Title

The Effect of a Sedation Wake-up Trial and Spontaneous Breathing Trial on the Occurrence of Delirium and Perception of Sleep in Critically Ill Trauma Patients

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THE EFFECT OF A SEDATION WAKE-UP TRIAL AND SPONTANEOUS BREATHING TRIAL ON THE OCCURRENCE OF DELIRIUM AND PERCEPTION OF SLEEP IN CRITICALLY ILL TRAUMA PATIENTS

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

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in

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of the

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[redacted]

Dedication

Because for You I exist… this dissertation is especially dedicated to my *God of Mercy,* the principal inspiration in my life. You gave me the opportunity to realize this important challenge in my professional career. Your grace and blessings have helped me along this important journey. It was an opportunity to recognize Your kindness and unconditional love. Thank you for giving me strength to take this road, and for the belief that You are my beginning and my end.

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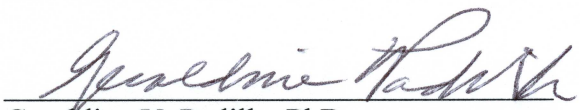
Chapter I of this dissertation contain a reprint of material published in *Intensive Care Medicine*. I wish to thank the publisher, Springer, for granting permission to reprint the entire article.

Research Advisor Statement

The publications represent research or scholarship comparable in scope and contribution to the portion of the standard dissertation it replaces.

The published material is substantially the product of the student's period of study at UCSF and was primarily written by the student.



Geraldine V. Padilla, PhD
Advisor and Dissertation Committee Chair

Abstract

The Effect of a Sedation Wake-up Trial and Spontaneous Breathing Trial on the Occurrence of Delirium and Perception of Sleep in Critically Ill Trauma Patients

Milagros I. Figueroa-Ramos
Doctor of Philosophy
University of California, San Francisco, 2010

Delirium and sleep deprivation are experienced by patients in intensive care units (ICUs) and have been associated with negative patient outcomes. Benzodiazepine, often used for sedation in critically ill patients, contributes to an imbalance of neurotransmitters that can influence the wake-sleep-regulatory system and the occurrence of delirium. This dissertation evaluated the effect of a sedation wake-up trial (SWT) and spontaneous breathing trial (SBT) on the occurrence of delirium, perception of sleep and other outcomes in trauma ICU (TICU) patients.

The first study was a prospective interventional trial that implemented the SWT plus SBT in TICU patients. The intervention group (IG, n = 20) experienced less delirium (OR 0.107; 95% CI: 0.025-0.459), recovered from drug-induced coma faster (RH 2.25; 95% CI: 1.08-4.65), and was liberated from the mechanical ventilator (RH 3.09; 95% CI: 1.45-6.60) and discharged from the TICU sooner (RH 4.20; 95% CI: 1.82-9.69) than the control group (CG, n = 20). Sleep perception was rated as bad and did not differ between groups.

A second report addressed the feasibility of conducting the SWT plus SBT based on the ability to implement the combined intervention, measure patients' physiological responses, and maintain patient safety. IG patients passed 67% of the 39 SWTs

performed. Those who did not pass presented RASS scores of +1 and +2, tachycardia, or showed ventilator asynchrony. Eighteen patients tolerated their first SBT and after the second SBT more than half of patients were discontinued from the mechanical ventilator. Physiological responses (i.e., heart rate, respiratory rate, and systolic blood pressure) increased significantly from the beginning to the end of the SWT. However, their overall means did not increase by 20%. Opioids were not interrupted during the SWT; however, at the end of six SWTs patients reported having pain.

The findings demonstrated that those TICU patients who received the combined intervention decreased in the occurrence of delirium and improved in several outcomes. However, this conclusion is limited by the non randomized design, the small sample, and the lack of control in the type of sedative given to both groups. The combined intervention was well tolerated, safe, and clinically feasible.

Approved by:

Geraldine V. Padilla, PhD
Advisor and Dissertation Committee Chair

Table of Contents

List of Tables

Chapter II

Chapter III

Chapter IV

List of Figures

Chapter II

Chapter III

Chapter IV

Chapter I

Introduction

Introduction

Delirium and sleep deprivation have been identified as common phenomena in critically ill patients. Of the three types: hypoactive, hyperactive, and mixed, the most common types of delirium in this population are hypoactive and mixed-type. Sleep in these patients is fragmented. The use of benzodiazepine for sleep and sedation has been associated with the development of delirium and sleep architecture alterations.

The following chapters of this dissertation include three manuscripts and a conclusion. The first manuscript is a literature review related to delirium and sleep in critically ill patients. This manuscript discusses the mechanisms that underlie the regulation of sleep-wake cycles as well as mechanisms of delirium; provides general definitions and concepts of both sleep and delirium and their manifestation in critically ill patients; and include the relationship between sleep and delirium as well as the influence of sedatives and analgesics on both.

Understanding that sedatives such as benzodiazepine could contribute to the occurrence of delirium and sleep disturbance, the second manuscript presents the report of a prospective interventional study that implemented a sedation wake-up trial (SWT) and a spontaneous breathing trial (SBT). The purpose of this study was to determine whether a SWT combined with a SBT results in a reduction of the occurrence of delirium and improvements in other outcomes in critically ill trauma patients. An intervention group who received the combined intervention (SWT plus SBT) was compared with a control group who received the usual care of the trauma intensive care unit (TICU) that consisted of the administration of continuous sedative infusions without SWT and without standardized SBT. Twenty patients per group were enrolled. Patients in the

intervention group had a decrease in the occurrence of delirium, days in coma, duration of mechanical ventilation, length of TICU stay, and total cumulative doses of benzodiazepines and propofol administered during their TICU stay.

The third manuscript is the report of the feasibility in conducting the SWT and SBT using data from patients in the intervention group from the prospective interventional study previously described. The results showed that this combined intervention was well tolerated and successfully implemented and is safe and clinically feasible for these trauma patients.

Chapter II

Sleep and Delirium in ICU Patients:
A Review of Mechanisms and Manifestations

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Abstract

Sleep deprivation and delirium are conditions commonly encountered in intensive care unit patients. Sleep in these patients is characterized by sleep fragmentation, an increase in light sleep, and a decrease of both slow wave sleep and rapid eye movement sleep. The most common types of delirium in this population are hypoactive and mixed-type.

Knowledge about the mechanisms of sleep and delirium has evolved over time, but these phenomena are not yet well understood. What is known, however, is that different areas in the brainstem transmit information to the thalamus and cortex necessary for sleep-wake regulation. Delirium is related to an imbalance in the synthesis, release, and inactivation of some neurotransmitters, particularly acetylcholine and dopamine.

The relationship between sleep deprivation and delirium has been studied for many years and has been viewed as reciprocal. The link between them may be ascribed to shared mechanisms. An imbalance in neurotransmitters as well as alteration of melatonin production may contribute to the pathogenesis of both phenomena. A better understanding of the mechanisms and factors that contribute to sleep deprivation and delirium can guide the development of new methods and models for prevention and treatment of these problems and consequently improve patient outcomes.

Introduction

Sleep deprivation and delirium are conditions commonly encountered in intensive care unit (ICU) patients, but they are not yet well understood. Although several hypotheses concerning their mechanisms have been advanced, the alteration in specific neurotransmitters associated with sleep and delirium is the foundation of current research. The link between sleep deprivation and delirium has been studied for many years. However, it is yet unknown whether delirium causes sleep deprivation or whether delirium is a disorder caused by altered sleep architecture or circadian rhythm desynchrony.

Although sleep functions are not well understood, it is clear that sleep is a dynamic as well as complex physiologic state necessary for life; when lacking, deprivation results in serious physiological consequences (Colten, Altevogt, & Institute of Medicine (U.S.) Committee on Sleep Medicine and Research, 2006). Delirium may also result in consequences that negatively influence patient outcomes, including mortality (Ely et al., 2004). Many risk factors have been implicated in the development of both sleep deprivation and delirium. Although some factors are unique to each phenomenon, other factors are shared by both. For example, sedatives and analgesics can contribute to the development of both sleep deprivation and delirium.

The purpose of this article is to review the mechanisms that underlie the regulation of sleep-wake cycles as well as mechanisms of delirium. We also provide general definitions and concepts of both sleep and delirium and their manifestation in ICU patients. Finally, we present the relationship between sleep and delirium as well as the influence of sedatives and analgesics on both.

Sleep

Sleep is a dynamic as well as complex physiologic state necessary for life. Sleep architecture is the structural organization of sleep (i.e., pattern of sleep stages and cycles). Non-rapid eye movement (NREM) and rapid eye movement (REM) constitute two phases of normal human sleep. Both NREM sleep and REM sleep have specific anatomical, physiological, and behavioral characteristics (Harris, 2005) (Table 1). Normally, both NREM and REM sleep alternate cyclically. Each sleep period consists of four to six cycles across the night, with durations of 90 to 110 minutes during which the person progresses from wake through light sleep to deep sleep (Carskadon & Dement, 2005).

Sleep Mechanisms

The mechanisms of sleep are not yet well defined; however, there exists a neural pathway that regulates the sleep-wake cycle (Saper, Scammell, & Lu, 2005b). This pathway principally consists of the ascending reticular activating system (ARAS); the basal forebrain and lateral hypothalamus areas; and the ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus. The ARAS and both basal forebrain and lateral hypothalamus areas contain neurotransmitters that mostly mediate wakefulness, but also sleep (Harris, 2005; Manns, Mainville, & Jones, 2001; Saper et al., 2005b; Verret et al., 2003). The VLPO is responsible for sleep onset (Saper et al., 2005b) (Table 2).

Regulation of sleep-wake cycles is thought to occur as an interaction between ARAS and VLPO neurons, commonly called the "flip-flop switch" because both ARAS and VLPO are mutually inhibitory (Saper et al., 2005b). That is, when ARAS is "on" (i.e., during wakefulness), it provokes VLPO to turn "off." When VLPO is "on" (i.e., during sleep), ARAS turns "off." Wakefulness is produced by active firing of

wakefulness-promoting neurons in the ARAS and inhibition of VLPO neurons, while sleep is promoted by activation of VLPO neurons and inhibition of ARAS neurons (Saper et al., 2005b) (Figures 1 and 2).

The "flip-flop switch" mechanism is stabilized by orexin (hypocretin), a peptide produced in the lateral hypothalamus (Sakurai, 2007). Orexin strengthens the ARAS (thereby maintaining wakefulness) and prevents inappropriate transition to the sleep state (Saper et al., 2005b). On the other hand, when VLPO is activated, it inhibits both monoaminergic and orexin neurons to maintain sleep (Sakurai, 2007).

In addition to the wake-sleep neuron-regulatory system, the Homeostatic Drive for Sleep (Process S) provides a useful explanation for waking and sleeping based on the observation that sleep debt accumulates during wakefulness (Colten et al., 2006). It is proposed that a substance that accumulates during prolonged wakefulness activates VLPO neurons and inhibits ARAS neurons, producing a transition to sleep (Saper, Cano, & Scammell, 2005a). Although it is not yet determined, it is thought that adenosine could be this sleep-promoting substance which accumulates in the basal forebrain and inhibits wake-promoting neurons in this area (Basheer, Strecker, Thakkar, & McCarley, 2004).

The sleep-wake cycle is also influenced by circadian rhythms. Circadian rhythm (also known as the Process C model) is regulated by the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus, usually referred to as the biological clock. The contribution of the SCN to the sleep-wake cycle depends on input received from the retinal ganglion cells, pineal gland, and ARAS, as well as output from the SCN projected indirectly to the ARAS and VLPO. The SCN is involved in regulating the secretion of

melatonin produced by the pineal gland (Colten et al., 2006) (see Figure 3). Melatonin is involved in the maintenance of circadian rhythms and sleep-wake cycles (Shigeta et al., 2001).

Sleep Deprivation

To maintain homeostasis between sleep and wakefulness, it is important that sleep-wake mechanisms work adequately. However, several factors can negatively influence these mechanisms by provoking an alteration in sleep-wake cycles that subsequently reduce quantity or quality of sleep. The consequences of sleep deprivation that will be addressed have been studied in non-ICU patients. Thus, further studies are necessary to elucidate the effect of sleep deprivation on ICU patient outcomes.

Consequences of sleep deprivation. The consequences of total or partial sleep deprivation have been categorized as physiological and behavioral. Physiological consequences include increase in pain sensitivity (Lautenbacher, Kundermann, & Krieg, 2006; Onen, Alloui, Gross, Eschallier, & Dubray, 2001), reduction in forced expiratory volume and forced vital capacity (Phillips, Cooper, & Burke, 1987), increases in sympathetic and decreases in parasympathetic cardiac modulation (Zhong et al., 2005), impaired immune response (Irwin et al., 1996; Ozturk et al., 1999) and alteration in metabolic and endocrine systems (Spiegel, Leproult, & Van Cauter, 1999). Behavioral consequences of sleep deprivation include impaired attention and psychomotor performance, increased daytime sleepiness, and impaired mood that includes fatigue and irritability (Bonnet & Arand, 2003).

The consequences of REM deprivation are similar to total sleep deprivation and include mood and memory alterations. Of importance to ICU patients is that REM

deprivation due to CNS depressant medications can be followed by a REM sleep rebound phenomenon if the medication is suddenly discontinued. REM rebound is defined as an above-normal percentage of REM sleep, often a 300% increase, after a period of suppressed REM sleep and includes exacerbations of autonomic activity normally seen during phasic REM periods (Carlson, 2007; Kavey & Ahshuler, 1979). Thus, REM rebound may cause an increase in heart rate, hypoxemia, cardiac arrhythmias, and hemodynamic instability (Gabor, Cooper, & Hanly, 2001; Rosenberg, Wildschiodtz, Pedersen, von Jessen, & Kehlet, 1994). Because of the cardiac and respiratory variability observed during this event, REM rebound can be dangerous for ICU patients (Gabor et al., 2001).

Sleep in ICU Patients

Two primary sleep disorders have been found in ICU patients: parasomnias and dyssomnias. Parasomnias include undesirable physiological or behavioral events occurring during specific sleep or sleep-wake transition phases, which are not associated with abnormalities of the sleep-wake cycle itself (American Academy of Sleep Medicine [AASM], 2005). REM sleep behavior disorder, one of the parasomnias which is characterized by loss of atonia, increase in musculoskeletal activity, and vivid dreams (AASM, 2005), has been reported in ICU patients with Guillian-Barré syndrome (Cochen et al., 2005). It is suggested that REM sleep behavior disorder may be associated with decreased blood flow in the brain, loss of dopaminergic neurons, or motor system alterations (Nofzinger, 2005).

According to the AASM (2005) dyssomnias include disorders related to the inability to initiate or maintain sleep. Specifically, circadian rhythm sleep disorder is a

dyssomnia with an irregular sleep-wake pattern that can affect ICU patients. Sleep in ICU patients is often fragmented due to frequent arousals and awakenings. Studies show that their sleep architecture is altered, with an increase in light sleep and less SWS and REM sleep; total sleep time averages between 2.1 and 8.8 hours and is not continuous (Aurell & Elmqvist, 1985; Cooper et al., 2000; Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Friese, Diaz-Arrastia, McBride, Frankel, & Gentilello, 2007; Gabor et al., 2003; Hilton, 1976). Indeed, sleep has been noted to occur in 50-67% of the night (Aurell & Elmqvist, 1985; Cooper et al., 2000; Hilton, 1976) and 54-57% of the day in ICU patients (Cooper et al., 2000; Freedman et al., 2001; Gabor et al., 2003; Hilton, 1976), suggesting that both circadian rhythms and sleep quality are affected. One of the predisposing factors for developing this type of dyssomnia is prolonged bed rest (AASM, 2005).

Disturbance of the light-dark cycle might also contribute to alteration in circadian rhythms (AASM, 2005). Light exposure is the main external cue for maintaining circadian rhythm, but ICU patients have limited natural light exposure. In addition, alteration in circadian rhythm has also been linked to melatonin secretion impairment in ICU patients (Olofsson, Alling, Lundberg, & Malmros, 2004; Shilo et al., 1999). For example, systemic inflammatory response, hormone interactions, medications, acuity of illness, mechanical ventilation, and environmental factors, could influence melatonin excretion rhythm (Bourne & Mills, 2006; Frisk, Olsson, Nylen, & Hahn, 2004; Mundigler et al., 2002; Olofsson et al., 2004).

Many factors contribute to disrupted sleep in ICU patients. Based on available evidence, noise, patient-care interaction, and the mode of mechanical ventilation are three

factors (Freedman et al., 2001; Freedman, Kotzer, & Schwab, 1999; Gabor et al., 2003; Hilton, 1976; Parthasarathy & Tobin, 2002). Specifically, patients in pressure support ventilation mode showed more arousals and awakenings than those patients in assist control ventilation (Parthasarathy & Tobin, 2002; Toublanc et al., 2007) or proportional assist ventilation (Bosma et al., 2007). However, a recent study did not find differences in frequency of arousals and awakenings among three mechanical ventilators modes (assist control, clinically adjusted pressure support, and automatic adjusted pressure support ventilation) (Cabello et al., 2008). Acuity of illness appears to influence sleep deprivation, but further studies are needed to investigate this relationship (Parthasarathy & Tobin, 2003). Most of the pharmacological therapies used in ICU patients have been shown to affect sleep architecture in studies with non-ICU patients (Achermann & Borbely, 1987; Bourne & Mills, 2004; Dimsdale, Norman, DeJardin, & Wallace, 2007; Kavey & Ahshuler, 1979; Mortazavi, Thompson, Baghdoyan, & Lydic, 1999; Shaw, Lavigne, Mayer, & Choiniere, 2005; Walder, Tramer, & Blois, 2001). A study with critically ill patients showed a reduction in REM sleep with intermittent benzodiazepine therapy (Hardin, Seyal, Stewart, & Bonekat, 2006). Figure 4 depicts sleep risk factors and potential outcomes. All of these factors might also interact to adversely affect sleep architecture and patient outcomes.

Sleep Measurements

The methods utilized to measure sleep are classified into three categories: physiologic, behavioral, and self-report. Polysomnography (PSG) is the gold standard to measure sleep; however, this physiologic method is expensive and time-consuming. Several studies have been conducted with PSG in ICU patients (Aurell & Elmqvist, 1985;

Cooper et al., 2000; Freedman et al., 2001; Hardin et al., 2006; Hilton, 1976; Parthasarathy & Tobin, 2002), but Watson and colleagues (2006) found several limitations in applicating the standardized Rechtschaffen and Kales' criteria to analyze PSG data in the 7 ICU patients they studied. Thus, PSG data in this population must be interpreted with caution. Processes electroencephalogram (EEG) such as bispectral index (BIS) has been used to measure sleep; however, there has been and identified overlap of BIS values between light sleep and REM sleep (Sleigh, Andrzejowski, Steyn-Ross, & Steyn-Ross, 1999) that could affect its validity.

Among the behavioral methods, observation and actigraphy have been utilized with ICU patients (Aurell & Elmqvist, 1985; Redeker, Ruggiero, & Hedges, 2004; Shilo et al., 1999). The validity of the observation method has not been well established. This technique is time-consuming and could be subject to observer bias and observer fatigue. Good accuracy between actigraphy and PSG has been demonstrated in non-ICU patients. However, overestimation of total sleep time and underestimation of awakenings were found with the use of actigraphy (de Souza et al., 2003). In addition, ICU patients are likely to decrease movement that may not be associated with sleep problems due to the use of sedation/analgesia, neuromuscular blockers, restraint, and weakness. To overcome these limitations, complementary tools, such as sleep diaries or video recording have been suggested. However, sleep diaries would be next to impossible to keep by must ICU patients.

Self-report questionnaires to assess sleep in the ICU population (Verran and Snyder-Halpern Sleep Scale [Fontaine, 1989], Richards-Campbell Sleep questionnaire [Richards, O'Sullivan, & Phillips, 2000], and Sleep in the ICU questionnaire [Freedman

et al., 1999]) did not show adequate psychometric properties and had several limitations. Recall bias is one potential limitation of these questionnaires. Their use is limited to conscious and stable patients, thereby important ICU populations are excluded and generalizability of the study results is compromised. Moreover, some of these questionnaires fail to assess characteristics of daytime sleep in ICU patients.

Delirium

Delirium is characterized by an acute onset of disturbance in consciousness in which cognition or perception is altered (First, Frances, & Pincus, 2004). It can fluctuate throughout the day and usually develops within a short period of time (hours to days) (First et al., 2004; Miller & Ely, 2007). Disturbance in consciousness includes inattention or the inability to focus on external stimuli and ideas (American Psychiatric Association [APA], 1999). Change in cognition can affect orientation, memory, and language (First et al., 2004). Perceptual disturbance includes illusions or hallucinations (APA, 1999). Delirium may be preceded by restlessness, anxiety, irritability, distractibility, or sleep disturbance (APA, 1999). In order to improve the recognition of delirium, it has been classified into three clinical subtypes: hyperactive, hypoactive, and mixed (Meagher, O'Hanlon, O'Mahony, Casey, & Trzepacz, 2000). Table 3 describes the characteristics of two delirium subtypes, hypoactive and hyperactive. Mixed delirium alternates between features of both hyperactive and hypoactive delirium (Meagher et al., 2000). Hypoactive delirium is more difficult to recognize and may be misdiagnosed as depression or dementia (Trzepacz, Meagher, & Wise, 2002) (see Table 4 for differences). The characteristics of hyperactive delirium permit its better recognition.

Delirium Mechanisms

The mechanisms of delirium are not fully understood. Nevertheless, it is suggested that they are related to an imbalance of neurotransmitters (van der Mast, 1998). A neuroanatomical pathway has been proposed for delirium that involves the thalamus, prefrontal cortex, fusiform cortex, posterior parietal cortex, and basal ganglia (Trzepacz, 2000).

The most prevalent hypothesis suggests that imbalances in acetylcholine and dopamine neurotransmitters are involved in the development of delirium (Trzepacz, 1999). More specifically, levels of acetylcholine are low and levels of dopamine are high (Trzepacz, 1996). However, a literature review performed by Trzepacz (2000) referred to some studies that suggested just the opposite: that either excess acetylcholine or deficiency in dopamine can provoke delirium. The relation of dopamine to delirium is based on the therapeutic effect of haloperidol, which is a potent dopamine blocker (Trzepacz, 1994). A retrospective study that selected use of haloperidol as an indicator of delirium occurrence found that dopamine administration was strongly associated with the need for haloperidol, suggesting that dopamine administration could be a risk factor for delirium (Sommer, Wise, & Kraemer, 2002).

Neurotransmitters other than acetylcholine and dopamine are also implicated in delirium, but their mechanism of action is not well established. These include serotonin, GABA, glutamate, histamine, and noradrenaline (Trzepacz, 1994, 1996). A study conducted with cardiac surgery patients with delirium found a significant decrease in plasma tryptophan, the precursor of serotonin, as well as a significant increase in phenylalanine, a precursor of dopamine and noradrenaline (van der Mast, van den Broek,

Fekkes, Pepplinkhuizen, & Habbema, 2000). The authors suggest that alteration in these amino acids may contribute to the development of delirium by a decrease in serotonin and increase in dopamine and noradrenaline.

Another delirium mechanism was explored by Lewis and Barnett (2004) based on the "abnormal tryptophan metabolism" model of delirium from an earlier study (Balan et al., 2003). Balan and colleagues (2003) showed that patients with hyperactive delirium had low levels of urinary 6-sulphatoxymelatonin (SMT), a melatonin metabolite, and patients with hypoactive delirium had higher levels of urinary 6-SMT. This model suggests the existence of two metabolic pathways for tryptophan's ability to enhance either hypoactive or hyperactive delirium.

Milbrandt and Angus (2005) discuss an "occult diffuse brain injury" mechanism for delirium. They suggest that ischemic damage and acute inflammation lead to brain injury and, consequently, to delirium. The authors based this hypothesis on the findings from several studies. One found that the development of septic encephalopathy was significantly associated with severe hypotension suggesting that ischemic damage could contribute to encephalopathy (Wijdicks & Stevens, 1992). Another revealed that serum levels of C-reactive protein (acute inflammation marker) were significantly higher in delirious patients who underwent a hip fracture surgical intervention (Beloosesky, Grinblat, Pirotsky, Weiss, & Hendel, 2004). Inflammation may also be related to delirium through an increase in cytokines (tumor necrosis factor, interleukin-1, and interleukin-2). However, the role of cytokines in delirium could also be due to their interference with neurotransmitter function (Flacker & Wei, 2001). Figure 5 depicts the proposed delirium mechanisms.

Delirium in ICU Patients

Delirium is common in ICU patients, reported to affect 11 to 87% of ICU patients (Aldemir, Ozen, Kara, Sir, & Bac, 2001; Balas et al., 2007; Bergeron, Dubois, Dumont, Dial, & Skrobik, 2001; Ely et al., 2001b; McNicoll et al., 2003). This prevalence varies according to patient's severity of illness and delirium measure or criteria used. Medical ICU patients predominantly develop a mixed-type delirium (55%), followed by hypoactive delirium (43.5%); only 1.6% showed hyperactive delirium (Peterson et al., 2006). In contrast, surgical and trauma ICU patients who developed delirium showed more hypoactive delirium (64% and 60%, respectively) than mixed-type (9% and 6%, respectively) or hyperactive delirium (0% and 1%, respectively) (Pandharipande et al., 2007).

There are many risk factors associated with delirium in ICU patients. In a study of 818 surgical ICU patients, 11% developed delirium diagnosed by a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) delirium criteria (Aldemir et al., 2001). They found many predisposing factors for delirium including hyperamylasemia, hypocalcemia, respiratory disease, hypotension, infection, fever, hyperbilirubinemia, hyponatremia, anemia, azotemia, metabolic acidosis, and increase in hepatic enzymes. In another study, hypertension was a risk factor for delirium in 198 medical and surgical ICU (Dubois, Bergeron, Dumont, Dial, & Skrobik, 2001). Both the Intensive Care Delirium Screening Checklist (ICDSC) and a psychiatric assessment were used to identify delirium in this study. They also found that a smoking history, hyperbilirubinemia, epidural route of analgesia, and morphine use were risk factors for delirium. Risk factors for delirium in thoracic postoperative patients include diabetes

mellitus, length of operation time, age, chemical imbalance, and sleep deprivation (Yildizeli et al., 2005).

Pandharipande and colleagues (2006) performed a study with 198 medical and coronary patients using the Confusion Assessment Method for the ICU (CAM-ICU) to identify delirium. They showed that lorazepam was an independent risk factor for daily transition to delirium (i.e., patients who received lorazepam were more likely to develop delirium the following day); every additional year above 65 years of age and an increase in Acute Physiology and Chronic Health Evaluation (APACHE) II score were also risk factors after adjusting for many covariates. A multivariate analysis revealed that an admission APACHE II score >14, history of hypertension, or alcoholism were significant risk factors for delirium in medical-surgical ICU patients (Ouimet, Kavanagh, Gottfried, & Skrobik, 2007). In another study, daily and cumulative doses of lorazepam were significantly higher in patients with delirium identified by CAM-ICU compared with nondelirious patients in 275 mechanically ventilated medical and coronary ICU patients (Ely et al., 2004). Micek and colleagues (2005) did not find differences in total doses of infusions of midazolam and fentanyl in 44 delirious versus 22 nondelirious patients identified by the CAM-ICU. However, they found that a significant number of delirious patients received continuous IV midazolam and fentanyl compared with non-delirious patients. In addition, use of physical restraints was a risk factor for delirium. Recently, Pandharipande and colleagues (2008) using the CAM-ICU, found that midazolam was an independent risk factor for delirium in trauma and surgical ICU patients. In addition, fentanyl was also found as an independent risk factor for delirium but only in surgical ICU patient.

Another possible risk factor for delirium in ICU patients is alteration in melatonin secretion. In 41 ICU patients who underwent thoracic esophagectomy, the association between delirium and serum melatonin concentration was explored (Miyazaki et al., 2003). Serum melatonin levels were measured every 6 hours over 4 days. Eleven patients (26.8%) developed delirium, and they were significantly older than those who did not develop delirium. Irregular patterns of melatonin secretion were associated with the development of delirium in the 11 patients. Although delirious patients tended to have abnormally low melatonin levels compared with non-delirious patients, differences were not significant, a finding that could have been due to sample size.

Other studies performed in delirious ICU patients have explored patient outcomes and genetic predisposition. Delirium influences patient outcomes, including mortality, longer length of stay, and higher ICU cost (Ely et al., 2001a; Ely et al., 2004; Milbrandt et al., 2004; Ouimet et al., 2007; Thomason et al., 2005). Figure 6 depicts risk factors for delirium as well as patient outcomes. Only one study has been conducted to determine genetic predisposition to delirium in ICU patients (Ely et al., 2007). The study showed a significant association between apolipoprotein E4 genotype and a longer duration of delirium.

Delirium Measurements

Among the delirium instruments, ICDSC and the CAM-ICU have good psychometrics properties and more feasible for use with ICU patients. Both are based on DSM-IV delirium criteria. The ICDSC developed by Bergeron and colleagues (2001) consists of eight domains (altered level of consciousness, inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate

speech or mood, sleep-wake cycle disturbance, and symptom fluctuation) with descriptions that facilitate its application. However, some domains can be difficult to assess or can be misinterpreted; and the ICDSC may be subject to variability in its interpretation. It has been shown to have an excellent sensitivity (99%); however, its specificity was lower at 64% (Bergeron et al., 2001), allowing other conditions to be identified incorrectly as delirium.

The CAM-ICU was developed to identify delirium in mechanically ventilated and nonventilated ICU patients (Ely et al., 2001c). This instrument uses an algorithm system with four domains: acute onset of mental status changes or fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The CAM-ICU has been validated in larger ICU population than the ICDSC and includes tools and questions that reduce subjectivity. While it requires training to use, is an easy instrument that takes approximately two minutes to administer.

Sleep Deprivation and Delirium

The relationship between sleep deprivation and delirium has been studied for many years. However, methodological issues related to the studies make it difficult to establish the relationship between these two phenomena. One can ask: does sleep deprivation contribute to delirium, or does delirium contribute to sleep deprivation? Studies conducted with cardiac surgical patients suggest that sleep deprivation is a result of delirium (Harrell & Othmer, 1987; Johns, Large, Masterton, & Dudley, 1974). However, in a review of 17 studies performed with different types of surgical patients who had delirium risk factors, sleep deprivation was not a risk factor for delirium (Dyer, Ashton, & Teasdale, 1995). Yet, Sveinsson (1975) found that sleep deprivation is a potential

precipitating factor for delirium in cardiac surgical patients, and Helton and colleagues (1980) found that patients with sleep deprivation were significantly more likely to develop delirium than patients without sleep deprivation.

Sleep deprivation was found to be a risk factor that predicted delirium in postoperative patients (Yildizeli et al., 2005). However, this study was a retrospective record review, and investigators did not report how sleep deprivation was measured. A prospective study performed with 27 ICU patients showed a significant association between delirium (measured by CAM-ICU) and altered sleep architecture (measured by PSG) during a one-night recording (Trompeo et al., 2005). They identified longer sleep onset latency, longer REM sleep latency, shorter REM sleep duration, and fewer REM sleep periods in patients with concomitant delirium.

Although the relationship between sleep disturbance and delirium has not been well established, the literature suggests that both phenomena share similar mechanisms. As noted earlier, imbalances in neurotransmitters as well as alteration of melatonin production may contribute to the pathogenesis of both phenomena (Figure 7).

Effect of Benzodiazepines and Opioids on Sleep and Delirium

Many medications can influence the wake-sleep-regulatory system by a direct effect on neurotransmitters and hormones (Bourne & Mills, 2004). Benzodiazepines and opioids can reduce both SWS and REM sleep via GABA type A and opioid mu receptors stimulation, respectively (Bourne & Mills, 2004). On the other hand, opioids can cause delirium by decreasing acetylcholine and increasing dopamine and glutamate activity (Roche, 2003). Benzodiazepines might play a role in hypoactive delirium by increasing GABA activity (Smith, Breitbart, & Platt, 1995). A theory of drug-induced delirium was

proposed by Gaudreau and Gagnon (2005) who identified the role of the thalamus in filtering information from cortical and stem regions of the brain. They established that medications like benzodiazepines and opioids interfere with neurotransmitter pathways to cause a transient thalamic filtering dysfunction that contributes to delirium.

In addition to the administration of benzodiazepines and opioids, the sudden discontinuation of these medications may influence sleep and delirium through development of a withdrawal syndrome (Brown, Albrecht, Pettit, McFadden, & Schermer, 2000; Cammarano, Pittet, Weitz, Schlobohm, & Marks, 1998). Benzodiazepine withdrawal decreases GABA activity which may lead to the development of hyperactive delirium (Smith et al., 1995). Sleep disturbance, specifically REM rebound, can result from benzodiazepine withdrawal (George & Robertson, 1987). In a review of several studies, Wang and Teichtahl (2007) concluded that opioid withdrawal was associated with alterations in sleep architecture. REM rebound may result from discontinuation of sedatives and opioids therapy (Bourne & Mills, 2004; Gabor et al., 2001; Knill, Moote, Skinner, & Rose, 1990). Knill and colleagues (1990) found that higher opioid doses correlated with marked SWS and REM sleep suppression; REM sleep reappears when opioid doses are reduced.

As previously mentioned, an alteration in melatonin secretion may contribute to sleep disturbances and delirium in postoperative or critically ill patients (Bourne & Mills, 2006). It is important to note that both opioids and benzodiazepines affect melatonin secretion. A study performed with an animal model (bovine pineal glands) showed that morphine significantly increased the activity of N-acetyltransferase, promoting melatonin synthesis (Govitrapong, Pariyanonth, & Ebadi, 1992). Melatonin levels decrease with

benzodiazepines in humans via the GABA system (McIntyre, Burrows, & Norman, 1988; Monteleone, Forziati, Orazzo, & Maj, 1989). Researchers noted that chronic benzodiazepine administration reduced melatonin through a reduction in the activity of N-acetyltransferase in a rat model (Djeridane & Touitou, 2001). However, findings related to the effects of opioids and benzodiazepines on melatonin are equivocal. Gogenur and colleagues (2007) did not find a correlation between opioid doses and melatonin level in 11 patients undergoing major abdominal surgery. In addition, Frisk et al. (2004) found a significant difference in excretion of 6-SMT (melatonin metabolite); excretion was higher with benzodiazepine therapy than with opioid or propofol therapy in an analyses of 257 collection periods. Larger studies are needed to better elucidate the effect of opioids and benzodiazepines on melatonin and Process S (sleep) and Process C (circadian) effects as well as delirium.

Conclusion

Despite significant advances in our understanding of the sleep-wake cycle and delirium mechanisms as well as how both influence ICU patient outcomes, significant gaps remain requiring elucidation. Largely unknown are the relationships between sleep deprivation and delirium; the interaction of sedatives and opioid analgesics with sleep and delirium; the effects of long-term continuous sedation and analgesia on sleep and delirium; the importance of sleep in the recovery of ICU patients; the impact of sleep fragmentation and delirium on patient outcomes; and the most valid and reliable method to measure sleep stages in ICU patients. Moreover, most hypotheses for sleep and delirium mechanisms have been established from studies in non-ICU patients. Therefore, studies are needed to test hypotheses in ICU patients. A better understanding of these

mechanisms, as well as the factors that contribute to both, can guide the development of new methods and models for prevention and treatment that consequently improve in ICU patient outcomes.

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References

Achermann, P., & Borbely, A. A. (1987). Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. *Human Neurobiology, 6*, 203-210.

Aldemir, M., Ozen, S., Kara, I. H., Sir, A., & Bac, B. (2001). Predisposing factors for delirium in the surgical intensive care unit. *Critical Care, 5*, 265-270.

American Academy of Sleep Medicine. (2005). *International classification of sleep disorders: Diagnostic and coding manual* (2nd ed.). Westchester, IL: American Academy of Sleep Medicine.

American Psychiatric Association. (1999). Practice guideline for the treatment of patients with delirium. Retrieved from http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=DeliriumPG_05-15-06

Aurell, J., & Elmqvist, D. (1985). Sleep in the surgical intensive care unit: Continuous polygraphic recording of sleep in nine patients receiving postoperative care. *British Medical Journal (Clinical Research Ed.), 290*, 1029-1032.

Balan, S., Leibovitz, A., Zila, S. O., Ruth, M., Chana, W., Yassica, B., . . . Habot, N. (2003). The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. *Journal of Neuropsychiatry and Clinical Neurosciences, 15*, 363-366.

Balas, M. C., Deutschman, C. S., Sullivan-Marx, E. M., Strumpf, N. E., Alston, R. P., & Richmond, T. S. (2007). Delirium in older patients in surgical intensive care units. *Journal of Nursing Scholarship, 39*, 147-154.

Basheer, R., Strecker, R. E., Thakkar, M. M., & McCarley, R. W. (2004). Adenosine and sleep-wake regulation. *Progress in Neurobiology, 73*, 379-396.

Beloosesky, Y., Grinblat, J., Pirotsky, A., Weiss, A., & Hendel, D. (2004). Different c-reactive protein kinetics in post-operative hip-fractured geriatric patients with and without complications. *Gerontology, 50*, 216-222.

Bergeron, N., Dubois, M. J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive care delirium screening checklist: Evaluation of a new screening tool. *Intensive Care Medicine, 27*, 859-864.

Bonnet, M. H., & Arand, D. L. (2003). Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Medicine Reviews, 7*, 297-310.

Bosma, K., Ferreyra, G., Ambrogio, C., Pasero, D., Mirabella, L., Braghiroli, A., . . . Ranieri, V.M. (2007). Patient-ventilator interaction and sleep in mechanically ventilated patients: Pressure support versus proportional assist ventilation. *Critical Care Medicine, 35*, 1048-1054.

Bourne, R. S., & Mills, G. H. (2004). Sleep disruption in critically ill patients: Pharmacological considerations. *Anaesthesia, 59*, 374-384.

Bourne, R. S., & Mills, G. H. (2006). Melatonin: Possible implications for the postoperative and critically ill patient. *Intensive Care Medicine, 32*, 371-379.

Brown, C., Albrecht, R., Pettit, H., McFadden, T., & Schermer, C. (2000). Opioid and benzodiazepine withdrawal syndrome in adult burn patients. *American Surgeon, 66*, 367-370.

Cabello, B., Thille, A. W., Drouot, X., Galia, F., Mancebo, J., d'Ortho, M. P., & Brochard, L. (2008). Sleep quality in mechanically ventilated patients: Comparison of three ventilatory modes. *Critical Care Medicine, 36*, 1749-1755.

Cammarano, W. B., Pittet, J. F., Weitz, S., Schlobohm, R. M., & Marks, J. D. (1998). Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Critical Care Medicine, 26,* 676-684.

Carlson, N. R. (2007). *Physiology of behavior* (9th ed.). Boston: Pearson Allyn & Bacon.

Carskadon, M. A., & Dement, W. C. (2005). Normal human sleep: An overview. In M. H. Kryger, T. Roth & W. C. Dement (Eds.), *Principles and practice of sleep medicine* (4th ed., pp. 13-23). Philadelphia: Elsevier Saunders.

Cochen, V., Arnulf, I., Demeret, S., Neulat, M. L., Gourlet, V., Drouot, X., . . . Bolgert, I. (2005). Vivid dreams, hallucinations, psychosis and REM sleep in guillain-barre syndrome. *Brain, 128,* 2535-2545.

Colten, H. R., Altevogt, B. M., & Institute of Medicine (U.S.). Committee on Sleep Medicine and Research. (2006). *Sleep disorders and sleep deprivation: An unmet public health problem*. Washington, DC: Institute of Medicine: National Academies Press.

Cooper, A. B., Thornley, K. S., Young, G. B., Slutsky, A. S., Stewart, T. E., & Hanly, P. J. (2000). Sleep in critically ill patients requiring mechanical ventilation. *Chest, 117,* 809-818.

de Souza, L., Benedito-Silva, A. A., Pires, M. L., Poyares, D., Tufik, S., & Calil, H. M. (2003). Further validation of actigraphy for sleep studies. *Sleep, 26,* 81-85.

Dimsdale, J. E., Norman, D., DeJardin, D., & Wallace, M. S. (2007). The effect of opioids on sleep architecture. *Journal of Clinical Sleep Medicine, 3,* 33-36.

Djeridane, Y., & Touitou, Y. (2001). Chronic diazepam administration differentially affects melatonin synthesis in rat pineal and harderian glands. *Psychopharmacology, 154,* 403-407.

Dubois, M. J., Bergeron, N., Dumont, M., Dial, S., & Skrobik, Y. (2001). Delirium in an intensive care unit: A study of risk factors. *Intensive Care Medicine, 27,* 1297-1304.

Dyer, C. B., Ashton, C. M., & Teasdale, T. A. (1995). Postoperative delirium. A review of 80 primary data-collection studies. *Archives of Internal Medicine, 155*, 461-465.

Ely, E. W., Gautam, S., Margolin, R., Francis, J., May, L., Speroff, T., . . . Inouye, S. K. (2001a). The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Medicine, 27,* 1892-1900.

Ely, E. W., Girard, T. D., Shintani, A. K., Jackson, J. C., Gordon, S. M., Thomason, J. W., . . . Laskowitz, D. T. (2007). Apolipoprotein e4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Critical Care Medicine, 35*, 112-117.

Ely, E. W., Inouye, S. K., Bernard, G. R., Gordon, S., Francis, J., May, L., . . . Dittus, R. (2001b). Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA, 286*, 2703-2710.

Ely, E. W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, R., . . . Inouye, S. K. (2001c). Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Critical Care Medicine, 29,* 1370-1379.

Ely, E. W., Shintani, A., Truman, B., Speroff, T., Gordon, S. M., Harrell, F. E., Jr., . . . Dittus, R. (2004). Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA, 291*, 1753-1762.

First, M. B., Frances, A., & Pincus, H. A. (2004). *DSM-IV-TR guidebook* (1st ed.). Washington, DC: American Psychiatric Pub.

Flacker, J. M., & Wei, J. Y. (2001). Endogenous anticholinergic substances may exist during acute illness in elderly medical patients. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 56*, M353-355.

Fontaine, D. K. (1989). Measurement of nocturnal sleep patterns in trauma patients. *Heart and Lung, 18*, 402-410.

Freedman, N. S., Gazendam, J., Levan, L., Pack, A. I., & Schwab, R. J. (2001). Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine, 163*, 451-457.

Freedman, N. S., Kotzer, N., & Schwab, R. J. (1999). Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine, 159*, 1155-1162.

Friese, R. S., Diaz-Arrastia, R., McBride, D., Frankel, H., & Gentilello, L. M. (2007). Quantity and quality of sleep in the surgical intensive care unit: Are our patients sleeping? *Journal of Trauma, 63*, 1210-1214.

Frisk, U., Olsson, J., Nylen, P., & Hahn, R. G. (2004). Low melatonin excretion during mechanical ventilation in the intensive care unit. *Clinical Science, 107*, 47-53.

Gabor, J. Y., Cooper, A. B., Crombach, S. A., Lee, B., Kadikar, N., Bettger, H. E., & Hanly, P. J. (2003). Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *American Journal of Respiratory and Critical Care Medicine, 167,* 708-715.

Gabor, J. Y., Cooper, A. B., & Hanly, P. J. (2001). Sleep disruption in the intensive care unit. *Current Opinion in Critical Care, 7,* 21-27.

Gaudreau, J. D., & Gagnon, P. (2005). Psychotogenic drugs and delirium pathogenesis: The central role of the thalamus. *Medical Hypotheses, 64,* 471-475.

George, C. F., & Robertson, D. (1987). Clinical consequences of abrupt drug withdrawal. *Medical Toxicology and Adverse Drug Experience, 2,* 367-382.

Gogenur, I., Ocak, U., Altunpinar, O., Middleton, B., Skene, D. J., & Rosenberg, J. (2007). Disturbances in melatonin, cortisol and core body temperature rhythms after major surgery. *World Journal of Surgery, 31,* 290-298.

Govitrapong, P., Pariyanonth, M., & Ebadi, M. (1992). The presence and actions of opioid receptors in bovine pineal gland. *Journal of Pineal Research, 13,* 124-132.

Hardin, K. A., Seyal, M., Stewart, T., & Bonekat, H. W. (2006). Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. *Chest, 129,* 1468-1477.

Harrell, R. G., & Othmer, E. (1987). Postcardiotomy confusion and sleep loss. *Journal of Clinical Psychiatry, 48,* 445-446.

Harris, C. D. (2005). Neurophysiology of sleep and wakefulness. *Respiratory Care Clinics of North America, 11,* 567-586.

Helton, M. C., Gordon, S. H., & Nunnery, S. L. (1980). The correlation between sleep deprivation and the intensive care unit syndrome. *Heart and Lung, 9*, 464-468.

Hilton, B. A. (1976). Quantity and quality of patients' sleep and sleep-disturbing factors in a respiratory intensive care unit. *Journal of Advanced Nursing, 1*, 453-468.

Irwin, M., McClintick, J., Costlow, C., Fortner, M., White, J., & Gillin, J. C. (1996). Partial night sleep deprivation reduces natural killer and cellular immune responses in humans. *The FASEB Journal, 10*, 643-653.

Johns, M. W., Large, A. A., Masterton, J. P., & Dudley, H. A. (1974). Sleep and delirium after open heart surgery. *British Journal of Surgery, 61*, 377-381.

Kavey, N. B., & Ahshuler, K. Z. (1979). Sleep in herniorrhaphy patients. *American Journal of Surgery, 138*, 683-687.

Knill, R. L., Moote, C. A., Skinner, M. I., & Rose, E. A. (1990). Anesthesia with abdominal surgery leads to intense rem sleep during the first postoperative week. *Anesthesiology, 73*, 52-61.

Lautenbacher, S., Kundermann, B., & Krieg, J. C. (2006). Sleep deprivation and pain perception. *Sleep Medicine Reviews, 10*, 357-369.

Lewis, M. C., & Barnett, S. R. (2004). Postoperative delirium: The tryptophan dyregulation model. *Medical Hypotheses, 63*, 402-406.

Manns, I. D., Mainville, L., & Jones, B. E. (2001). Evidence for glutamate, in addition to acetylcholine and gaba, neurotransmitter synthesis in basal forebrain neurons projecting to the entorhinal cortex. *Neuroscience, 107*, 249-263.

McIntyre, I. M., Burrows, G. D., & Norman, T. R. (1988). Suppression of plasma melatonin by a single dose of the benzodiazepine alprazolam in humans. *Biological Psychiatry, 24*, 108-112.

McNicoll, L., Pisani, M. A., Zhang, Y., Ely, E. W., Siegel, M. D., & Inouye, S. K. (2003). Delirium in the intensive care unit: Occurrence and clinical course in older patients. *Journal of the American Geriatrics Society, 51*, 591-598.

Meagher, D. J., O'Hanlon, D., O'Mahony, E., Casey, P. R., & Trzepacz, P. T. (2000). Relationship between symptoms and motoric subtype of delirium. *Journal of Neuropsychiatry and Clinical Neurosciences, 12*, 51-56.

Micek, S. T., Anand, N. J., Laible, B. R., Shannon, W. D., & Kollef, M. H. (2005). Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. *Critical Care Medicine, 33*, 1260-1265.

Milbrandt, E. B., & Angus, D. C. (2005). Potential mechanisms and markers of critical illness-associated cognitive dysfunction. *Current Opinion in Critical Care, 11*, 355-359.

Milbrandt, E. B., Deppen, S., Harrison, P. L., Shintani, A. K., Speroff, T., Stiles, R. A., . . . Ely, E. W. (2004). Costs associated with delirium in mechanically ventilated patients. *Critical Care Medicine, 32*, 955-962.

Miller, R. R., 3rd, & Ely, E. W. (2007). Delirium and cognitive dysfunction in the intensive care unit. *Current Psychiatry Reports, 9*, 26-34.

Miyazaki, T., Kuwano, H., Kato, H., Ando, H., Kimura, H., Inose, T., . . . Tsukada, K. (2003). Correlation between serum melatonin circadian rhythm and intensive care unit psychosis after thoracic esophagectomy. *Surgery, 133*, 662-668.

Monteleone, P., Forziati, D., Orazzo, C., & Maj, M. (1989). Preliminary observations on the suppression of nocturnal plasma melatonin levels by short-term administration of diazepam in humans. *Journal of Pineal Research, 6,* 253-258.

Mortazavi, S., Thompson, J., Baghdoyan, H. A., & Lydic, R. (1999). Fentanyl and morphine, but not remifentanil, inhibit acetylcholine release in pontine regions modulating arousal. *Anesthesiology, 90,* 1070-1077.

Mundigler, G., Delle-Karth, G., Koreny, M., Zehetgruber, M., Steindl-Munda, P., Marktl, W., . . . Siostrzonek, P. (2002). Impaired circadian rhythm of melatonin secretion in sedated critically ill patients with severe sepsis. *Critical Care Medicine, 30,* 536-540.

Nofzinger, E. A. (2005). Functional neuroimaging of sleep. *Seminars in Neurology, 25,* 9-18.

Olofsson, K., Alling, C., Lundberg, D., & Malmros, C. (2004). Abolished circadian rhythm of melatonin secretion in sedated and artificially ventilated intensive care patients. *Acta Anaesthesiologica Scandinavica, 48,* 679-684.

Onen, S. H., Alloui, A., Gross, A., Eschallier, A., & Dubray, C. (2001). The effects of total sleep deprivation, selective sleep interruption and sleep recovery on pain tolerance thresholds in healthy subjects. *Journal of Sleep Research, 10,* 35-42.

Ouimet, S., Kavanagh, B. P., Gottfried, S. B., & Skrobik, Y. (2007). Incidence, risk factors and consequences of ICU delirium. *Intensive Care Medicine, 33,* 66-73.

Ozturk, L., Pelin, Z., Karadeniz, D., Kaynak, H., Cakar, L., & Gozukirmizi, E. (1999). Effects of 48 hours sleep deprivation on human immune profile. *Sleep Reserch Online, 2,* 107-111.

Pandharipande, P., Cotton, B. A., Shintani, A., Thompson, J., Costabile, S., Truman Pun, B., . . . Ely, E. W. (2007). Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Medicine, 33*, 1726-1731.

Pandharipande, P., Cotton, B. A., Shintani, A., Thompson, J., Pun, B. T., Morris, J. A., Jr., . . . Ely, E. W. (2008). Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *Journal of Trauma, 65*, 34-41.

Pandharipande, P., Shintani, A., Peterson, J., Pun, B. T., Wilkinson, G. R., Dittus, R. S., . . . Ely, E. W. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology, 104*, 21-26.

Parthasarathy, S., & Tobin, M. J. (2002). Effect of ventilator mode on sleep quality in critically ill patients. *American Journal of Respiratory and Critical Care Medicine, 166*, 1423-1429.

Parthasarathy, S., & Tobin, M. J. (2003). Is sleep disruption related to severity of critical illness? *American Journal of Respiratory and Critical Care Medicine, 167*, A968.

Peterson, J. F., Pun, B. T., Dittus, R. S., Thomason, J. W., Jackson, J. C., Shintani, A. K., . . . Ely, E. W. (2006). Delirium and its motoric subtypes: A study of 614 critically ill patients. *Journal of the American Geriatrics Society, 54*, 479-484.

Phillips, B. A., Cooper, K. R., & Burke, T. V. (1987). The effect of sleep loss on breathing in chronic obstructive pulmonary disease. *Chest, 91*, 29-32.

Redeker, N. S., Ruggiero, J., & Hedges, C. (2004). Patterns and predictors of sleep pattern disturbance after cardiac surgery. *Research in Nursing and Health, 27*, 217-224.

Richards, K. C., O'Sullivan, P. S., & Phillips, R. L. (2000). Measurement of sleep in critically ill patients. *Journal of Nursing Measurement, 8,* 131-144.

Roche, V. (2003). Southwestern internal medicine conference. Etiology and management of delirium. *American Journal of the Medical Sciences, 325,* 20-30.

Rosenberg, J., Wildschiodtz, G., Pedersen, M. H., von Jessen, F., & Kehlet, H. (1994). Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. *British Journal of Anaesthesia, 72,* 145-150.

Sakurai, T. (2007). The neural circuit of orexin (hypocretin): Maintaining sleep and wakefulness. *Nature Reviews Neuroscience, 8,* 171-181.

Saper, C. B., Cano, G., & Scammell, T. E. (2005a). Homeostatic, circadian, and emotional regulation of sleep. *Journal of Comparative Neurology, 493,* 92-98.

Saper, C. B., Scammell, T. E., & Lu, J. (2005b). Hypothalamic regulation of sleep and circadian rhythms. *Nature, 437,* 1257-1263.

Shaw, I. R., Lavigne, G., Mayer, P., & Choiniere, M. (2005). Acute intravenous administration of morphine perturbs sleep architecture in healthy pain-free young adults: A preliminary study. *Sleep, 28,* 677-682.

Shigeta, H., Yasui, A., Nimura, Y., Machida, N., Kageyama, M., Miura, M., . . . Ikeda, K. (2001). Postoperative delirium and melatonin levels in elderly patients. *American Journal of Surgery, 182,* 449-454.

Shilo, L., Dagan, Y., Smorjik, Y., Weinberg, U., Dolev, S., Komptel, B., . . . Shenkman, L. (1999). Patients in the intensive care unit suffer from severe lack of sleep associated with loss of normal melatonin secretion pattern. *American Journal of the Medical Sciences, 317,* 278-281.

Sleigh, J. W., Andrzejowski, J., Steyn-Ross, A., & Steyn-Ross, M. (1999). The bispectral index: A measure of depth of sleep? *Anesthesia and Analgesia, 88,* 659-661.

Smith, M. J., Breitbart, W. S., & Platt, M. M. (1995). A critique of instruments and methods to detect, diagnose, and rate delirium. *Journal of Pain and Symptom Management, 10,* 35-77.

Sommer, B. R., Wise, L. C., & Kraemer, H. C. (2002). Is dopamine administration possibly a risk factor for delirium? *Critical Care Medicine, 30,* 1508-1511.

Spiegel, K., Leproult, R., & Van Cauter, E. (1999). Impact of sleep debt on metabolic and endocrine function. *Lancet, 354,* 1435-1439.

Sveinsson, I. S. (1975). Postoperative psychosis after heart surgery. *Journal of Thoracic and Cardiovascular Surgery, 70,* 717-726.

Thomason, J. W., Shintani, A., Peterson, J. F., Pun, B. T., Jackson, J. C., & Ely, E. W. (2005). Intensive care unit delirium is an independent predictor of longer hospital stay: A prospective analysis of 261 non-ventilated patients. *Critical Care, 9,* R375-381.

Toublanc, B., Rose, D., Glerant, J. C., Francois, G., Mayeux, I., Rodenstein, D., . . . Jounieaux, V. (2007). Assist-control ventilation vs. Low levels of pressure support ventilation on sleep quality in intubated ICU patients. *Intensive Care Medicine, 33,* 1148-1154.

Trompeo, A. C., Vidi, Y., Locane, M., Braghiroli, A., Rana, N., Rizzuto, A., . . . Ranieri, V. M. (2005). The influence of sleep disorders on the occurrence of delirium in critically ill patients [abstract]. *Intensive Care Medicine,* s94.

Trzepacz, P. T. (1994). The neuropathogenesis of delirium. A need to focus our research. *Psychosomatics, 35*, 374-391.

Trzepacz, P. T. (1996). Delirium. Advances in diagnosis, pathophysiology, and treatment. *Psychiatric Clinics of North America, 19*, 429-448.

Trzepacz, P. T. (1999). Update on the neuropathogenesis of delirium. *Dementia and Geriatric Cognitive Disorders, 10*, 330-334.

Trzepacz, P. T. (2000). Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Seminars in Clinical Neuropsychiatry, 5*, 132-148.

Trzepacz, P. T., Meagher, D. J., & Wise, M. G. (2002). Neuropsychiatric aspects of delirium. In S. C. Yudofsky, R. E. Hales & American Psychiatric Publishing. (Eds.), *The American Psychiatric publishing textbook of neuropsychiatry and clinical neurosciences* (4th ed., pp. 525-564). Washington, DC: American Psychiatric Pub.

van der Mast, R. C. (1998). Pathophysiology of delirium. *Journal of Geriatric Psychiatry and Neurology, 11*, 138-145.

van der Mast, R. C., van den Broek, W. W., Fekkes, D., Pepplinkhuizen, L., & Habbema, J. D. (2000). Is delirium after cardiac surgery related to plasma amino acids and physical condition? *Journal of Neuropsychiatry and Clinical Neurosciences, 12*, 57-63.

Verret, L., Goutagny, R., Fort, P., Cagnon, L., Salvert, D., Leger, L., . . . Luppi, P. H. (2003). A role of melanin-concentrating hormone producing neurons in the central regulation of paradoxical sleep. *BMC Neuroscience, 4*, 19.

Walder, B., Tramer, M. R., & Blois, R. (2001). The effects of two single doses of tramadol on sleep: A randomized, cross-over trial in healthy volunteers. *European Journal of Anaesthesiology, 18,* 36-42.

Wang, D., & Teichtahl, H. (2007). Opioids, sleep architecture and sleep-disordered breathing. *Sleep Medical Reviews*, *11*, 35-46.

Watson, P. L., Ely, W., Malow, B., & Pandharipande, P. P. (2006). Scoring sleep in critically ill patients: Limitations in standard methodology and the need for revised criteria. *Critical Care Medicine, 34,* A83.

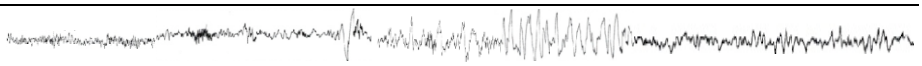
Wijdicks, E. F., & Stevens, M. (1992). The role of hypotension in septic encephalopathy following surgical procedures. *Archives of Neurology, 49,* 653-656.

Yildizeli, B., Ozyurtkan, M. O., Batirel, H. F., Kuscu, K., Bekiroglu, N., & Yuksel, M. (2005). Factors associated with postoperative delirium after thoracic surgery. *Annals of Thoracic Surgery, 79*, 1004-1009.

Zhong, X., Hilton, H. J., Gates, G. J., Jelic, S., Stern, Y., Bartels, M. N., . . . Basner, R. C. (2005). Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. *Journal of Applied Physiology, 98*, 2024-2032.

Table 1

Characteristics of NREM and REM sleep

	Sleep Stages			
	NREM			REM
Characteristics	Stage 1	Stage 2	SWS	
EEG				
% of the TST	2-5%	45- 55%	15-20%	20-25%
Wave	Low voltage; Mixed frequency activity	Intermittent sleep spindles and K-complexes	High voltage; Slow Delta waves	Low-voltage amplitude; Saw-tooth waves high frequency EEG
Physiologic	↓CBF (brain stem and cerebellum in Stage1 and 2) ↓CBF (cortex in SWS) ↑GH and ↓corticosteroids and catecholamines (SWS) ↓HR, ↓BP, ↓RR (more regular than REMs) ↑PAP ↓CO ↓Brain temperature Arousal threshold increase through the stages			↑CBF, Cardio- respiratory irregularities[a] (↑HR,↑RR and BP variations); ↑Brain temperature[b]; Pupil change[b]; High arousal threshold[b]
Behavioral	Leg movement; Changes in posture; Talking; Sleep walking; Dreams (at sleep onset and Stage 2)			Muscle atonia[b] Muscle twitches[a]; Rapid eye movement[a]; Dreams

NREM, non rapid eye movement; REM, rapid eye movement; SWS, slow wave sleep; EEG, Electroencephalogram; TST, total sleep time; CBF, cerebral blood flow; GH, growth hormone; HR, heart rate; BP, blood pressure; RR, respiratory rate; PAP, pulmonary arterial pressure; CO, cardiac output; ↑, increase; ↓, decrease.

[a] REM sleep phasic characteristics; [b] REM sleep tonic characteristics.

Table 2

Components of the Wake-Sleep-Regulatory System

Components	Projection	Substance	Effect
ARAS 1st Pathway			
PPT	Thalamus	Acetylcholine	Wakefulness REM sleep
LDT	Thalamus	Acetylcholine	Wakefulness REM sleep
ARAS 2nd Pathway			
TM	Forebrain	Histamine	Wakefulness Suppress NREM
LC	Forebrain	Noradrenaline	Wakefulness Suppress REM
Raphe[a]	Forebrain	Serotonin (5-HT)	NREM sleep Wakefulness Suppress REM
vPAG	Forebrain	Dopamine	Wakefulness REM sleep
Other Components			
LH area	Forebrain ARAS	Melatonin Orexin Glutamate	REM sleep Wakefulness Wakefulness
BF area	Forebrain	Acetylcholine GABA Glutamate	Wakefulness REM sleep Sleep Wakefulness
VLPO			
VLPO cluster and VLPO extended	ARAS	GABA and Galanin	Sleep

ARAS, ascending reticular activating pathway; PPT, pedunculopontine nucleus; LDT, laterodorsal tegmental nucleus; TM, tuberomammillary nucleus; LC, locus coeruleus nucleus; vPAG, ventral periacueductal grey matter; LH, lateral hypothalamic; BF, basal forebrain; GABA, gamma-amino-butiric acid; VLPO, ventrolateral preoptic.

[a] Raphe, dorsal and median raphe nuclei.

Table 3

Physiologic and Behavioral Characteristics according to Two Delirium Sub-types

	Delirium Subtypes	
Characteristics	**Hyperactive**	**Hypoactive**
% in ICU	0- 6%	43.5 - 94%
Level of consciousness	Hyperalert/vigilant Distractibility	Lethargy, ↓ Alertness Inattention
Cognition	Diffuse deficits Speech loud, incomprehensible, rapid and disorganized Disorientation	Diffuse deficits Slow speech/quiet
Perceptual disturbances	Hallucination Delusions	Lack of perceptual disturbance
Physiologic	Low-voltage fast EEG ↑ or normal cerebral metabolic activity ↓ GABA activity	Slow/diffuse EEG ↓ Cerebral metabolic activity ↑ GABA activity
Behaviors	↑ Psychomotor activity Restless Excitable Combative Mood liability	↓ Psychomotor activity Apathetic ↓ Stimuli response Withdraws
Possible Etiology	Benzodiazepine withdrawal Alcohol/drug withdrawal Drug intoxication	Benzodiazepine intoxication Hepatic encephalopathy Hypercapnea Hypoxia Metabolic disturbance
Outcome	Best	Worst

↑, increase; ↓, decrease; GABA, gamma-amino-butiric acid

Table 4

Differences between Sleep Deprivation, Delirium, Depression, and Dementia (Modified from Trzepacz et al. (2002)

Features	**Sleep Deprivation**	**Delirium**	**Depression**	**Dementia**
Onset	Variable	Acute (hour /days)	Variable (weeks/months)	Insidious (month/years)
Course	Variable	Fluctuating	Variable	Progresses slowly
Level of consciousness	Impaired	Impaired	Usually normal	Usually normal
Attention	Impaired	Inattention	Minimal deficit	Relatively normal
Memory	Disrupted memory consolidation	Impaired (immediate and short-term memory)	Usually intact (short-term memory deficit)	Impaired (immediate and recent events)
Thinking	Inhability to concentrate	Disorganized	Intact (inhability to concentrate, negative thoughts)	Dificulty with abstractions, finding words, decreased judgments
Orientation	Intact	Disoriented (time and place)	Selective disorientation	Intact in early dementia (worse with progression)
Reversibility	Reversible	Reversible	Potential	Progressive

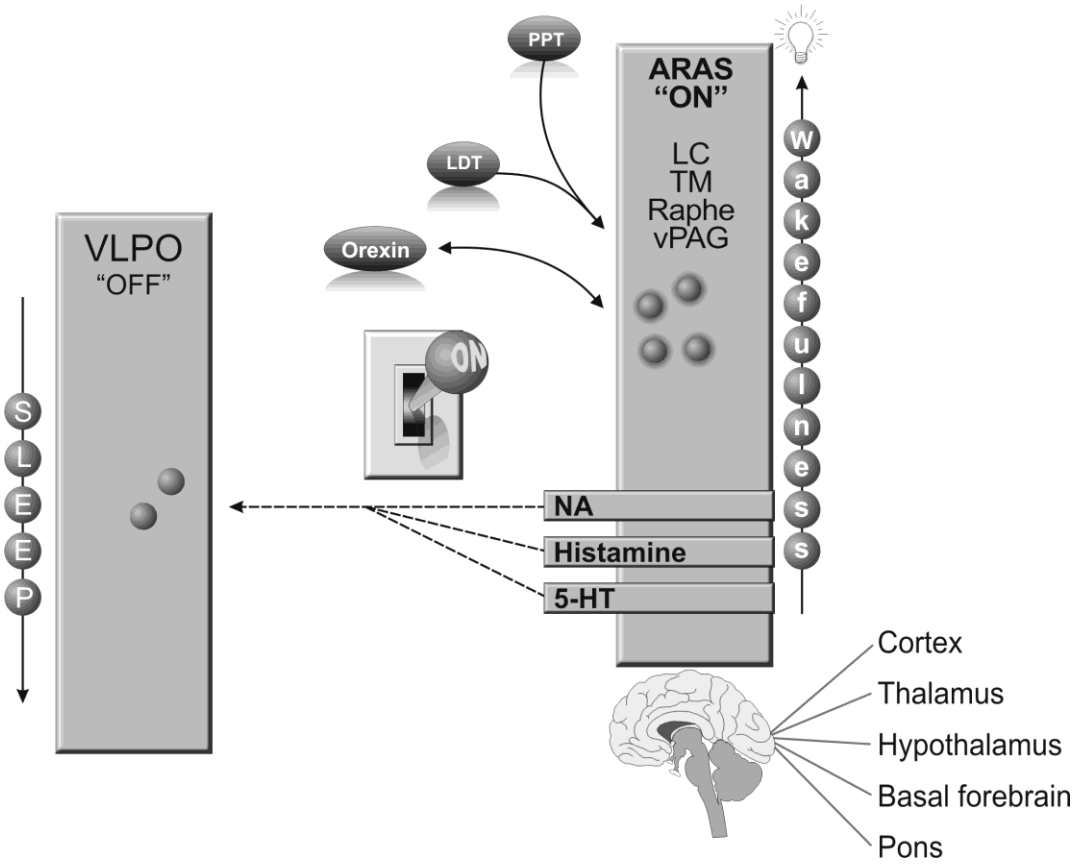


Figure 1. Representation of the "flip-flop switch" mechanism that regulates sleep-wake-cycle. Ascending reticula activating system (ARAS) is "On" during wakefulness by active firing from wakefulness-promoting neurons (pedunculopontine PPT; laterodorsal tegmental, LDT; locus coeruleus, LC; tuberomammillary, TM; dorsal and median raphe nuclei; and ventral periaqueductal grey, vPAG,). Neurotransmitters (noradrenaline, NA; histamine, and serotonin, 5-HT) are released from the ARAS neurons to inhibit ventrolateral preoptic (VLPO) neurons which provoke VLPO to turn "Off". Orexin peptide strengthens the ARAS by direct excitation of the monoaminergic neurons, while monoaminergic neurons simultaneously send an inhibitory influence to orexin neurons. Solid arrow represents excitatory input, dashed arrow represents inhibitory input.

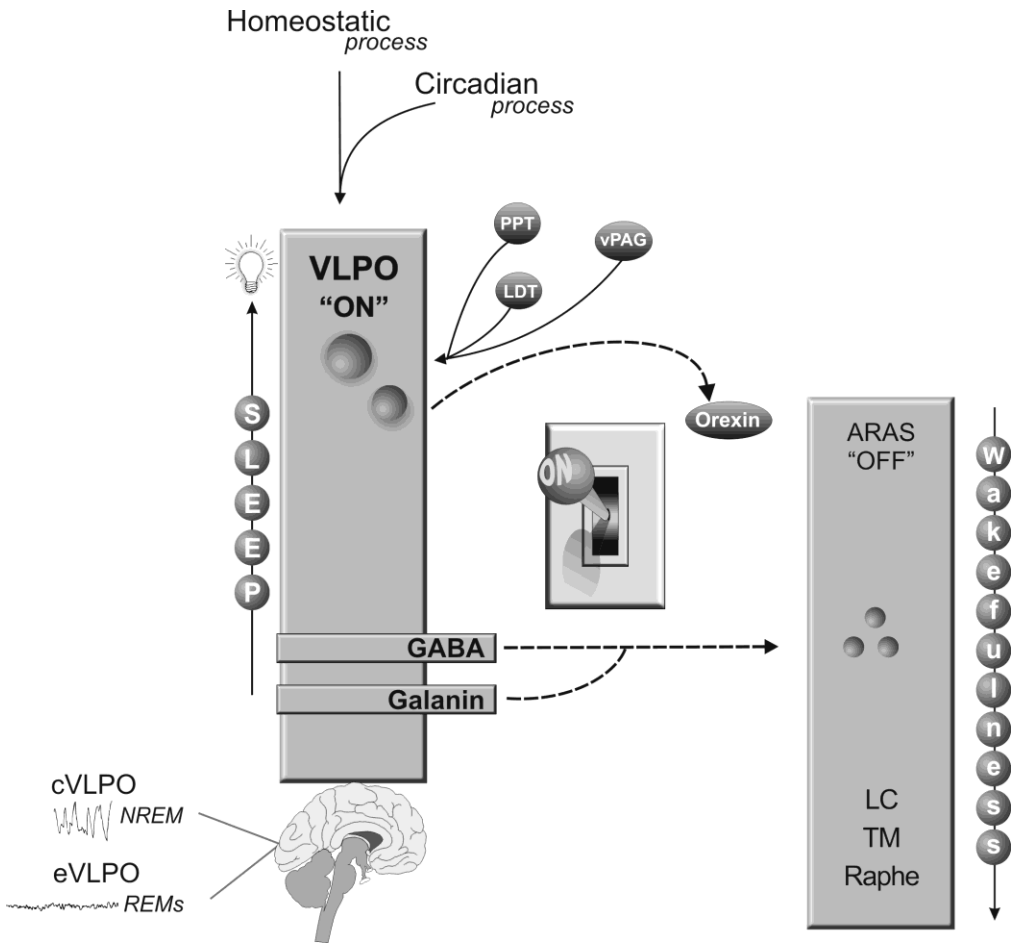


Figure 2. Representation of the "flip-flop switch" mechanism that regulates sleep-wake-cycle. Ventrolateral preoptic (VLPO) nucleous is "On" during sleep by activation of both VLPO cluster (cVLPO) and VLPO extended (eVLPO) neurons. These neurons release gamma-amino-butiric acid (GABA) and galanin and inhibit both ascending reticular activating (ARAS) neurons (locus coeruleus, LC; tuberomammillary, TM; and dorsal and median raphe nuclei) and orexin peptide. These provoke ARAS to turn "Off". Cholinergic neurons (pedunculopontine, PPT and laterodorsal tegmenta, LDT) and ventral periaqueductal grey (vPAG) promotes REM sleep. Homeostatic and circadian processes influence VLPO. Solid arrow represents excitatory input, dashed arrow represents inhibitory input.

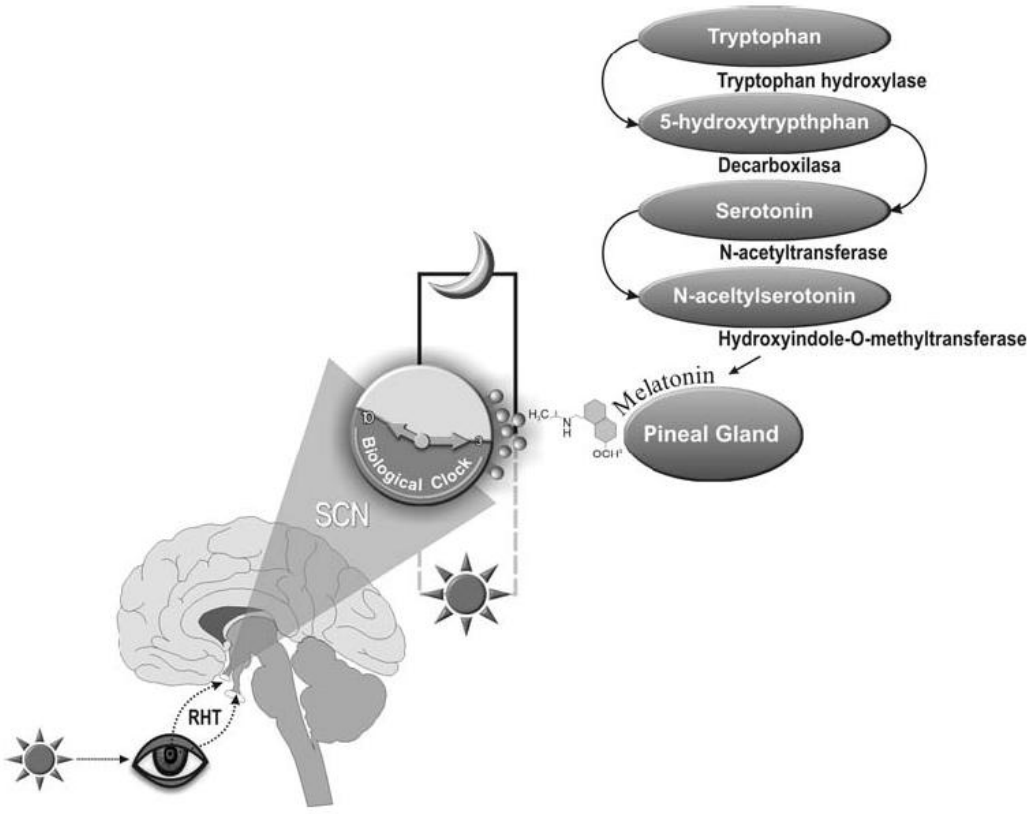


Figure 3. The suprachiasmatic nucleus (SCN) by receiving the information from light and dark environmental stimuli through the retina, regulates the secretion of melatonin produced by the pineal gland. Tryptophan starts the synthesis of melatonin through intermediates (5-hydroxytryptophan, serotonin, and N-acetylserotonin).
RHT, retinohypothalamic tract.

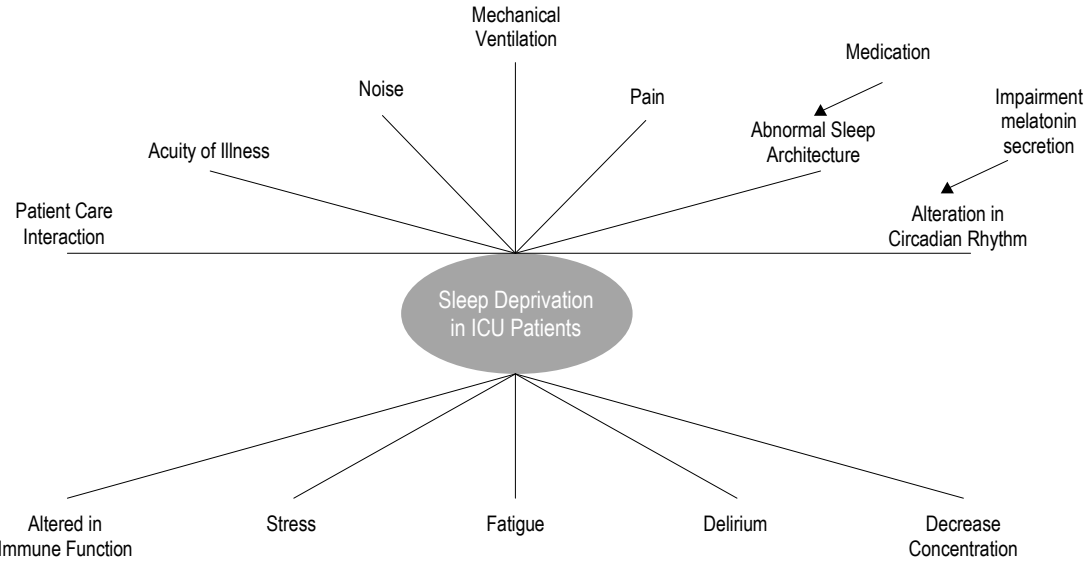


Figure 4. Risk factors and potential outcomes of sleep deprivation in ICU patients.

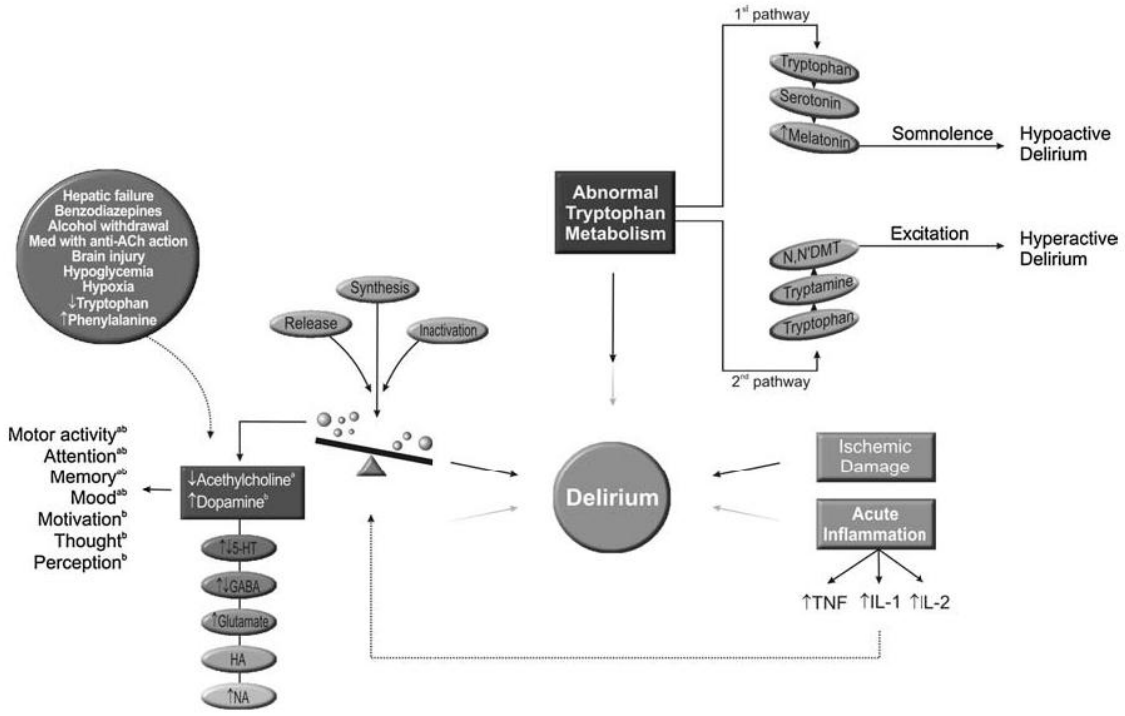


Figure 5. Representation of the three hypotheses of delirium mechanisms: (1) imbalance (release, synthesis, and inactivation) in neurotransmitters induced by the factors within the circle, (2) abnormal tryptophan metabolism constitutes two principal pathways that lead to either hyperactive or hypoactive delirium, (3) occult diffuse brain injury by ischemic damage or acute inflammation (increase in cytokines: tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-2 (IL-2). Cytokines could interfere with neurotransmitter function. Med, medications; anti-Ach, anticholinergic; 5-HT, serotonin; GABA, gamma-amino-butiric acid; HA, histamine; NA, noradrenaline, DMT, N,N'dimethylathryptamine ; ↑, increase; ↓, decrease.

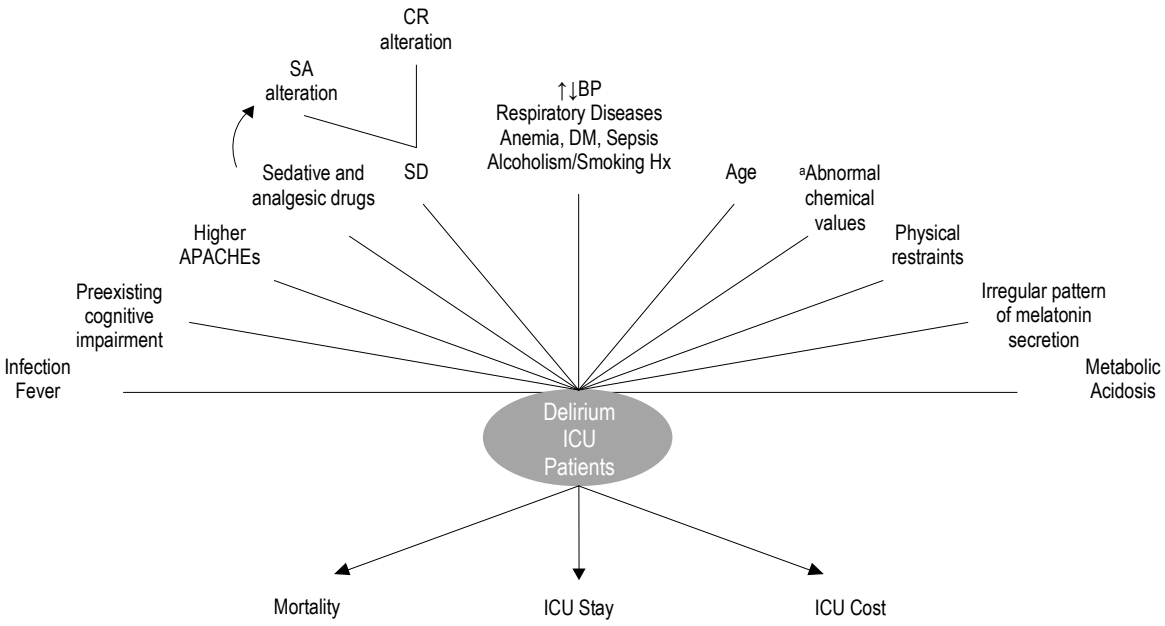


Figure 6. Risk factors and outcomes of delirium in ICU patients. SA, sleep architecture; CR, circadian rhythms; SD, sleep deprivation; ↑, increase; ↓, decrease. [a]Hypocalcemia, hyponatremia, hyperamylasemia, hyperbilirubinemia, increase in hepatic enzymes, and azotemia.

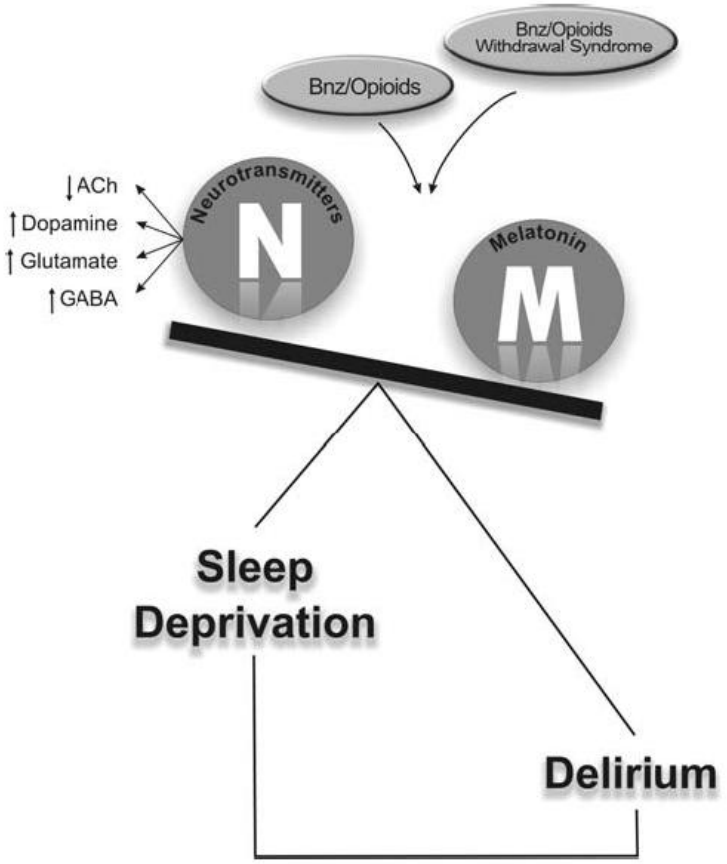


Figure 7. Benzodiazepine/opioids use and benzodiazepine/opioids withdrawal syndrome can contribute to an imbalance in neurotransmitters and alteration in melatonin production. These can be involved in the relationship between sleep deprivation and delirium. Bnz, benzodiazepines; ACh, acetylcholine; GABA, gamma-amino-butiric acid; ↑, increase; ↓, decrease.

Chapter III

The Effect of a Sedation Wake-up Trial and
Spontaneous Breathing Trial on the Occurrence of Delirium
and Perception of Sleep in Critically Ill Trauma Patients

Abstract

Delirium is associated with negative outcomes in intensive care unit (ICU) patients. The administration of benzodiazepines could lead to delirium. Implementation of a daily sedation wake-up trial (SWT) and spontaneous breathing trial (SBT) has shown significant reductions in the administration of sedatives, shorter duration of mechanical ventilation, and shorter length of ICU stay in medical ICU patients.

A prospective interventional trial was used to determine whether a SWT combined with a SBT results in a reduction in the occurrence of delirium and improvements in other outcomes in critically ill trauma patients. Patients with baseline neurological or psychiatric diseases, head trauma, and history of alcoholism or drug dependence were excluded. A total of 40 mechanically ventilated trauma patients were enrolled in the study. Patients in the control group (CG) (n = 20) received continuous sedative infusions without SWT and without standardized SBT based on the standard clinical practice of the trauma ICU (TICU), while patients in the intervention group (IG) (n = 20) received the combined intervention of SWT plus SBT according to the study protocol.

Eighty percent of patients in the CG developed delirium versus 30% in the IG. Being in the CG (OR 0.100; 95% CI: 0.016- 0.629) and being older (OR 1.07, 95% CI: 1.010-1.131) significantly predicted delirium occurrence. The CG demonstrated more hypoactive delirium, while the IG demonstrated more mixed delirium. Total cumulative and daily dose of benzodiazepines and propofol during TICU stay were significantly higher in the CG. Patients in the IG recovered from drug-induced coma faster (RH 2.25; 95% CI: 1.08-4.65) and were liberated from the mechanical ventilator (RH 3.09; 95% CI: 1.45-6.60) and discharged from the TICU sooner (RH 4.20; 95% CI: 1.82-9.69).

Complications, clinical events, and adverse events were not different between groups. This study demonstrates, with limitations, the contribution of the combined intervention of SWT and SBT to improve clinical outcomes in these trauma patients.

Introduction

Delirium is common in critically ill patients and has been associated with negative patient outcomes: increased mortality, longer length of stay, and higher intensive care unit (ICU) cost (Ely et al., 2001a; Ely et al., 2004a; Milbrandt et al., 2004; Ouimet et al., 2007; Thomason et al., 2005). Patients in ICU are exposed to several factors that could lead to delirium including the administration of benzodiazepines and opioids (Ely et al., 2004a; Pandharipande et al., 2008; Pandharipande et al., 2006). Benzodiazepine may lead to hypoactive delirium by increasing GABA activity which alters levels of potentially delirogenic neurotransmitters (Smith, Breitbart, & Platt, 1995) and opioids can cause delirium by decreasing acetylcholine and increasing dopamine and glutamate activity (Roche, 2003). To the contrary, benzodiazepine withdrawal may lead to hyperactive delirium by decreasing GABA activity (Smith, et al, 1995).

Research has shown that medical and cardiac patients who receive lorazepam are more likely to develop delirium (Pandharipande et al., 2006) and that daily and cumulative doses of lorazepam are significantly higher in patients with delirium compared to patients without delirium (Ely et al., 2004a). Midazolam, another benzodiazepine, was found to be an independent risk factor for delirium in trauma and surgical ICU patients. The opioid, fentanyl, was also an independent risk factor for delirium but only in a the surgical patients (Pandharipande et al., 2008).

Studies using a protocol-driven approach to daily interruption of sedative infusion, also known as a sedation wake-up trial (SWT), have been done to determine the effectiveness of SWT in improving patient outcomes (Carson et al., 2006; Kress, Pohlman, O'Connor, & Hall, 2000). Through the implementation of this intervention,

there was a significant reduction in the administration of sedatives and analgesics, a shorter duration of mechanical ventilation, and a briefer length of stay in the ICU (Carson et al., 2006; Kress et al., 2000).

SWT has not been studied in trauma ICU (TICU) patients. Since SWT reduces the total dose of sedatives administered, this intervention may contribute to decreasing the occurrence of delirium in this population. A SWT intervention, combined with a daily spontaneous breathing trial (SBT) protocol, led to a significant reduction in total dose of benzodiazepines used post-enrollment (p =.02), a shorter ICU stay (p = .04), and an increase in ventilator-free days (p = .02) in medical ICU patients, all measures of patient improvement (Girard et al., 2008). Therefore, a prospective interventional trial was conducted to determine whether a SWT combined with a SBT results in a reduction of the occurrence of delirium and improvements in other outcomes in critically ill trauma patients.

The first aim of the study was to compare the following outcomes in a group of patients who received SWT plus SBT versus a group of patients who received usual care: (a) occurrence of delirium; (b) duration of delirium; (c) prevalence of type of delirium; (d) changes in delirium status across time; (e) total cumulative doses and average daily doses of both sedatives and analgesics; (f) number of complications, clinical events, and adverse events; (g) duration of drug-induced coma; (h) duration of mechanical ventilation; (i) length of TICU stay; (j) length of hospital stay; and (k) change in sleep perception across time. The second aim was to explore the best predictors of the occurrence of delirium. Finally, the third aim was to establish interrater reliability of both the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and

Richmond Agitation Sedation Scale (RASS) Spanish versions and to establish the correlation between scores on the Bispectral Index (BIS), a measure of level of consciousness, and scores on the RASS, a measure of agitation and sedation, in a sample of TICU patients.

Method

Setting and Study Subjects

This study was conducted in the TICU at the Trauma Hospital in the Medical Center of San Juan, Puerto Rico. This unit receives critically ill patients after a motor vehicle crash, gunshot injury, penetrating injury, or fall. All consecutive patients admitted to the TICU were screened during their first 24 hours of admission between July 29, 2008 and August 10, 2009. The principal investigator (MIF) determined each patient's study eligibility. Patients were able to participate if they were ≥ 21 years of age, receiving mechanical ventilation, receiving a continuous sedative infusion, and deeply sedated (RASS -4) or unarousable (RASS -5) (Sessler et al., 2002). Patients were excluded if they were determined to have baseline neurological or psychiatric diseases, head trauma, acute neurological injury with a Glasgow Coma Scale score < 8, a history of alcoholism or drug dependence, who were both deaf and blind, or whose death was expected within 24 hours (i.e., Acute Physiology and Chronic Health Evaluation [APACHE] II ≥ 30) (Knaus, Draper, Wagner, & Zimmerman, 1985).

The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus and the Committee on Human Research of the University of California, San Francisco approved this study. This study was registered at ClinicalTrial.gov, number NCT00714194.

Measures

Delirium was measured with the CAM-ICU, Spanish version (Vanderbilt University, 2002). The CAM-ICU is an instrument developed to identify delirium in mechanically ventilated and non-ventilated ICU patients (Ely et al., 2001c). This instrument uses an algorithm system that includes four domains. Delirium is diagnosed if the patient is positive in three of the four domains: acute onset of mental status changes or fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. The CAM-ICU has been validated in large ICU sample (Ely et al., 2001b; Ely et al., 2001c) and includes tools and questions that reduce subjectivity (permission was granted by Doctor E. Wesly Ely to use the CAM-ICU Spanish version for this study.)

Sedation and agitation levels were measured with the RASS (Sessler et al., 2002). This instrument consists of an assessment of three principal states: agitation (+1 to +4), calm/alert (0), and sedation (-1 to -5). The RASS is easy to use and has high compliance, acceptability, and usefulness for ICU patients. In addition, it has excellent psychometric properties (Ely et al., 2003; Sessler et al., 2002). Motoric subtypes of delirium were classified according to Peterson et al. (2006) criteria as: (a) hypoactive, CAM-ICU positive with a RASS 0 to -3; (b) hyperactive, CAM-ICU positive with a RASS +1 to +4; and (c) mixed, positive CAM-ICU assessments that alternate between hyperactive and hypoactive.

A non-invasive physiological monitor BIS (A-2000 BIS-XP™, Aspect Medical Systems, Norwood, MA) was used to estimate the patient's level of consciousness. The BIS monitoring system uses a sensor placed on the patient's forehead to detect electrical

signals from the brain. Signals are received by a digital converter and then displayed on a monitor screen. BIS scores range from 0 (isoelectrical line) to 100 (alert). The score decreases according to the depth of sedation.

Sleep perception was measured with the Patient's Sleep Perception questionnaire developed for this study based upon previous ICU sleep instruments that were deemed too long for ICU patients (Freedman, Kotzer, & Schwab, 1999) or did not include ICU patient's daytime sleep (Richards, 1987) to be feasible or adequate for use with ICU patients. This instrument includes seven items answered by a 0 to 10 numeric rating scale. The 0 corresponds to the answer that describes the best sleep perception, whereas 10 corresponds to the worst sleep perception. Questions were asked about the overall quality of sleep, number of awakenings, sleep satisfaction, and the type of dreams experienced during both day and night time.

Baseline measures. Baseline measures included patient demographics, diagnosis, length of stay before TICU admission (i.e., in the stabilizing unit and/or recovery room until TICU admission), cumulative doses of sedatives and analgesics received, in mg/kg, before TICU admission (i.e., administered in stabilizing unit and/or recovery room until TICU admission, excluding sedatives and analgesics administered in the operating room). Physiological measures (heart rate [HR], respiratory rate [RR], blood pressure [BP], and oxygen saturation [SpO_2]), APACHE II score, agitation/sedation level per RASS, and level of consciousness per BIS were obtained the day of enrollment which corresponded to the first 24 or 48 hours of TICU admission.

Outcomes measures. These measures included the occurrence and number of days in delirium during TICU stay, days in drug-induced coma (RASS -4 or -5) during TICU

stay, daily RASS score during TICU stay, total daily doses and cumulative doses of sedatives and analgesics in mg/kg before first delirium measurement (i.e., before TICU admission and during TICU stay before first delirium measurement) and during total TICU stay, days on mechanical ventilation, length of TICU stay, total hospital stay, complications (e.g. sepsis, acute respiratory distress syndrome), clinical events (i.e., tracheostomy and death) and, adverse events (i.e., self-extubation, self-removal of tubes or catheters [e.g. central catheter, chest tube]).

Procedure

All patients in the TICU that met inclusion criteria were enrolled in the study using a sequential assignment method. Enrollment started with the control group (CG) and was followed by the intervention group (IG). An authorized patient representative signed the informed consent. Once patients were able to consent, their desire to continue or terminate participation in the study and approval to use the previously obtained data were documented and signed in the consent form. All patients except those who died ($n = 5$) and one patient who developed a neurological impairment in TICU signed the consent form.

Patients in the CG received the usual care of the TICU that consisted of the administration of continuous sedative infusions without SWT and without standardized SBT, while patients in the IG received the combined intervention of SWT plus SBT according to the study protocol. Type, amount, and frequency of sedative administration were determined by physician discretion in both groups. Patients in the IG received the SWT if they met the criteria detailed in Figure 1. The SWT was started with the interruption of continuous sedative infusion in the morning (between 7:00 a.m. and 8:00

a.m.) for a maximum of 4 hours. The SWT was stopped if a patient developed failure criteria to the SWT detailed in Figure 1. Once a patient failed the SWT, the continuous sedative infusion was resumed at half of the previous dose adjusting to the target level of sedation established. In addition, a sedative IV bolus was given if a patient showed a RASS of +3 or +4. For those patients who did not fail and showed RASS scores between 0 and -5 at the end of the SWT, the continuous sedative infusion was discontinued and changed to scheduled intermittent doses to treat further agitation or anxiety. Since pain management is a cornerstone of clinical practice in this population, continuous infusions or intermittent doses of opioids were not interrupted during the SWT.

Physiological measures, RASS, and BIS were measured prior to the SWT. Physiological measures, RASS, BIS, delirium, and pain were measured at the end of the SWT or when the patient was awake or developed agitation before resumption of the continuous sedative infusion (these data are discuss in the third manuscript of this dissertation). Significant changes in physiological measures (HR > 20% from baseline or > 120 beats/min, systolic BP > 20% from baseline or > 180 mmHg, RR > 20/min, and SpO_2 < 90%) or the presence of pain were reported to the physician and nurse in charge for their determination of the patient's subsequent management.

Patients who passed the SWT with a RASS score of 0 to -2 were screened for the SBT (see Figure 1). However, if a patient met the SBT criteria, then the mechanical ventilator mode was changed to continuous positive airway pressure (CPAP) for two hours or until the patient met SBT failure criteria detailed in Figure 1. The decision to extubate a patient was made by the physician in charge.

Delirium was evaluated three times a day (at approximately 8:00 a.m., 2:00 p.m., and 8:00 p.m.) for a maximum of three days after discontinuation of continuous intravenous (IV) deep sedation. If patients remained delirious after the three days of consecutive evaluation of delirium, the CAM-ICU was performed daily until the patient no longer exhibited delirium. Independent CAM-ICU ratings were performed in a blinded fashion by the principal investigator (MIF) and co-investigator (CMA) at the second evaluation day, with an interval of five minutes between ratings. Sleep perception was evaluated daily after continuous IV sedation discontinuation, for a maximum of three days. The Sleep Perception questionnaire was read to patients in the morning by the principal investigator. Patients responded by nodding or closing their eyes for a "yes" response to a question. Daily simultaneous RASS ratings during the patient's entire TICU stay were also done by MIF and CMA. The simultaneous rating consisted of both observers rating the same patient at the same interaction according to Ely et al. (2003). The principal investigator was blinded to the patient's BIS score. Daily BIS scores were obtained by the co-investigator.

Power Analysis

N-Query Advisor® 5.0 was used to calculate the sample size needed to address one aspect of the primary aim through a simple logistic regression analysis; that is, to determine a significant difference in the occurrence of delirium between groups. A power analysis indicated that 91 patients per group was needed to have sufficient (80%) power to detect a difference between groups if the odds ratio was 2.67 with a two-tailed alpha of .05 level of significance. This odds ratio effect size estimation was based on results of previous studies in which there was an 80% occurrence of delirium in ICU

patients (Ely et al., 2001a; Ely et al., 2001b; Ely et al., 2004) and the assumption that the IG would have a lower occurrence of delirium (approximately 60%). The difference between 80% and 60% is equivalent to an odds ratio of 2.67.

It was proposed that the sequential method of recruitment and enrollment would be used to assign the first 20 patients to CG and the next 20 to IG. If a comparison of data from the two groups did not show the effect of the SWT on the critical variable of delirium occurrence, then data collection would continue using the sequential assignment method, alternating CG and IG with cohorts of 10 patients at a time. This method would proceed until a delirium effect was detected or until the a priori sample size of 182 (i.e., 91 patients per group) was reached. If a comparison of the data from the two groups showed an effect with the first cohort of 20 patients per group, recruitment would end.

A post hoc power analysis was done using the actual odds ratio (9.33) in the occurrence of delirium when IG was the reference group. Results showed that the actual effect size was much larger than the originally estimated size, and 19 patients per group were sufficient to detect statistical differences between groups.

Statistical Analysis

Data for patient demographics, baseline characteristics, and total amount of sedatives and analgesics administered were not normally distributed and, thus, were tested non-parametrically with Mann-Whitney *U* tests. To investigate if CG patients and IG patients differ in the occurrence of delirium after deep sedation discontinuation, a simple logistic regression was done. A multiple logistic regression was used to investigate the best predictors of the occurrence of delirium. Multilevel logistic regression was conducted to compare change in delirium status and multilevel regression

for change in sleep perception. A Cox proportional hazards regression model was used to compare groups on five key outcome variables: days in delirium, days in drug-induced coma, duration on mechanical ventilation, and length of stay in both TICU and the hospital. Age, motoric subtypes of delirium, complications, clinical events, and adverse events between groups were compared using Chi square. Cohen's kappa statistic was used to determine interrater reliability of both the RASS and CAM-ICU Spanish versions. Spearman Rho correlation was performed to estimate the association between RASS scores and BIS scores, and multilevel regression was used to predict RASS scores from BIS scores across time. Patients who died before the first delirium measurement were not included in the data analysis. Both odds and hazard ratios analysis used the CG as the reference group. Statistical analyses were performed using SPSS® version 16.0 and STATA® version 11.0.

Results

Patients were enrolled between July 29, 2008 and August 10, 2009. The recruitment process is shown in Figure 2. A total of 40 patients, 20 per group, were included in the analysis. Demographics and baseline clinical characteristics were similar in both groups (see Table 1).

Delirium

Sixteen patients (80%) developed delirium in the CG, whereas only six (30%) did so in the IG. The odds of being delirious decreased by 89% in the IG compared to the CG (OR 0.107; 95% CI: 0.025- 0.459, p = .003). An overall multiple logistic regression model in which delirium occurrence was the dependent variable and included group assignment, age, and benzodiazepine and propofol received before the first delirium

measurement was significant (χ^2 = 19.29, *df* = 4, *n* = 40, *p* = .001). After controlling for age, benzodiazepine, and propofol the odds of being delirious decreased by 90% in the IG compared to the CG (OR 0.100; 95% CI: 0.016- 0.629, *p* = .014). In addition, for every one year increase in age, the odds of being delirious increased by 7% when group assignment, benzodiazepine, and propofol were controlled (OR 1.07, 95% CI: 1.010- 1.131, *p* = .021). However, benzodiazepine and propofol were not significant contributors to the model after controlling for the other variables.

Although the occurrence of delirium was lower in IG patients, they tended to have longer periods of delirium than patients in the CG, but this was not statistically significant (relative hazard [RH] 0.25; CI: 0.054- 1.11, *p* = .07) (see Table 2). The delirium motoric subtype was significantly different between groups (χ^2 = 15.9, *df* = 3, *n* = 40, *p* = .001). The CG showed more hypoactive delirium while the IG showed more mixed delirium (see Figure 3).

Of the 22 patients who developed delirium, 21 (CG = 15, IG = 6) emerged from drug-induced coma into delirium; one from the CG emerged from drug-induced coma into an intact cognitive status. However, after a second drug-induced coma period, delirium was detected in this patient 48 hours after the first CAM-ICU measurement. A multilevel logistic regression showed a significant change in delirium status across time during the first three days measured. For every one unit increase in measurement time (8 hr), the odds of being delirious decreased by 51% (OR 0.49, 95% CI: 0.24- 0.96, *p* = .04). However, changes in delirium status between groups (*p* = .98) and the interaction between group and time (*p* = .44) were not significant. Thirty six percent of patients who

developed delirium showed a fluctuating pattern. In addition, delirium persisted in two IG patients up until the time of transfer.

Benzodiazepines and Opioids

Patients in the CG received more sedatives than those in the IG; however, they had a longer length of stay in TICU before the first delirium measurement (Table 3). Total cumulative dose of benzodiazepines prior to the first measurement of delirium and total cumulative and daily dose of benzodiazepines and propofol during TICU were found to be significantly different between groups. In contrast, opioid doses were not significantly different between groups.

Complications and Events

Complications of injury developed in the TICU were not statistically different between groups. Patients in both CG (65%) and IG (60%) developed one or more complications (see Table 4). Moreover, differences between groups in clinical and adverse events were not found to be statistically significant. These results are summarized in Table 4.

Other Outcomes

The rate of recovering from drug-induced coma was two times faster in the IG than in the CG (RH 2.25; 95% CI: 1.08- 4.65, $p = .03$) (see Table 2 and Figure 4). This means that the IG patients recovered from drug-induced coma sooner than CG patients. The rate of being liberated from the mechanical ventilator was three times greater in the IG than in the CG, after adjusting for complications (RH 3.09; 95% CI: 1.45- 6.60, $p = .004$) (see Table 2 and Figure 5). This means that IG patients were liberated from the mechanical ventilator significantly sooner than patients in the CG. The rate of discharge from the

TICU was four times greater in the IG than the CG, after adjusting for complications (RH 4.20; 95% CI: 1.82- 9.69, p = .001) (see Table 2 and Figure 6). Although differences between groups were not found to be statistically significant, patients in the IG had a longer length of hospital stay, after adjusting for complications (see Table 2).

Sleep Perception

The Patient's Sleep Perception questionnaire had considerable missing data. This was due to patients' inability to respond or to patients being transferred out of the TICU (*n's* reported in Table 5). The questionnaire showed high internal consistency, Cronbach's α = .81. Data from each item of the questionnaire were skewed; therefore a single mean score of the sum of the items was used to do the multilevel regression analysis. Although, in general, IG patients reported greater difficulty with sleep (see Table 5), there were no significant differences in sleep perception between groups on the first day (p = .93); in linear change across time, ignoring group assignment (p = .20); and in the interaction between group and time (p = .85). The sleep perception mean (*SD*) of the sum of the items across three days was 6.5 (2.4). Types of dreams reported by patients across three days are depicted in Figure 7.

CAM-ICU, RASS, and BIS

A total of 37 paired assessments of CAM-ICU were performed on the patient's second day of delirium measurement. The strength of agreement between raters was almost perfect according to Landis and Koch (1977), (κ = 0.95; 95% CI: 0.84- 1.00). The Cohen's κ for RASS measured at baseline using 39 paired assessments was almost perfect (κ = 0.95; 95% CI: 0.85- 1.00) between raters. In 450 paired observations of

RASS from baseline until the 14th day of study enrollment the Cohen's κ was 0.96 (95% CI: 0.94- 0.98) of agreement.

There was no correlation between RASS scores (i.e., -4 or -5) and BIS scores at baseline in the sample of 40 patients (r = .14, p = .39). However, when these 40 patients were monitored from baseline to the 14th day of study enrollment (i.e., 317 paired assessments), the correlation became much stronger (r = .72, p < .0005). A multilevel regression analysis showed a significant association between BIS and RASS across time, including baseline measures. For a 10% increase in BIS there was an expected 0.6 increase on the RASS (t = 18.92, p < .0005). Level of consciousness from the RASS score was grouped into three categories: (1) RASS 0 to -1, alert with sustained eye contact; (2) RASS -2 to -3, arousable by verbal stimulation without sustained eye contact; and (3) RASS -4 to -5, unarousable by verbal stimulation according to Ely and colleagues (2004b). For each of the three levels of consciousness derived from RASS, the median (interquartile ranges [IQR]) BIS score was 81.5 (IQR 74- 87.5), 65 (IQR 55- 73), and 46 (IQR 41- 52), respectively (see Figure 8). In addition, the minimum and maximum ranges of BIS score for each category were 64 to 95, 30 to 96, and 41 to 52, respectively.

Discussion

This study evaluated the effect of using a sedation wake-up trial plus spontaneous breathing trial in 20 patients compared to 20 controls on several outcomes in critically ill trauma patients. Although SWT has been studied with different ICU patient populations (Carson et al., 2006; de Wit, Gennings, Jenvey, & Epstein, 2008; Kress et al., 2000; Mehta et al., 2008), this combined intervention (SWT plus SBT) has been studied only in medical ICU patients (Girard et al., 2008).

Our study demonstrated that the trauma patient group receiving SWT plus SBT had a lower occurrence of delirium compared to the control patients. It was not possible to control for type of sedation; some patients were on benzodiazepines, some on propofol, and some on both. Furthermore, the intermittent sedation could not be separated from the total dose of sedation. For those two reasons, the significant differences in delirium cannot be exclusively attributed to the SWT and SBT interventions. In contrast to our findings, Girard et al. (2008) did not find significant differences in the occurrence of delirium between medical patients who received both interventions and those who did not. This difference could be explained from our exclusion of patients with a history of alcohol or drug dependence and psychiatric disease who are considered to be high risk for delirium. Girard and colleagues did not report whether their patients had a history of these conditions. Furthermore, patients in our IG sample on average received lower amounts of benzodiazepines and propofol prior to the first measurement of delirium than patients in the CG; this may also have contributed to a lower risk of developing delirium. However, amount of benzodiazepines and propofol were not significantly associated with delirium in our sample. One potential explanation for this lack of a significant association is the skewed distribution of the cumulative doses of benzodiazepine and/or propofol that occurred in both groups before the first delirium measurement. Other studies found that exposure to benzodiazepines was an independent predictor of delirium in medical, surgical, and trauma ICU patients (Pandharipande et al., 2008; Pandharipande et al., 2006).

It is important to remark that we selected patients who were in drug-induced coma (RASS -4 to -5) at baseline; therefore, the occurrence of delirium was measured only in

patients who emerged from drug-induced coma into delirium. It is important to reiterate that CG patients were in coma for a longer period of time than the IG patients. Some (Ouimet et al., 2007) found that coma (RASS -5) induced by medication (i.e., sedatives and analgesics) was a high risk factor for delirium; however, coma induced by medical conditions was not. We did not enroll patients who were in medically-induced coma.

Duration of delirium was longer in the IG (i.e., 3.5 days) than in the CG (i.e., 2 days), although not significant in our sample. This finding was contrary to that found by Girard and colleagues (2008) who reported similar duration of delirium between groups in their sample of 335 patients. The fact that our IG patients spent more time in delirium could be skewed by data from two older IG patients who spent 10 and 13 days of their TICU stay in delirium. A post hoc power analysis showed that, although the effect size for differences in days in delirium between our groups was large, our small sample did not have enough power to detect this effect as significant.

Our data showed that hypoactive delirium was higher in the CG, while mixed delirium was more pronounced in the IG. Findings from the CG were similar to another cohort of TICU patients who presented with more hypoactive delirium (60%), followed by mixed (6%), and hyperactive delirium (1%) (Pandharipande et al., 2007). A possible explanation for the differences between groups may be that our CG patients received more benzodiazepine which may lead to hypoactive delirium by increasing GABA activity. To the contrary, the IG was exposed to daily SWT followed by a 50% decrease of continuous sedative IV infusion, or they were switched to intermittent benzodiazepine therapy, which could result in a greater recovery from sedation. Consequently, IG

patients could have experienced withdrawal syndrome from decreasing GABA activity which could increase the probability of experiencing periods of hyperactive delirium.

Patients in the IG received lesser amounts of sedative during their TICU stay, as was found in other studies that implemented SWT (Girard et al., 2008; Kress et al., 2000; Mehta et al., 2008). Less time on mechanical ventilation and shorter ICU length of stay were also found in the IG, as seen in previous studies (Girard et al., 2008; Kress et al., 2000). This could be a direct consequence of the SWT. IG patients received lesser amount of sedative and were more awake, thus allowing for early mechanical ventilator weaning and extubation after the SBT and early TICU discharge. In contrast to Kress and colleagues (2000), but similar to other studies (Girard et al., 2008; Mehta et al., 2008), we did not find significant differences in amount of opioid use. However, there was a trend toward higher daily doses of opioids received by patients in the IG. This finding was not surprising since continuous infusion or intermittent doses of opioids were in place so as to not interrupt pain management.

Rates of self-extubation were not different between groups, supporting other study findings (Kress et al., 2000). However, Girard and colleagues (2008) found a significant increase in self-extubation in those who received the SWT plus SBT. This difference in self-extubation could be related to a potential bias. Since self-extubation was one of the study outcomes, researchers and nursing staff could apply interventions such as increased close observation or use of physical restrains in our IG patients to prevent self-extubations. Finally, in contrast to findings by Schweickert and colleagues (2004) in their large sample, we did not a find significantly lower rate of ventilator associated

pneumonia (VAP) in the IG. The lack of differences in VAP between our IG and CG could be due to the lack of power in our study for this variable.

In terms of sleep perception, missing data were a problem since patients were followed for only three days in TICU after continuous sedative infusion discontinuation. In future research patients need to be followed throughout the TICU stay and, perhaps, even further. Despite missing data, our results are consistent with other studies that showed that ICU patients experience sleep fragmentation, perceive their sleep quality as bad, and are not satisfied with their sleep (Freedman et al., 1999; Nicolas et al., 2008). The reason why patients in our IG perceived worse sleep than CG patients, although not significant, might be that they were more awake and consequently more aware of ICU noises and patient-care interactions that are known factors that disrupt a patients' sleep (Freedman, Gazendam, Levan, Pack, & Schwab, 2001; Freedman et al., 1999; Gabor et al., 2003). Critically ill patients consistently show sleep disturbance during their ICU stay. It is necessary, however, to persist in the search and implementation of new alternatives that support improvement in the quality of sleep. Further research is warranted to determine the best practices to improve sleep in ICU patients.

There was strong agreement between raters ($\kappa = 0.75$ to 0.96) for the CAM-ICU English version (Ely et al., 2001b; Ely et al., 2001c; Pun et al., 2005). A recent study (Tobar et al., 2010) that validated a new Spanish version of CAM-ICU showed an almost perfect agreement ($\kappa = 0.91$), as was found in our study. Our data showed a similar strength of agreement on simultaneous ratings of RASS compared with a previous study (English version), $\kappa = 0.91$ (Ely et al., 2003). However, the fact that one of the raters was not blinded to the BIS score could have biased the results. Substantial evidence supports

the use of the CAM-ICU and RASS as reliable and feasible instruments that provide clinicians and researchers with the opportunity to perform a systematic assessment of delirium and sedation/agitation levels in TICU patients.

The weak correlation between BIS scores and RASS scores at baseline is due to the restriction of range of the RASS scores at that time (-4 or -5) which reduces variability. In this study, the median BIS scores among the three levels of consciousness of RASS were lower compared to a previous study (Ely et al., 2004b). In addition, although there was no overlap among the interquartile ranges of the BIS score for each of the three RASS categories as was shown by Ely et al. (2004b), a considerable overlap was demonstrated among the minimum and maximum ranges of the BIS score with the three RASS categories. This finding limits the usefulness of BIS monitoring as a unique measure of sedation in ICU patients.

Several limitations must be considered when interpreting findings from this study. Randomization was not used; however, groups were similar in baseline measures. The design was sequential; all data from the CG were collected first, followed by the IG. This type of design is subject to threats to internal validity such as different dropout rates between groups or different environmental conditions during the CG period and the IG period. However, a randomized clinical trial, while more rigorous, also has some inherent problems. For example, there could be intervention contamination between groups when patients are recruited from the same site. Also, randomization does not assure IG and CG equivalence. As stated earlier, an important limitation to the significant differences in delirium found between the IG and the CG was the lack of control in the type of sedative given to both groups.

The two raters were not blinded to IG and CG group assignment; therefore, the data were subject to investigator bias toward greater improvement in IG patient outcomes. The use of the specification strategy to avoid confounding factors delayed the recruitment process and limits the generalizability of the results to selected trauma patients (i.e., those without baseline neurological or psychiatric diseases, head trauma or acute neurological, or history of alcoholism or drug dependence) (Newman, Browner, & Hulley, 2007).

Although differences between groups were found in many variables and recognizing that we had a small sample, post-hoc power analyses for other variables (i.e., gender, days in delirium, total hospital stay, and total cumulative dose of propofol before first delirium measurement) were done. These power analyses showed that the study was underpowered for those variables. The variability of these data were too large and the sample size too small to detect significant group differences. This provides preliminary information that should be tested in a larger sample.

Content validity of the Patient's Sleep Perception questionnaire was performed by investigators who are experts in the field of sleep and critical care. However, construct and criterion validity were not performed because of the limited sample size. Data derived from this questionnaire should be interpreted with caution.

Finally, pain presence was assessed at the end of each SWT in those IG patients who were able to respond. However, since SWT was not done in CG patients, we were not able to compare this outcome between groups. In addition, pain was not assessed in both groups along the TICU stay.

In conclusion, this study demonstrates, with limitations, the contribution of the combined intervention of SWT and SBT to improve clinical outcomes in selected trauma

patients. Critically ill trauma patients who received the combined intervention decreased in the occurrence of delirium, days in drug-induced coma, duration of mechanical ventilation, length of TICU stay, and total cumulative doses of benzodiazepines and propofol received during their stay in TICU. Data from the study reported here tend to support the theory concerning the action of benzodiazepines on delirium. The CG, which received a greater cumulative dose of benzodiazepines, experienced more hypoactive delirium than the IG. However, the IG, which received a lesser cumulative dose of benzodiazepines and experienced intermittent withdrawal of benzodiazepines, showed more of a mix of both hypoactive and hyperactive delirium. This conclusion is limited by the non randomized design, the small sample, and the lack of control in the type of sedatives given to both groups.

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References

Carson, S. S., Kress, J. P., Rodgers, J. E., Vinayak, A., Campbell-Bright, S., Levitt, J., . . . Hall, J. (2006). A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. *Critical Care Medicine, 34*, 1326-1332.

Chan, J. D., Treece, P. D., Engelberg, R. A., Crowley, L., Rubenfeld, G. D., Steinberg, K. P., & Curtis, J. R. (2004). Narcotic and benzodiazepine use after withdrawal of life support: Association with time to death? *Chest, 126*, 286-293.

de Wit, M., Gennings, C., Jenvey, W. I., & Epstein, S. K. (2008). Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. *Critical Care, 12*, R70.

Ely, E. W., Gautam, S., Margolin, R., Francis, J., May, L., Speroff, T., . . . Inouye, S. K. (2001a). The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Medicine, 27*, 1892-1900.

Ely, E. W., Inouye, S. K., Bernard, G. R., Gordon, S., Francis, J., May, L., . . . Dittus, R. (2001b). Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA, 286*, 2703-2710.

Ely, E. W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, R., . . . Inouye, S. K. (2001c). Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Critical Care Medicine, 29*, 1370-1379.

Ely, E. W., Shintani, A., Truman, B., Speroff, T., Gordon, S. M., Harrell, F. E., Jr., . . . Dittus, R. (2004a). Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA, 291*, 1753-1762.

Ely, E. W., Truman, B., Manzi, D. J., Sigl, J. C., Shintani, A., & Bernard, G. R. (2004b). Consciousness monitoring in ventilated patients: Bispectral EEG monitors arousal not delirium. *Intensive Care Medicine, 30*, 1537-1543.

Ely, E. W., Truman, B., Shintani, A., Thomason, J. W., Wheeler, A. P., Gordon, S., . . . Bernard, G. R. (2003). Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA, 289*, 2983-2991.

Freedman, N. S., Gazendam, J., Levan, L., Pack, A. I., & Schwab, R. J. (2001). Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine, 163*, 451-457.

Freedman, N. S., Kotzer, N., & Schwab, R. J. (1999). Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *American Journal of Respiratory and Critical Care Medicine, 159*, 1155-1162.

Gabor, J. Y., Cooper, A. B., Crombach, S. A., Lee, B., Kadikar, N., Bettger, H. E., & Hanly, P. J. (2003). Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *American Journal of Respiratory and Critical Care Medicine, 167*, 708-715.

Girard, T. D., Kress, J. P., Fuchs, B. D., Thomason, J. W., Schweickert, W. D., Pun, B. T., . . . Ely, E. W. (2008). Efficacy and safety of a paired sedation and ventilator

weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): A randomised controlled trial. *Lancet, 371*, 126-134.

Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). Apache II: A severity of disease classification system. *Critical Care Medicine, 13*, 818-829.

Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine, 342*, 1471-1477.

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics, 33*, 159-174.

Mehta, S., Burry, L., Martínez-Motta, J. C., Stewart, T. E., Hallett, D., McDonald, E., . . . Cook, D. J. (2008). A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: A pilot trial. *Critical Care Medicine, 36*, 2092-2099.

Milbrandt, E. B., Deppen, S., Harrison, P. L., Shintani, A. K., Speroff, T., Stiles, R. A., . . . Ely, E. W. (2004). Costs associated with delirium in mechanically ventilated patients. *Critical Care Medicine, 32*, 955-962.

Newman, T. B., Browner, W. S., & Hulley, S. B. (2007). Enhancing causal inference in observational studies. In S. B. Hulley, S. R. Cummings, W. S. Browner, D. G. Grady & T. B. Newman (Eds.), *Designing clinical research* (3rd ed., pp. 127- 146). Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Nicolas, A., Aizpitarte, E., Iruarrizaga, A., Vazquez, M., Margall, A., & Asiain, C. (2008). Perception of night-time sleep by surgical patients in an intensive care unit. *Nursing in Critical Care, 13*, 25-33.

Ouimet, S., Kavanagh, B. P., Gottfried, S. B., & Skrobik, Y. (2007). Incidence, risk factors and consequences of ICU delirium. *Intensive Care Medicine, 33*, 66-73.

Pandharipande, P., Cotton, B. A., Shintani, A., Thompson, J., Costabile, S., Truman Pun, B., . . . Ely, E. W. (2007). Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Medicine, 33*, 1726-1731.

Pandharipande, P., Cotton, B. A., Shintani, A., Thompson, J., Pun, B. T., Morris, J. A., Jr., . . . Ely, E. W. (2008). Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *Journal of Trauma, 65*, 34-41.

Pandharipande, P., Shintani, A., Peterson, J., Pun, B. T., Wilkinson, G. R., Dittus, R. S., . . . Ely, E. W. (2006). Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology, 104*, 21-26.

Peterson, J. F., Pun, B. T., Dittus, R. S., Thomason, J. W., Jackson, J. C., Shintani, A. K., . . . Ely, E. W. (2006). Delirium and its motoric subtypes: A study of 614 critically ill patients. *Journal of the American Geriatrics Society, 54*, 479-484.

Pun, B. T., Gordon, S. M., Peterson, J. F., Shintani, A. K., Jackson, J. C., Foss, J., . . . Ely, E. W. (2005). Large-scale implementation of sedation and delirium monitoring in the intensive care unit: A report from two medical centers. *Critical Care Medicine, 33*, 1199-1205.

Richards, K. C. (1987). Techniques for measurement of sleep in critical care. *Focus on Critical Care, 14*, 34-40.

Roche, V. (2003). Southwestern internal medicine conference. Etiology and management of delirium. *American Journal of the Medical Sciences, 325*, 20-30.

Schweickert, W. D., Gehlbach, B. K., Pohlman, A. S., Hall, J. B., & Kress, J. P. (2004). Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Critical Care Medicine, 32,* 1272-1276.

Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K. A., . . . Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine, 166*, 1338-1344.

Smith, M. J., Breitbart, W. S., & Platt, M. M. (1995). A critique of instruments and methods to detect, diagnose, and rate delirium. *Journal of Pain and Symptom Management, 10,* 35-77.

Thomason, J. W., Shintani, A., Peterson, J. F., Pun, B. T., Jackson, J. C., & Ely, E. W. (2005). Intensive care unit delirium is an independent predictor of longer hospital stay: A prospective analysis of 261 non-ventilated patients. *Critical Care, 9,* R375-381.

Tobar, E., Romero, C., Galleguillos, T., Fuentes, P., Cornejo, R., Lira, M. T., . . . Ely, E. W. (2010). [Confusion assessment method for diagnosing delirium in ICU patients (CAM-ICU): Cultural adaptation and validation of the Spanish version.]. *Medicina Intensiva, 34*, 4-13.

Vanderbilt University. (2002). El método para la evaluación de la confusión en la UCI (CAM-ICU). [The confusion assessment method for the ICU (CAM-ICU)]. Retrieved from http://www.icudelirium.org/docs/CAM_ICU_training_Spanish.pdf

Table 1

Demographics and Baseline Characteristics

Characteristics	**Control Group**	**Intervention Group**
	(*n* = 20)	**(*n* = 20)**
Age	34 (24-50)	31 (23-58)
Gender		
Female	7 (35%)	3 (25%)
Male	13(65%)	17 (85%)
Weight (kg)	75 (66-98)	83 (73-96)
APACHE II score	12 (10-13)	11 (10-14)
RASS	-5 (-5 to -4)	-4 (-5 to -4)
Bispectral Index	49 (40-61)	46 (43-55)
Mechanism of Trauma		
Motor vehicle crash	11 (55%)	7 (35%)
Gunshot wound	6 (30%)	8 (40%)
Falls	2 (10%)	4 (20%)
Stab wound	1 (5%)	1 (5%)
Surgical Status		
Surgical	16 (80%)	17 (85%)
Non surgical	4 (20%)	3 (15%)
LOS before TICU admission*	3.0 (1.0-4.8)	3.0 (1.0-6.0)
Sedatives and analgesics administered before TICU admission:		
Benzodiazepines (mg/kg)†	**(*n* = 13)**	**(*n* = 12)**
Days before TICU admission	4.0 (2.5-6.5)	4.5 (3.0-7.5)
Total cumulative dose	3.0 (0.2-6.5)	3.3 (0.9-7.6)
Average daily dose	0.5 (0.1-1.9)	1.0 (0.3-1.3)
Propofol (mg/kg)	**(*n* = 8)**	**(*n* = 5)**
Days before TICU admission	4.0 (3.3-5.8)	3 (1.5-8.0)
Total cumulative dose	32.8 (2.0-99.3)	9.5 (3.3-439.6)
Average daily dose	9.6 (0.5-31.6)	5.1 (1.9-47.7)
Opioids (mg/kg)‡	**(*n* = 17)**	**(*n* = 15)**
Days before TICU admission	4.0 (2.0-5.5)	4.0 (2.0-8.0)
Total cumulative dose	1.1 (0.4-1.5)	1.6 (0.6-3.6)
Average daily dose	0.3 (0.1-0.5)	0.4 (0.2-0.8)

Data presented as median (interquartile ranges) or frequency (%). APACHE II, Acute Physiology and Chronic Health Evaluation II; RASS, Richmond Agitation Sedation Scale; LOS, length of stay; TICU, Trauma Intensive Care Unit. * From stabilizing unit and/or recovery room until TICU admission; † calculated in lorazepam equivalents; ‡ calculated in morphine equivalents (Chan et al., 2004).

Table 2

Outcomes

Outcomes	**Control Group Median (IQR)**	**Intervention Group Median (IQR)**	***Wald Statistic/χ^2**	***p value**
	(*n* = 16)	**(*n* = 6)**		
Days in Delirium	2 (1- 3)	3.5 (1.8- 10.8)	3.31	.07
	(*n* = 20)	**(*n* = 20)**		
Days on MV	15 (11.3- 27.3)	12.5 (7- 19.3)	8.48	.004
LOS TICU	16 (11.3- 28)	10.5 (6.3- 18.8)	11.36	.001
LOS Hospital	25.5 (20.3- 53.8)	30 (19- 42.5)	2.35	.125
Days in Drug-induced Coma	6 (2.3- 10.6)	2 (2- 5)	4.73	.03

IQR, Interquartile ranges; MV, mechanical ventilation; LOS, length of stay; TICU, Trauma Intensive Care Unit. *Reported from Cox-regression analysis.

Table 3

Doses of Sedative and Analgesic

Sedative and Analgesic	Control Group Median (IQR)	Intervention Group Median (IQR)	Z Test Statistic	*p* value
Benzodiazepines (mg/kg)†				
Before 1st delirium measurement*:	**(*n* = 19)**	**(*n* = 20)**		
Length of stay	13 (11-16)	9 (4.3-10.8)		
Total cumulative dose	13.8 (7.1-35.5)	4.8 (2.3-12.5)	-2.53	.01
Average daily dose	1.2 (0.7-1.9)	0.6 (0.4-1.3)	-1.91	.06
TICU stay:	**(*n* = 18)**	**(*n* = 20)**		
Length of stay	16 (13.5-29.5)	10.5 (6.3-18.8)		
Total cumulative dose	13.8 (8.1-48.6)	4.1 (1.5-19.7)	-2.57	.01
Average daily dose	1.1 (0.7-2.1)	0.5 (0.2-1.1)	-2.16	.03
Propofol (mg/kg)				
Before 1st delirium measurement*:	**(*n* = 14)**	**(*n* = 8)**		
Length of stay	13.5 (10.8-15.3)	8 (4.3-19.3)		
Total cumulative dose	121.5 (35.9-357.8)	36.3 (5.1-225.5)	-.96	.37
Average daily dose	18.8 (1.0-31.5)	18.0 (0.6-39.1)	-.27	.82
TICU stay:	**(*n* = 12)**	**(*n* = 9)**		
Length of stay	15.5 (11-32.8)	15 (9-20.5)		
Total cumulative dose	346.1 (122.1-519.9)	17.9 (3.1-60.9)	-3.06	.001
Average daily dose	17.4 (4.3-47.3)	1.2 (0.2-8.9)	-2.35	.02
Opioids (mg/kg)‡				
Before 1st delirium measurement*:	**(*n* = 20)**	**(*n* = 20)**		
Length of stay	13 (10.3-15.8)	9 (4.3-10.8)		
Total cumulative dose	4.3 (1.7-10.3)	5.0 (1.8-8.9)	-.38	.72
Average daily dose	0.5 (0.2-0.8)	0.6 (0.2-1.0)	-1.03	.31
TICU stay:	**(*n* = 20)**	**(*n* = 20)**		
Length of stay	16 (11.3-28)	10.5 (6.3-18.8)		
Total cumulative dose	4.3 (1.9-11.4)	5.5 (2.1-10.9)	-1.62	.88
Average daily dose	0.2 (0.2-0.7)	0.5 (0.2-1.1)	-1.92	.06

Data are presented as median (interquartile ranges) from sample statistics. Z test and *p*-values reported from Mann-Whitney *U* test. TICU, Trauma Intensive Care Unit; † calculated in lorazepam equivalents; ‡calculated in morphine equivalents (Chan et al., 2004); * before TICU admission and during TICU stay before first delirium measurement.

Table 4

Complications, Clinical Events, and Adverse Events

Complication and Event	CG Frequency (%) (*n* = 20)	IG Frequency (%) (*n* = 20)
Patients with complications*	**13 (65%)**	**12 (60%)**
Acute respiratory distress syndrome	7 (35%)	7 (35%)
Sepsis	3 (15%)	5 (25%)
Ventilator associate pneumonia	7 (35%)	4 (20%)
Hypertensive crisis	0 (0%)	1 (5%)
Acute renal failure	1 (5%)	0 (0%)
Multiple organ failure	1 (5%)	0 (0%)
Clinical Events	**9 (45%)**	**8 (40%)**
Tracheostomy	5 (25%)	7 (35%)
Reason for tracheostomy:		
Prolonged intubation	2 (40%)	2 (29%)
Failed extubation	2 (40%)	1 (14%)
Failed weaning	1 (20%)	2 (29%)
Abundant tracheal secretions	0 (0%)	2 (29%)
Death	4 (20%)	1 (14%)
Adverse Events	**7 (35%)**	**3 (15%)**
Self-extubation with no re-intubation	0 (0%)	1 (5%)
Self-extubation requiring re-intubation	3 (15%)	1 (5%)
Failed extubation (re-intubation within 24hrs)	4 (20%)	1 (5%)

*Some patients had one or more types of complications.

Table 5

Patient's Sleep Perception across the Three Days

Item	Day	CG Mean (*SD*)	*n*	IG Mean (*SD*)	*n*	EG Mean (*SD*)
Your overall quality of sleep last night was: *(0 = excellent and 10 = poor)*	1	5.6 (3.5)	14	8.1 (2.8)	15	6.9 (3.4)
	2	4.6 (3.7)	7	6.3 (3.8)	14	5.8 (3.8)
	3	6.0 (3.7)	6	8.1 (2.4)	10	7.3 (3.1)
How disrupted was your sleep during last night? *(0 = not disrupted and 10 = very disrupted)*	1	6.1 (3.8)	14	6.7 (3.6)	15	6.5 (3.6)
	2	5.2 (4.5)	7	6.1 (4.3)	14	5.8 (4.3)
	3	4.7 (3.8)	6	8.2 (2.3)	10	6.9 (3.4)
How many times did you wake-up during last night? *(0 = never and 10 = many times)*	1	4.8 (3.2)	14	6.8 (3.2)	14	5.8 (3.3)
	2	3.2 (2.9)	6	5.4 (4.1)	14	4.8 (3.9)
	3	5.7 (4.1)	6	7.0 (3.3)	10	6.5 (3.5)
How satisfied were you with last night sleep? *(0 = very satisfied and 10 = very unsatisfied)*	1	8.1 (3.0)	14	6.7 (3.7)	15	7.4 (3.4)
	2	5.0 (4.4)	6	6.1 (3.9)	14	5.8 (4.0)
	3	9.3 (.82)	6	8.9 (2.2)	10	9.1 (1.8)
Your overall quality of sleep yesterday during the day was: *(0 = excellent and 10 = poor)*	1	6.1 (3.2)	14	7.9 (1.9)	13	7.0 (2.8)
	2	5.3 (4.0)	7	5.2 (4.1)	14	5.2 (3.9)
	3	6.2 (2.4)	5	6.3 (2.4)	10	6.3 (2.3)
How disrupted was your sleep yesterday during the day? *(0 = not disrupted and 10 = very disrupted)*	1	6.1 (2.7)	14	7.9 (2.8)	14	7.0 (2.9)
	2	3.0 (3.8)	7	6.9 (3.8)	14	5.6 (4.2)
	3	2.8 (4.1)	5	6.7 (3.0)	10	5.4 (3.8)
How satisfied were you with yesterday day sleep? *(0 = very satisfied and 10 = very unsatisfied)*	1	7.7 (2.3)	14	7.9 (2.0)	14	7.8 (2.4)
	2	4.3 (4.8)	7	6.1 (3.8)	14	5.6 (4.1)
	3	8.6 (2.1)	5	6.9 (2.2)	10	7.5 (2.9)

Means (*SD*) of Patient's Sleep Perception questionnaire for each group and entire group by day are provided but the multilevel statistics is based on the sum of the item scores. IG, intervention; CG, control group, EG, entire group.

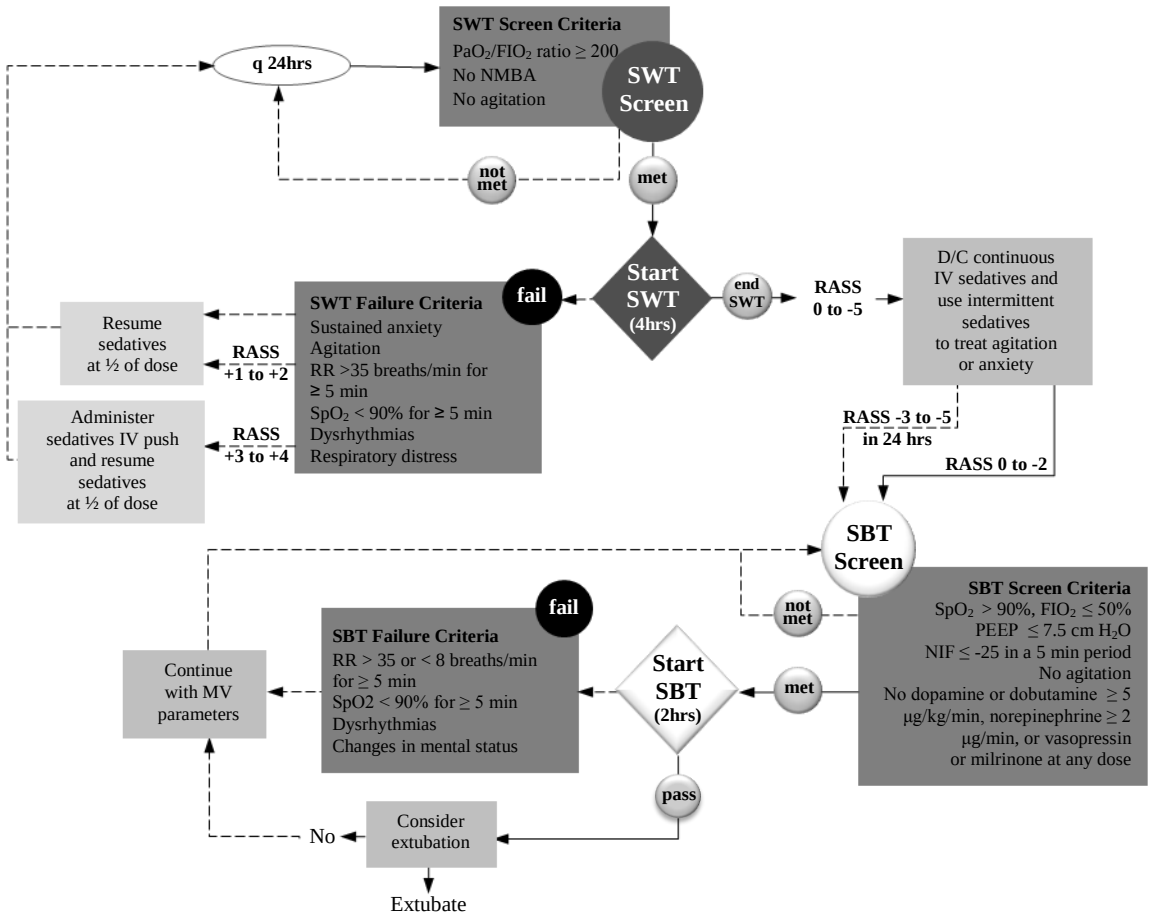

Figure 1. Sedation wake-up trial (SWT) and spontaneous breathing trial (SBT) protocol. PaO_2, partial oxygen pressure; FIO_2, fraction of inspired oxygen; NMBA, neuromuscular blockers agent; RR, respiratory rate; SpO_2, saturation of peripheral oxygen; RASS, Richmond Agitation Sedation Scale; D/C, discontinue; IV, intravenous; PEEP, positive end-expiratory pressure, NIF, negative inspiratory force; MV, mechanical ventilation.

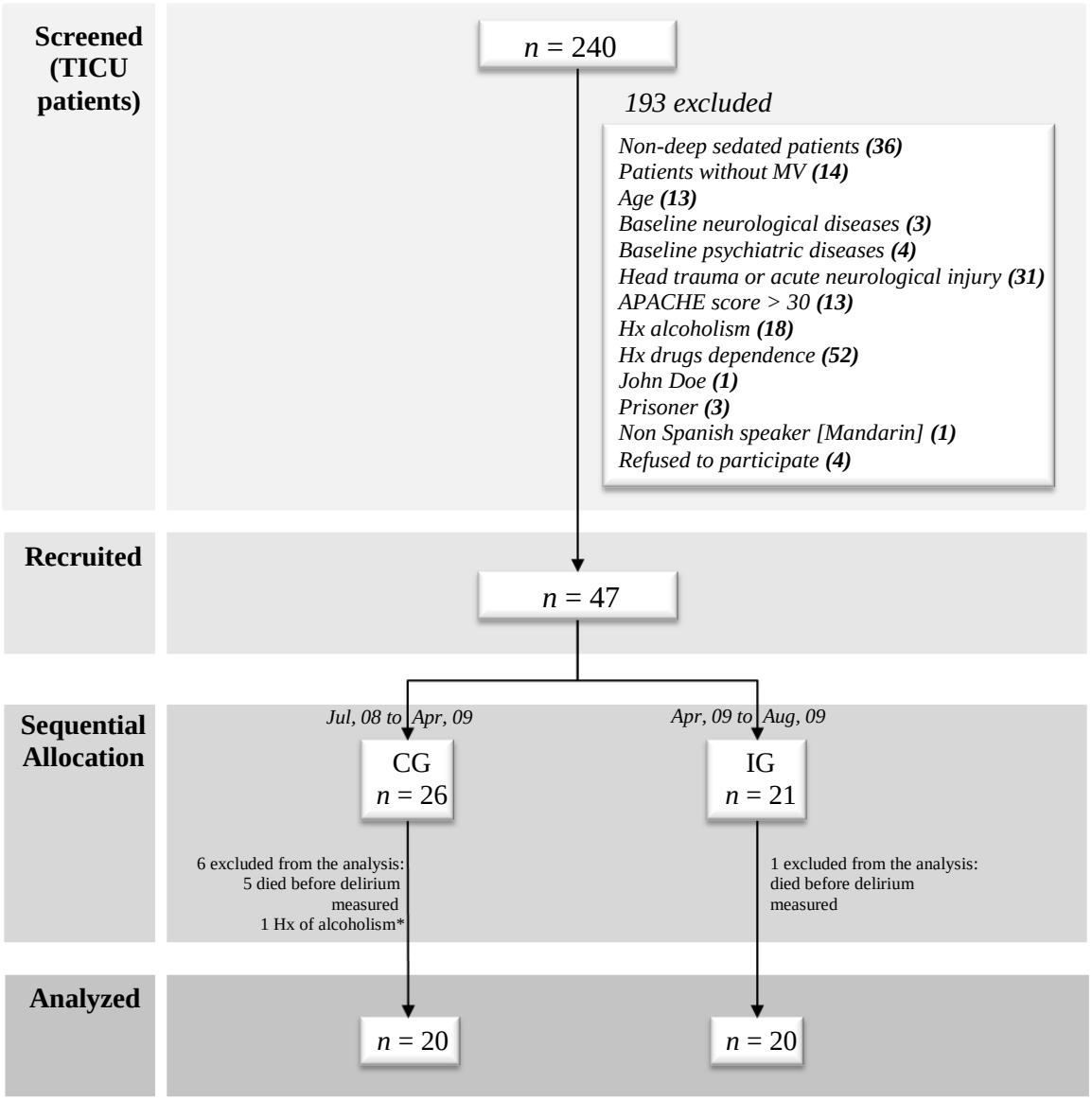

Figure 2. Flow diagram of the study. TICU, Trauma Intensive Care Unit; MV, mechanical ventilation; APACHE, Acute Physiology and Chronic Health Evaluation score; Hx, history; CG, control group; IG, intervention group. *Patient was withdrawn due to a history of alcoholism confirmed later.

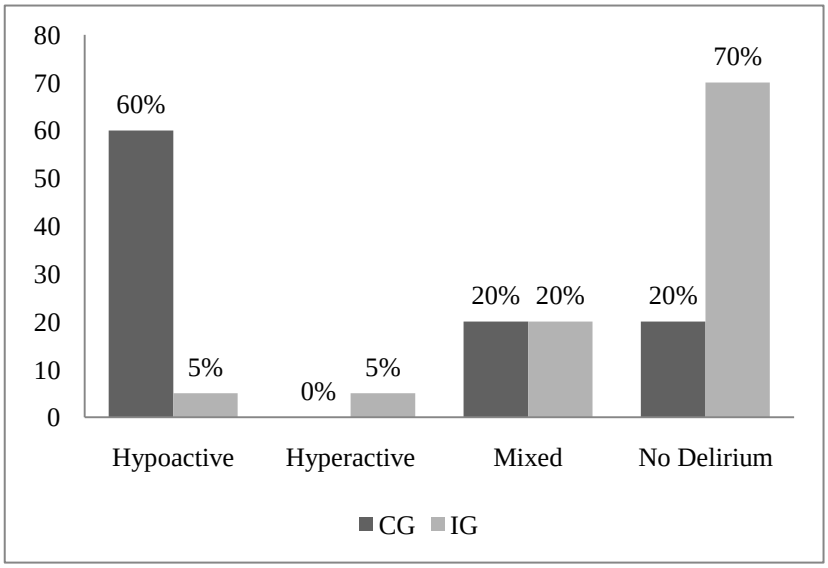

Figure 3. Frequency of occurrence and type of delirium (across all measures). CG, control group; IG, intervention group.

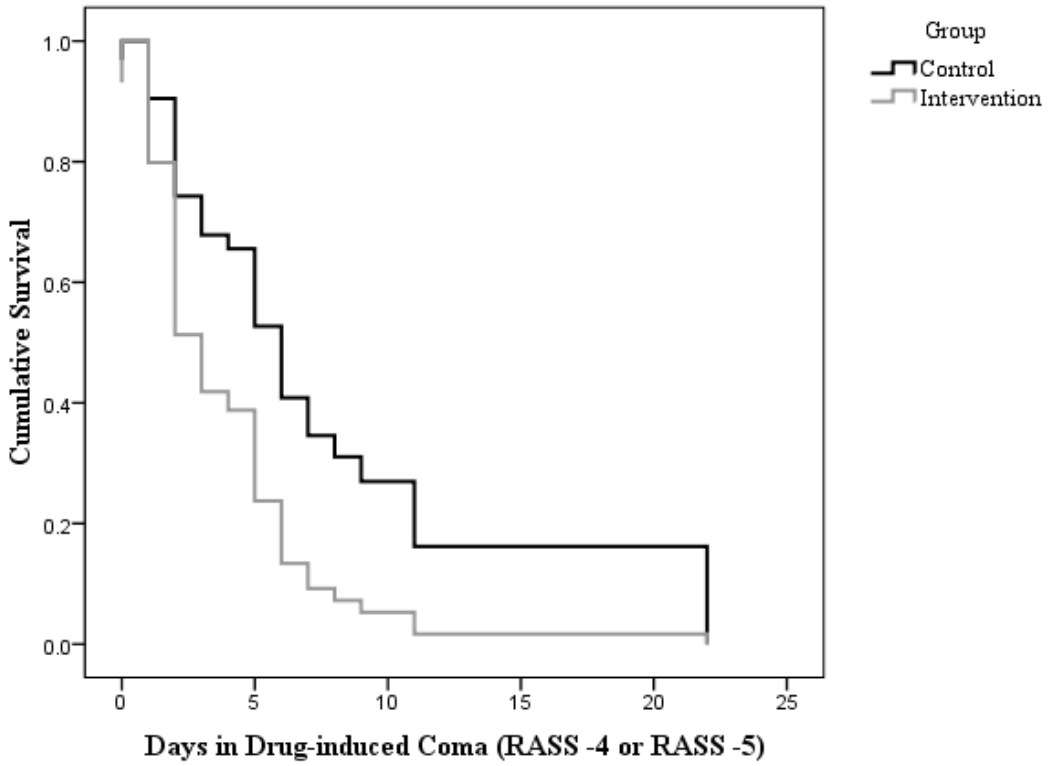

Figure 4. Survival curves for time to recover from drug-induced coma. RASS, Richmond Agitation Sedation Scale.

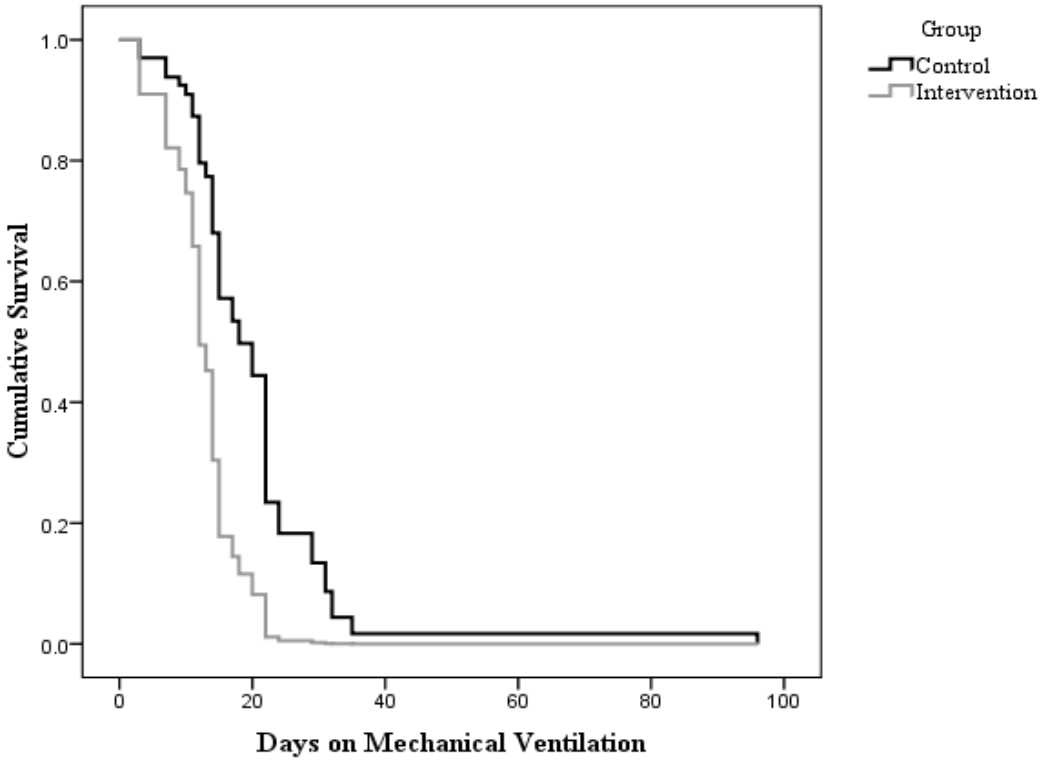

Figure 5. Survival curves for time to liberation from the mechanical ventilator.

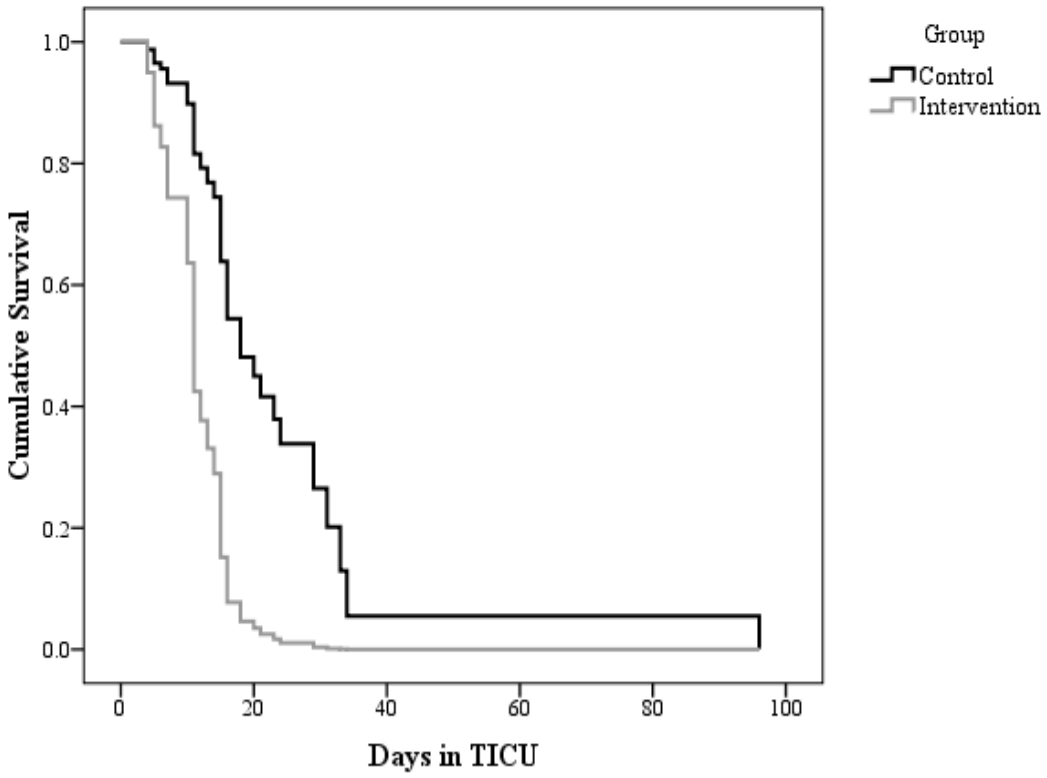

Figure 6. Survival curves for time to discharge from the Trauma Intensive Care Unit (TICU).

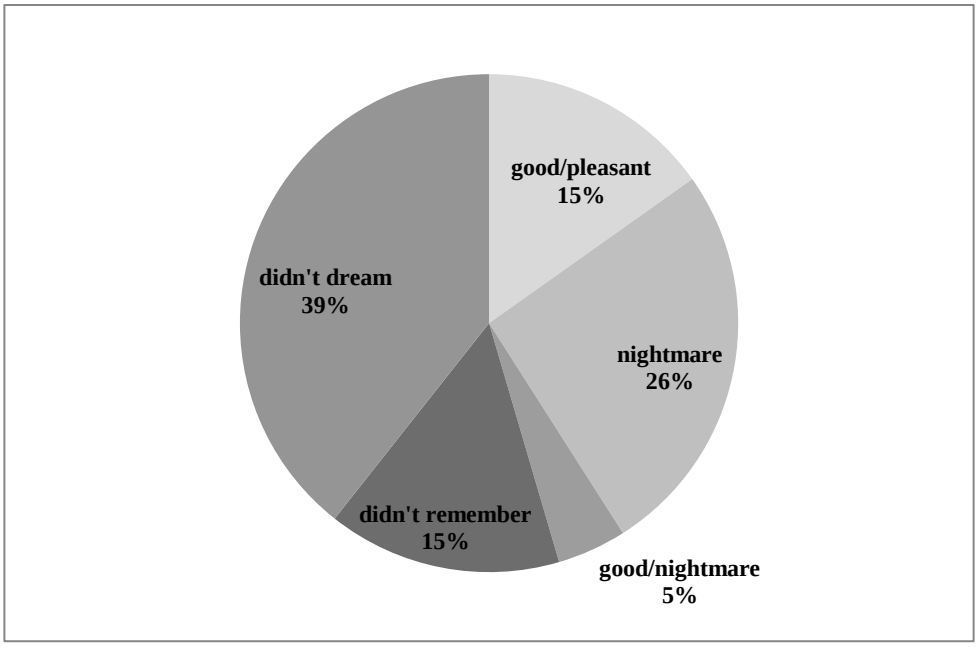

Figure 7. Types of dreams.

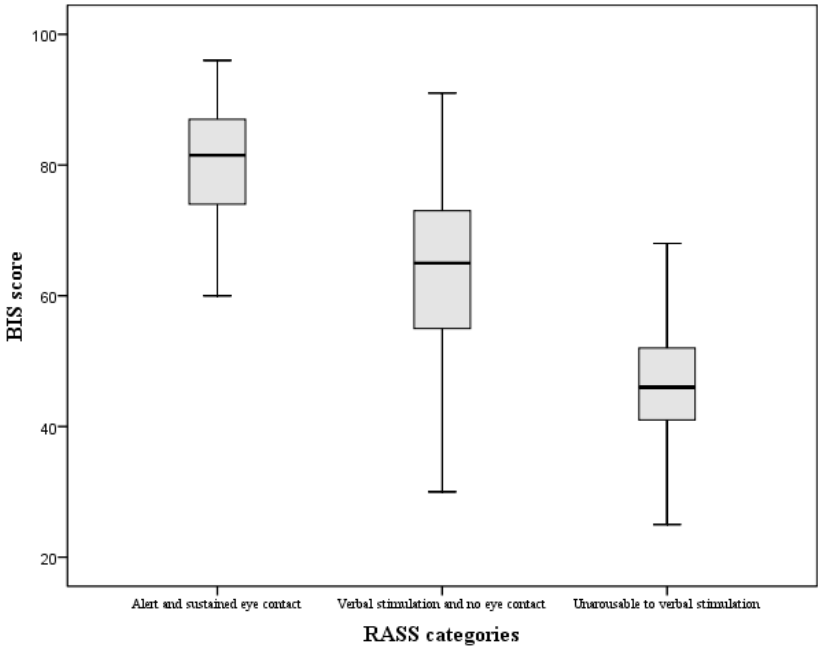

*Figure 8***.** Box plots for bispectral index (BIS) score versus Richmond Agitation Sedation Scale (RASS) categories. Horizontal bar, median value; boxes, interquartile ranges (25^{th} -75^{th}).

Chapter IV

Feasibility of a Sedation Wake-up Trial and Spontaneous Breathing Trial in Critically Ill Trauma Patients

Abstract

Patients in trauma intensive care units (ICUs) on mechanical ventilation often receive continuous intravenous sedatives. Although sedation is necessary in the majority of cases, negative consequences of sedation due to inappropriate management can occur. A sedation wake-up trial (SWT) is an option for managing sedation in ICU patients. In addition, a combined intervention of SWT plus a spontaneous breathing trial (SBT) has contributed to improved patient outcomes.

The goal of this report is to determine the feasibility of conducting a SWT plus a SBT in trauma patients based on the ability to implement the combined intervention; measure and describe patients' physiological responses; and maintain patient safety. Data were used from a prospective intervention study that determined whether a SWT plus a SBT contribute to a reduction in the occurrence of delirium in critically ill trauma patients.

Twenty patients in the intervention group were screened 88 times for a SWT. Patients passed 67% of the 39 SWTs performed; those who failed presented RASS scores of +1 and +2 (70%), tachycardia (15%), or ventilator asynchrony (15%). Eighteen patients tolerated their first SBT, and after the second SBT, more than half of the patients were discontinued from the mechanical ventilator. A multilevel regression analysis showed that there was a significant increase from the beginning to the end of the SWT in RASS scores (p = .008), BIS scores (p = .011), heart rate (HR) (p = .021), respiratory rate (RR) (p = .043), and systolic blood pressure (BP) (p = .04). Although HR, RR, and systolic BP increased significantly, their overall mean did not increase by 20% and treatment was not required. Opioids were not interrupted during the SWT; however, four

patients reported having pain at the end of six SWTs and were treated. Only one self-extubation occurred during the SBT.

In conclusion, SWT plus SBT was well tolerated and successfully implemented. This combined intervention provides an alternative to the management of sedation in this mechanically ventilated trauma population. In addition, our data showed that it is not necessary to withhold continuous analgesic infusions during the SWT.

Introduction

Patients in trauma intensive care units (TICUs) on mechanical ventilation often receive continuous intravenous (IV) sedatives as part of supportive treatment. Sedatives are often given in order to improve patient comfort and safety and to minimize distress due to the complexity of ICU care (Hooper & Girard, 2009; Sessler & Pedram, 2009). Sedation management in critically ill trauma patients is a multifaceted challenge. Complications (e.g., acute respiratory distress syndrome [ARDS] and sepsis) as a result of the mechanisms of the injury make sedation management more challenging in this population (Robinson et al., 2008).

Although sedation is necessary in the majority of cases, negative consequences of sedation due to inappropriate management can occur. Over-sedation could lead to prolonged mechanical ventilation, increased length of stay, increased neurological tests, and greater delirium (Sessler & Pedram, 2009). Under-sedation could lead to anxiety, ventilator asynchrony, increased nursing workload, wound dehiscence, and self-removal of tubes (Dasta & Kane-Gill, 2009). An established individualized target sedation level according to the patient's clinical condition could enhance patients' responses to sedation management (Riker & Fraser, 2009). In addition, it is important to take into account the use of sedation guidelines or a protocol to achieve appropriate sedation (Sessler & Pedram, 2009).

Daily interruption of sedation, also known as a sedation wake-up trial (SWT), was introduced as an option for managing sedation in ICU patients. It resulted in improved patient outcomes (i.e., decrease in duration of mechanical ventilation, length of ICU stay, and quantity of benzodiazepine administered) (Kress, Pohlman, O'Connor, & Hall, 2000).

The addition of a spontaneous breathing trial (SBT) to a SWT has also contributed to improved patient outcomes (Girard et al., 2008). Some studies have addressed the benefits, feasibility, and safety of the SWT (Girard et al., 2008; Kress et al., 2003; Kress et al., 2007; Schweickert, Gehlbach, Pohlman, Hall, & Kress, 2004) but not in trauma patients. Indeed, it has been suggested that SWTs performed in young trauma patients could be dangerous and not well tolerated (Robinson et al., 2008).

The goal of this report is to determine the feasibility and safety of conducting a SWT plus a SBT in trauma patients. The specific aim was to explore the screening criteria for both the SWT and SBT; patient responses to the combined intervention including failure and pass criteria, physiological measures (heart rate [HR], blood pressure [BP], respiratory rate [RR], oxygen saturation [SpO_2]), agitation/sedation levels, and level of consciousness before and at the end of the SWT; delirium and pain during each SWT; length of time to awakening after sedative interruption; and patient safety based on the occurrence of adverse events related to the SWT and SBT. A secondary aim was to explore reasons why patients remain on a mechanical ventilator after successfully passing a SBT.

Methods

The database used was from a prospective interventional study that determined whether a SWT plus SBT contributes to a reduction in the occurrence of delirium in critically ill trauma patients. Data from patients in the intervention group who received the SWT plus SBT were analyzed. The Institutional Review Board of the University of Puerto Rico, Medical Sciences Campus and the Committee on Human Research of the

University of California, San Francisco approved the study. The ClinicalTrial.gov identifier for the study is NCT00714194.

Setting and Study Subjects

The study was conducted in the TICU of the Trauma Hospital at the Medical Center of San Juan, Puerto Rico. All consecutive patients admitted to the TICU were screened during their first 24 hours of admission. Patients who were ≥ 21 years of age, receiving mechanical ventilation and a continuous sedative infusion, and having a Richmond Agitation Sedation Scale (RASS) score of -4 or -5 were included in the study. Patients excluded from the study were those who had baseline neurological or psychiatric diseases, head trauma or acute neurological injury with a Glasgow Coma Scale score < 8, a history of alcoholism or drug dependence, who were both deaf and blind, or whose death was expected within 24 hours (i.e., Acute Physiology and Chronic Health Evaluation [APACHE] II score ≥ 30) (Knaus, Draper, Wagner, & Zimmerman, 1985).

Measures

The RASS was used to measure agitation and sedation levels based on three states: agitation (+1 to +4), calm/alert (0), and sedation (-1 to -5) (Ely et al., 2003; Sessler et al., 2002). A non-invasive physiological monitor, the Bispectral Index (A-2000 BIS-XP™, Aspect Medical Systems, Norwood, MA), was used to measure level of consciousness. BIS scores range from 0 (isoelectrical line) to 100 (alert), with scores decreasing according to the depth of sedation.

The presence of pain was measured by asking patients to answer by nodding their head or closing their eyes for a "yes" response. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Spanish version, was used to measure delirium

(Vanderbilt University, 2002). The CAM-ICU is an instrument that has been validated in large ICU populations (Ely et al., 2001a; Ely et al., 2001b; Guenther et al., 2009; Tobar et al., 2010). The CAM-ICU has four domains: acute onset of changes or fluctuations in the course of mental status, inattention, disorganized thinking, and an altered level of consciousness.

Procedure

Informed consent was obtained from authorized patient representatives. When they were able to consent, patients documented on a consent form their desire to continue or to terminate their participation in the study and their approval to use the previously obtained data.

SWT procedure. Every morning after the day of admission, patients were screened to receive a SWT. The screening criteria for the SWT were: PaO_2/FIO_2 ratio ≥ 200, not receiving neuromuscular blocking agents (NMBA), and no agitation. If patients met the screening criteria, the SWT was started with interruption of continuous IV sedatives in the morning (between 7:00 a.m. and 8:00 a.m.) for a maximum of 4 hours. Because these trauma patients required pain management, the continuous infusion or the scheduled intermittent dose of opioid was not interrupted during the SWT. Continuous sedation was resumed at half of the previous dose adjusting to the target level of sedation established if patients failed the SWT. In addition, a bolus of sedatives was given if patients showed a RASS of +3 to +4. Criteria for failure of the SWT included: sustained anxiety, agitation, respiratory rate ≥ 35 breaths per minute for 5 minutes or longer, SpO_2 < 90% for 5 minutes or longer, acute cardiac dysrhythmia, or respiratory distress. For those patients who did not fail and showed a RASS score between 0 and -5 at the end of

the SWT, the sedative treatment was changed to intermittent doses to treat further agitation or anxiety.

Physiological measures, the RASS, and the BIS were measured before the initiation of the SWT. Physiological measures, RASS, BIS, delirium, and presence of pain were measured at the end of the SWT. The end of the SWT was established when patients increased their RASS score and were able to perform at least three of the following oral commands: open their eyes, use their eyes to follow the investigator, squeeze a hand, and stick out their tongue; when they developed agitation before resumption of sedatives; or after completion of 4 hours of SWT. Significant changes in physiological measures (HR > 20% from baseline or > 120 beats/min, systolic BP > 20% from baseline or > 180 mmHg, RR > 20/min, and SpO_2 < 90%), and the presence of pain or delirium were reported to the physician and nurse in charge.

SBT procedure. Patients who passed the SWT with a RASS score of 0 to -2 were screened for the SBT. The SBT criteria included: SpO_2 > 90%, fraction of inspired oxygen (FIO_2) ≤ 50%, positive end-expiratory pressure (PEEP) ≤ 7.5 cm H_2O, negative inspiratory force (NIF) ≤ -25 in a 5-minute period, no agitation, and no significant use of vasopressors or inotropes (dopamine or dobutamine ≥ 5 μg/kg per min, norepinephrine ≥ 2 μg/min, or vasopressin or milrinone at any dose). If the patient met the criteria, then the mechanical ventilator mode was changed to continuous positive airway pressure (CPAP) for two hours or until the patient failed the SBT. The failure criteria included: RR > 35 or < 8 breaths per minute for ≥ 5 minutes, SpO_2 ≤ 90% for ≥ 5 minutes, cardiac arrhythmias, changes in mental status, or respiratory distress. Patient extubation was

determined by the physician in charge. The study protocol was followed by the principal investigator (MIF) and/or co-investigator (CMA).

Statistical Analysis

Descriptive statistics were used to explore screening criteria for both SWT and SBT and the following patient responses: failure and pass criteria for SWT and SBT, occurrence of delirium or pain at the end of each SWT, and length of time to awakening after sedative interruption. A multilevel regression model was used to compare changes in physiological measures, RASS scores, and BIS scores before and at the end of the SWT. Descriptive statistics were also used to explore adverse events related to the SWT and SBT and to explore reasons that patients remained on mechanical ventilator after passing the SBT. Statistical analyses were performed using SPSS® version 16.0 and STATA® version 11.0.

Results

Patients were enrolled between April 20, 2009 and August 10, 2009. A total of 20 patients were included in the analysis. The data are expressed as median (interquartile ranges [IQR]). The majority of patients were male (*n* = 17, 85%), 31 (IQR 23-58) years of age and had a median APACHE II score of 11 (IQR 10-14). The mechanisms of trauma were gunshot wounds (*n* = 8, 40%), motor vehicle crashes (*n* = 7, 35%), falls (*n* = 4, 20%), and stab wounds (*n* = 1, 5%). Seventeen patients (85%) required surgical intervention.

Screening Criteria

Sedation wake-up trial. The 20 patients were screened 88 times for a SWT. They did not meet the screening criteria 51 times (58%) due to a PaO_2/FIO_2 ratio < 200 (90%),

NMBA (8%), or agitation (2%). Sixteen patients met the SWT screening criteria the first day after study enrollment; those who did not (n = 4), met the screening criteria by the 7th day (IQR 3-9.5) after enrollment.

Spontaneous breathing trial. The SBT was performed on 19 patients. One patient died before meeting the SBT screening criteria. The 19 patients with RASS scores of 0 to -2 were screened 74 times for eligibility for SBTs. In 25 attempts (34%), patients did not meet the screening criteria due to FIO_2 > 50% (44%), NIF > -25 (40%), and PEEP ≥ 7.5 (16%).

Patient Responses to the SWT and SBT

SWT fail and pass criteria. Patients passed 67% of the 39 SWTs performed and sedative continuous infusion was switched to intermittent sedative doses. Specific findings from the SWTs are summarized in Table 1. After being changed to intermittent sedative dosing, patients showed daily RASS scores of 0 (IQR -1-0) in 113 daily RASS assessments. Of these, RASS scores were +1 in five daily assessments. Thirteen of 20 patients passed the SWT the first day after enrollment. The median SWT for the sample was 1 (IQR 1-3) per patient before being switched from continuous to intermittent sedative administration. One patient failed all six SWTs performed before he died.

First SWT. Because more than half of the patients received only one SWT, this part includes an in-depth description of the first SWT performed among 20 patients. For the first SWT, patients were receiving midazolam (n = 15, 75%), propofol (n = 4, 20%), or lorazepam (n = 1, 5%). The length of time for the first SWT is summarized in Table 2. At the end of the first SWT, seven patients awoke with a RASS score of 0 to -2; nine had RASS scores of -3; one -4; one -5; and two patients had positive RASS +1 and +2,

respectively. Of the 20 patients, four failed the SWT due to positive RASS scores, tachycardia, or ventilator asynchrony. Six patients who passed their first SWT required a restart of continuous IV sedatives after being switched to intermittent dosing due to a second surgical intervention and/or development of ARDS (n = 4), failed extubation (n = 1) or further agitation (n = 1).

SBT fail and pass criteria. Patients passed 98% of the 49 SBTs performed. One patient did not tolerate one SBT due to a decrease in SpO_2. The findings from the SBTs, including the reasons that patient remained on the mechanical ventilator after successfully passing the SBT, are illustrated in Figure 1.

Changes in physiological measures. A multilevel regression analysis showed that there was a significant increase from the beginning to the end of the SWT for RASS scores, BIS scores, and all physiological measures, except for diastolic BP and SpO_2 (see Table 3). As expected, RASS and BIS scores increased significantly. Although HR, RR, and systolic BP increased significantly, their overall means did not increase by 20% from the beginning to the end of the SWT.

Pain and delirium. At the end of the 39 SWTs performed, four patients reported having pain in 6 SWTs (15%); nine patients experienced no pain in 12 SWTs (31%); and 14 patients were unable to report pain in 21 SWTs (54%). Those who reported having pain did not show restlessness (RASS +1) or agitation (RASS +2) at the end of the SWT. Patients were receiving continuous opioid infusions during 23 SWTs (59%) and intermittent opioids during 16 (41%). The fact that continuous opioid infusions were not stopped during the SWT did not prevent the patients from awakening or increasing their RASS scores. Only one patient was still deeply sedated (RASS score -4) at the end of

one SWT. The rate of continuous IV opioids was increased or a bolus of morphine IV was given by medical order to those patients who reported having pain at the end of the SWT.

Four patients exhibited delirium (two hypoactive and two hyperactive) at the end of 4 SWTs (10%). Nine patients had no delirium at the end of 14 SWTs (36%). Fourteen patients were unable to perform the CAM-ICU at the end of 21 SWTs (54%). The presence of delirium was reported to the physician in charge.

Adverse Events

Two patients self-extubated: one did not require re-intubation and the other required re-intubation. However, these self-extubations did not occur during the four hours of the SWT. One patient failed extubation after having passed the SBT and was reintubated.

Discussion

This study demonstrated the feasibility of conducting a SWT plus a SBT in trauma patients. SWTs plus SBTs were performed in 19 patients; one patient received only one of the interventions (i.e., SWT) because he died before he met the SBT screening criteria. This patient failed all six SWTs.

The majority of the patients who did not meet the screening criteria for SWT had ARDS with a PaO_2/FIO_2 ratio less than 200. Sedation is used in patients with ARDS to prevent mechanical ventilation resistance and to decrease oxygen consumption (Michaels, 2004). Although continuous IV sedatives were not stopped in patients with ARDS until the condition was resolved, the rate of infusion was adjusted according to patients' needs and medical orders.

We found that the majority of patients were young, required only one SWT and passed it on the first day after study enrollment, which usually corresponded to the first and second day after TICU admission. Moreover, most study participants did not develop any further restlessness or agitation that required restarting continuous IV sedatives. Based on this information, it is important to consider whether these patients really required continuous sedative infusion. Perhaps they would have benefited from intermittent sedative dosing or analgesics only.

Both the selection of patients with RASS scores of 0 to -2 and the application of specific screening and failure criteria guided the successful implementation of the SBTs. Eighteen patients tolerated their first SBT and, after the second day of SBT, more than half of the patients were liberated from the mechanical ventilator. Although patients passed the SBT, some of them were not extubated because they showed risk factors for extubation failure (i.e., abundant secretions, rapid shallow breathing [f/V_T] > 100 breaths/minute/ml, and absence of cuff air leak) observed by the trauma medical staff. In sixteen occasions (33%), patients successfully passed the SBT and did not exhibit risk factors for extubation failure; however, they were not extubated and mechanical ventilation was continued by medical decision.

We found some discrepancies in terms of the rate of failure of screening criteria and the rate of completion of both interventions when compared to those from the study by Girard et al. (2008). Our patients did not meet the SWT screening criteria 58% of the time versus 18% for the Girard study. This difference between both studies could be related because of our inclusion of a PaO_2/FIO_2 ratio $\geq$ 200 as a SWT screening criterion. Patients in our study passed the SWT 27% fewer times than did patients in the Girard

study. Patients met screening SBT criteria at same proportion in both studies (66%). However, our study showed an extremely low rate of SBT failures compared to the Girard study (2% versus 47%). A possible explanation for this discrepancy could be the differences in types of patient (i.e., trauma versus medical) or the duration of the study. We studied patients during their entire TICU stay (up to 33 days) instead of the 28 days in the Girard study.

Concerns related to patient responses to the implementation of SWTs have been described previously (Heffner, 2000; O'Connor, Bucknall, & Manias, 2009; Tanios, de Wit, Epstein, & Devlin, 2009). Our results are similar to those in a study with coronary risk patients (Kress et al., 2007), in which changes in physiological measures increased significantly from the beginning to the end of the SWT. However, the mean increase was not greater than 20%. In our study, only four patients demonstrated 20% increases in HR, systolic BP, or diastolic BP. These values decreased after restarting the continuous sedative infusion. No consequences were observed from these physiological changes, and no further treatment was required.

O'Connor et al. (2009) established in their review that although pain can be present during the SWT and may be associated with anxiety, pain has not been explored in previous SWT studies. Our study addressed this gap by measuring pain at the end of each SWT. We found that some patients were able to report the presence or absence of pain at the end of SWTs. Moreover, the presence of pain at the end of SWTs was not associated with positive RASS scores. Pain assessment at the end of the SWT provided the opportunity to optimize pain management and improve patient comfort.

Patient safety concerns related to removal of devices during the SWT have been described previously (Kress et al., 2000; Tanios et al., 2009). The 10% incidence of self-extubation for patients in the intervention group in our study was the same as for the Girard et al. (2008) study. The self-extubation rate was lower than the rate among other ICU patients which has been reported to be as high as 21% (Yeh, Lee, Ho, Chiang, & Lin, 2004).

Several limitations need to be addressed. The sample size was small, and the majority of patients were male. The results cannot be generalized to all trauma ICU populations. This study excluded patients with head trauma or who had a history of illicit drug dependence or alcoholism who represent a high percentage of patients admitted to this TICU. Because, in more than the half of SWTs, patients were unable to self-report their pain, the behavioral pain scale (Payen et al., 2001) or the critical care pain observation tool (Gelinas & Johnston, 2007) could be used to measure pain behaviors. Patient comfort was not measured after continuous sedation therapy was switched to intermittent sedative dosing; however, restlessness was noted in only five daily RASS assessments.

In conclusion, SWT plus SBT is clinically feasible and appears to be a safe intervention for trauma patients. Based on our results, this combined intervention was well tolerated and successfully implemented in the small sample. The SWT plus SBT intervention provides an alternative to the management of sedation in this mechanically ventilated trauma population. In addition, our data showed that it is not necessary to withhold analgesic continuous infusions during the SWT, thus preventing pain rebound.

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References

Dasta, J. F., & Kane-Gill, S. (2009). Pharmacoeconomics of sedation in the ICU. *Critical Care Clinics, 25*, 571-583.

Ely, E. W., Inouye, S. K., Bernard, G. R., Gordon, S., Francis, J., May, L., . . . Dittus, R. (2001a). Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA, 286*, 2703-2710.

Ely, E. W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, R., . . . Inouye, S. K. (2001b). Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Critical Care Medicine, 29*, 1370-1379.

Ely, E. W., Truman, B., Shintani, A., Thomason, J. W., Wheeler, A. P., Gordon, S., . . . Bernard, G. R. (2003). Monitoring sedation status over time in ICU patients: Reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA, 289*, 2983-2991.

Gelinas, C., & Johnston, C. (2007). Pain assessment in the critically ill ventilated adult: Validation of the critical-care pain observation tool and physiologic indicators. *Clinical Journal of Pain, 23*, 497-505.

Girard, T. D., Kress, J. P., Fuchs, B. D., Thomason, J. W., Schweickert, W. D., Pun, B. T., . . . Ely, E. W. (2008). Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (awakening and breathing controlled trial): A randomised controlled trial. *Lancet, 371*, 126-134.

Guenther, U., Popp, J., Koecher, L., Muders, T., Wrigge, H., Ely, E. W., & Putensen, C. (2010). Validity and reliability of the CAM-ICU flowsheet to diagnose delirium in surgical ICU patients. *Journal of Critical Care, 25*,144-51.

Heffner, J. E. (2000). A wake-up call in the intensive care unit. *New England Journal of Medicine, 342*, 1520-1522.

Hooper, M. H., & Girard, T. D. (2009). Sedation and weaning from mechanical ventilation: Linking spontaneous awakening trials and spontaneous breathing trials to improve patient outcomes. *Critical Care Clinics, 25*, 515-525.

Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: A severity of disease classification system. *Critical Care Medicine, 13*, 818-829.

Kress, J. P., Gehlbach, B., Lacy, M., Pliskin, N., Pohlman, A. S., & Hall, J. B. (2003). The long-term psychological effects of daily sedative interruption on critically ill patients. *American Journal of Respiratory and Critical Care Medicine, 168*, 1457-1461.

Kress, J. P., Pohlman, A. S., O'Connor, M. F., & Hall, J. B. (2000). Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New England Journal of Medicine, 342*, 1471-1477.

Kress, J. P., Vinayak, A. G., Levitt, J., Schweickert, W. D., Gehlbach, B. K., Zimmerman, F., . . . Hall, J. B. (2007). Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Critical Care Medicine, 35*, 365-371.

Michaels, A. J. (2004). Management of post traumatic respiratory failure. *Critical Care Clinics, 20*, 83-99.

O'Connor, M., Bucknall, T., & Manias, E. (2009). A critical review of daily sedation interruption in the intensive care unit. *Journal of Clinical Nursing, 18*, 1239-1249.

Payen, J. F., Bru, O., Bosson, J. L., Lagrasta, A., Novel, E., Deschaux, I., . . . Jacquot, C. (2001). Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Critical Care Medicine, 29*, 2258-2263.

Riker, R. R., & Fraser, G. L. (2009). Altering intensive care sedation paradigms to improve patient outcomes. *Critical Care Clinics, 25*, 527-538.

Robinson, B. R., Mueller, E. W., Henson, K., Branson, R. D., Barsoum, S., & Tsuei, B. J. (2008). An analgesia-delirium-sedation protocol for critically ill trauma patients reduces ventilator days and hospital length of stay. *Journal of Trauma, 65*, 517-526.

Schweickert, W. D., Gehlbach, B. K., Pohlman, A. S., Hall, J. B., & Kress, J. P. (2004). Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Critical Care Medicine, 32*, 1272-1276.

Sessler, C. N., Gosnell, M. S., Grap, M. J., Brophy, G. M., O'Neal, P. V., Keane, K. A., . . . Elswick, R. K. (2002). The Richmond Agitation-Sedation Scale: Validity and reliability in adult intensive care unit patients. *American Journal of Respiratory and Critical Care Medicine, 166*, 1338-1344.

Sessler, C. N., & Pedram, S. (2009). Protocolized and target-based sedation and analgesia in the ICU. *Critical Care Clinics, 25*, 489-513.

Tanios, M. A., de Wit, M., Epstein, S. K., & Devlin, J. W. (2009). Perceived barriers to the use of sedation protocols and daily sedation interruption: A multidisciplinary survey. *Journal of Critical Care, 24*, 66-73.

Tobar, E., Romero, C., Galleguillos, T., Fuentes, P., Cornejo, R., Lira, M. T., . . . Ely, W. E. (2010). [Confusion assessment method for diagnosing delirium in ICU patients (CAM-ICU): Cultural adaptation and validation of the Spanish version.]. *Medicina Intensiva, 34*, 4-13.

Vanderbilt University. (2002). El método para la evaluación de la confusión en la UCI (CAM-ICU). [The confusion assessment method for the ICU (CAM-ICU)]. Retrieved from http://www.icudelirium.org/docs/CAM_ICU_training_Spanish.pdf

Yeh, S. H., Lee, L. N., Ho, T. H., Chiang, M. C., & Lin, L. W. (2004). Implications of nursing care in the occurrence and consequences of unplanned extubation in adult intensive care units. *International Journal of Nursing Studies, 41,* 255-262.

Table 1

Sedation Wake-up Trial

Sedation Wake-up Trial	**Frequency**	**(%)**
Total	39	
Passed	26	(67)
RASS 0	6	(23)
RASS -1	4	(15)
RASS -2	5	(19)
RASS -3	9	(35)
RASS -4	1	(4)
RASS -5	1	(4)
Failed	13	(33)
RASS +1 to +2	9	(70)
Tachycardia	2	(15)
Ventilator asynchrony	2	(15)
Sedation decision at the end of SWT		
Intermittent dose	26	(67)
Half dose	5	(13)
Same dose	6	(15)
Bolus and same dose	2	(5)

SWT, sedation wake-up trial; RASS, Richmond Agitation Sedation Scale

Table 2

Length of Time of the First SWT

Length of Time	***n* (%)**
≤ ½ hour	2 (10)
> ½ hour, ≤ 1 hour	2 (10)
> 1hour, ≤ 2 hour	4 (20)
> 2hour, ≤ 3 hour	4 (20)
> 3hour, ≤ 4 hour	8 (40)

SWT, sedation wake-up trial

Table 3

Changes in RASS, BIS, and Physiological Measures during SWT

Parameter	**Beginning SWT**	**End SWT**	**Estimated Change**	***p*-value**
RASS	-3 ± 2	-1 ± 2	↑ 1.2	.008
BIS	56 ± 17	69 ± 15	↑ 11	.011
HR	101 ± 18	111 ± 23	↑ 7.8	.021
RR	17 ± 4	20 ± 6	↑ 2.5	.043
SBP	129 ± 17	137 ± 14	↑ 7.2	.04
DBP	70 ± 9	75 ± 13	↑ 2.7	.29
SpO_2	100 (99-100)	99 (98-100)	↓0.18*	.36

Data are presented as mean ± *SD* or as median and interquartile range from sample statistics. Estimated change and *p*-values reported from the multilevel regression analysis. *Change in means from the original scale converted back from a natural log scale. RASS, Richmond Agitation Sedation Scale; BIS, bispectral index; SWT, sedation wake-up trial; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, saturation of peripheral oxygen; ↑, increase; ↓, decrease.

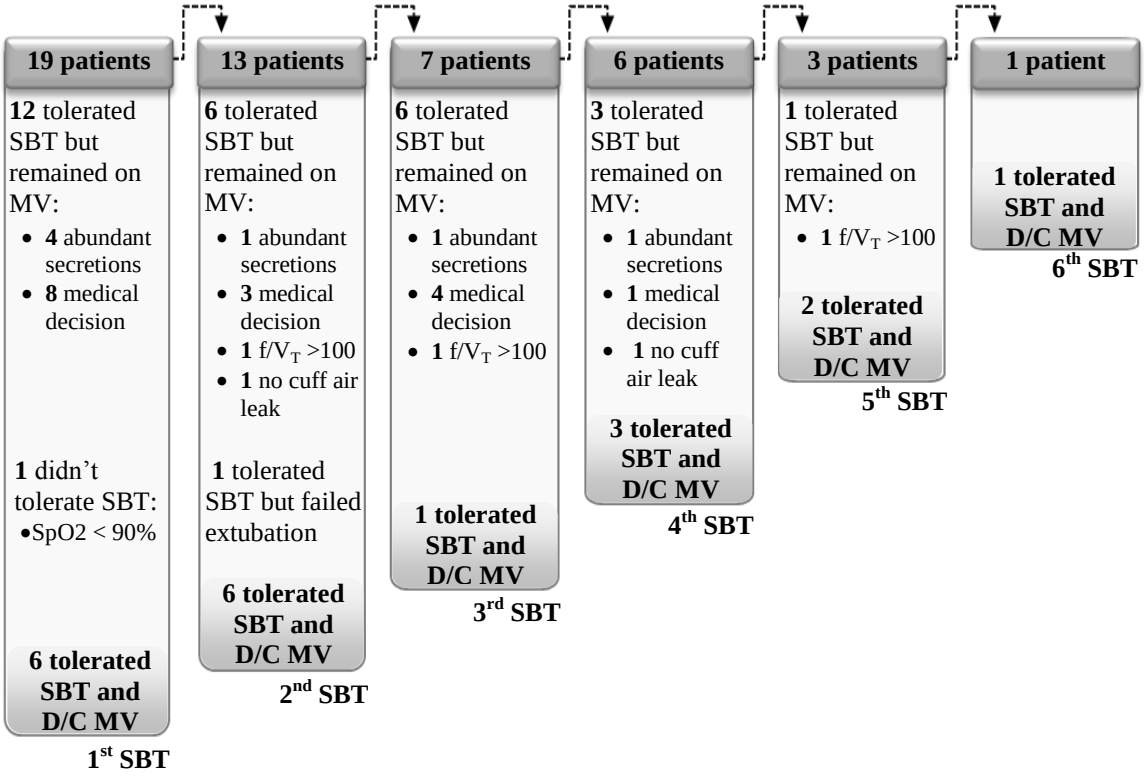

Figure 1. Spontaneous breathing trial (SBT). D/C, discontinued; MV, mechanical ventilation; SpO_2, saturation of peripheral oxygen; f/V_T, breathing frequency-tidal volume ratio (> 100 breaths/minute/ml).

Chapter V

Conclusion

Conclusion

Delirium and sleep disturbance are complex and highly prevalent phenomena among critically ill patients. Although the relationship between delirium and sleep disturbance has not been well established, the link between them suggests that both phenomena share similar mechanisms. Many risk factors have been implicated in the development of delirium and sleep disturbance in critically ill patients. These factors might also interact to adversely affect sleep architecture and patient outcomes. Although some factors are unique to each phenomenon, sedatives and analgesics are shared by both. Benzodiazepines negatively influence sleep mechanisms by provoking a reduction in the quantity and quality of sleep and also are related to the occurrence of delirium. Specifically, theories hold that the use of benzodiazepines and opioids could reduce slow wave sleep and REM sleep via gamma-amino-butiric acid (GABA) and opioid mu receptor stimulation. The use of benzodiazepine also may lead to hypoactive delirium by increasing GABA activity which alters levels of potentially delirogenic neurotransmitters. To the contrary, benzodiazepine withdrawal could lead to sleep disturbance, specifically REM rebound and as a consequence of a decrease in GABA activity may lead to hyperactive delirium.

Studies have demonstrated that a sedation wake-up trail reduced total amount of sedative administered. Therefore, this intervention may contribute to decreasing the occurrence of delirium by reducing the cumulative dose of sedatives. Since a sedation wake-up trial combined with a spontaneous breathing trial has also demonstrated improved patient outcomes, this combined intervention was implemented to explore its effect on the occurrence of delirium, patients' sleep perception, and other outcomes in critically ill trauma patients.

Findings of the first research report (Chapter III) demonstrated the contribution of the combined intervention in a sample of critically ill trauma patients. Those who received the combined intervention showed decreased occurrence of delirium, days in coma, duration in mechanical ventilation, length of TICU stay, and cumulative doses of benzodiazepines and propofol during the TICU stay. Furthermore, patients in the intervention group sample received lower amounts of benzodiazepines prior to the first measurement of delirium than patients in the control group.

In terms of sleep perception, our results are consistent with other studies that showed that ICU patients experience sleep fragmentation, perceive their sleep quality as bad, and are not satisfied with their sleep. However, differences in sleep perception were not significantly different between groups. It is important to recognize that construct and criterion validity were not performed on the Patient's Sleep Perception questionnaire to determine its psychometric properties. Therefore, the data derived from this questionnaire should be interpreted with caution. A future study to determine the validity of the Patient's Sleep Perception questionnaire is warranted with a larger sample.

The second research report (Chapter IV) showed that the implementation of the sedation wake-up trial and spontaneous breathing trial in these critically ill trauma patients was feasible. This combined intervention was well tolerated and successfully implemented in this population. The sedation wake-up trial provides clinicians with the opportunity to estimate pain and optimize their sedation treatment according to the patients' needs. In addition, it is not necessary to withhold analgesic continuous infusion during the sedation wake-up trial, thus preventing pain rebound. This combined intervention provides a safe alternative to the management of sedation in this

mechanically ventilated trauma population. However, the results cannot be generalized to all trauma ICU populations. This study excluded patients with head trauma or who had a history of illicit drug dependence or alcoholism who represent a high percentage of patients admitted to TICU. Further studies should include this type of patient to determine if the sedation wake-up trial is appropriate to use in this population or if the use of an alternate sedation protocol is better for them.

This study had several limitations. The design was sequential; all data from the CG were collected first followed by the IG. This type of design is subject to threats to internal validity such as different dropout rates between groups or different environmental conditions during CG period and IG period. A randomized clinical trial, while more rigorous, also has some inherent problems. For example, there could be intervention contamination between groups when patients are recruited from the same site. Also, randomization does not assure IG and CG equivalence. The lack of control in the type of sedative given to both groups may account for the significant differences found in delirium between the IG and the CG. Another methodological issue of this study that could lead to bias is that the investigators were not blinded to group assignment; therefore, a future study that includes a blinded strategy is needed. In addition, a larger sample is required to overcome the power issues in some of the variables in this study such as gender, days in delirium, total hospital stay, and total cumulative dose of propofol before the first delirium measurement.

Although the RASS score was measured daily in each patient after continuous sedative infusion discontinuation, it will be interesting to know the RASS scores at different times during the day in order to determine if a pattern exists in response to

intermittent sedative doses. In addition, in future studies, pain and comfort should be measured at different times during the day throughout the entire TICU stay. More than half of the patients in the sedation wake-up trials were not able to report their pain. Therefore, other measures than self-reported pain should be implemented in future studies.

In summary, data from the study reported here tend to support the theory concerning the action of benzodiazepines on delirium. The control group, which received a greater cumulative dose of benzodiazepines, experienced more hypoactive delirium than the intervention group. However, the intervention group, which received a lesser cumulative dose of benzodiazepines and experienced intermittent withdrawal of benzodiazepines, showed more of a mix of both hypoactive and hyperactive delirium.

APPENDICES

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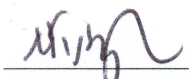

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