were recorded continuously during all times a subject was receiving sedation during the study period. Data from the BIS were downloaded to a USB drive and transferred to a laptop for storage and analysis. There are multiple sources of artifact and noise in the electronic signal and BIS values with a signal quality index (SQI) less than 50 were discarded. Additionally, BIS values with electromyographic (EMG) values greater than 50 were also discarded. In all there were 19,385 samplings of valid BIS values used in the analysis (Table 10). Each BIS sample represents a 1-minute signal-processed average BIS value. When data from both groups were combined, the overall mean BIS value was 50.7398 with a standard deviation of 14.1635. Due to the large sample size, the difference in mean BIS scores for the Ramsay-alone group (51.15) compared to the BIS-augmentation group mean (50.38) is statistically significant. However this difference is likely clinically insignificant.

Table 10.

Descriptive statistics for BIS values.

Group	N	Mean	Standard Deviation	Skewness	min / max
Both Groups Combined	19,385	50.7398	14.1635	.7205	2 / 97
Ramsay-alone	9012	51.1542	13.5583	.4981	20 / 96
BIS-augmentation	10,373	50.3798	14.6601	.8827	2 / 97

Glasgow Coma Scale Scores

The severity of the injury was measured by the admission Glasgow Coma Score (GCS). This study included only subjects who were intubated and on mechanical ventilatory support at the start of the study period, however, not all subjects were intubated at the time of their admission. Descriptive statistics for the GCS scores were explored for the two groups individually and for all subjects combined (Table 11). Overall, the mean admission GCS (8.58) was noted to have a wide range (12) that included all possible GCS scores. There was no significant differences in the Ramsay-alone group GCS scores (mean = 9.24) compared to the BIS-augmentation group GCS scores (mean = 7.92; $F = 3.84$, $p = .0559$).

Table 11.

Descriptive statistics for GCS scores.

Group	N	Mean	Standard Deviation	Skewness	min / max
Both Groups Combined	51	8.5800	2.4502	.1985	3 / 15
Ramsay-alone	25	9.2400	2.1848	.9952	6 / 15
BIS-augmentation	26	7.9200	2.5645	-.0164	3 / 14

*GCS scores on admission to hospital, not at time of consent/enrollment.

APACHE®IV Scores

The Acute Physiology and Chronic Health Evaluation (APACHE®IV) score provides for prognosis of mortality and length of ICU stay. Higher APACHE®IV scores correlate with higher morbidity, or longer lengths of stay, or both. Descriptive statistics for APACHE®IV scores were explored for the two groups individually as well as for the combined data set of all subjects in the study (Table 12). Overall, the APACHE®IV score (67.76) was noted to have a wide range (102). There was a significant difference in the Ramsay-alone group APACHE scores (mean = 61.64) compared to the BIS-augmentation group APACHE scores (mean = 73.88; F = 4.93, p = .0312) indicating that subjects in the BIS-augmentation group had a higher expected length of stay and higher mortality rate.

Table 12.

Descriptive statistics for APACHE-IV scores

Group	N	Mean	Standard Deviation	Skewness	min / max
Both Groups Combined	51	67.7600	20.2591	.7622	29 / 131
Ramsay-alone	25	61.6400	16.0439	.0252	29 / 91
BIS-augmentation	26	73.8800	22.4171	.7551	46 / 131

Research Question Results

The primary research question was tested using an alpha level = .025. As described in chapter IV the decision to perform an interim data analysis was predicated on partitioning the planned original alpha of .05 into two equal parts. As described below, the data were sufficient to reject the null hypothesis (no difference in drug use) with alpha set at .025. The decision was made to accept the alternative hypothesis that there is less sedation drug use for

patients when nurses monitor sedation with BIS augmentation of Ramsay than when nurses monitor patients with Ramsay alone. Following this decision, all other models were explored with alpha set at .05.

Results for the Primary Research Question

The first research question, which asked, "Is there less sedation drug use for patients when nurses monitor sedation with BIS augmentation of Ramsay than when nurses monitor patients with Ramsay alone?" This question was explored using ANOVA and ANCOVA. In the first exploration, ANOVA was used to explore a model constructed only using the total volume of propofol infused (no covariates) over the course of the entire 12-hour shift (Table 13). The difference in the mean propofol volume infused in the BIS-augmentation group (97.51ml, SD=92.71) compared to the Ramsay-alone group (175.36ml, SD=131.72) was found to be statistically significant (F=6.00, p=0.018) and explained 11% of the variance in scores (r^2=0.11).

Propofol is typically prescribed in micrograms per kilogram per minute (mcg/kg/min), therefore a model was constructed to explore the mean rate (mcg/kg/min) of propofol infusion. The difference in the mean rate of propofol infusion in the BIS-Augmentation group (mean = 15.35 mcg/kg/min, SD=12.80) compared to the Ramsay-alone group (mean = 30.19 mcg/kg/min, SD=22.23) was found to be statistically significant (F=8.63, p=0.005, r^2=0.15).

Table 13.

Comparison of mean propofol volume infused and mean propofol infusion rate.

Dependent Variable	BIS-Augmentation Mean	Ramsay-Alone Mean	F	p value	r^2 Value
Propofol Volume	97.51 ml	175.36 ml	6.00	.0180	.11
Propofol Rate	15.35 mcg/kg/min	30.19 mcg/kg/min	8.63	.0050	.15

Examining Covariates for the Primary Research

The first research question included two sub-questions which where explored with ANCOVA. The four-step approach to examining covariates described by Cody and Smith (2006) was used. The first step using this approach is to test the relationship between the primary dependent variable and the hypothesized covariate. Next, a t-test is performed to explore for a difference in the primary dependent variable between the two groups (i.e. BIS-augmentation group and Ramsay-alone group). Third, the general linear model is used with an interaction term to examine if the slopes are different for the primary dependent variable. Finally, the least square means in the general linear model with the covariate is explored to assess for a significant difference in the dependent variable after adjusting for the hypothesized covariate. In this final model, the Type III sum of squares was examined. The covariates were explored individually and jointly (Table 14) which resulted in four new models. Each model is explored individually in a separate paragraph below.

The first sub-question (research question 1.a.) asked, "Does injury severity act as a covariate for sedation drug use in neurocritically ill patients?" For this question, two models were tested in which GCS (a tool for measuring injury severity) was the covariate. To facilitate the reader the first model is a fully illustrated example (Figure 14 - Figure 17). The 4-step approach illustrated in this example was used to examine injury severity (GCS), illness

(APACHE®IV), and the combination of injury illness and injury severity as covariates of total propofol volume (ml) and the propofol rate (mcg/kg/min).

Table 14.

Comparison of mean propofol volume and mean propofol infusion rates with covariates in the model.

Dependent Variable	Covariate	BIS-Augmentation Least Squares Means	Ramsay-Alone Least Squares Means	F observed	p value
Total Propofol Volume (total milliliters)	none	97.51	175.36	6.00	.0180
	GCS	97.28	173.30	5.03	.0297
	APACHE®IV	101.53	169.06	3.99	.0515
Propofol Rate (mcg/kg/min)	none	15.35	30.19	8.63	.0050
	GCS	14.67	30.30	8.45	.0055
	APACHE®IV	15.55	29.42	6.63	.0132

GCS as a covariate of total propofol volume

The first model explored GCS as a covariate of propofol volume using the approach described above. As described above, using the Cody and Smith (2006) approach, Step 1 (Figure 14) answers the question "Does propofol volume correlate with GCS?" An examination of the output from step 1 found that propofol volume is not highly correlated with GCS ($r = .1504$, $p = .2973$).

Figure 14.

Step 1 for exploring covariates using SAS.

SAS PROGRAM

```
PROC CORR data = combomcg;
Var proptotal admitgcs;
run;
```

SAS OUTPUT

```
                                Total drug by volume
                                  GCS as a covariate

                                  The CORR Procedure

                              Pearson Correlation Coefficients
                                 Prob > |r| under H0: Rho=0
                                    Number of Observations

                                            proptotal      AdmitGCS

                           proptotal         1.00000       0.15037
                                                           0.2973
                                                51            50

                           AdmitGCS          0.15037       1.00000
                                              0.2973
                                                50            50
```

Step 2 (Figure 15) is performed using a t-test. This step answers two key questions. First, “Is there a difference in total propofol volume infused for the BIS-augmentation group versus the Ramsay -alone group?” Second, “Is there a difference in GCS for the BIS-augmentation group versus the Ramsay-alone group?” The SAS output shows a significant difference in propofol volume (p=.0180), but no significant difference in GCS (p=.0559) for the two groups (BIS-augmentation group, Ramsay alone group).

Figure 15.

Step 2 for exploring covariates using SAS.

SAS PROGRAM

```
PROC TTEST data = combomcg;
class group;
VAR proptotal admitgcs;
run;
```

SAS OUTPUT

Total drug by volume
GCS as a covariate

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
proptotal	Pooled	Equal	49	2.45	0.0180
AdmitGCS	Pooled	Equal	48	1.96	0.0559

Step 3 (Figure 16) introduces an interaction term to examine the relationship between propofol volume and GCS scores. The SAS output shows no significant difference in the propofol/GCS relationship by group (F = .50, p = .4836).

Figure 16.

Step 3 for exploring covariates using SAS.

SAS PROGRAM

```
PROC GLM data = combomcg;
class group;
model proptotal = group admitgcs group*admitgcs;
run;
```

SAS OUTPUT

Total drug by volume
GCS as a covariate
The GLM Procedure

Dependent Variable: proptotal

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	89611.8967	29870.6322	2.22	0.0983
Error	46	618532.7915	13446.3650		
Corrected Total	49	708144.6882			

R-Square	Coeff Var	Root MSE	proptotal Mean
0.126545	85.70850	115.9585	135.2940

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Group	1	80264.21780	80264.21780	5.97	0.0185
AdmitGCS	1	2641.10299	2641.10299	0.20	0.6597
AdmitGCS*Group	1	6706.57592	6706.57592	0.50	0.4836

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Group	1	103.950065	103.950065	0.01	0.9303
AdmitGCS	1	4064.119068	4064.119068	0.30	0.5851
AdmitGCS*Group	1	6706.575916	6706.575916	0.50	0.4836

Step 4 (Figure 17) is the final step in exploring GCS as a covariate of total propofol volume. This step tests for difference in the least square means using the Type III sums of squares. The SAS output shows that there is still a significant difference in propofol volume for the two groups after adjusting for GCS (F = 5.03, p = .0297).

Figure 17.

Step 4 for exploring covariates using SAS.

SAS PROGRAM

```
PROC GLM data = combomcg;
class group;
model proptotal = group admitgcs;
LSmeans group;
run;
```

SAS OUTPUT

Total drug by volume
GCS as a covariate
The GLM Procedure

Dependent Variable: proptotal

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	82905.3208	41452.6604	3.12	0.0536
Error	47	625239.3674	13302.9653		
Corrected Total	49	708144.6882			

R-Square	Coeff Var	Root MSE	proptotal Mean
0.117074	85.25026	115.3385	135.2940

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Group	1	80264.21780	80264.21780	6.03	0.0178
AdmitGCS	1	2641.10299	2641.10299	0.20	0.6580

Source	DF	Type III SS	Mean Square	F Value	Pr > F
Group	1	66892.93620	66892.93620	5.03	0.0297
AdmitGCS	1	2641.10299	2641.10299	0.20	0.6580

Least Squares Means

Group	proptotal LSMEAN
0	173.304900
1	97.283100

This first model explores injury severity (GCS) as a covariate of the total volume of propofol infused. The results from step 1 demonstrate that propofol volume is not highly

correlated with GCS (r = .1504, p = .2973). The results from step 2 demonstrate a significant difference in propofol volume (p = .0180), but no significant difference in GCS (p = .0559) for the two groups. The results from step 3 indicate that there is not a significant difference in the propofol/GCS relationship when examined by group (F = .50, p = .4836). Finally, shows that although the model with GCS as a covariate remains statistically significant (F = 5.03, p = .0297) the critical value of F is less than the critical value of F for the model without GCS (F = 6.00, p = .0180). Thus, because the potential covariate GCS does not appear to relate to the response variable propofol in this model, and because it does not appear to affect the relationship of Group with propofol, it is not useful as a covariate and should not be used as a covariate.

GCS as a covariate of propofol infusion rate

The second model was constructed to explore GCS as a covariate of the rate (mcg/kg/min) of propofol infused. Step 1 examines the question "Does the propofol infusion rate correlate with GCS?" The infusion rate is not highly correlated with injury severity scores (r = .08952, p = .5364). Next a t-test was performed which provides evidence of a significant difference in the propofol infusion rate, but not in the GCS scores for the two groups. Third, the addition of an interaction term fails to show a significant difference in the relationship between propofol rate and GCS by group (F = .08, p = .7738). Finally, a model with GCS as a covariate of propofol infusion rate remains statistically significant (F = 8.45, p = .0055), but does not increase the power to test for treatment differences when compared to the model without GCS (F = 8.63, p = .0050). Thus, because the potential covariate GCS does not appear to relate to the response variable propofol in this model, and because it does

not appear to affect the relationship of group with propofol, it is not useful as a covariate and should not be used as a covariate.

APACHE®IV as a covariate of total propofol volume

The second sub-question (1.b.) asked, "Is illness severity a covariate for sedation drug use in neurocritically ill patients?" For this question, two models (one for propofol volume and one for propofol rate) were again tested in which APACHE®IV scores (a tool for measuring illness severity) was the covariate. The model exploring APACHE®IV as a covariate of propofol volume was explored first. The first step, examining the correlation between propofol volume and APACHE®IV resulted in no significant correlation (r= -0.26, p=.068). The t-test provided evidence to support a significant difference in both propofol volume (p=.018) and in APACHE®IV (p=.0312). When the interaction term was introduced, there was no difference in the propofol volume/APACHE®IV relationship by group (F=.88, p=.3539). Finally, the model with APACHE®IV and propofol volume was not statistically significant (F = 3.99, p = .0515). Therefore it did not increase the power to test for treatment differences when compared to the model without APACHE®IV (F = 8.63, p = .0050). Thus, because the potential covariate APACHE®IV does not appear to relate to the response variable propofol in this model, and because it does not appear to affect the relationship of group with propofol volume, it is not useful as a covariate and should not be used as a covariate.

APACHE®IV as a covariate of propofol infusion rate

Exploring the second sub-question (1b) using the rate of propofol administration instead of the volume yields similar results. The first step, correlation, found that the propofol infusion rate is not highly correlated with APACHE®IV (r= -0.2410, p=.0918). The

t-test again provides evidence to support a significant difference in propofol rate (p=.0050) and in APACHE®IV (p=.03120). The introduction of an interaction term shows that there is no significant difference in the relationship of propofol infusion rates to APACHE®IV scores by group (F=1.32, p=.2571). The model with APACHE®IV and propofol rate, although statistically significant (F=6.63, p=.0132), does not increase the power to test for treatment differences when compared to the model without APACHE®IV (F=8.63, p=.0050). Thus, because the potential covariate APACHE®IV does not appear to relate to the response variable propofol in this model, and because it does not appear to affect the relationship of Group with propofol infusion rate, it is not useful as a covariate and should not be used as a covariate.

Results for the Second Research Question

The second research question, "Is BIS-augmentation of sedation assessment associated with a decrease time to wake-up (recovery time) when nurses are instructed to interrupt sedation and obtain a neurologic examination, compared to us of Ramsay alone?" was then examined. This question was answered using ANOVA to explore variance estimates to determine if there are significant differences in mean recovery rates between the two groups. The difference in mean recovery time for the BIS-augmentation group (mean = 1.44 minutes, SD = 2.18) compared to the mean recovery time for the Ramsay-Alone group (mean = 9.47 minutes, SD = 7.57) was found to be statistically significant ($F = 24.48$, $p < .0001$).

Results for the Third Research Question

The third research question asked, "Are there differences in the number of events associated with undersedation for patients assigned to the BIS augmentation group compared

to patients assigned to Ramsay alone?" This question was measured by observation and chart review. During the study period there were zero events of undersedation in both groups where undersedation events were defined as unplanned self-extubation, self removal of invasive lines and/or monitoring devices, ventilatory asynchrony, attempts to exit the bed and physical threat to self or staff. With the absolute number of events in both groups equal to zero, there is clear evidence to fail to reject the null hypothesis of no difference.

Planned Post-hoc Analyses

Several additional post-hoc explorations of the data were deemed reasonable. The planned post-hoc analyses were performed to explore intervention fidelity and historical bias. Intervention fidelity was explored as the percent of time at goal Ramsay and the percent of time at goal BIS. It is possible that if BIS scores permit nurses to safely use less sedation then those nurses could develop a tendency to use less sedation even when BIS is not being used (historical bias). To test this assumption, the null hypothesis of no change in mean propofol infusion rates over the 6-months during which data were collected was examined.

Intervention fidelity

Intervention fidelity was first explored in relation to Ramsay documented by the nurses. Ramsay scores were examined for the Ramsay-alone group and for the BIS-augmentation group (Table 15). There were 265 Ramsay scores documented in the 51 subjects. Assessment of Ramsay were made more frequently in the BIS-augmentation group (143 assessments of 26 subjects, or an average of 5.5 times per shift) compared to the Ramsay-alone group (122 assessments of 25 subjects, or an average of 4.9 times per shift). However, a two-tailed t-test of this difference failed to reject the null hypothesis of no difference (t critical =2.01, p=.55). The mean value of Ramsay assigned to subjects in each

group was also explored. For the Ramsay-alone group, the mean value assigned was 4.28 and for the BIS-augmentation the mean value assigned was 4.06. This difference was neither statistically different (t critical for two-tail = 1.96, p=.22), nor clinically significant (Ramsay is scored as a whole number). Thus nurses caring for subjects in both groups were equally likely to achieve the goal of maintaining a Ramsay score of 4.

Table 15.

Intervention fidelity of Ramsay assessments.

Group	n	Total assessment document	Documentations per shift	Documented Mean Score
Ramsay-alone	25	122	4.88	4.28
BIS-augmentation	26	143	5.50	4.06

The second step in exploring intervention fidelity was to explore BIS scores. To accomplish this analysis, BIS data were transformed such that BIS values less than 60 were scored as 'target=1' (lower than goal), BIS values between 60 and 70 were scored as 'target=2' (at goal), and BIS values over 70 were scored as 'target=3' (greater than goal). Clean BIS data was defined by the investigator as BIS values associated with less than 50 decibels of EMG and a signal quality index greater than 50. Of the 26 subjects in the BIS-augmentation group, there were clean BIS data (data obtained from the BIS monitor that was neither corrupt, nor had excessive artifact) for 21 subjects. In this group, there were 7824 minutes of clean BIS data. There were 910 minutes during which the BIS value was recorded as being between 60 and 70. This translates into a mean of 43.33 minutes for each subject.

Propofol rate change over time

An examination of change in mean propofol infusion rates over the 7-month course of data collection was also a planned post-hoc analysis. This was explored modeling the mean propofol infusion rates for the entire set (both groups), for the Ramsay-alone group, and for the BIS-augmentation group over time and testing the null hypothesis that the slope was equal to zero. When all subjects from both groups were combined, the intercept was 19.67 and the slope (.1138) was not significantly different from zero ($p = .5423$). When only subjects randomized to the Ramsay-alone group were used in the model, the intercept was 25.79 and the slope (.1879) was not significantly different from zero ($p = .5137$). When only subjects randomized to the BIS-augmentation group were included in the model, the intercept was 9.07 and again, the slope (.1918) was not significantly different from zero. Given the available data, there was no significant change in propofol infusion rates over time.

Un-planned Post-hoc Analysis

Under consideration is the hypothesis that subjects may have been preferentially weaned from mechanical ventilation during the study. All subjects began the study with the requirement that they be on mechanical ventilatory support and require continuous intravenous sedation with propofol. The decision to extubate was made by the medical team without input from the study investigators. Of the 51 subjects, 6 were successfully extubated during the 12-hour shift being studied here. Of these, 3 were subjects in the Ramsay-alone group, and 3 were subjects in the BIS-augmentation group. Given that 3 of 26 subjects in the BIS-augmentation group and 3 of 25 subjects in the Ramsay-alone group were extubated, a formal statistical analysis was not performed. There is inadequate data to support rejecting the null hypothesis that the extubation rates are equal.

CHAPTER VI

DISCUSSION

This final chapter discusses the interpretations of the results presented in chapter V. The results are discussed as they relate to the reality of the clinical setting. Particular attention is focused on providing theoretical alternative explanations for the results and examining models that support further research in the realm of nurse-driven conscious sedation.

Major findings

BIS-augmentation of sedation reduces sedative use

The use of BIS-monitoring as an adjunct to sedation assessment resulted in a significant decreased use of sedation. Sedation use outcome data were explored both as propofol volume and the propofol infusion rate. However, despite this positive finding, the models explained only a small percentage of the variance in scores (11% when propofol volume is the dependent variable and 15% when propofol infusion rate is the dependent variable). From the clinical perspective, explaining 11% or 15% of the variance through a single intervention is a reasonable result. Both sedation assessment and the adjustment of sedative based on that assessment is subject to a wide variety of influences. The following section will discuss the results of the first research question, "Is there less sedation drug use for patients when nurses monitor sedation with BIS augmentation of Ramsay than when nurses monitor patients with Ramsay alone?" These results will be discussed within the fuller context of the clinical setting.

The amount of sedative infused was the primary dependent variable. Specifically, the first research question asked if there was less sedation drug used. Herein, amount can be defined as volume and/or as the amount each minute per given unit of weight (which is equivalent to stating the rate). Nurses document propofol in mcg/kg/min, but often discuss propofol as the amount given, (i.e. "I gave him a 3ml bolus of propofol and now he's getting 30 ml an hour). Further, despite the ability of the infusion pump to automatically calculate the rate in mcg/kg/min many nurses often initially set the infusion pump by the volume a patient will receive not by the mcg/kg/min. This demonstrates that while weight is a key variable in drug distribution and it is important to explore how the rate of administration is impacted by BIS-augmentation, it may be important to also understand how BIS-augmentation impacts propofol volume. Therefore, each time propofol use was explored, both volume and rate were explored separately. The amount of propofol use was decreased with BIS-augmentation for both propofol measured as volume and propofol measured as rate.

Injury severity and illness severity are not covariates of sedation use

In randomized studies, the purpose of including a covariate in the model is to examine if the effect of the covariate results in a substantial increase in the amount of variance explained (Munro, 2005). Maxwell and Delaney (2004) write that if the covariate is significant, then including the covariate in the model will provide a greater power of detecting a difference between two randomized groups (if there is indeed a difference). This study examined both injury severity scores and illness severity scores as potential covariates. Neither when sedation was explored as volume, nor when sedation was explored as the rate of infusion did either potential covariate relate to the amount of propofol nor did they affect the relationship between the group (Ramsay-alone and BIS-augmentation) and propofol.

Given the available data, neither the subject's severity of injury nor their severity of illness are useful as covariates.

BIS-augmentation is associated with a more rapid emergence from sedation

The second research question explored the length of time required to recover from sedation and found that BIS-augmented sedation is associated with a significantly shortened period of time. Subjects in the Ramsay-alone group experienced longer periods of time from the moment that sedation was stopped until the moment that they were judged to be free of the effect of sedation compared to subjects in the BIS-augmentation group. Clinically, this makes sense because most sedation has a dose-dependent response. In other words, the more drug a subject receives, the greater the effect of that drug. The more sedation a subject receives, the longer the subject will remain sedated (Burchardi, 2004; Cortinez et al., 2004; Hogarth & Hall, 2004). Given that subjects in the BIS-augmentation group received less sedation than subjects in the Ramsay-along group it is not unreasonable to expect that they would awaken more rapidly once the sedation was stopped.

BIS-augmentation does not impact undersedation events

A statistical analysis of the data for the third research question was not required. The logic supporting this question was that BIS-augmentation would decrease sedative use. The decreased sedative use would result in patients being kept at a lighter level of sedation and the lighter levels of sedation would result in subjects being awake more often. In turn, if subjects were awake more often, they would experience more instances of undersedation. This, in fact, was not the case. There were zero undersedation events in each group. Therefore, BIS-augmentation of sedation is not associated with a change in the number of undersedation events.

Intervention Fidelity

Despite the positive findings, the study had only limited intervention fidelity. Nurses taking care of patients who were subjects in the study were instructed to document Ramsay scores at least once every 2 hours for all subjects in the study (both Ramsay-alone, and BIS-augmentation group), and, for subjects in the BIS-augmentation group, to adjust the sedation to maintain a BIS value between 60 and 70. Nurses documented 265 of the 306 (87%) of the Ramsay scores that would have been expected (51 subjects with 6 Ramsay assessments per shift) if nurses did document once every 2 hours. This represents that nurses were able to perform the Ramsay assessments.

The nurses were able to maintain sedation at a goal BIS between 60 and 70 for an average of only 43 minutes per subject. This is especially interesting given that the intervention was successful in reducing sedation drug use. There are no studies to suggest that the ideal range for BIS is 10-points (60-70), and this target may have been too narrow. It is not known if the nurses observed subjects near the goal BIS and made a decision based on that information. For example, if a subject had a BIS value of 59, the nurse may have felt that to be "close enough" yet the subject would still be scored as "not at goal." A more complete exploration of BIS values and intervention fidelity is found later in this chapter during the discussion of clinical implications.

Limitations

The best model explains only 15% of the variance in the amount of sedation used. The interpretation of the results from this study are limited by the wide array of variables that are either known to influence, or hypothetically influence sedation assessment in the clinical practice arena. Specific limitations include: use of the Ramsay scale, individual nursing

characteristics, shift variability, differences in sedation agents, as well as the unit design and staffing plan will be discussed in this section.

The Ramsay scale was the primary observational assessment tool used in this study, but it is not a validated sedation assessment tool. The decision to use the Ramsay scale stems from the fact that this study explored current sedation practice in the NCCU, and at the time of the study, the Ramsay scale was the only scale used. However, in the time since the study was proposed, in a study of 241 nurses, Olson, Lynn, Thoyre and Graffagnino (2007) found that the Ramsay scale was not reliable for scoring sedation. Thus, despite earlier studies (Ely et al., 2003; Haberthur, Lehmann, & Ritz, 1996; Schulte-Tamburen et al., 1999) that reported adequate reliability of the Ramsay scale, the Ramsay scale is not a reliable tool for assessing sedation. Therefore, it could be argued that this study should have been completed with a more recently validated sedation assessment tool such as the Richmond Agitation-Sedation Scale (Sessler et al., 2002). The counter to this position is that the introduction of a new sedation assessment scale along with the introduction of BIS is no longer a test of the effect of BIS-augmentation versus current practice, but rather a test of the effect of two new tools (BIS and the new scale) versus one new tool (the new scale). Given the results of this current study, future studies with more validated tools are warranted.

Every subject in the study was cared for by a nurse working in the NCCU, but not all provide identical care. It is a limitation of this study that there was not a test of which nurse cared for which subject, nor if any one nurse cared for more than one subject. It is reasonable to expect that there are variables that can be attributed to the nurse that contribute to the variance in sedation practice. This study was designed to explore how BIS-augmentation affected current practice, it was therefore not desirable to have only one nurse care for all 51

subjects in the study. Although a full list of such variables is not present in current literature, a 2001 (Weinert, Chlan, & Gross) study found that social, personal and professional factors attributed to nurses and physicians influence sedation delivery. Therefore a more reasonable approach is to gather pilot data from which specific hypotheses about specific nursing characteristics could be tested. For the purposes of this study, there were no controls placed on which nurses cared for which subjects, and the charge nurse (who is responsible for making care assignments) was blinded to the dependent variable. Each subject had an equal likelihood of being cared for by a nurse who was either more or less likely to use additional sedation based on the attributes of the nurse.

Another limitation of this study is that all of the data were collected during the day shift and nursing care is provided 24-hours a day. Although limiting data collection to a single shift increases the internal validity of the study, it leaves several questions unanswered. It remains unknown whether sedation assessments would have been different on the night shift. It is also unknown whether patients require more or less sedation at night than they do during the day time; which may be influenced by light and sound stimuli that results from the increased activity of visitors and staff that is an inherent component of the day shift in an ICU (Gabor et al., 2003; Gelling, 1999). As discussed in the section on unit of analysis, a 24-hour study period provides both advantages and disadvantages. The primary advantage is the increased external validity. The primary disadvantage is the need to increase sample size and account for repeated measures wherein each shift represents a measure and not all subjects would contribute 2 shifts (some subjects would be moved out of the NCCU during the 24-hour period).

The decision to use propofol (and not all sedative medications) as the dependent variable is, like other decisions, a decision to balance internal and external validity. The assumption supporting this decision was that propofol would remain the primary sedative agent used in the NCCU at the time of the study. The assumption was supported, however, a newer sedative agent (dexmedetomidine) is increasingly being used in the NCCU. Dexmedetomidine (precedex) is a centrally acting selective alpha receptor agonist with a relatively high ratio of [alpha]^{2}/[alpha]1-activity (Hsu et al., 2004). The mechanism of action for dexmedetomidine is believed to be a pathway that leads to inhibition histamine release which in turn inhibits arousal in the cortex and forebrain (Cortinez et al., 2004). Because the mechanism of action and the neuronal pathways that are affected by dexmedetomidine are different from those of propofol, it remains unclear whether sedation assessment with BIS (which relies on signal from the frontal lobe of the brain) would provide the same or similar information when dexmedetomidine is used as when propofol is used. Future explorations of these differences would add to the body of knowledge regarding sedation assessment.

Not accounting for the unit staffing plan and the physical properties of the NCCU is a limitation of this study that was unrecognized in the study design phase. The physical location of the patient may have an impact on how much sedative they receive, but there is no hard evidence to support this assumption. It is the routine of the NCCU that medical rounds begin in room 16 (one end of the hall) and progress to room 1 (the other end). Thus, if a subject is ready for extubation, that decision (and the decision to stop sedation) will be made several hours earlier if the subject has been admitted to room 16 compared to the same subject being admitted to room 1. Randomization should control for this and provide that any one subject has an equal likelihood of being admitted to any one of the 16 beds. However,

there are staff preferences (such as the propensity to admit subjects into rooms 1 through 8 when more than one bed is empty and available) that may not be accounted for. In addition to when the subject meets the medical rounding team, the subject's distance from the nursing station may play a role in sedative use. To date there are no published studies that explore this variable, however in an unpublished study, Olson and Laskowitz (Olson & Laskowitz, 2007) found that the proximity to the nurses station correlated with the likelihood of observing a patient to be awake.

The staffing ratio and staffing plan were also not accounted for in the study. The ratio of patients to nurses in the NCCU is usually 2:1 or 1:1. If a nurse is singled (assigned to care for one and only one patient) then it is reasonable to assume that the nurse will be able to provide more frequent observations of the patient. There were no data collected regarding whether a subject in the study was being cared for by a nurse who was singled. Most often, the decision to single a nurse is based on the acuity of the patient. The GCS and APACHE®IV scores are markers of injury and illness severity, but they are not an adequate correlate of acuity which includes variables such as family presence and required nursing care activities (Miranda, de Rijk, & Schaufeli, 1996; Pyykko et al., 2004). BIS provides continual data monitoring and alarms may be set to notify the nurse when a subject has a high or low BIS score. Thus, two arguments exist: first, that BIS-augmentation may be more beneficial when the nurse is caring for two patients (because she can delegate some of the responsibility of patient monitoring to technology), second, that BIS-augmentation may be more beneficial to the nurse who is singled and has the time available to observe the BIS values more frequently. It is not possible to conclude from this study how BIS-augmentation contributes differently when the staffing ratio is 2:1 versus 1:1.

Limitations to determining sedative use

Unit of Analysis

Data were abstracted from each subject's electronic patient record as the volume of propofol (ml) infused each hour for 12 consecutive hours during a single 12-hour nursing shift. The unit of analysis was, therefore, a single nursing shift. Several arguments present themselves. First, should the unit of analysis have been shorter or longer? Also, because propofol infusion is most often prescribed as a component of rate (mcg/kg/min) was it appropriate to collect data in ml/shift?

The use of a single nursing shift enhanced the internal validity of the study and is the appropriate unit of analysis for this study. A single nursing shift indicates that one, and only one nurse has the primary responsibility of determining the amount of propofol infused. Equally arguable is the fact that no nurse is likely to function in isolation and it is likely that input was provided by other nurses, physicians, and nurse practitioners who worked the same shift. However, the nurse assigned as the primary care RN would still retain the task and responsibility of making any adjustments.

Recording the volume of propofol infused during the previous hour provides more accurate data than does recording the propofol rate at the top of the hour. Nurses often change the propofol infusion rate, but rarely does this change occur precisely at the top of any given hour. Recording the total volume of propofol infused provides data that includes rate adjustments. For example, at the start of the hour, the rate is 50 mcg/kg/min, and at 45 minutes into the hour the rate is changed to 30 mcg/kg/min, then at 59 minutes into the hour the rate is cut to 20 mcg/kg/min. The value displayed on the electronic record is 20mcg/kg/min, but this does not accurately represent the mean infusion rate.

The unit of analysis was a single (full) 12-hour shift, but represents only one shift, and may not necessarily be reflective of a proportion of the true total amount of propofol infused during the patient's length of stay in the NCCU. Each study period began at 8:00 a.m. and lasted 12-hours. This approach enhanced internal validity, but limits external validity. Subjects were admitted to the NCCU at various times throughout the day and informed consent was obtained from their legally authorized representative. Not all subjects experienced an equal amount of time on propofol prior to the 8:00 a.m. start of the study. However, a t-test of the mean number of hours for which propofol was infusing demonstrates that the mean number of hours for the Ramsay-alone group (17.8 hours) compared to the BIS-augmentation group (17.0 hours) was not significantly different (p=.8515).

Using a smaller unit of analysis would limit the findings. A smaller unit of analysis (1 hour) is not appropriate because it fails to control for patients who are taken off of propofol or extubated precisely because the BIS-augmentation provided additional data that was not available without BIS monitoring. Thus, if only a single hour of data was used, it would likely fail to capture the response to BIS, wherein sedation assessments are not performed when patients are not receiving sedation.

A larger unit of analysis, while appropriate, was beyond the scope of this dissertation. A larger unit of analysis would be useful to explore the total volume of propofol given over the entire course of stay. However, it is not possible to pre-randomize critically ill patients and all patients in the study received some propofol for various lengths of time before the onset of the study period. Therefore, any exploration of this data would require adjusting for the amount of propofol the subject received prior to being enrolled in the study. Additionally, multiple nurses would care for one subject. A study of the sedation use over the total length

of NCCU stay should include variables associated with individual nurses and an analysis plan that examines the effect.

Finally, the unit of analysis was a day-shift; a 12-hour nursing shift that began at 8:00 a.m. and thus explored sedation assessment only when day-shift nurses were caring for subjects. It is assumed that the day-shift is fundamentally different than the night-shift (7:00 p.m. – 7:00 a.m.) in some manner than impacts drug delivery, although this is not yet documented in current literature. Other factors such as the level of unit acuity, family presence, management presence and personal beliefs about sedation requirements during day and nighttime could also vary by shift. The attending physician rounds begin in the morning, and it is the decision of the rounding team (guided by the attending physician) to extubate patients. This dramatically decreases the number of planned-extubation events that occur after 7:00 p.m. This fact alone is sufficient to compromise internal validity if subjects were cared for on both the day and night shift.

Potential covariates

This data set included only 51 subjects and was powered to detect a difference in propofol use; it is not unreasonable to suggest that specific variables do exist that should be used as covariates. Glasgow Coma Scale scores as a marker of injury severity and APACHE®IV scores as a marker of illness severity were not found to be covariates in this sample, however, a larger data set with specific a-priori hypotheses about subsets of injury severity and illness severity might be still be designed to more specifically explore these potential covariates.

Numerous other possible covariates could also have been explored, but were not studied here. Certainly, if multiple shifts were included, nursing shift, or specific attributes of

the nurse (experience level) could be explored as potential covariates. The length of time on mechanical ventilation is linked to the requirement of sedation because of the need to keep the patient free from self-harm (self-extubation) and the desire to prevent the patient from experiencing unpleasant events (being intubated). The decision to extubate is based on multiple factors (MacIntyre, 2004). Often overlooked are the personal and professional attributes of the medical and nursing teams. In many critical care settings, especially university type settings, the attending physician changes from week to week, or even daily. In the NCCU, if the physician is not familiar with the patient there may be a decreased likelihood of extubation. The decision to extubate should be made solely on the basis of the individual's readiness to be weaned from mechanical ventilation, but this is not always the case (Epstein, 2002). Simple factors such as location may also play a role in the decision to extubate and thereby the need for sedation (Couchman, Wetzig, Coyer, & Wheeler, 2007).

Patient location and the physical properties of the ICU may determine when the patient is seen. In the 16-bed NCCU, physician rounds start at one end of the hall and progress sequentially until the last patient is seen. Logic dictates that some patient must be the first and some other, the last. Nurses may preferentially adjust sedation differently if they are likely to participate in rounds early versus late in the day. This decision may be based on other patients that the nurse is caring for, or the influence of family presence in the ICU.

Family presence has been explored by different authors as influencing a variety of outcomes (Doornbos, 1996; Tullmann & Dracup, 2000). The effect of the family and of family presence on sedation practice has not been documented. Kaplow and Hardin (Kaplow & Hardin, 2007) support an environment wherein the family is an integral component of care. This could result in situations that lead nurses towards using either more sedation (e.g.

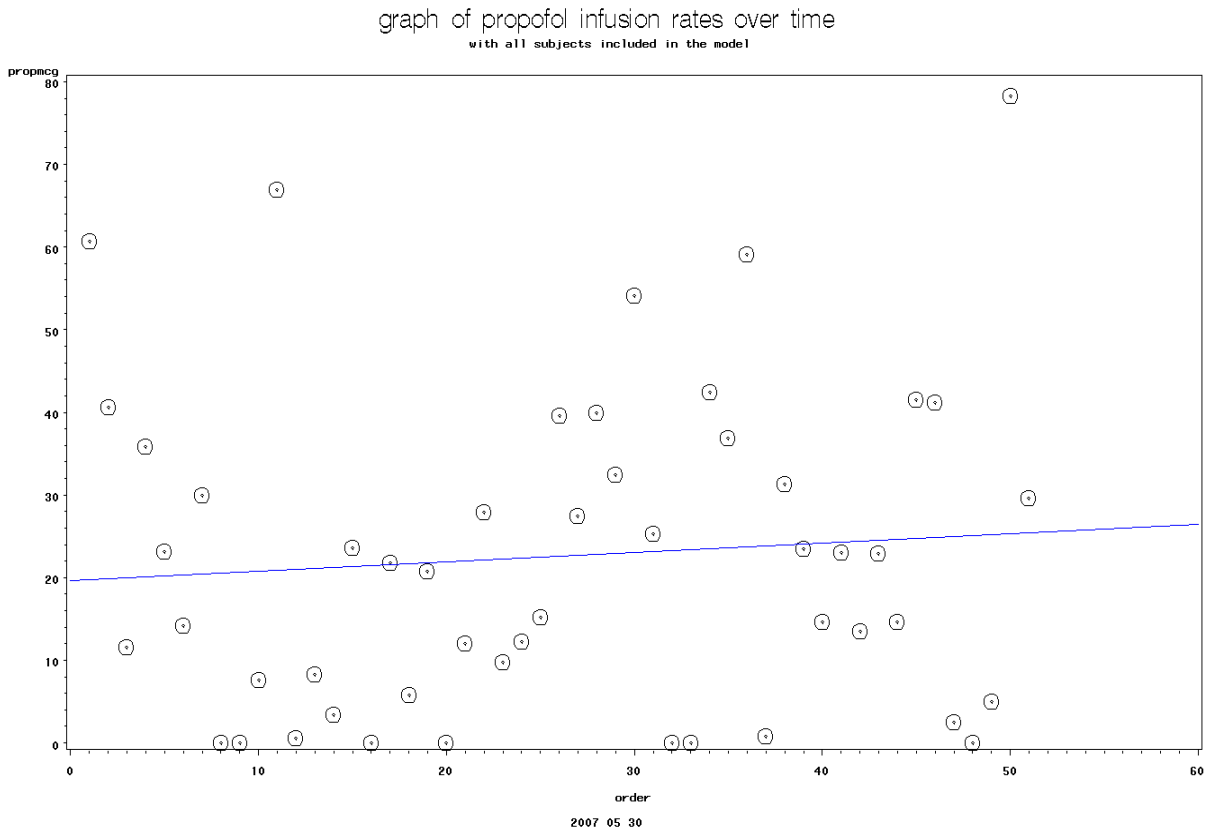
so that patients continue to look peaceful and family members are not disturbed), or less sedation (e.g. because the family presence helps calm the frightened patient who now no longer requires sedation). The effect of family, although not explored in this study could play a significant role in determining sedation use.

Development of a Historical Bias

The presence of a historical bias may have been a limitation to the results. If the amount of sedation being used decreased for both groups over time, then it is possible that the influence of BIS-augmentation extends beyond the patients who were assigned to the BIS-augmentation group. To explore for a historical bias the mean propofol infusion rate (mcg/kg/min) for each subject was plotted using SAS v9.1 for Windows. The question driving this exploration of the data was whether nurses had become so familiar with lower rates of propofol infusion that subjects in both the Ramsay-alone and in the BIS-augmentation group were simultaneously seeing lowered infusion rates compared to historical uses. When data from both groups were included in the model, there was no significant change in propofol infusion rate over time using a general linear model. This examines whether there was a change in the mean propofol rate as nurses were exposed to more patients being in the study. The results (Figure 18) show enrollment along the x-axis where time is used as ordinal-level data. On first glance, the data appear to have a non-linear relationship that possibly demonstrates a change in the effect of augmenting sedation assessments with BIS as more subjects were enrolled in the study. On further examination (Figure 19) this was not the case. The data are insufficient to support a historical bias.

Figure 18.

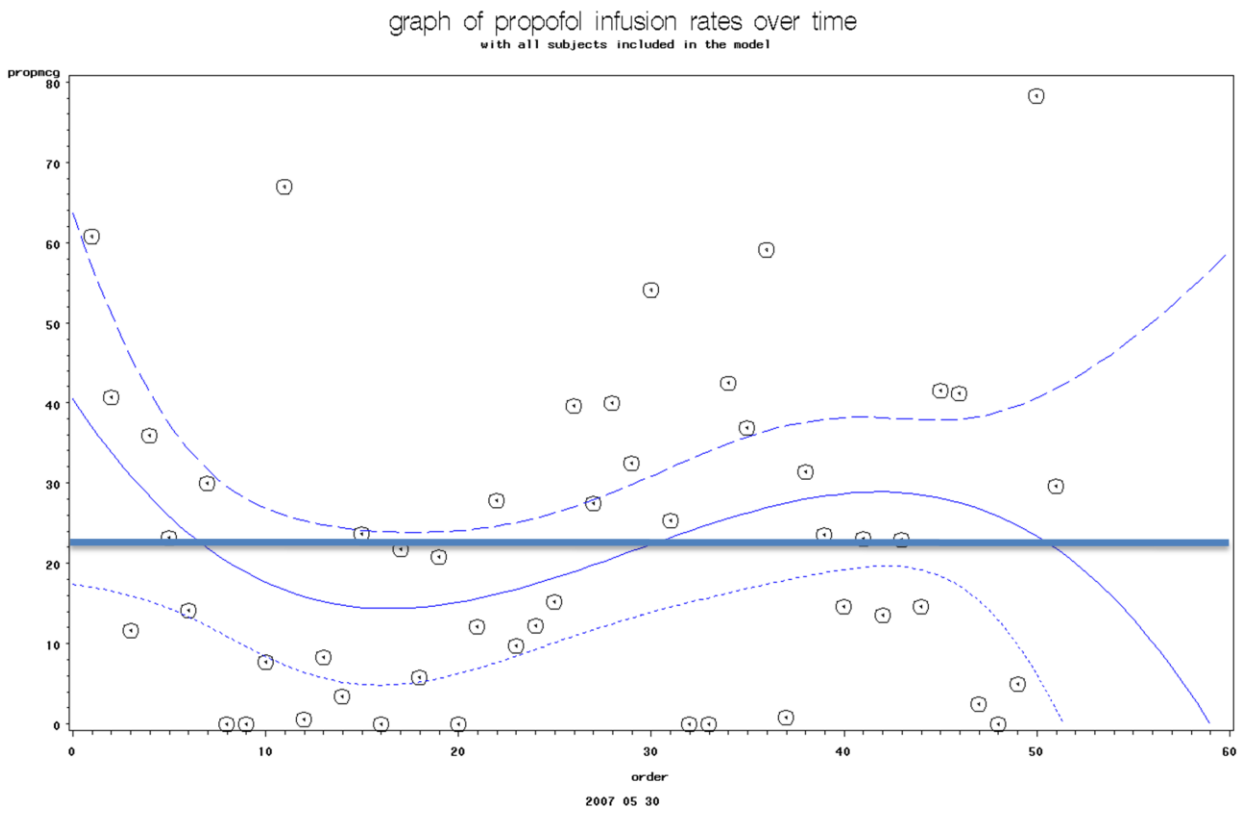
Does enrollment order predict propofol rate?



- Data from all subjects (both groups) are included. The X-axis represents the order in which subjects were enrolled. The Y-axis represents infusion rate in mcg/kg/min.

Figure 19.

Cubic relationship of mean propofol rates over time.



Data from all subjects (both groups) are included. The mean and 95% confidence limits for a cubic regression plot are shown. A line with slope=0 has been added to the figure.

Limitations to measuring recovery time

The second research question explored the recovery time and found that BIS-augmented sedation assessment was associated with shorter recovery times. In this study, the recovery time was evaluated at 4:00 p.m. on the day of the study. The time of the day at which the recovery time measure took place was determined by an advance practice nurse who was not affiliated with the study, but was experienced in caring for and assessing neurocritically ill patients.

Although the recovery time was defined a priori to occur at 4:00 p.m. this may have, in fact, been a limiting factor. The decision to use only one specific time point was made under the assumption that it would increase the internal validity of the study. However, in the NCCU all patients receive a neurological examination at least once every 2 hours (q2h). In order to obtain an accurate exam, the nurse must turn off any sedative medications. Therefore, all patients have a recovery time at least q2h, but this was measured once in this study. The justification for this decision is the logic that earlier exams would not be reflective of the effect of the intervention and all subjects would be available at 4:00 p.m. based on current NCCU routines. This assumption was not entirely correct. Of the 51 subject, 3 were not available at 4:00 p.m. (2 in the Ramsay-alone group, 1 in the BIS-augmentation group); 3 subjects in the Ramsay-alone group did not have a 4:00 p.m. recovery assessment because the nurse felt that the subject was not stable enough for the sedation to be stopped; and 2 subjects (one in each group) did not have a 4:00 p.m. exam because only palliative care was being provided. Thus, the data from only 43 of the original 51 subjects (84%) were included in the analysis of recovery time.

Despite these limitations, the difference in the mean recovery times was significant and appears to be real. Given that there was a fairly even distribution of recovery times in the Ramsay-alone group, the skewed distribution of recovery times in the BIS-augmentation provides additional support for rejecting the null hypothesis (figure 13). In the BIS-augmentation group, there were a total of 14 subjects who roused from sedation in less than 1 minute, 10 of these roused from sedation in less than 30-seconds. The recovery time can not be less than 0, therefore it is not unreasonable that the data be skewed if the intervention was, in fact, successful in reducing recovery time. The goal was a BIS value 60-70, a value that

has been cited as being minimally conscious. It is likely that, because subjects were on less sedation, and were already minimal conscious, it took only a small stimulus to bring them to a wakeful state. Interestingly, a Ramsay value of 4 should have also produced this effect because a Ramsay of 4 is defined as "asleep, but has a brisk response to light glabellar tap or loud auditory stimulus." If in fact, subjects were truly able to be maintained at this state in the Ramsay-alone group, it is likely that they too would have experienced shorter recovery times.

Research Question 3

The third research question asked if there were differences in the rates of undersedation events for the two groups. This question was not explored statistically, however, it bears comment. A fundamental underlying assumption in this study was that patients are chronically oversedated. The risk of decreasing sedation would seem to be that the pendulum is swung too far and the patient experiences episodes of undersedation. While there are no strict definitions or measures of undersedation, convention supports that events such as unplanned self-extubation and ventilatory dysynchrony are indicators that a patient is not adequately sedated.

Understanding the implications of the null and alternative hypotheses is key to interpreting the results of having no events in either research group. If the null hypothesis for this question were "There is no difference in undersedation event for the Ramsay-alone group compared to the BIS-augmentation group" then accepting the null hypothesis would support the use of BIS. There were zero undersedation events during the course of the study. However, it remains inappropriate to wholeheartedly accept the null hypothesis because undersedation events are rare. This study only followed subjects for a single 12-hour shift

and patients are rarely admitted to the NCCU for such a short period of time. It may be that there was not a large enough time frame to see undersedation events come to light. Finally, it is possible that the Hawthorne effect ensured that subjects were more closely monitored. If subjects were monitored more closely than what is normal, that fact alone explains the zero-event rate and the only reasonable conclusion is, "subjects in 12-hour long sedation studies are less likely to experience undersedation events than subjects who are not in 12-hour long sedation studies. No truly meaningful conclusions can be drawn from exploring this research question given the data.

Clinical Implications

This study provides support that the use of BIS monitoring, when combined with current methods of observational assessment, is associated with a decrease in the amount of sedative used to maintain an adequate level of sedation for neurocritically ill patients. The results of the study are most clearly applicable to patients with neurological injuries but may be relevant to other populations. BIS-augmented sedation assessment has been extensively studied as a component of intra-operative care and found to be associated with a decrease in sedative use (Gan et al., 1997; Johansen, 2006; Song, Joshi, & White, 1997). Other authors disagree and find that BIS-augmented sedation is not associated with a decrease in sedative use (De Deyne et al., 1998; Struys et al., 1998). Although there is a large volume of BIS and critical care related studies that have been published, most have focused on how BIS compares to other forms of sedation assessment. In this study, BIS-augmentation of current sedation assessment was associated with a significant decrease in sedative use. Numerous authors have agreed that critically ill patients are chronically oversedated; as such, BIS-use

should be considered as a means of augmenting current sedation assessment in the critical care setting.

Decreasing the amount of sedation is good for the patient

Patients are chronically oversedated and improving sedation assessment will decrease the amount of sedative patients receive. Increased sedation is associated with higher risk of infection, prolonged length of mechanical ventilation, longer hospital stay, increased cost and increased mortality (Anis, Wang, Leon, & Hall, 2002; Ostermann et al., 2000; Rodrigues Junior & do Amaral, 2004; Weinert & Calvin, 2007). There are multiple domains to the patient's response to sedation and the Ramsay scale, which is the current standard of care, and sole method of assessing sedation in many hospitals throughout the world, assesses only one domain; the patient's ability to physically respond to stimulation while being sedated (De Jonghe et al., 2000; Hansen-Flaschen, Cowen, & Polomano, 1994; Olson et al., 2007).

This study evaluated the effect of BIS-augmented sedation assessment on sedation use; the comparison group (Ramsay-alone) used only the standard of care for sedation assessment. In this study, BIS was not designed to replace nor suppress any other forms of sedation assessment. Rather, BIS was to be used as an adjunct to current practice. There are multiple domains involved in sedation assessment. The domains consciousness, agitation, anxiety, sleep and patient-ventilator asynchrony were described by De Jong et al (2005) as paralleling the goals of sedation. The ability to react to stimulus and the response to pain have also been proposed as individual domains of the patient's response to sedation (Burchardi, 2004; Olson et al., 2005; Riker & Fraser, 2002). The domain of tolerance introduces the concept that unique physiologic response may impact the response to sedation and thereby the nurses perception of the patient's needs (De Jonghe et al., 2003). Other

authors have explored concrete physical properties such as respiratory response, alertness and facial tension as individual domains or component of domains (Ambuel, Hamlett, Marx, & Blumer, 1992).

The BIS was designed to evaluate the hypnotic state of anesthetized patients (Johansen, 2006). In this study, BIS-augmentation explained 11% and 15% of the variance in scores. Given the aforementioned wide array of possible domains, it seems reasonable that BIS-augmentation would not explain all of the variance. The results obtained from an exploration of intervention fidelity further support that BIS-augmentation, although it clearly provides additional information, does not fully explain the sedation assessment paradigm.

Intervention Fidelity

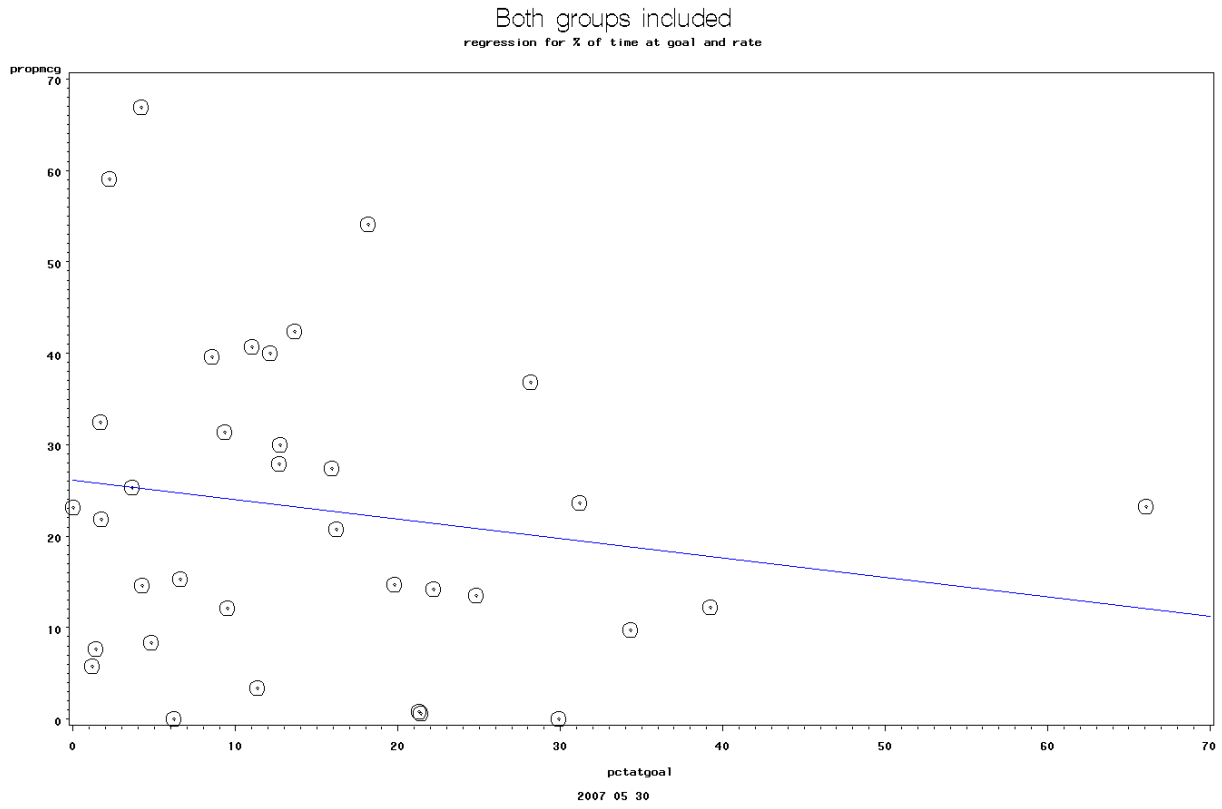
The analysis of intervention fidelity supports that, if the subject was assigned to the BIS-augmentation group, the more the nurse was able to keep the patient at goal BIS, the less sedation was required despite both groups being kept at a Ramsay level of 4. The next several paragraphs will be useful in demonstrating how the combination of group assignment (BIS-augmentation) and the percent of time spent at target BIS goal (60-70) explains a greater percent of the variance in sedation use (26%) than when only group assignment is used. This implies that the addition of BIS monitoring to current sedation practice could have a more profound impact if a mechanism were devised that would improve intervention fidelity. Further evidence of the link between keeping the patient at a goal BIS (between 60 and 70) and a decrease in the amount of sedation can be seen in the (as yet insignificant) trend towards less sedation when the BIS goal is maintained.

There is a general, but not significant, trend noted that the percent of time spent at goal sedation is inversely correlated with sedative use (the goal Ramsay = 4, the goal BIS =

60-70). The sample size and the influence of outliers greatly impacts these data. This is visually represented by a series of scatter plots (SAS v 9.1). In each of the plots, the horizontal (X-axis) represents the percent of time spent at goal sedation and the vertical (Y-axis) represents propofol use. The first of these (Figure20) shows a scatter plot and regression line for all subjects in both groups. The percent of time spent at goal BIS ranged from 0 to 66%. The mean propofol infusion rate ranged from 1 to 68 mcg/kg/min. Despite the clear outlier (a subject in the Ramsay-alone group) there is a developing trend that may signal the presence of an inverse relationship.

Figure 20.

Scatter plot for both groups combined.

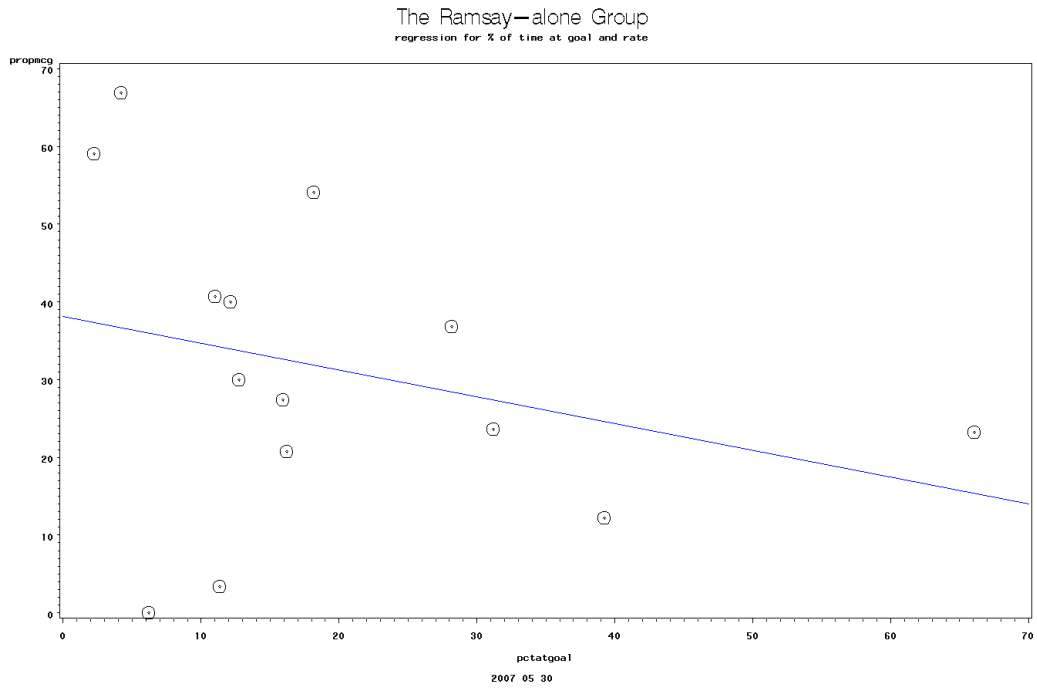


- This plot examines if the percent of time at goal BIS for both groups combined is a predictor of propofol infusion rates. The x axis represents the percent of time BIS values were 60-70. The y axis represents propofol infusion rates in mcg/kg/min.

Two additional figures were produced to further explore the intervention fidelity data (Figure 21 and Figure 22). Each of these figures also use the percent of time at goal as the x-axis. Figure 21 uses only data from subjects randomized to the Ramsay-alone group. Interestingly, despite the nurses being blinded to the BIS score, the percent of time at goal BIS ranged from 2% to 66%, which compares favorably to the BIS-augmentation group (Figure 22) who spent from 0% to 34% of the time at goal BIS. As noted in Figure 21, the small sample size and presence of outliers greatly impacts the ability to draw conclusions from this data.

Figure 21.

Scatter plot for the Ramsay-alone group.



- Using data from only the Ramsay-alone group, this plot examines if the percent of time at goal BIS is a predictor of propofol infusion rates. The x axis represents the percent of time BIS values were 60-70. The y axis represents propofol infusion rates in mcg/kg/min.

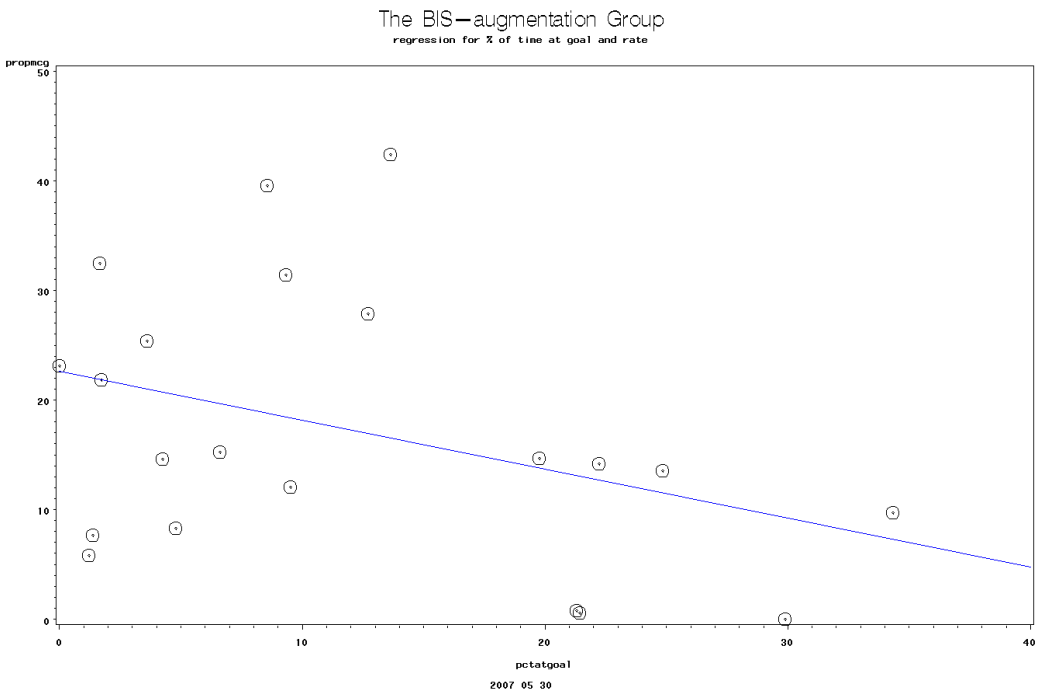
Multiple issues with sampling of BIS data impair the conclusion that can be drawn. Only 35 of the 51 subjects contributed BIS data to this analysis. Reasons for attrition

included hardware issues, staff nurses removing the BIS from the patient, staff nurses turning the BIS monitor off, and subjects with excessive diaphoresis (BIS not adhering). It must be clearly noted that not all BIS values were included in the analysis and not all subjects contributed BIS data. BIS values with high EMG (>50dB) and BIS values with low signal quality (<50dB) were deleted from analysis based on the manufacturer recommendations (Aspect Medical Systems, 2004). BIS data represents the average BIS for the previous 1-minute. The total number of minutes per subject ranged from 0 to 716 (there were 720 possible sampling points in each 12-hour shift). If a subject was extubated, their need for sedation was often eliminated and therefore the BIS would have been discontinued. The percent of time at goal BIS was calculated only using that data obtained during the sedation period.

It is also not known how often the nurses used the BIS in their assessment. Nurses were not asked to document more frequently than what is dictated by hospital policy, which is every 2 hours. Also, nurses do not routinely document every minor assessment (Gillespie & Curzio, 1996). Critical care nurses often perform more than one task at any one given moment in time (e.g. observe the BIS value and suction the patient while teaching the family member why hand-washing is important). It is not always practical to evaluate nursing care by looking at only one event because the events can not be said to be mutually exhaustive (Miranda, de Rijk, & Schaufeli, 1996; Olson, 2004; Pyykko et al., 2004).

Figure 22.

Scatter plot for the BIS-augmentation group.



- Using data only from the BIS-augmentation group, this plot examines if the percent of time at goal BIS is a predictor of propofol infusion rates. The x axis represents the percent of time BIS values were 60-70. The y axis represents propofol infusion rates in mcg/kg/min.

Despite these limitations, the results (Table 16) demonstrate that the percent of time at target combined with group assignment helps to predict propofol infusion rate (F=6.93, <.0001). Furthermore, when the percent of time at target sedation was used, a greater proportion of the variance (26%) was explained than when only group assignment (15%) was used. This is noted in a model which was created to explore how group assignment and intervention fidelity taken together help to predict the propofol infusion rate. This regression model ($\gamma = \beta_0 + \beta_1 + \beta_2 = \epsilon$), and output statement (Table 16) demonstrate that percent of time at target combined with group assignment helps to predict propofol infusion rate (F=6.93, <.0001). This model explains a larger proportion of variance (26%) than does the original model (Table 13).

Table 16.

SAS output modeling for intervention fidelity (two variables).

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	2533.65683	1266.82842	5.52	0.0087
Error	32	7341.81185	229.43162		
Corrected Total	34	9875.46869			

Root MSE	15.14700	R-Square	0.2566
Dependent Mean	22.87827	Adj R-Sq	0.2101
Coeff Var	66.20694		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|	Type I SS	Type II SS
Intercept	1	38.85466	5.60518	6.93	<.0001	18320	11025
pctatgoal	1	-0.38223	0.19735	-1.94	0.0616	285.99486	860.67621
group	1	-17.01862	5.43733	-3.13	0.0037	2247.66198	2247.66198

- Testing whether a combination of group assignment and the percent of time at target BIS helps to predict the propofol infusion rate.

Implications of a shortened recovery time

Subjects in the BIS-augmentation group had a shorter recovery time than did their counterparts in the Ramsay-alone group. The positive implications to this result are primarily theoretical, but clinically relevant. In the NCCU, it is important to awaken patients from sedation for the purpose of obtaining a neurologic exam. A decrease in the amount of time it takes to begin that exam will reduce the negative patient outcomes associated with halting sedation (Olson et al., 2005). The patient who is maintained in a state of conscious sedation receives minimal sedative infusion and will quickly awaken when the sedation is removed (Kost, 1998). The additional implication is that if the patient requires less time to arouse from sedation, then it follows that the nurse will also experience a shortened time for which he/she is required to monitor for emergence from sedation, thus saving nursing time and effort, and freeing the nurse to engage in other tasks.

The decrease in recovery time may also have direct physical benefits that have not yet been fully explored. Specific biochemical markers such as lactate, glutamate and pyruvate, that have been identified as substrates of cerebral metabolic activity have noted to be of prognostic value (Engstrom et al., 2005; Samuelsson et al., 2007; Stahl, Ungerstedt, & Nordstrom, 2001). There is a theoretical link between the worsening in lactate/pyruvate ratios and glutamate levels when sedation is interrupted (Miller & Reves, 2000). The cause of these changes is linked to the side effects and secondary effects of most sedative medications (decreased blood pressure and decreased intracranial pressure). When patients awaken, they experience a sudden increase in cerebral blood flow, cerebral blood volume and intracranial pressure, which may result in increased secondary brain injury (Olson et al., 2005; Soukup et al., 2002). This relates back to the Coma Cue-Response Theoretical Framework, which was introduced in Chapter I of this dissertation as the primary framework (Olson & Graffagnino, 2005). Namely, more optimally timed interventions will reduce secondary brain injury and result in recovery from coma.

BIS-augmentation represents safe practice

The implications of the results from the third research question are simple and straightforward. Despite a theoretical link and several authors who have argued that BIS monitoring is potentially harmful because of the risk of undersedation, there is no evidence to support these assertions (Nasraway et al., 2002; Tonner, Paris, & Scholz, 2006; Vivien et al., 2003). In this study there were zero undersedation events in either group. It must be noted that this study was not powered to detect a difference in undersedation events, and undersedation events are notably rare. However, should these results be replicated in a larger

study, they would support continued use of BIS as an adjunct to current sedation assessment tools.

Future research in BIS-augmented sedation assessment

This study, like most, has generated a new set of questions. As BIS monitoring becomes more ingrained in practice, discovering the limitations of EEG-derived parameters will become as important as uncovering the advantages of incorporating them into daily assessment routines.

BIS and the amount of sedation

The examination of the first research question found that BIS-augmentation does decrease the amount of sedation a patient receives. This study was performed during a single 12-hour shift in a neurocritical care unit and it would be important to extend future studies to include additional shifts and longer periods of time (the entire length of stay in the ICU). Future studies should be designed that explore the question of different patient populations and nurse-patient dyads. Some very specific questions are generated: Do these results hold true for patients with different diagnoses? Is there a difference in the effect of BIS-augmentation for nurses with different levels of education or different attitudes toward sedation? Is there a difference in the effect of adding BIS to sedation assessment for the day and night shift nursing staff? Would the same or similar results be seen with other medications used to induce sedation? In this study, propofol was used to help control for internal validity and future studies should seek to expand the external validity of these results with larger samples and different populations.

Exploring intervention fidelity was difficult and techniques to improving the fidelity and more accurately tracking fidelity are needed. Even when a given subject's BIS score was

with the 60-70 range, there was no means of noting whether the nurse was present in the room, took notice, or took action based on BIS data. There was no mechanism of noting whether the nurse used short 'snapshots' of the BIS value, or whether he/she observed the trended BIS value (both of which are displayed simultaneously on the monitor screen). Measuring intervention fidelity by exploring the percent of time the BIS was within the prescribed range does not capture the full richness of what all the variables were that nurses used to make their decision to alter or not alter the sedation.

Although there was no significant change in amount of propofol used over the course of the study, there were variations noted at different times during the months of data collection that could be seen in the scatter-plot and these should be explored more fully. It is, indeed, quite likely that these observations are completely random, but they may also represent some heretofore unsuspected trend. Just as there is an increase each summer in the number of motorcycle-related injuries, there may be seasonal differences in how patients are cared for. Ultimately, it must be noted that the current study was able to explain only a small, but significant, proportion of the variance in sedation use. Clearly, there are other factors that should and must be examined.

Does reduced recovery time really matter?

The desire to reduce recovery time remains largely theoretical at present and future studies should be aimed towards examining outcomes related to decreasing the recovery time. If a decreased recovery time is associated with a decrease in secondary brain injury, then those factors associated with secondary brain injury should be included in future designs. Research questions exploring the impact of reduced recovery times on ICP, and biochemical markers such as lactate and pyruvate should be developed. To be fully

comprehensive, these models would need to evolve to include how other body systems, which secondarily impact the brain, are also affected. In the example that a sedative like propofol is associated with hypotension, then increased propofol would eventually require that the medical team treat the circulatory system with fluid volume resuscitation, vasopressors, or both. When the propofol is turned off, the patient is at risk for sudden increase in blood pressure as a result of fluid or vasopressor resuscitation efforts (Bader, Arbour, & Palmer, 2005; Bader & Palmer, 2000). Future studies of BIS monitoring and recovery times could be modeled to include these more complex cascades of events, but will require tighter controls, increased intervention fidelity, and quite likely, larger sample sizes.

How does BIS monitoring affect undersedation event rates

In this study, there were no differences in undersedation event rates for the two groups, and future studies should seek to more clearly support or refute these results. For this study, the goal BIS range was 60-70, and although this range has some evidentiary support, there is no consensus on what the perfect BIS score is or should be, nor how great or small the range in BIS scores should be (Johansen, 2006; Leblanc, Dasta, & Kane-Gill, 2006; Olson, Cheek, & Morgenlander, 2004). It has been noted that undersedation events are rare and the method of tracking undersedation events in this study was through examining the medical record for documented evidence. Given that undersedation events are rare, and may not always be documented, future studies should seek to include larger time frames as the unit of analysis (the entire length of stay) and to devise tools to more accurately track and record undersedation events.

Conclusion

BIS-augmented sedation assessment should be considered for the routine use of monitoring and caring for neurocritically ill patients who require sedation. Sedation assessment augmented by BIS monitoring is associated with a decrease in the amount of propofol used to maintain a safe level of sedation. Compared to subjects who were sedated and monitored using only the Ramsay scale, subjects in the BIS-augmentation group experienced significantly shorter recovery times when sedation was interrupted for a neurological examination. There was no difference in the number of undersedation events associated, and therefore BIS monitoring provides a safe adjunct to current sedation assessment. This study provides the strongest evidence to date that BIS-augmented sedation assessment is associated with improved patient outcomes. Physiologic sedation assessment tools with EEG-derived parameters such as BIS should no longer be seen as a remote possibility for replacing nursing judgment but rather they should be incorporated, and studied, as an adjunct and a compliment to observational methods of sedation assessment.

Appendix A.

Instructions given to nurses who cared for patients in the study.

Instructions for:
Combining Objective and Subjective Sedation Assessment Tools

Thank you for taking part in this study. These are instructions for nurses who will be caring for patients who are subjects in the "Combining Objective and Subjective Sedation Assessment Tools" study.

These instructions apply to all patients who are enrolled in the study. The instructions apply to equally to patients in the control group and patients in the intervention group. The study is designed to look for relationships in BIS and Glasgow Coma Scores (GCS).

Patients who are in the study will be randomized to either the control group (sedation monitoring with modified-Ramsay alone), or the intervention group (sedation monitoring with modified-Ramsay and BIS). It is important to note that for the entire time a study patient is in the Neuro ICU, any time he/she receives sedation, he/she will be monitored according to his/her group assignment.

As a nurse taking care of the patient, you should recognize that the modified-Ramsay scale is the current standard of care at Duke. Sedation assessment begins with the modified-Ramsay scale. The modified-Ramsay scale is a 1-item scale with 6 different levels of sedation. Levels 1 - 3 of the modified-Ramsay scale indicate that the patient is awake and levels 4 – 6 indicate that the patient is asleep.

- Level 1 - patient is anxious, agitated or restless
- Level 2 – patient is cooperative, agitated or restless
- Level 3 – patient responds to vocal commands only
- Level 4 – patient is asleep and responds to gentle shaking or loud auditory stimulus
- Level 5 – patient is asleep and does not respond to gentle shaking our loud stimulus, but responds to pain
- Level 6 – patient is unarousable and does not respond to pain or noxious stimuli

There is no change in the standard of practice at Duke. Modified-Ramsay scores should be documented in CareVue^{tm} at least once every 2 hours. (You may refer to "ICU Sedation, with/without Neuromuscular Blockade, Monitoring Protocol (ICU's only)" which is attached to this instruction sheet and is also available on the Duke Intranet.)

Patients in the intervention group will receive BIS monitoring in addition to modified-Ramsay. If you are taking care of a patient who has been randomized to the intervention group, your assessment will begin with the modified-Ramsay scale and then you may incorporate information (values) from the BIS monitor. Only adjust sedation using data from the BIS monitor so long as the Ramsay score is equal to 4. For example, it is better to have a modified-Ramsay 4 and BIS 80 than it is to have a BIS 65 and modified-Ramsay 3. In other words, the goal is to have a modified-Ramsay 4 and BIS 60-70 but the priority is the modified Ramsay score.

In this study, the desired range for BIS is a goal of 60-70. BIS scores should be recorded on CareVue^{tm} at least once each hour. Follow the instructions in the Duke protocol ("Bispectral Index Monitor (BIS) Management Protocol" which is attached to this instruction sheet and is also available on the Duke Intranet) to place the BIS sensor strip. For patients with a unilateral brain injury, place the sensor over the contra-lateral (non-injured) brain. Ensure that the sensor strip is placed with the circle # 1 at the center of the forehead and the outer-most circle between the corner of the eye and the hairline. Ensure adhesion of the sensor by firmly pressing all edges.

Electromyography (EMG) and signal quality index (SQI) are components of BIS monitoring. Excessive EMG (more than 50%) can skew BIS readings. If this happens the BIS value will appear as a halo instead of being bold. Interpret BIS readings with > 50 % EMG as unreliable. The SQI indicates how well the BIS monitor is able to interpret the electrical signal. If the SQI is <50% the BIS value will appear as a halo instead of being bold. Interpret BIS readings with <50% SQI as unreliable.

You may keep this instruction sheet for your own records. If you lose this set of instructions you may ask for, and receive, a new copy at any time. Please contact DaiWai Olson with any questions or requests.

References

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