COMPARATIVE EFFECTIVENESS OF ANALGESIC SEDATION AS PRIMARY SEDATION IN MEDICAL ICU PATIENTS VS. CONVENTIONAL SEDATION AND ANALGESIA REGIMENS

BY

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ABSTRACT

Background: Most critically ill patients experience pain, fear, and anxiety as part of their illness while in the Intensive Care Unit (ICU). These emotions may be amplified during the provision of life-sustaining therapies, such as mechanical ventilation (MV). Pharmacotherapy including analgesics, sedatives, and antipsychotics are considered the standard of care to optimize patient safety and comfort during MV. Although the use of analgesics, sedatives, and antipsychotic therapies in the ICU is commonplace; adverse effects, unpredictable pharmacokinetics, and inappropriate dose titrations often hinder achieving the optimal level of effectiveness.[2-4] Under-treatment may lead to significant pain, agitation, myocardial ischemia, ventilator dyssynchrony, intravenous line removal, self-extubation, and post-discharge complications, including post-traumatic stress disorder (PTSD). In contrast, over-sedation has been associated with prolonged mechanical ventilation, development of decubitus skin ulcers, hospital-acquired infections, PTSD, delirium, prolonged ICU and hospital length of stay (LOS), and an increase in overall hospital costs. The aims of this study were to see if the use of analgosedation (fentanyl alone) would be non-inferior to conventional regimen (CR) in time-to-extubation and determine factors that affect ICU length of stay, mortality and re-intubation within 24 hours.

Methods: The study design was a retrospective matched observational study. After inclusion/exclusion criteria were applied 254 patients were identified in the study group. Propensity score matching was used to ensure that treatment groups were similar in terms of admission diagnosis, intubation reason, and APACHE II score. A total sample of 86 patients were selected into the analytical group with 43 patients each in the fentanyl alone group (FA) and CR group to show that the effect of fentanyl alone in a sedation protocol is not worse than that of the conventional regimen Kaplan Meier methods and Cox proportional hazard models

were used to analyze the primary outcome of interest; time-to-extubation. Covariates included in the Cox regression model included age, gender, ICU days, substance abuse history, number of admissions in the previous year, and insurance status. Using general linear regression modeling, we explored the effect of patient socio-demographic and clinical characteristics on ICU length of stay. Binary logistic regression modeling was used to assess the effect of patient socio-demographic and clinical characteristics risk of ICU mortality, and also for re-intubation within 24 hours.

Results: Differences in patient socio-demographics characteristics between the two groups was observed for ventilator days (5.7 days FA vs. 8.3 CR $p = 0.04$) and history of psychiatric problems and medication (17.4% vs. 2% $p < 0.001$). In the Cox proportional hazards regression models, the univariate/unadjusted models demonstrated non-inferiority between the two groups [HR= 0.7, 95% CI = (0.47, 1.18). This was confirm after adjusting for patient socio-demographic and clinical characteristics HR= 0.99, 95% CI = (0.6, 1.63). The ICU length of stay was significantly different between the two treatment groups in both the univariate model [HR= 0.9, 95% CI = (0.83, 0.93)] and after adjusting for patient socio-demographic and clinical characteristics [HR= 0.9, 95% CI = (0.82, 0.92)]. Females were observed to likely have reduced time-to-extubation in the adjusted model [HR = 0.5, 95% CI = (0.32, 0.88)]. In the analyses on secondary outcomes, ICU length of stay was determined to depend on the gender of the patient. Females were more likely than males to be admitted for a shorter length of time in the ICU ($p < 0.001$). There was no statistically significant difference in the duration of admission in the ICU between patients who received FA and CR ($p = 0.3$). In the assessments of the risks of death in the ICU and re-intubation within 24 hours whiles on admission at the ICU, the binary logistic

regression models comparing the risks in the FA and CR groups showed that the treatment groups were similar in terms of the risks.

Discussion: It was shown that Fentanyl-Alone in a sedation protocol was not worse off than that of the Conventional regimen in terms of duration of intubation. A larger trial is needed to determine if the analgosedation with fentanyl will provide any superior benefits in the duration of intubation. In this trial females demonstrated a much reduced length of time intubated compared to males and also the duration of admission at the ICU. A much structured study with sufficient power to determine the nature and intensity of these differences will needed. If the findings here are confirmed, it should provide some meaningful directions in health care particularly the relationship between gender and these outcomes. Finally this trial adds to the literature by being the first to use time-to-event analysis in patients receiving analgosedation.

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INTRODUCTION

The Public Health Issue

Most critically ill patients experience pain, fear, and anxiety as part of their illness while in the Intensive Care Unit (ICU). These emotions may be amplified during the provision of life-sustaining therapies, such as mechanical ventilation (MV). Thirty-seven percent of all patients who are admitted into an ICU will be placed on a mechanical ventilator.[1] Pharmacotherapy including analgesics, sedatives, and antipsychotics are considered the standard of care to optimize patient safety and comfort during MV.[2] As with all other therapeutics, a complete past medical history with regard to psychological function and current medication use (e.g. opioids and benzodiazepines) must be obtained in order to understand the baseline needs of the individual patient. It is important to note that each underlying disease state will directly influence the choice of pharmacotherapy; therefore, applying evidence-based medicine to the ICU population should be focused towards prioritizing patient comfort and outcomes, given the principle condition and comorbidities.

Although the use of analgesics, sedatives, and antipsychotic therapies in the ICU is commonplace; adverse effects, unpredictable pharmacokinetics, and inappropriate dose titrations often hinder achieving the optimal level of effectiveness.[2-4] Under-treatment may lead to significant pain, agitation, myocardial ischemia, ventilator dyssynchrony, intravenous line removal, self-extubation, and post-discharge complications, including post-traumatic stress disorder (PTSD). In contrast, over-sedation has been associated with prolonged mechanical ventilation, development of decubitus skin ulcers, hospital-acquired infections, PTSD, delirium, prolonged ICU and hospital length of stay (LOS), and an increase in overall hospital costs.[5,6] However, use of a multidisciplinary care team and an ICU-specific sedation and analgesia

protocol can limit morbidity and mortality defined above.[2,7,8] Delirium is a strong predictor of adverse outcomes and is one of the first iatrogenic events following admission to the ICU that has demonstrated long-term and short-term effects[9]. These affects include increased mortality and morbidity[10]. Patients who experience delirium have increased ICU and hospital LOS, which are associated with an increase in cost to the health system.[11]

The majority of patients in the ICU, who experience pain, will experience pain recall after transferring out of the ICU.12-14 Therefore, according to the 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit, pain should be monitored and treated.4 These guidelines are meant to: (a) ensure that patients are pain free and comfortable, and (b) reduce ventilator time. The ideal regimen for patients receiving MV should have adequate coverage for pain and anxiety, as well as providing favorable pharmacokinetics (rapid onset/offset of action, short half-life, few drug interactions, and minimal accumulation).[15] Fentanyl and other opioids have been reviewed as monotherapy, meaning when taken in conjunction with other agents they successfully control pain and provide sedative for those mechanically ventilated due to a short onset of action. The Society of Critical Care Medicine (SCCM) guidelines state that Fentanyl may provide immediate sedation and comfort. This approach is referred to as "analgosedation"; however, there is very little data to support this strategy.[16]

Purpose of this Study

This study, through a retrospective cohort of medical ICU patients, compared a Fentanyl-alone (FA) regimen to a conventional regimen (CR) to show that the effect of fentanyl alone in a sedation protocol is not worse than that of the conventional regimen in terms of critical outcomes like the duration of admission in the ICU, duration of intubation of patients, risk of mortality

whiles on admission at the ICU, and risk of re-intubation with 24 hours after a temporary extubation. The conventional regimen is defined as receiving a sedation medication (Propofol, Midazolam, Lorazepam, or Dexmedetomidine) continuously in tandem with an analgesic medication (Fentanyl). Since there is minimal evidence on Fentanyl as monotherapy, the study findings could potentially change practice, resulting in improved patient care and reduced exposure to potential complications associated with mechanical ventilation. The results of this study will help clinicians determine optimal medications for patients in an ICU who are mechanically-ventilated to help decrease ventilator-dependent and hospital days.

Aims

In a retrospective cohort of medical ICU patients, this study we compared a Fentanyl-alone (FA) group to a conventional regimen. Conventional regimen is defined as receiving a sedation medication (Propofol, Midazolam, Lorazepam, or Dexmedetomidine) continuously in tandem with an analgesic medication (Fentanyl).

1. The decrease in sedation will not be associated in any reduced benefits in ventilator support compared to the conventional regimen
2. To determine the effects of analgosedation (Fentanyl) on ICU length of stay, ICU- and ICU-mortality, and the proportion of re-intubations within 24 hours among the cases examined

Inclusion/Exclusion Criteria

Selection into the study required the patient to have been admitted to the MICU at the Via Christi Hospital on St. Francis St from 1/1/2010 to 5/31/2013. Patients were also required to have been mechanically ventilated for a minimum of forty-eight hours and had received analgesic medications (Fentanyl) and/or sedation medication (propofol, midazolam, lorazepam,

and Dexmedetomidine. Patients were excluded if they were prisoners, pregnant, minors, receiving neuromuscular blockers (NMBA), were admitted for trauma or have a central nervous system pathology (acute stroke, traumatic brain injury, intracranial hemorrhage, active seizures, end stage Parkinson's, dementia, post cardiac arrest etc.) Finally, patients were excluded if they were receiving spinal or epidural infusions.

BACKGROUND AND LITERATURE REVIEW

Pain Management among Critically Ill Patients

Analgesics

Pain occurs in critically-ill MV patients for various reasons, including discomfort from surgical wounds and provision of endotracheal tubes. From the patient's perspective, MV can be uncomfortable. Mechanical ventilation prevents patients from communicating effectively, therefore symptoms of pain, delirium, and hypoxemia can manifest as "agitation". This agitation can lead to self-extubation and potential harm to the patient and staff.[17] According to some evidence, adequate pain control is vital and potentially achieved with little to no sedative administration.[16] It is also important to remember that a significant number of critically ill patients expire during their ICU stay and providing comfortable transition to death is key for the family and presumably the patient.

Sedation

Sedation is the provision of analgesia and satisfaction of the anxiolytic, hypnotic, and amnestic needs of the patient. Sedatives are frequently used to facilitate care in the ICU to prevent recall of treatment and reduce anxiety. This care includes primary nursing responsibilities such as endotracheal suctioning, wound dressings, and prevention of adverse events such as self-extubation.[18] Patients may experience anxiety from the events surrounding an ICU admission secondary to an inability to communicate and/or sleep deprivation.[2,16-20] Another use for sedation includes the desire to produce an amnestic effect in order to blunt the overall ICU experience, pain recall and lessen the risk of post-traumatic stress disorder (PTSD).[19] However, this practice has been challenged by recent literature stating that less sedation may reduce the risk of PTSD.[20]

However, pain assessment in patients who are mechanically-ventilated is difficult due to the patient's inability to communicate. Pain assessment becomes subjective due to altered sensorium and decreased mentation. It is recommended that clinicians should assess non-communicative patients with subjective measurements of body movement, ventilator synchrony, and facial expressions, in addition to dynamic changes in vital signs (heart rate, respiratory rate, and blood pressure).[2,21-24]

Sedation Medications

The most common sedation medications in current use include Propofol, Lorazepam, Midazolam and Dexmedetomidine. Propofol is commonly used because it has a short half-life and has predictable sedative and hypnotic effects. This allows Propofol to be administered to patients who require frequent neurological exams. Thus, titration to clinical response and daily evaluation of sedation are important during use of Propofol infusions for ICU sedation. It is chiefly eliminated by hepatic conjugation to inactive metabolites, which are excreted by the kidney. Neither metabolism nor clearance has been affected by hepatic and renal insufficiency, which makes it a desirable pharmacotherapeutic agent in the ICU. However, Propofol also has potential adverse effects including Propofol Infusion Syndrome (PRIS), infection, and hypertriglyceridemia, if high-doses are administered for greater than 72 hours.[25,26]

Benzodiazepines are extensively used sedatives in the ICU and exert their effect by binding to the gamma-aminobutyric acid receptor (GABA) complex.[27-30] Benzodiazepines induce anterograde amnesia, respiratory depression, and are opioid-sparing. Two benzodiazepines that have been studied in MV ICU patients include Lorazepam and Midazolam. Both of these drugs have been shown to be effective in reducing anxiety and improving comfort to the MV patient.[31] Midazolam and Lorazepam are highly lipophilic and accumulate in

peripheral tissues during continuous intravenous infusion, which has been shown to increase the half-life of the medication and the pharmacodynamic effects.[6] The effects of accumulation may be reduced by providing a daily drug holiday and maintaining the lowest infusion dose that produces satisfactory sedation. [32-35] Benzodiazepines have been shown to increase the risk of delirium in approximately 70% of mechanically ventilated patients.[36] Among medical ICU patients, delirium has been shown to be a strong predictor of increased ventilator duration, longer ICU stay, long-term cognitive impairment, or even death.[37]

Dexmedetomidine (Precedex©) is a centrally acting alpha-2 agonist. Dexmedetomidine promotes anxiolysis and sedation; however, it does not cause respiratory depression.[38] The side effect profile consists of hypotension and bradycardia, which can lead to complete heart block. Dexmedetomidine has shown the ability to reduce the amount of time a patient is delirious and has been proven to be safe for extended infusions. [39]

Pain Medications

Fentanyl is a highly lipophilic synthetic opioid with a rapid-onset of action (1-3 minutes) and a short duration of activity upon intravenous administration. This makes Fentanyl ideal for clinical situations that require rapid and short-sustained analgesic activity. Fentanyl has little effect on the cardiovascular system and can be used without issue in hemodynamically unstable patients. Opioids, such as Fentanyl, have been reviewed as monotherapy, or in conjunction with other agents, to help control pain for those mechanically ventilated due to its short onset of action. The SCCM guidelines state that Fentanyl may provide immediate sedation and comfort; however, there is very little data to support this.[4] One published multi-centered study compared Remifentanil with a "conventional regimen".[16] Patients were randomized to receive either Remifentanil with or without Propofol vs. conventional regimen, which was defined as sedation

agent (Propofol, Midazolam, or Lorazepam) or analgesic (Morphine or Fentanyl). Infusions started simultaneously **Table 1**. Remifentanil was administered alone until a ceiling dose was reached; then propfol was added. The primary outcome variable was duration of MV, defined as the time from the start of the study regimen until extubation. Patients who received conventional sedation were on the ventilator 1.2 days longer compared to patients who received a Remifentanil-based analgesia **Table 2**.[16]

Table 1. Exposure of Medication Combination in the Rozendaal, FW et al.[16]

Drug, %	Conventional Sedation & Analgesia, %* n = 109	Remifentanil n = 96
Analgesic Meds		
Morphine	58%	-
Fentanyl	38%	-
Remifentanil	-	100%
Sedation Meds		
Midazolam	81%	-
Propofol	46%	65%
Lorazepam	7%	-

*Does not add up to 100%, some patients received more than one therapy

Table 2. Outcomes of Analgosedation in the Rozendaal, FW et al Study[16]

Ventilator Outcomes	Conventional Sedation & Analgesia n = 109	Remifentanil n = 96	P Value
Duration of MV(mean days) + (95% CI)	5.1 (3.5, 6.7)	3.9 (2.6, 5.2)	0.025
Weaning time (mean hours) + (95% CI)	24.8 (21.4, 28.1)	5.9 (0.8, 11)	0.0001

HYPOTHESIS

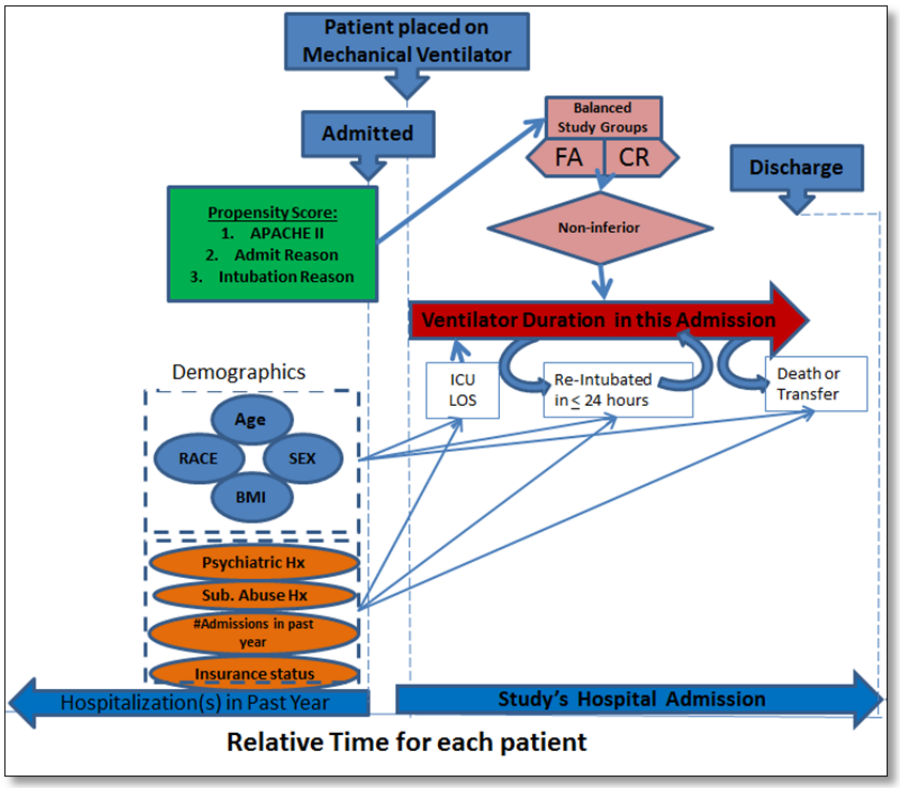
ICU patients from 1/1/2010 to 5/31/13, who were mechanically ventilated and obtained analgesia alone from Fentanyl alone in a sedation protocol is not worse of in terms of the length of time-to-extubation than those who received conventional sedation, defined as a continuous infusion of a sedation agent (Midazolam, Lorazepam, Propofol, or Dexmedetomidine) in tandem with analgesia (Fentanyl).

STUDY DESIGN

This research was a retrospective, observational, cohort study. The researcher conducted a retrospective chart review of mechanically ventilated patients admitted to the medical ICU at Via Christi Hospitals, Wichita, Inc. between January 1, 2010 and May 31, 2013. (Figure 1)

Conceptual Model

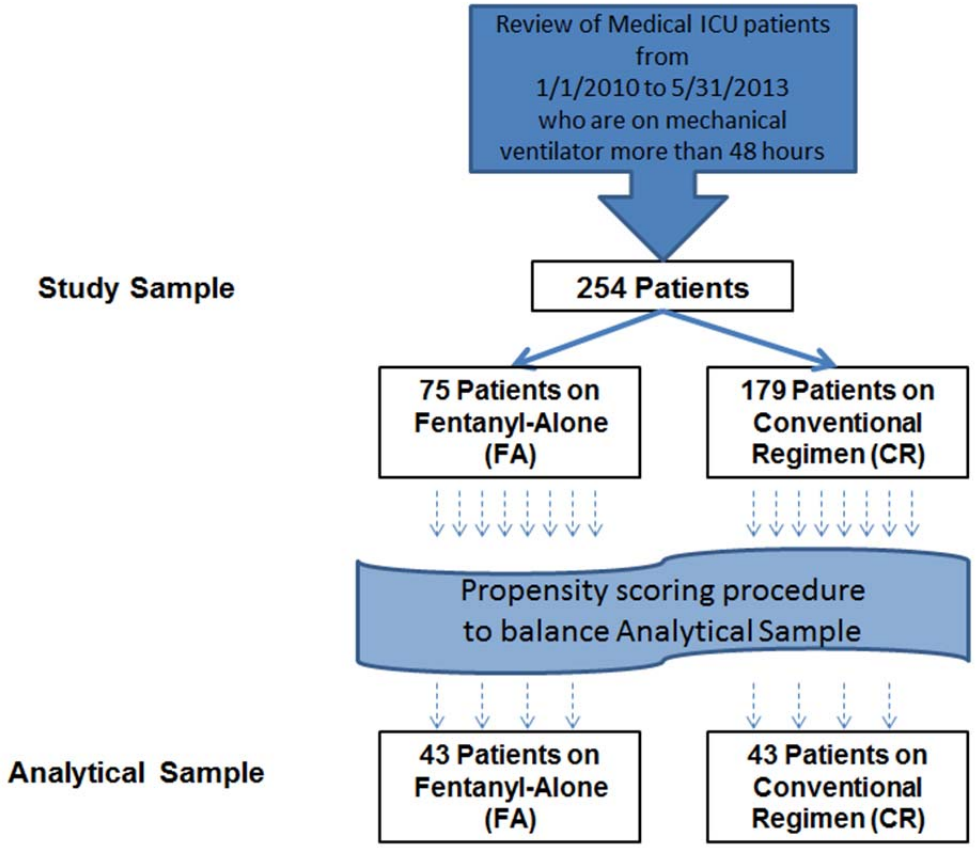
Figure 1. Structure of Analytical Strategy



Study Sample and Analytical Sample

As shown in Figure 2 the identification of all patients in the Medical ICU who were on mechanical ventilation (MV) during the period of January 1, 2010 through May, 31 2013 garnered 254 potential subjects for analysis after meeting inclusion and exclusion criteria (Table 3). However, in an effort to ensure that the treatment groups were balanced in terms of critical confounding factors, propensity scoring matching methods (described below) were applied which after isolating patients on the Fentanyl-Alone (FA) regimen, selected a patient matched to be similar in the matching characteristics (detailed below) who had received the Conventional Regimen (CR). The resulting, propensity-balanced, observational cohorts contained 43 patients in each study group.

Figure 2. Study Sample and Analytical Sample



STUDY LOCATIONS

The site involved in this research includes Via Christi Hospitals, Wichita Inc., St. Francis Campus.

As this project is a retrospective chart review, access was only allowed for VCH-W Principal Investigator to on-line hospital patient records (Mirror Image, respiratory records, and on-line hospital pharmacy records (Siemens Pharmacy System) was required.

METHODS

This was a retrospective chart review approved by The University of Kansas School of Medicine-Wichita Human Subjects Committee and Via Christi Health Institutional Review Board. The study was based on data routinely collected in hospital records for patients admitted to the Medical ICU (MICU). All patients admitted to the MICU at Via Christi Hospitals, Wichita Inc., Saint Francis Campus, who were placed on a MV between January 1, 2010 and May 31, 2013 and who met inclusion criteria, were selected. The exclusion criteria are specified in Table 3. The process of selection had it that patients were first identified from a pharmacy-based routine report based on medication prescribed, and use of ventilator. Once a patient list was obtained, the researcher reviewed all relevant information and entered the extracted information into an electronic database (Microsoft Excel and Access) for analysis. All statistical analyses were carried out using SAS software 9.2 (SAS Institute Inc., Cary, NC).

Table 3. Subject Inclusion/Exclusion

Inclusion Criteria (eligible to participate)	Exclusion Criteria (ineligible to participate)
● Age 18 or older ● Mechanically ventilated ≥48 hours ● Admitted to Via Christi Hospital on St. Francis Street between 1/1/2010 and 5/31/2013 ● Patients receiving IV infusions of Lorazepam, Midazolam, Dexmedetomidine, Propofol, and Fentanyl	● Prisoners ● Pregnant women ● Patients who were receiving neuromuscular blockers outside rapid sequence intubation ● Trauma patients ● Burn patients ● Patients with serious central nervous pathology (acute stroke, traumatic brain injury, intracranial hemorrhage, active seizures, end stage Parkinson's, dementia, post cardiac arrest etc.) ● Epidural or spinal epidurals

BALANCING GROUPS: FENTANYL-ALONE & CONVENTIONAL REGIMEN

Patients in the Fentanyl-Alone (FA) group were matched to a comparison group of Conventional Regimen (CR) using propensity scoring techniques as depicted in **Figure 1**. The propensity score matching algorithm determined the propensity score defined as an individual's probability of being treated with the intervention of interest relative to the alternative treatment given an appropriate set of patient socio-demographic and clinical characteristics about that individual. The purpose of propensity score matching is to reduce the numbers of potential confounders between the two groups, thus balancing the observational groups on factors expected to affect the dependent measures. These "matching factors" were selected based on their potential to reduce differences between the groups. In this study, the matching factors were patient Apache scores and diagnosis at admission.

APACHE Score

The APACHE scoring system was designed to aid in determining ICU admission criteria. Today, the APACHE II scoring system is used as a predictive model for mortality. Breakpoints of less than 25 and greater or equal to 25 are based on data demonstrating that patients with high APACHE scores have approximately 55% higher mortality rates compared to a 30% mortality rate for APACHE lower scores.

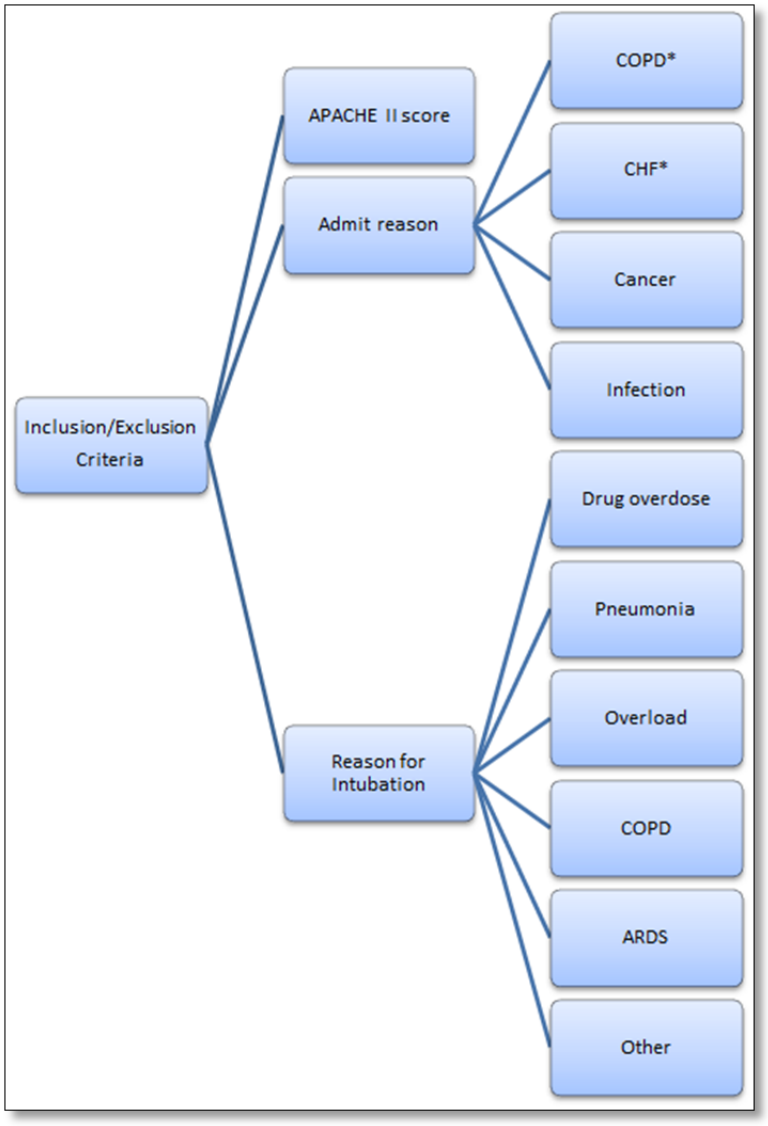
Admitting Diagnosis

The admission diagnosis was selected due to the expected variation in mortality and morbidity for each diagnosis. Congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cancer, infection, and other conditions were anticipated to provide similar mortality and morbidity characteristics in both FA and CR groups.

Ventilator Modes

The ventilator mode can affect sedation and analgesic requirements. All of the patients in this study were on conventional ventilator modes, which should reduce the requirements needed for sedation and analgesia.

Figure 3. Propensity Matching Criteria



* CHF = Congested Heart Failure

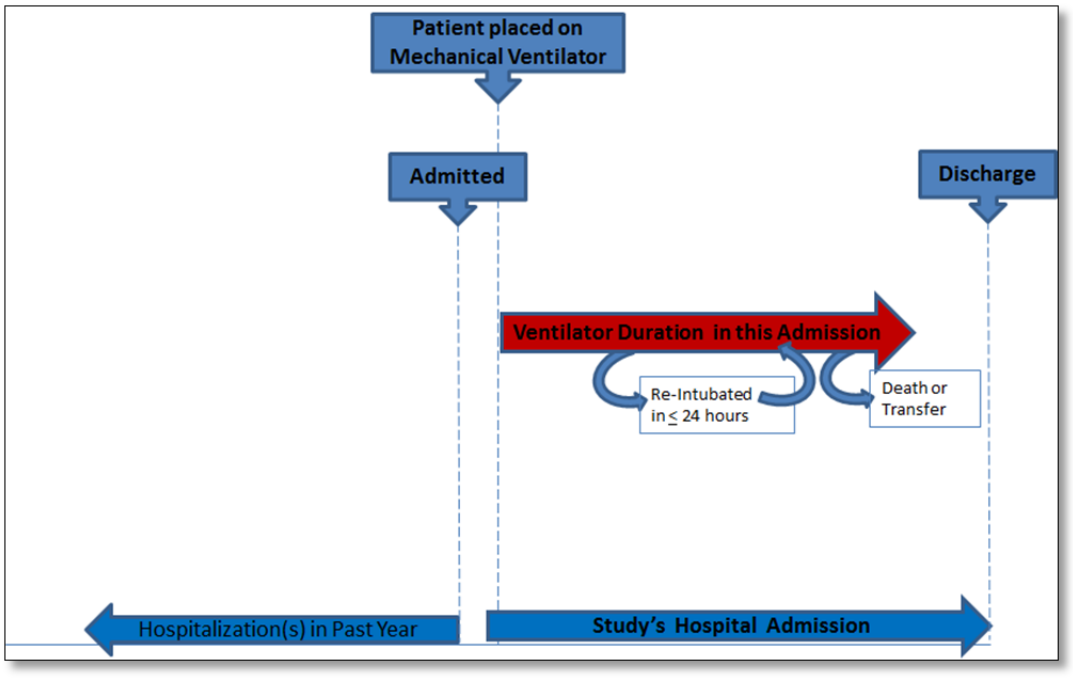
* COPD = Chronic Obstructive Pulmonary Disease

OUTCOMES

Primary Outcome Measure

The primary outcome measure was duration (days) from intubation to extubation within 28 days from ICU admission. Patients who died whiles on admission at the ICU and during the period of intubation, had extubation not according to the medical protocol, was transferred to another institution, or was still intubated at the end of the 28 days of observation were considered censored to the time-to-event analysis. This 28-day cutoff in patient observation is according to a Food and a Drug Administration (FDA) recommendation for new pharmacotherapeutic agents designed for critically-ill patients, which suggests 28 days to be the optimal time to determine beneficial outcomes in the critically-ill. [40-42] The study time frame and structure of the primary outcome measure are shown in Figure 4.

Figure 4. Primary Outcome Measure and Timeline



Secondary Outcome Measures

Secondary outcome measures included: ICU length of stay, ICU mortality, and proportion of re-intubations within 24 hours. ICU length of stay was measured from date of ICU admission to ICU discharge. Mortality was determined by discharge disposition of death in the electronic record and location when the event occurred. Re-intubation within 24 hours was used as a surrogate marker for failed extubation.

Covariates

Covariates that were used in this study included gender, dosage of medication, substance abuse history, Source of payment, BMI, count of patients re-intubated within 24 hours of extubation and number of admissions in past year.

Statistical Analysis: Descriptive Analysis

Summary description of baseline characteristics of patients in the two treatment groups were assessed using frequency distributions for categorical variables and means and standard deviations for continuous variables. We compared all baseline variables for both groups to identify any clinically meaningful imbalances that may influence the primary outcome. All analyses were conducted using SAS software 9.2 (SAS Institute Inc., Cary, NC)

Multivariable Analytical Strategy: To address the primary and secondary outcomes that comprehensively addressed the research objectives of this study, we adopted the following multivariable analysis strategy (Shown in Table 4).

First, the univariate unadjusted effect of patient characteristics on patient time-to-extubation (days) compared between the propensity-balanced groups was conducted. The influence of key predictors on patient probability of extubation was further examined in a multivariable Cox Proportional Hazards regression model.

Table 4. Definition of Variables

Variable	Definition
Ventilator days	Time (days) spent on the mechanical ventilator
ICU days	Time spent admitted to the ICU
ICU mortality	Patients who died in the ICU
Re-intubation within 24 hours	Patients placed back on the ventilator $\leq$ 24 hours from extubation

Table 5. Analytical Strategy

Outcomes	Measure
Time-to-extubation	Kaplan Meier & Cox Proportional Hazard Model
ICU days	Linear Regression
ICU mortality	Logistic Regression
Re-intubation within 24 hours	Logistic Regression

Further analyses were conducted to understand the factors that predict the secondary outcomes: number of ICU days, mortality within the ICU and re-intubation within 24-hours of extubation.

Statistical Analysis: Analysis of Primary Outcome Measure

We compared the primary outcome (time-to-extubation) between FA patients and the CR group. Kaplan-Meier (KM) survival analysis methods were utilized to determine the differences in time-to-extubation between the two treatment strategies. Unadjusted rates of time-to-extubation between the propensity-balanced cohorts, with 95% confidence intervals, were compared using log-rank tests. In addition, Cox proportional hazards regression model was used to determine the effects of patient and disease characteristics on the likelihood of extubation and to further examine their influences on the measure of effect, while adjusting for possible confounding variables.

The Cox proportional hazards regression model was used to determine if admission age, gender, substance abuse history, ICU length of stay, BMI categorical, race, Insurance status, re-intubation within 24 hours, and number of hospital visits in the last year to provide insight to the difference found between the two groups in time-to-extubation. The predictors were selected based on the assumed clinical effect each predictor has on successful extubation. Forest plots were used to present the parameter estimates.

Statistical Analysis: Analysis of Secondary Outcome Measures

ICU Length of Stay

The t-test was used to compare the statistical difference in ICU length of stay. The linear regression model was then used to determine if age, psychiatric history, substance abuse history, study group, race source of payment, gender, re-intubation within 24 hours, BMI, number of admissions in past year, and substance abuse history could provide insight to differences between the two propensity-balanced groups in ICU length of stay. The predictors were selected based on an assumed clinical effect on ICU length of stay, and evidence in the literature.[16,17] The critical coefficients included study group, BMI, age, substance abuse history, and psychiatric history.

Different sedation medications have significantly different half-lives and therefore could account for increase in length of ICU stay. Patients who are in the obese BMI category are associated with increase length of stay. Re-intubation within 24 hours is an assessment of extubation failure and is associated with an ICU length of ICU stay. There is a potential effect source of payment, gender, number of admissions in past year, and substance abuse history with ICU length of stay. The specification of the model is shown below.

$$\text{LOS} = \hat{\beta}_0 + \hat{\beta}_1 \times \text{age} + \hat{\beta}_2 \times \text{Psychiatric history} + \hat{\beta}_3 \times \text{Study group} + \hat{\beta}_4 \times \text{Race} + \hat{\beta}_5 \times \text{Substance abuse history} + \hat{\beta}_6 \times \text{Source of payment} + \hat{\beta}_7 \times \text{number of admissions in past year} + \hat{\beta}_8 \times \text{Gender} + \hat{\beta}_9 \times \text{Re} - \text{intubation within 24 hours} + \hat{\beta}_{10} \times \text{BMI Groups}$$

ICU Mortality

ICU mortality was defined as a dichotomous variable (Yes/No). Due to the potential low cell counts, Fisher's exact test was chosen to determine any association ICU mortality outcomes and treatment groups. This binary logistic regression modeling technique was used to determine if patient characteristics such as age, gender, treatment group, race, psychiatric history, source of payment, number of admissions in past year, BMI group, and substance abuse history will explain ICU mortality differences between the two groups. The predictors were selected based on their assumed effect each predictor has on mortality. Study grouping it was expected would determine if sedation choices made a difference in ICU Mortality, which would in turn affect duration to extubation. BMI categories, it was supposed, might have some effect on mortality through increased half-life of pharmacotherapy and increased morbidity of patients with amassed BMI. Psychiatric history was selected on the assumption that patients who have mental illness may have an increased risk of mortality. Age and gender are used in the model to determine their impact on mortality. Source of payment, number of admissions in past year, and substance abuse history was also assessed as potential confounders of the risk of ICU mortality.

$$\text{logit}\left(\text{mortality:}\frac{\text{Yes}}{\text{No}}\right)$$

$$= \hat{\beta}_0 + \hat{\beta}_1 \times \text{age} + \hat{\beta}_2 \times \text{Psychiatric history} + \hat{\beta}_3 \times \text{Study group} + \hat{\beta}_4$$

$$\times \text{Race} + \hat{\beta}_5 \times \text{Substance abuse history} + \hat{\beta}_6 \times \text{Source of payment} + \hat{\beta}_7$$

$$\times \text{number of admissions in past year} + \hat{\beta}_8 \times \text{Gender} + \hat{\beta}_9 \times \text{Re}$$

$$- \text{intubation within 24 hours} + \hat{\beta}_{10} \times \text{BMI Groups}$$

Proportion of Re-intubations within 24 Hours

Re-intubation within 24 hours was defined as a dichotomous variable (Y/N). Due to the potential low cell counts, Fisher's exact test was chosen to determine any association re-intubation within 24 hours outcomes and treatment groups. This binary logistic regression modeling technique was used to determine if patient characteristics such as age, gender, treatment group, race, psychiatric history, source of payment, number of admissions in past year, BMI group, and substance abuse history will explain re-intubation within 24 hours differences between the two groups. The predictors were selected based on the assumed effect each predictor has on re-intubation. Study group would determine if sedation choices made a difference in re-intubation, which would in turn effect duration to extubation. BMI categories might have an effect on re-intubation due to the lipophilicity of the pharmacotherapeutic agents. Psychiatric history was selected on the assumption that patients who have mental illness may have an increased risk of re-intubation. Age and Gender is used in the model to determine their impact on re-intubation. There is a potential effect source of payment, number of admissions in past year, and substance abuse history with ICU re-intubation.

$$\text{logit}\left(\text{re}-\text{intubation}:\frac{\text{Yes}}{\text{No}}\right)$$

$$= \hat{\beta}_0 + \hat{\beta}_1 \times \text{age} + \hat{\beta}_2 \times \text{Psychiatric history} + \hat{\beta}_3 \times \text{Study group} + \hat{\beta}_4 \times \text{Race} + \hat{\beta}_5 \times \text{Substance abuse history} + \hat{\beta}_6 \times \text{Source of payment} + \hat{\beta}_7 \times \text{number of admissions in past year} + \hat{\beta}_8 \times \text{Gender} + \beta_9 \times \text{ICU los} + \hat{\beta}_{10} \times \text{BMI Groups}$$

Results

Patients were identified from the hospital electronic health records by sedation agents used during ICU stay. A total of two hundred and fifty-four patients met the requirements for inclusion into the study. Propensity scoring matched patients based on APACHE scores, admission diagnosis, and intubation reason. Propensity scoring was used to reduce confounders between the two groups, and achieve the best balancing in these observational groups.

A total of eighty-six patients were included in the study with forty-three in each group. The mean [$\pm$ Standard deviation (SD)] or percentages were reported between the two groups: age FA 62..5 $\pm$ 13.9 vs. CR 65.2 $\pm$ 14.3 (p =0.382), gender FA 65% were male vs. CR 48.% male (p = 0.127), ICU days FA 10.6 $\pm$ 11.6 vs. CR 13.5 $\pm$ 10.5 (p=0.227) and ICU mortality FA 19.8% vs. CR 16.3% (p=0.5). There was no difference between the groups in relationship to the BMI categories (p = 0.9). There was no difference between the groups average number of prior admissions in the last year. 0.7 $\pm$ 1.2 FA and 1.1 $\pm$ 1.3 (p = 0.095). The only difference between the two groups was a reduction in ventilator days – the primary outcome measure 5.7$\pm$ 4.7 FA and 8.3$\pm$ 6.4 CR, (p = 0.039). Insurance was classified into three groups with public 65% and private insurance 16%. The insurance classification of "other" was 8%, which included mostly patients without any insurance or customers, who were cash paying. Table 6 highlights the demographics of the study populations.

Table 6. Demographics and Descriptive Variables

Study Group	Fentanyl-Alone (FA) N = 43	Conventional Regimen (CR) N = 43	Total	P value
Age, (Mean + SD)	62.5 + 13.9	65.2 + 14.3	63.8 + 14.1	0.382
Gender (Male), n (%)	28 (65.1)	21 (48.8)	49 (57)	0.127
Admission Diagnosis*, n (%)				0.945
Infection Chronic Obstructive Pulmonary Disease Other Renal failure Congested Heart Failure Diabetic ketoacidosis	17 (19.8) 12 (13.9) 8 (9.3) 3 (3.5) 2 (2.3) 1 (1.2)	16 (18.6) 14 (16.3) 5 (5.8) 4 (4.7) 4 (4.7) 0 (0)	33 (38.4) 26 (30.2) 13 (15.1) 7 (8.1) 6 (7) 1 (1.2)	
Reason for Intubation*, n (%)				0.965
Pneumonia Chronic Obstructive Pulmonary Disease Overload Acute Respiratory Distress Syndrome Overdose Other	15 (17.4) 8 (9.3) 8 (9.3) 8 (9.3) 3 (3.5) 1 (1.2)	14 (16.3) 10 (11.6) 10 (11.6) 6 (7) 2 (2.3) 1 (1.2)	29 (33.7) 18 (20.9) 18 (20.9) 14 (16.3) 5 (5.8) 2 (2.3)	
Weight (kg), (Mean + SD)	86.4 + 25.7	83.7 + 25.7	84.8 + 25.6	0.553
BMI, n (%)				
Normal < 25 Overweight > 25 <30 Obese > 30	16 (18.6) 7 (8.1) 20 (18.6)	17 (19.8) 8 (9.3) 18 (21)	33 (38.3) 15 (17.4) 38 (44.2)	0.904
APACHE II*, (Mean + SD)	23.4 + 5.3	22.6 + 4.7	23 + 5	0.431
Ventilator days, Mean + SD	5.7 + 4.7	8.3 + 6.4	6.9 + 5.7	0.039
ICU days, (Mean + SD)	10.6 + 11.6	13.5 + 10.5	12.6 + 11.1	0.227
Hospital days, (Mean + SD)	15.4 + 13.5	17.5 + 13	16.4 + 13.3	0.467
Re-intubation < 24 hours, n (%)	4 (4.7)	7 (8.1)	11 (12.8)	0.355
Mortality, n (%)	17 (19.8)	14 (16.3)	31 (36)	0.501
Number of admissions last year, (Mean + SD)	1.1 + 1.3	0.7 + 1.2	0.9 + 1.2	0.095
History of Substance abuse, n (%)	6 (7)	7 (8.1)	13 (15.1)	0.764
Psychiatric History, n (%)	15 (17.4)	2 (2.3)	17 (19.8)	0.001
Insurance, n (%)				0.924
Public Private Other	32 (37.2) 7 (8.1) 4 (4.7)	33 (33.9) 7 (8.1) 3 (3.5)	65 (75.6) 14 (16.3) 7 (8.1)	

*Variables used in propensity score

Time-to-Extubation – Primary Outcome

The time-to-extubation between the FA and CR groups was analyzed using time-to event analysis with Cox proportional hazards regression. Patients were censored by death, self-extubation and all extubations not according to medical protocol, transfer to another institution, re-intubation within 24 hours, and intubation up to 28 days and beyond. Accounting for censoring of the time-to-extubation allows the patient to attribute time up to the point of censoring.

Kaplan Meier analysis with the log-rank test was used to determine any univariate differences between the two groups in the time-to-extubation.(Figure 5) The graph shows that there is not a significant difference between the two groups with the two lines crossing multiple times (p= 0.2)

Using backward elimination in the model selection process, which variables had any relevant effect on the time-to-extubation outcome were included in the final model. The backward elimination selection procedure used a probability to stay value of 0.25.

In the multivariable Cox proportional hazards regression models, the univariate unadjusted models demonstrated that Fentanyl alone in a sedation protocol was not worse of in terms of the length of time-to-extubation than those who received conventional sedation [HR = 0.7, 95% CI = (0.47, 1.18)] and this was confirmed in when we accounted to patient socio-demographic and clinical characteristics in the adjusted model. This was interesting due to the differences shown between the two groups with univariate t test (p= 0.039). Several variables were not selected for inclusion into the adjusted model including race, age, re-intubation within less than 24 hours, and number of hospital visits in the last year. The only variable that demonstrated a significant difference in both the univariate and adjusted model was the duration

of admission at the ICU [Unadjusted HR = 0.9, 95% CI = (0.83, 0.93); Adjusted HR = 0.9, 95% CI = (0.82, 0.92)]. Shorter ICU days were observed to be associated with reduced duration of ventilation. This could be explained because the majority of patients who inhabit the ICU are ventilated and ICU length of stay is highly correlated to patient's time on the ventilator. Other variables included in the model were the gender, insurance status, and substance abuse history. Females showed a significant reduction in the time-to-extubation in the adjusted model [HR 0.5, 95% CI = (0.32, 0.88)]. Both insurance status and substance abuse history did not show a statistically significant effect on duration of patient intubation. (Figure 6)

Figure 5. Kaplan Meier Graph

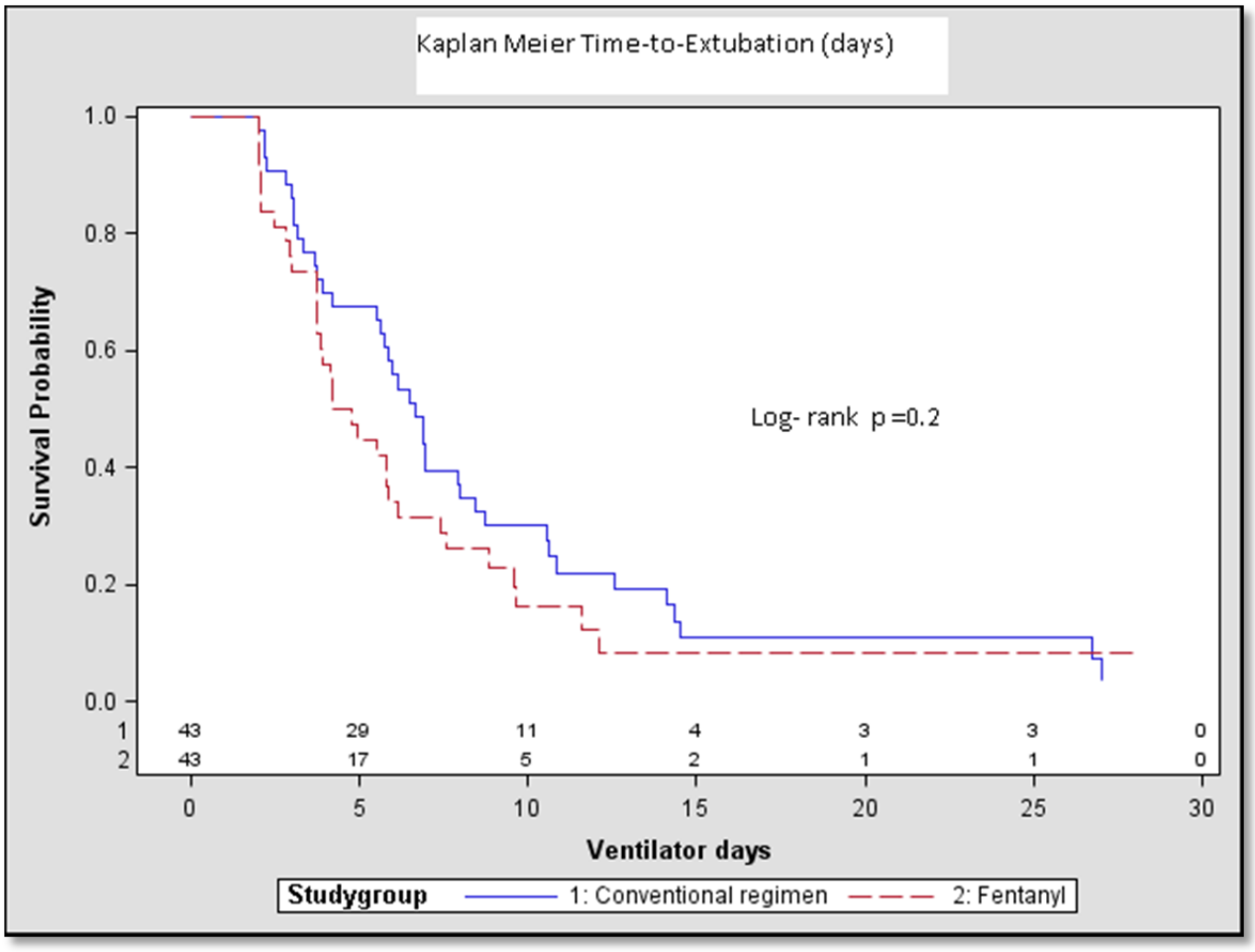
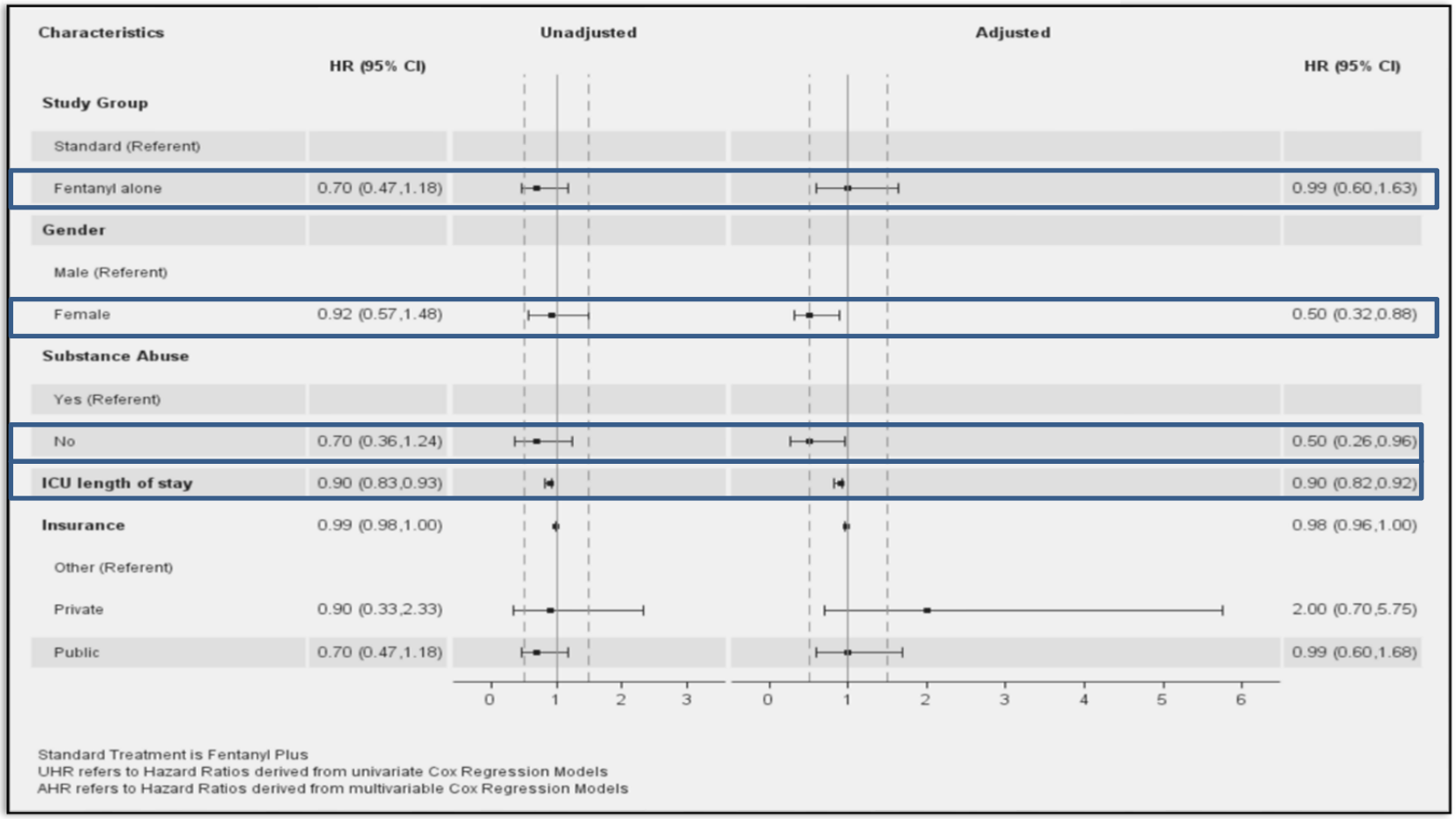


Figure 6. Cox Proportional Hazard Model



Secondary Outcomes

ICU Length of Stay

General linear regression modeling technique was used to determine predictors of ICU length of stay. The univariate unadjusted model variables that showed any significant effect on ICU length of stay included the gender. Females were associated with a surprising reduction in ICU length of stay (Parameter estimate -5.6, $p < 0.001$) compared to males. Patients who were re-intubated within 24 hours of first extubation also had a significantly longer length of stay in the unadjusted model (Parameter estimate 9.4, $p < 0.001$). This may be expected as patients who fail extubation are known to have a longer ICU length of stay. Patients in the FA group did not have a statistically significant reduction in ICU length of stay in either the unadjusted ($p >0.05$) or adjusted model ($p >0.05$) compared to the CR group. In the adjusted model the only variable that showed any significant reduction on ICU length of stay was gender. Females were more likely than males to have a reduction in the ICU length of stay (parameter estimate -7.1, 95% p value < 0.001). Having public insurance was associated with a significant increase in ICU length of stay (parameter estimate 10.4, $p < 0.001$). The gender difference on length of stay and public insurance are discussed further in the discussion section. All other variables in the adjusted model did not show any trend or significant difference in the length of ICU stay. (Table 7)

Table 7. ICU Days Linear Regression Model

		Unadjusted Model (Univariate Statistics)				Adjusted Multivariable Model			
Parameter	Ref Category	Parameter Estimate	95% Confidence Limits		P value	Parameter Estimate	95% Confidence Limits		P value
Intercept						17.7	3.8	31.6	0.0
Age		0.0	-0.2	0.2	0.9	-0.2	-0.4	0.0	0.1
Number of hosp visits in the last year		-1.3	-3.3	0.6	0.2	-0.7	-2.7	1.3	0.5
Insurance Private	Other	4.1	-6.2	14.3	0.4	8.3	-2.9	19.4	0.1
Insurance Public	Other	5.4	-3.4	14.2	0.2	10.4	0.0	20.8	0.0
Fentanyl	CR	-2.9	0.2	-7.7	-1.2	-2.6	-7.8	2.6	0.3
Female	Male	-5.6	-10.3	-0.9	0.0	-7.1	-12.2	-1.9	0.0
Re-intubation within 24 hours (Y/N)	No	9.4	2.5	16.3	0.0	7.0	-0.4	14.5	0.1
Substance Abuse (Y/N)	No	-1.7	-8.4	5.0	0.6	-3.1	-11.0	4.7	0.4
Psychiatric history (Y/N)	No	5.4	-11.3	0.5	0.1	-3.2	-9.7	3.4	0.3
Race Other vs. White	White	0.3	0.9	-6.6	7.2	0.9	-6.1	8.0	0.8
BMIC Obese	Normal	1.7	-3.6	7.0	0.5	1.7	-3.8	7.3	0.5
BMIC Overweight	Normal	1.1	-5.8	8.1	0.7	0.6	-6.3	7.5	0.9

Risk of ICU Mortality

Binary logistic regression was used to determine variables that would potentially reduce or increase the risk of ICU mortality. In the multivariable logistic regression model, there were no trends in mortality with age [OR=1.0, 95% CI = (1.0, 1.1)] and ICU days [OR=1.0, 95% CI = (1.0, 1.1)]. The CR group did show a trend towards less mortality [OR=0.7, 95% CI = (0.3, 1.8)]. Insurance status did not have any statistically significant effect on the risk of mortality [OR(Private) = 2.5, 95% CI = (0.3, 22.4); OR (Public) = 2.7, 95% CI = (0.4, 19.4)]. None of the other variables showed any significant effect or trend in mortality in both the unadjusted or adjusted models (Table 8).

Table 8. Relative Risk of Mortality

		Unadjusted Model (Univariate Statistics)			**Adjusted Multivariable Model**		
Effect	**Ref**	**Odds Ratio**	**95% Confidence Limits**		**Odds Ratio**	**95% Confidence Limits**	
Age (years)		1.0	1.0	1.1	1.1	1.0	1.1
ICU length of Stay		1.0	1.0	1.1	1.0	1.0	1.1
insurance Private vs. Other	Other	2.5	0.3	22.4	0.8	0.1	9.1
insurance Public vs. Other	Other	2.7	0.4	19.4	0.7	0.1	7.3
Conventional regimen vs. Fentanyl	Fentanyl	0.7	0.3	1.8	0.6	0.2	1.8
Race Other vs White	White	0.6	0.2	2.3	0.6	0.1	2.8
Psychiatric History (Y/N)	No	1.8	0.6	5.2	1.7	0.4	7.3
Substance Abuse (Y/N)	No	0.3	0.1	1.5	0.8	0.1	4.8
BMI Obese vs. Normal	Normal	0.3	0.1	0.7	0.2	0.1	0.6
BMI Overweight vs. Normal	Normal	0.3	0.1	1.2	0.3	0.1	1.3
Number of hosp visits in the last year		0.9	0.6	1.3	0.8	0.5	1.3

Risk of Re-Intubation within 24 hours of Extubation

This model was used to assess the relative risks of being re-intubated within twenty-fours of extubation comparing the FA group to the CR group. This model was used to determine what factors predict when extubation fails. Only eleven patients out of the eighty-six were re-intubated, which goes along with the demographics table showing no difference between the two groups. There were no significant differences with any of the variables in the unadjusted or adjusted model. Age, ICU length of stay, gender, race, substance abuse, and number of hospital visits had 95% CI for the odds ratios than enclosed the null value (Table 8). Patients with a BMI in the overweight category had an odds ratio of 3.8 as compared to normal, but again this was not statistically significance. Since re-intubation seems a rare event in this group, a larger population of patients undergoing MV may be needed to have a meaningful discussion. (Table 9)

Table 9. Relative Risk of Re-intubation

		Unadjusted			Adjusted		
			95%			95%	
Effect	Ref	Odds Ratio	Confidence Limits		Odds Ratio	Confidence Limits	
Age (years)		1.1	1.0	1.1	1.1	1.0	1.1
ICU length of Stay		1.0	1.0	1.1	1.0	1.0	1.1
insurance Private vs. Other	Other	1.7	0.0	56.5	0.8	0.0	29.8
insurance Public vs. Other	Other	2.8	0.1	65.1	1.0	0.0	29.4
Gender Female	Male	0.5	0.1	1.9	0.5	0.1	2.1
Conventional regimen vs. Fentanyl	CR	1.8	0.5	6.4	0.7	0.2	3.0
Psychiatric History (Y/N)	No	0.5	0.1	3.3	1.2	0.2	8.4
Race Other vs White	White	0.8	0.1	5.3	2.1	0.3	14.6
BMI Obese vs. Normal	Normal	3.5	0.8	16.0	3.4	0.7	16.0
BMI Overweight vs. Normal	Normal	1.3	0.1	11.5	1.4	0.2	10.8
Substance Abuse (Y/N)	No	0.7	0.1	4.7	0.7	0.1	6.5
Number of hospitalizations in the past year		0.9	0.5	1.6	0.9	0.5	1.6

Discussion

The aim of this study was to compare the FA group to CR in reduction in time to extubation and ICU length of stay, in hospital mortality, and proportion of re-intubations within 24 hours among the two groups. To acquire balanced retrospective cohort of patients, a propensity scoring technique was used based on APACHE II scores, reasons for intubation, and admission diagnosis. This provided an effective method of selecting patients since the characteristics of the two groups were well matched at the selection of patients who met initial inclusion and exclusion criteria.

The comparison of FA to CR was to show that the effect of a Fentanyl alone on the duration of intubation was not worse off than that of conventional regimen. No difference was shown in the Cox proportional hazard regression model. This is interesting in the fact that this was first time this type of analysis had been done (time-to-event) and the results demonstrated that groups are comparable. This information coupled with the univariate analysis where FA had statistically significant reduction in the mean ventilator days will lead to larger retrospective (multicenter) or prospective randomized control trials to elucidate the potential advantage between the two groups.

In the Cox proportional hazard model the critical estimate was ICU length of stay. This should not be a surprising since there is expected a relationship between ventilator days and ICU length of stay. A study by Arabi et al. researching resource utilization of patients with prolonged stays in the ICU, demonstrated that ICU length of stay and ventilator days had a high correlation ($r^2 = 0.89$, $p < 0.001$)[43].

The other variable to have an effect in the model was being gender. Females were more likely than males to have a reduced time to extubation. The authors could not find any data

correlating gender affecting time to extubation. It is difficult to determine whether this is just an artifact of the data set (was selected from a single center) or selection bias and sample size. It is anticipated that, this will be conformed in a larger much more structured study later.

Secondary Outcomes Discussion

In the linear regression model the Fentanyl alone group appeared to not affect ICU length of stay, after adjusting for other variables and balancing the comparison with propensity scores, which should remove any medical difference to the extent possible in this data. Among ICU patients and especially when dealing with sedation and mechanical ventilation, there are several variables that can affect outcomes. In a recent trial where sedation vacations were compared to light sedation protocol, there was not a difference in the length of ventilator days[44]. A study by Strom et al. where patients with no sedation (morphine boluses allowed for pain) compared to sedation with a daily interruption verified a significant increase in ventilator free days in the no sedation group ($p < 0.05$)[45]. These two trials have a couple of things in common, such as low nursing to patient ratios (1:1 in the no sedation study) and extensive education provided to the nurses in sedation practices. The inability to show a difference between the two groups in ICU days may be influenced by the quality of care and the education provided to the clinicians at the point of care. On the other hand, as discussed previously, the correlation between ventilator days and ICU length of stay leads one to believe that sedation choice will not affect ICU length of stay unless it first reduces ventilator days. Larger multicenter trials are needed to determine the effect of sedation on ICU length of stay.

The final two models looked at mortality and re-intubation within 24 hours of extubation. Neither model showed any significant differences in the risks of mortality or re-intubation

related to any of the variables. Mortality is affected by several factors that were controlled with the propensity matching.

Strengths

This trial used propensity scoring which allowed the authors to match cases in an observational retrospective sample on multiple variables. This allowed for a well-matched study and decreased the retrospective selection bias. This is the first trial that looked at time-to-extubation. Previous research on analgosedation has focused on the ability to increase ventilator free days or comparing time spent in the optimal level of sedation.

Limitations

This was a single center retrospective study in a community teaching hospital medical ICU. Even with propensity scoring the risk of selection bias is still present. Some of the secondary analysis had limited events occur, which makes it hard to analyze the model.

Conclusion

A single-center retrospective cohort study demonstrated that fentanyl alone and conventional regimen are non-inferior to each other in the time-to-event analysis. This study was a pilot study and therefore larger more robust study is needed to ascertain the true clinical difference between the two groups.

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44. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* Nov 21 2012;308(19):1985-1992.
45. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet.* Feb 6 2010;375(9713):475-480.

Appendices

KU IRB Approval Letter

KU SCHOOL OF MEDICINE WICHITA
The University of Kansas

August 12, 2013

HSC Number:	**220131613VC**
Project Title:	**Comparative Effectiveness of Analgesic Sedation as Primary Sedation in Medical ICU Patients vs. Conventional Sedation and Analgesia Regimens**
Primary Investigator:	**Bradham, Douglas D DrPH, MS, MPH**
Protocol Number:	**Version 1; June 26, 2013**
Sponsor:	**NA**
Status:	**Approved to rely on Via Christi**

Dear Investigator:

This is to certify that the KUSM-W Office of Compliance has reviewed your research proposal and has determined that your project meets the criteria for reliance upon Via Christi IRB.

You may only start the study after it has been approved by the Via Christi IRB. From this point forward, please submit all documents related to this project to Via Christi for IRB approval.

If you have any questions regarding the human subject protection process, please do not hesitate to contact me at (316) 293-2610 or jryan3@kumc.edu.

Sincerely,

Jamie Ryan, BA
Office of Compliance

Office of Compliance
1010 N. Kansas | Wichita, KS 67214-3199 | (316) 293-2600 | Fax (316) 293-2628

Via Christi IRB Approval

Via Christi Hospitals Wichita, Inc. Institutional Review Board

IRB Reviewer Findings

Benefit/Risk Assessment: ☐ Less Than Minimal Risk ☑ Minimal Risk

☑ Approved Term of Approval: One Year

☐ Conditionally Approved as follows_____

☐ Disapproved

☐ Deferred

☐ More Than Minimal Risk - Full Board Review Required

The project meets all of the following criteria for waiver of consent:

☑ The research in its entirety involves no greater than minimal risk.

☑ The waiver of informed consent will not adversely affect the rights and welfare of the subjects.

☑ It is not practicable to conduct the research without the waiver.

☑ Whenever appropriate, subjects will be provided with additional pertinent information after their participation.

The project meets all of the following criteria for waiver of authorization:

☑ The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals based on, at least, the presence of the following elements:

- ☑ An adequate plan to protect the identifiers from improper use and disclosure;
- ☑ An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law; and
- ☑ Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of protected health information would be permitted by HIPAA/Privacy regulations.

☑ The research could not practicably be conducted without the alteration or waiver.

☑ The research could not practicably be conducted without access to and use of the protected health information.

I find the research study to meet the qualifications for Expedited Review in the following category(s):

☐ Category I - Clinical studies of drugs and medical devices only when condition (a) or (b) is met:

a. Research on drugs for which an investigational new drug application (21CFR312) is not required.

b. Research on medical devices for which (i) an investigational device exemption application (21CFR812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

NOTE: While this may be an allowable category of expedited review, the minimal risk threshold may be exceede by the very nature of the studies involving drugs and/or devices.

☐ Category II - Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

a. From healthy, nonpregnant adults (18 and older) who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

b. From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

NOTE: Expedited review of research that falls into this category which involves very small children an infants warrants a cautionary approach based on health status, frequency of venipuncture, and bloo volumes. Although the physical risks may be very low, consideration should also be given to needle phobi associated with children's real and perceived fear of venipuncture.

☐ Category III - Prospective collection of biological specimens for research purposes by noninvasive means.

NOTE: Specimens collected for use in research involving DNA testing or searching for a new way to test fc pathogenic organisms which could be deemed potentially sensitive should be carefully reviewed. Such studie may require referral to the full IRB as the research may present more than minimal risk to subjects.

☐ Category IV - Collection of data through noninvasive procedures routinely employed in clinical practice.

NOTE: Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinel employed in clinical practice, excluding procedures involving xrays or microwaves. Where medical devices ar employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety an effectiveness of the medical device are not generally eligible for expedited review, including studies of cleare medical devices for new indications.

☒ Category V - Research involving materials collected for nonresearch purposes.

Research involving materials (data, documents, records, or specimens) that have been collected for any reason o will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).

Research utilizing retrospectively or prospectively collected, routine medical record information or leftove specimens collected at the time of clinical care would qualify if the information is NOT considered sensitive an any potential breach of confidentiality would not be damaging to the subject. Research using the medical record of HIV-positive patients is an example of a study that should not be reviewed by the expedited method.

☐ Category VI - Collection of data from recordings made for research purposes

NOTE: The IRB must review the types of information that would be recorded and determine whether the stud would involve information considered sensitive or potentially damaging to the subject's financial standing employability, insurability, reputation, etc., if his or her voice or image (still or moving) could be identified. The IRI must ensure that appropriate safeguards are in place to prevent any potential harm that may be associated with breach of confidentiality.

EXAMPLE: If the subject is asked to verbally describe his or her working conditions in a sweatshop, and his c her voice could be recognized, appropriate mechanisms should be used to disguise the subject's voice to prever any potential harm such as the loss of employment. Such a study should not be reviewed by expedited method.

☐ Category VII - Research on group characteristics or behavior or survey, interview, program evaluation, etc.

Research on group characteristics or behavior (including, but not limited to, research on perception, cognitior motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or researcl employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or qualit assurance methodologies.

NOTE: Survey research studies on intelligence or other traits involving specific populations require carefu analysis because this type of research, pending on the nature of the questions, could result in stigmatization of segment of society.

EXAMPLE: The results of a study involving standardized IQ scores of a particular ethnic group correlated wit their socioeconomic status and the educational levels of their parents may be stigmatizing. This would b particularly true if confidentiality were breached. Although this research fits the expeditable category the potentia issues of privacy and confidentiality must be considered. Such research should be reviewed by the full IRB.

OR – I am referring this submission for full board review for the following reason(s) _____

_____

REVIEWER COMMENTS, if any: _____

_____

IRB Reviewer Signature

8/29/13

Date of Review

PowerPoint

1

MSCR Thesis:
Comparative Effectiveness of Analgesic Sedation as Primary Sedation in Medical ICU Patients vs. Conventional Sedation and Analgesia Regimens

Scott Taylor, PharmD, BCPS
Douglas D Bradham, Dr.P.H - Chair
Philip Twumasi-Ankrah, PhD
Jim Haan MD, FACS

Via Christi HEALTH

2

Acknowledgements

- Committee Members
  - Douglas D Bradham, Dr.P.H – Chair
    - Professor
    - Department of Preventive Medicine and Public Health at the University of Kansas School of Medicine-Wichita
  - Philip Twumasi-Ankrah, PhD
    - Assistant Professor
    - Department of Preventive Medicine and Public Health at the University of Kansas School of Medicine-Wichita
  - Jim Haan MD, FACS
    - Medical Director of Trauma/Via Christi Health

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3

BACKGROUND

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Origins of mechanical ventilation

The era of intensive care medicine began with positive-pressure ventilation

- Negative-pressure ventilators ("iron lungs")
  - Non-invasive ventilation first used in Boston Children's Hospital in 1928
  - Used extensively during polio outbreaks in 1940s – 1950s
- Positive-pressure ventilators
  - Invasive ventilation first used at Massachusetts General Hospital in 1955
  - Now the modern standard of mechanical ventilation

The iron lung created negative pressure in abdomen as well as the chest, decreasing cardiac output.

Iron lung polio ward at Rancho Los Amigos Hospital in 1953.

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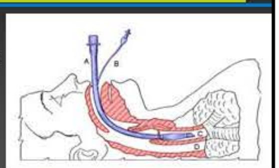
Mechanical Ventilation Today

Reasons for intubation

- Acute respiratory support
  - Intrinsic lung disorder
    - COPD
    - Pneumonia
    - H1N1
  - Inability to protect airway
    - Drug overdose
    - Head injury



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5

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Definitions

Intubation

- Insertion of a tube into the trachea for purposes of anesthesia, airway maintenance, prevention of aspiration of secretions, lung ventilation, or prevention of entrance of foreign material into the airway; the tube goes through the mouth or nose

Extubation

- Removal of tube from the trachea

ICU

- Intensive care unit

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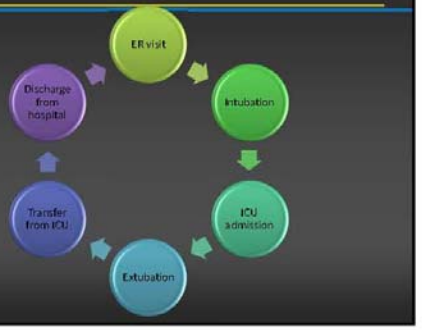
Patient Flow

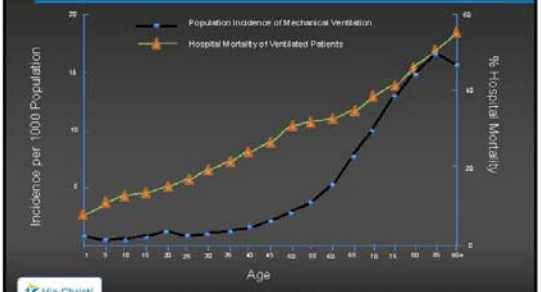


Mechanical Ventilation

- Epidemiology
  - 2005, discharge records from 6 states
  - Represented 23% of the US population
    - 6.5 million hospital visits
    - 180,000 patients received mechanical ventilation (MV)

Wunsch, H et al. *Crit Care Med.* 2010;38:1947-1953

In-Hospital Incidence/Mortality 2005



Wunsch, H et al. *Crit Care Med.* 2010;38:1947-1953

National Significance

Variable	2005 National Estimates
Total US population	296 million
Total MV hospitalizations	790,257
MV hospitalizations per 1000 population	2.7
Total hospital deaths with MV	273,412
Deaths per 1000 population exposed	0.9
Total hospital costs for MV patients	$27 billion

Wunsch, H et al. *Crit Care Med.* 2010;38:1947-1953

ICU Costs/Outcomes

- 2000-2005
  - Annual ICU costs 56-82 million
    - 13.4 % of hospital costs
    - 4.1 % of national health expenditures
    - 0.66% of GDP
- Outcomes
  - Days on the ventilator (ventilator days)
    - Increase risk of Ventilator Associated Pneumonia (VAP)
    - Risk of delirium
  - All of this leads to increase risk of mortality

Halpern NA, et al. *Crit Care Med.* 2010;38:65-71

SEDATION AND ANALGESIA

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Goals of Analgesia and Sedation

Provide comfort and safety

- Provide adequate pain control[1]
- Optimize safety for patients and their caregivers[2]
- Enhance patient comfort[1]
- Facilitate mechanical ventilation[3]
- Reduce anxiety[1]
- Prevent delirium[1]
- Induce sleep when required[1]
- Induce appropriate level of amnesia[3]

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[1]Ely EW, et al. *JAMA*. 2003;289:2983-2991.
[2]Blanchard AR. *Postgrad Med*. 2002;111:59-74.
[3]Kress JP, et al. *Am J Respir Crit Care Med*. 2002;166:1024–1028.

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Need for Analgesia and Sedation in the ICU
Physiological and Neurobehavioral Considerations

- Failure to address pain in acute care patients may lead to:
  - Agitation and anxiety
  - Hypermetabolic states
  - Increased endogenous catecholamine activity
  - Myocardial ischemia
- Acute care patients may demonstrate periods of disorientation during which psychotic behavior occurs
- Certain types of sedation can reduce the risk of harm to the patient or others

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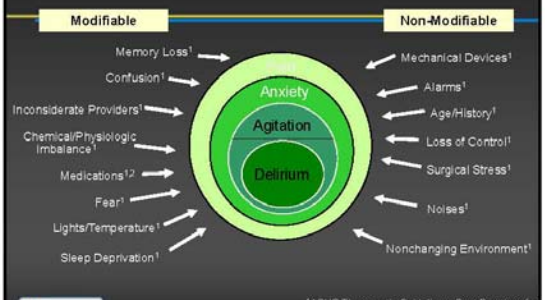
Kress JP, et al. *Am J Respir Crit Care Med*. 2002;166:1024–1028.

15

Factors Leading to Agitation



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[1]ASHP Therapeutic Guidelines. *Best Practices for Heath-System Pharmacy*. 2003-2004:498-512.
[2]McKinley S, et al. *Am J Crit Care*. 2004;13:146-152.

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Targeting Patient Comfort

On-target sedation:

- Decreases weaning period[1]
- Is not associated with muscular atrophy[1]
- Decreases LOS and cost[2]
- Provides cardiovascular[1] and intraoperative hemodynamic stability[3]
- Improves patient safety[1,3]
- Facilitates neurological assessment[3]

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[1]McGaffigan PA. *Crit Care Nursing*. 2002;Feb Suppl:29-36.
[2]Dasta et al. *Pharmacotherapy*. 2006;26:798-805.
[3]Arbour R. *Am J Crit Care Nursing*. 2004;13:65-73.

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Monitoring

- Subjective Assessment of Sedation
  - To predetermined endpoints
    - Over-sedation
    - Under-sedation
- Sedation scales
  - Improve continuity of care
    - Between caregivers
    - Prevent excessive sedation
    - Decrease LOS

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Sedation Scales

Richmond Agitation Sedation Scale (RASS) *

Score	Term	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive	
+2	Agitated	Frequent non-purposeful movement, fights ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (≥10 seconds)	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)	Verbal Stimulation
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)	Verbal Stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation	Physical Stimulation
-5	Unarousable	No response to voice or physical stimulation	Physical Stimulation

Procedure for RASS Assessment

1. Observe patient
   a. Patient is alert, restless, or agitated. **(score 0 to +4)**
2. If not alert, state patient's name and say to open eyes and look at speaker.
   b. Patient awakens with sustained eye opening and eye contact. **(score –1)**
   c. Patient awakens with eye opening and eye contact, but not sustained. **(score –2)**
   d. Patient has any movement in response to voice but no eye contact. **(score –3)**
3. When no response to verbal stimulation, physically stimulate patient by shaking shoulder and/or rubbing sternum.
   e. Patient has any movement to physical stimulation. **(score –4)**
   f. Patient has no response to any stimulation. **(score –5)**

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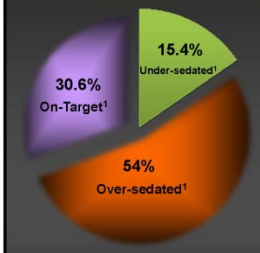
Incidence of Incorrect Sedation



- Continuous sedation carries the risks associated with over-sedation and may increase the duration of mechanical ventilation (MV)
- MV patients accrue significantly more cost during their ICU stay than non-MV patients
  - $31,574 versus $12,931, $P<0.001$[3]
- Sedation should be titrated to achieve a cooperative patient and daily wake-up, a JCAHO requirement

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[1]Kaplan L, et al. *Crit Care*. 2000;4(suppl 1):S110.
[2]Kress et al. *N Engl J Med*. 2000;342:1471-1477.
[3]Dasta JF, et al. *Crit Care Med*. 2005;33:1266-1271.

20

What Is "over-sedation"?

- N = 274 patients from 2001 to 2003
- Sedatives administered during 85% of 18,050 4-hour time intervals
- 1 in 3 patients (32%) were unarousable
- 1 in 5 patients (21%) had no spontaneous motor activity
- Little variation over 24 hours in level of consciousness, motor activity, or drug dose given
- **Only 2.6% were rated over-sedated**

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Weinert CR, et al. *Crit Care Med*. 2007;35:393-401.

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Importance of Optimizing Levels of Sedation

Under-sedation	Over-sedation
Delirium[2]	Delirium[2]
Anxiety[1]	Respiratory depression[4]
Ventilator dysynchrony[2]	
Dislodging invasive lines/ devices[1]	Lack of patient cooperation for assessment and therapeutic measures[1]
May increase posttraumatic stress syndrome[1]	Inability to communicate with health care providers or family members[1]
Increased O_2 consumption[1]	Prolonged weaning[3]
Hyperactivity[1]	Hypoactivity[1]
Minimal amnesia[2]	

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[1]McGaffigan PA. *Crit Care Nursing*. 2002;Feb Suppl:29-36.
[2]ASHP Therapeutic Guidelines. *Best Practices for Heath-System Pharmacy*. 2003:2004:486-512.
[3]Carrasco G. *Crit Care*. 2000;4:217–225.
[4]Blanchard AR. *Postgrad Med*. 2002;111:59-74.

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Costs and Effects of under-sedation	Costs and Effects of over-sedation
Increased staffing needs (nursing and respiratory care)	Inability to adequately examine the patient
Patient/family discomfort and dissatisfaction	Increased costs of diagnostic imaging and other tests
Decreased staff satisfaction	Possible delayed diagnosis of treatable problems
Need for an appropriate use of paralysis	Prolonged mechanical ventilation time
Adverse physiologic consequences	Prolonged stay in acute care settings
Reflex shift to over-sedation	Prolonged hospital stay

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Kress JP, et al. *N Engl J Med*. 2000;342:1471-1477.

23

Introduction to Delirium

- Definition
  - Acute onset of impaired cognitive function
  - Fluctuating course
  - Impaired attention and ability to manage new information
  - Altered level of consciousness

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Ely W et al *JAMA*. 2001;286:2703-10.

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Delirium as a Predictor of Mortality

- Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit.
- To determine if delirium is an independent predictor of clinical outcomes
  - 6 month mortality
  - ICU LOS
  - Hospital LOS

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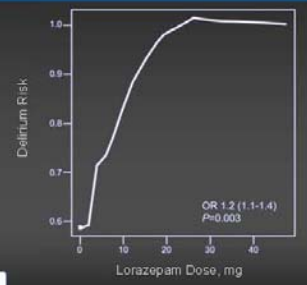
Ely EW, et al.. JAMA 2004; 29: 1753- 1762.

Risk for Transitioning to Delirium



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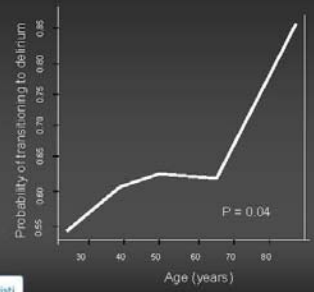
Pandharipande et al. *Anesthesiology*. 2006;104:21-6

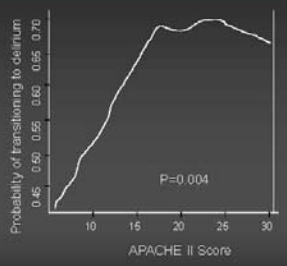
Age & delirium risk



Via Christi HEALTH

Pandharipande et al. *Anesthesiology*. 2006;104:21-6

Severity of illness and delirium risk



Via Christi HEALTH

Pandharipande et al. *Anesthesiology*. 2006;104:21-6

Serious Complications Associated With Delirium

Response	Number (%)
Prolonged ventilation	179 (20)
Patient injury	179 (20)
Respiratory complications	176 (19)
Self-extubation	80 (9)
Sepsis/shock	60 (7)
Prolonged LOS	58 (6)
Over-sedation	52 (6)
Death	36 (4)

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Ely EW, et al. *Crit Care Med*. 2004;32:106-112

"We are using less sedation than we were a decade ago, but we've got a long way to go before we'll be under-sedating our patients."

– Tim Girard on the implications of the ABC trial

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SCCM Pain Agitation and Delirium (PAD) Guidelines

Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit

Juliana Barr, MD, FCCM[1]; Gilles L. Fraser, PharmD, FCCM[2]; Kathleen Puntillo, RN, PhD, FAAN, FCCM[3]; E. Wesley Ely, MD, MPH, FACP, FCCM[4]; Céline Gélinas, RN, PhD[5]; Joseph F. Dasta, MSc, FCCM, FCCP[6]; Judy E. Davidson, DNP, RN[7]; John W. Devlin, PharmD, FCCM, FCCP[8]; John P. Kress, MD[9]; Aaron M. Jeffe, DO[10]; Douglas B. Coursin, MD[11]; Daniel L. Herr, MD, MS, FCCM[12]; Avery Tung, MD[13]; Bryce R. H. Robinson, MD, FACS[14]; Dorrie K. Fontaine, PhD, RN, FAAN[15]; Michael A. Ramsay, MD[16]; Richard R. Riker, MD, FCCM[17]; Curtis N. Sessler, MD, FCCP, FCCM[18]; Brenda Pun, MSN, RN, ACNP[19]; Joanna Skrobik, MD, FRCP[20]; Roman Jaeschke, MD[21]

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Crit Care Med 2013 Jan;30(1):117-141

PAD Recommendations

- Treat pain 1st (not new)
  - Use validated pain scoring systems
  - Not subjective "I think they look like they are in pain"
  - Vital signs (or observational pain scales) should not be used alone
- What does this mean?
  - Maybe Fentanyl should be the first therapy started on a patient (who is not being resuscitated)

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Crit Care Med 2013 Jan;30(1):117-141

Deep vs. Light Sedation of ICU Patients

Pre-PAD Guidelines

Post-PAD Guidelines

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Analgosedation

- The use of pain medications alone to maintain adequate pain control and sedation
- Used to provide a comfortable awake patient

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Analgosedation

- Limited data (10 published trials cited on slide 64)
  - Majority used remifentanil
    - Abnormal pharmacokinetics
    - Not widely used in U.S. ICUs
  - Wide range of outcomes measures
    - Ventilator days
    - Time to ICU discharge
    - Ventilator free days
    - Time spent at optimal sedation score

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Motivation for Study

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Purpose of Study

- To determine if analgosedation fentanyl alone (FA), compared to conventional regimen (CR), will reduce time-to-extubation.
- Reducing time-to-extubation is a desirable outcome, but there are limited data on the use of fentanyl alone to reduce time to extubation.

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Definitions – Study Groups

- Fentanyl Alone (FA)
  - Patients who receive fentanyl only for pain and sedation
- Conventional Regimen (CR)
  - Continuous infusion of a sedation agent (midazolam, lorezapam, propofol, or dexmedetomidine) in tandem with analgesia (fentanyl or morphine)

Hypotheses

- Primary
  - ICU patients who were mechanically ventilated and obtained fentanyl alone will not be inferior in time to extubation compared to those who received conventional regimen
- Secondary
  - The fentanyl alone group will have fewer days in the ICU compared to conventional regimen
  - The fentanyl alone group will have lower ICU mortality compared to conventional regimen
  - Patients in the fentanyl group will have fewer re-intubations within 24 hours as compared to the conventional regimen

Methods

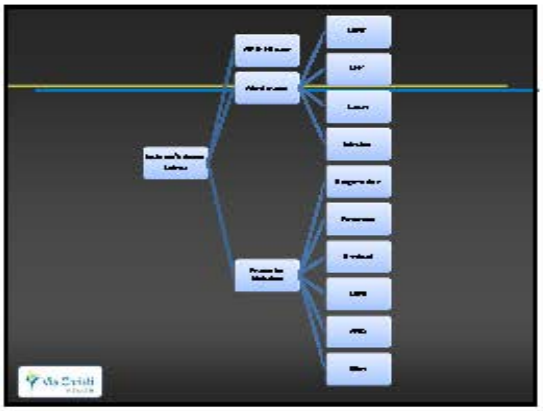
- DESIGN: Retrospective Cohort Matched Study
- Study Period
  - 1/1/2010 – 5/31/2013
- Patient Care Setting
  - Via Christi Health – St. Francis Medical ICU
    - Open ICU
    - Pulmonology consults
- IRB approved (8/12/2013, 8/29/2013)
  - University of Kansas School of Medicine – Wichita Human Subjects Committee
  - Via Christi Health Institutional Review Board

Inclusion/Exclusion Criteria

Inclusion Criteria (eligible to participate)	Exclusion Criteria (ineligible to participate)
Age 18 or older	Prisoners
Mechanically ventilated >48 hours	Pregnant women
Admitted to Via Christi Hospital on St. Francis Street between 1/1/2010 and 5/31/2013	Patients who were receiving neuromuscular blockers outside rapid sequence intubation
Patients receiving IV infusions of Lorazepam, Midazolam, Dexmedetomidine, Propofol, and Fentanyl	Trauma patients
	Burn patients
	Patients with serious central nervous pathology (i.e. acute stroke, traumatic brain injury, intracranial hemorrhage, active seizures, end stage Parkinson's, dementia, post cardiac arrest etc.)
	Epidural or spinal epidurals

Case Matching by Propensity

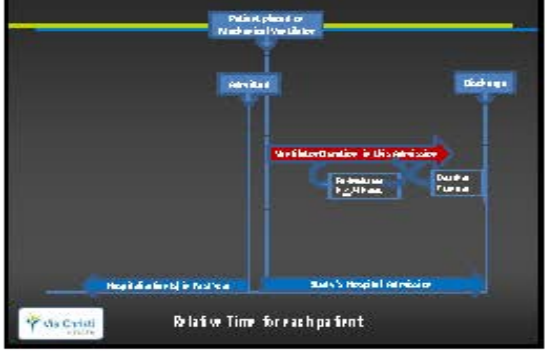
- Defined
  - An individual's conditional probability of being assigned to the intervention or control given the complete set of all information about the individual.
- Purpose
  - To reduce the numbers of confounders between the two groups and achieves balance, in a observational study
- Matching variables
  - APACHE II score
  - Admission diagnosis
  - Reason for intubation



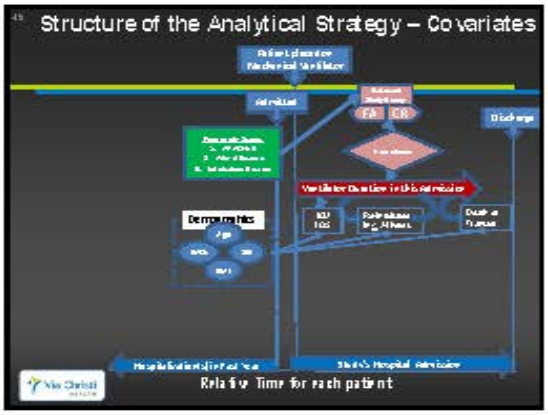
Study Outcome Variables

- Primary – time-to-extubation
  - Duration (days) from intubation to extubation within 28 days from ICU admission.
  - Censoring
    - Death
    - Extubation
    - Transfer to another institution
    - 28 days
- Secondary
  - ICU length of stay (days)
  - Hospital mortality (1,0= Y/N)
  - Re-intubation within 24 hours (1,0= Y/N)

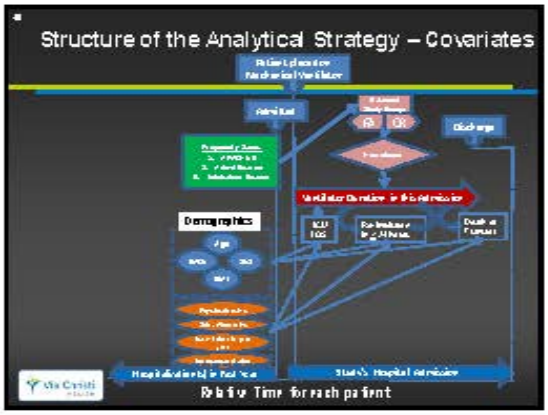
Study Period Time Frames & Primary Outcome



Structure of the Analytical Strategy – Covariates



Structure of the Analytical Strategy – Covariates



Covariates

- Study group
- Age
- Gender
- Race
  - White
  - Non-White
- Substance abuse (Y/N)
  - Stated alcohol or drug abuse in history & physical?
- Psychiatric history (Y/N)
  - Any psychiatric conditions or meds?
- ICU days
- Re-intubation within 24 hours? (Y/N)
- Number of admissions within the last year
- BMI
  - Normal < 25
  - Overweight ≥ 25 < 30
  - Obese ≥ 30
- Insurance
  - Public
    - Government funded
  - Private
    - Purchased or employer provided
  - Other
    - No Insurance

Statistical Analysis

- Demographics
  - Continuous variables
    - Parametric variables were evaluated using Student's t test
  - Categorical variables were evaluated using Chi-square or Fisher Exact test
- All statistical analysis were evaluated at 5% significance
- Statistical software used
  - SAS Institute Inc., Cary, NC

Statistical Analysis

- Primary Outcome
  - Time-to-extubation
    - Kaplan – Meier (KM) analysis
    - Cox Proportional Hazards regression model
- Secondary Outcomes
  - ICU days
    - Linear regression
  - ICU mortality
    - Logistic regression
  - Re-intubation within 24 hours
    - Logistic regression

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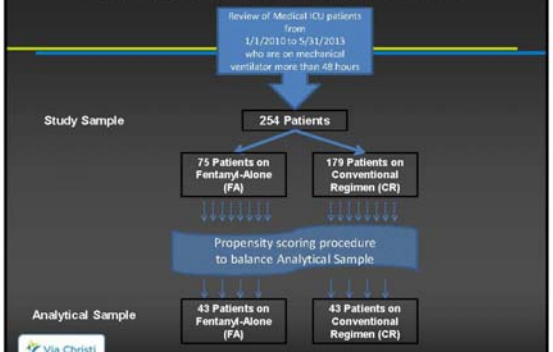
Study Sample and Analytical Sample



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Demographics, by Study Group

Study group	Fentanyl Alone (N = 43)	Conventional Regimen (N = 43)	Total	P value
				0.38
Age, Mean ± SD	62.5 ± 13.9	65.2 ± 14.3	63.8 ± 14.1	
Gender (Male) n (%)	28 (65.1)	21 (48.8)	49 (57)	0.13
Admission Diagnosis* n (%)				0.95
Infection	17 (19.8)	16 (18.6)	33 (38.4)	
Chronic Obstructive Pulmonary Disease	12 (13.9)	14 (16.3)	26 (30.2)	
Other	8 (9.3)	5 (5.8)	13 (15.1)	
Renal failure	3 (3.5)	4 (4.7)	7 (8.1)	
Congested Heart Failure	2 (2.3)	4 (4.7)	6 (7)	
Diabetic Ketoacidosis	1 (1.2)	0 (0)	1 (1.2)	
Reason for Intubation* n (%)				0.97
Pneumonia	15 (17.4)	14 (16.3)	29 (33.7)	
Chronic Obstructive Pulmonary Disease	8 (9.3)	10 (11.6)	18 (20.9)	
Overload	8 (9.3)	10 (11.6)	18 (20.9)	
Acute Respiratory Distress Syndrome	8 (9.3)	6 (7)	14 (16.3)	
Overdose	3 (3.5)	2 (2.3)	5 (5.8)	
Other	1 (1.2)	1 (1.2)	2 (2.3)	
Weight (kg), Mean ± SD	86.4 ± 25.7	83.7 ± 25.7	84.8 ± 25.6	0.55

*Variables used in propensity score

Demographics, by Study Group (cont'd.)

Study group	Fentanyl (N = 43)	CR (N = 43)	Total	P value
BMI, n (%)				0.90
Normal < 25	16 (18.6)	17 (19.8)	33 (38.3)	
Overweight ≥ 25 <30	7 (8.1)	8 (9.3)	15 (17.4)	
Obese ≥ 30	20 (18.6)	18 (21)	38 (44.2)	
APACHE II*, Mean ± SD	23.4 ± 5.3	22.6 ± 4.7	23 ± 5	0.43
Ventilator days, Mean ± SD	5.7 ± 4.7	8.3 ± 6.4	6.9 ± 5.7	0.04
ICU days, Mean ± SD	10.6 ± 11.6	13.5 ± 10.5	12.6 ± 11.1	0.23
Hospital days, Mean ± SD	15.4 ± 13.5	17.5 ± 13	16.4 ± 13.3	0.47
Re-intubation ≤ 24 hours, n (%)	4 (4.7)	7 (8.1)	11 (12.8)	0.36
ICU Mortality (Y/N), n (%)	17, (19.8)	14, (16.3)	31, (36)	0.50
Number of admissions last year, Mean ± SD	1.1 ± 1.3	0.7 ± 1.2	0.9 ± 1.2	0.09
History of Substance abuse (Y/N), n (%)	6 (7)	7 (8.1)	13 (15.1)	0.76
Psychiatric History (Y/N), n (%)	15 (17.4)	2 (2.3)	17 (19.8)	0.001
Insurance, n (%)				0.92
Public	32 (37.2)	33 (33.9)	65 (75.6)	
Private	7 (8.1)	7 (8.1)	14 (16.3)	
Other	4 (4.7)	3 (3.5)	7 (8.1)	

*Variables used in propensity score

Hypotheses

- Primary
  - ICU patients who were mechanically ventilated and obtained fentanyl alone will not be inferior in time to extubation compared to those who received conventional regimen
- Secondary
  - The fentanyl alone group will not be inferior in the number of days in the ICU compared to conventional regimen
  - The fentanyl alone group will not be inferior in ICU mortality compared to conventional regimen
  - Patients in the fentanyl alone group will not be inferior in the number of re-intubations within 24 hours as compared to the conventional regimen

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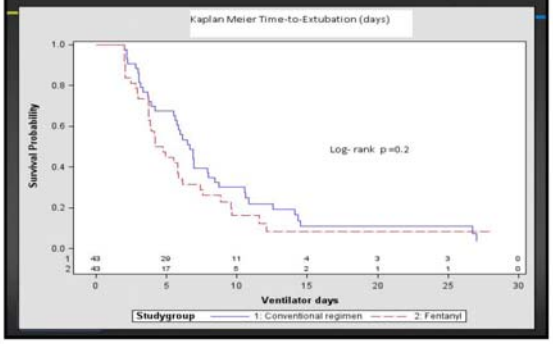
KM Time-to-Extubation(days)



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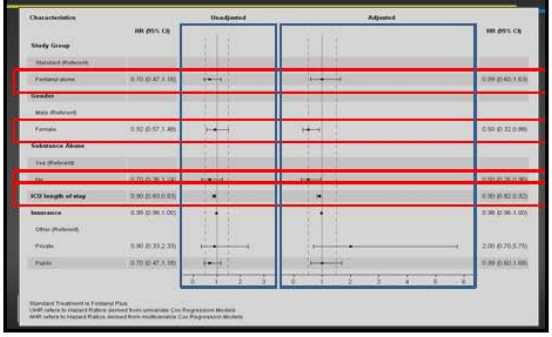
Cox Proportional Hazard Model



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Cox Proportional Hazard Model Unadjusted

- FA vs. CR were shown to be non-inferior between the two groups
  - Hazard ratio (HR) 0.7 (p = 0.2)
- Significant variable
  - ICU days HR 0.9 (p < 0.001)

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Cox Proportional Hazard Model Adjusted

- Significant variables
  - ICU days HR 0.9 (p < 0.001)
  - Female HR 0.5 (p = 0.006)
  - Substance abuse HR 0.5 (p = 0.036)
- FA and CR were similar in the time-to-extubation HR 0.9 (p = 0.98)
- ICU days and ventilator time have been shown to be highly correlated[1]
- Being female and no history of substance abuse reduced the time-to-extubation by 50%

Arabi Y, et al. *Int J Qual in Health Care* 2002;14:403-410

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ICU – Length of Stay

		Unadjusted				Adjusted			
Parameter	Ref Category	Parameter Estimate	95% Confidence Limits		P value	Parameter Estimate	95% Confidence Limits		P value
Intercept						17.7	3.8	31.6	0.0
Age		0.0	-0.2	0.2	0.9	-0.2	-0.4	0.0	0.1
Number of hosp visits in the last year		-1.3	-3.3	0.6	0.2	-0.7	-2.7	1.3	0.5
Insurance Private	Other	4.1	-6.2	14.3	0.4	8.3	-2.9	19.4	0.1
Insurance Public	Other	5.4	-3.4	14.2	0.2	10.4	0.0	20.8	0.05
Fentanyl Alone	CR	-2.9	0.2	-7.7	-1.2	-2.6	-7.8	2.6	0.3
Female	Male	-5.6	-10.3	-0.9	0.0	-7.1	-12.2	-1.9	0.0
Re-intubation within 24 hours	No	9.4	2.5	16.3	0.0	7.0	-0.4	14.5	0.1
Substance Abuse (Y/N)	No	-1.7	-8.4	5.0	0.6	-3.1	-11.0	4.7	0.4
Psychiatric history (Y/N)	No	5.4	-11.3	0.5	0.1	-3.2	-9.7	3.4	0.3
Race Other vs. White	White	0.3	0.9	-6.6	7.2	0.9	-6.1	8.0	0.8
BMI Obese	Normal	1.7	-3.6	7.0	0.5	1.7	-3.8	7.3	0.5
BMI Overweight	Normal	1.1	-5.8	8.1	0.7	0.6	-6.3	7.5	0.9

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ICU length of Stay Linear regression

- The FA and CR analytical groups were shown to be non-inferior in the linear regression
- The unadjusted model's variables that showed a significant difference included: female gender, which showed a surprising reduction in ICU length of stay (Parameter estimate -5.6, p < 0.001)
- Patients who were re-intubated within 24 hours had a significantly longer length of stay in the unadjusted model (Parameter estimate 9.4, p < 0.001)
  - Not surprising as patients who fail extubation are known to have a longer ICU length of stay
- In the adjusted model, the only parameter that showed a significant reduction in ICU length of stay was female gender (Parameter estimate -7.1, p value < 0.001)

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ICU Mortality

		Unadjusted			Adjusted		
Effect	Ref	Odds Ratio	95% CI		Odds Ratio	95% CI	
Age (years)		1.0	1.0	1.1	1.1	1.0	1.1
ICU length of Stay		1.0	1.0	1.1	1.0	1.0	1.1
Insurance Private vs. Other	Other	2.6	0.3	22.4	0.8	0.1	9.1
Insurance Public vs. Other	Other	2.7	0.4	19.4	0.7	0.1	7.3
Fentanyl Alone	CR	0.7	0.3	1.8	0.6	0.2	1.8
Race Other vs White	White	0.6	0.2	2.3	0.6	0.1	2.8
Psychiatric History (Y/N)	No	1.8	0.6	5.2	1.7	0.4	7.3
Substance Abuse (Y/N)	No	0.3	0.1	1.5	0.8	0.1	4.8
BMI Obese vs. Normal	Normal	0.3	0.1	0.7	0.2	0.1	0.6
BMI Overweight vs. Normal	Normal	0.3	0.1	1.2	0.3	0.1	1.3
Number of hosp visits in the last year		0.9	0.6	1.3	0.8	0.5	1.3

Re-intubation within 24 Hours

N = [illegible]		Unadjusted			Adjusted		
Effect	Ref	Odds Ratio	95% CI		Odds Ratio	95% CI	
Age (years)		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ICU length of Stay		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Insurance Private vs. Other	Other	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Insurance Public vs. Other	Other	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gender Female	Male	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Fentanyl Alone	CR	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Psychiatric History (Y/N)	No	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Race Other vs. White	White	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BMI Obese vs. Normal	Normal	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
BMI Overweight vs. Normal	Normal	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Substance Abuse (Y/N)	No	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Mortality and Re-intubation within 24 hours

- FA and CR were non-inferior in mortality and re-intubations within 24 hours
- Logistic regression was used to determine variables that would potentially reduce or increase the odds for mortality
  - Age and ICU days had an odds ratio = 1
  - No other variables showed a trend towards significance
- The last analysis was used to determine the odds of being re-intubated within twenty-fours of extubation.
  - This model only had eleven patients re-intubated within 24 hours
  - There were no significant differences with any of the variables in the unadjusted or adjusted model. Age, ICU length of stay, gender, race, substance abuse, and number of hospital visits had odds ratios < 1, but none of them were statistically significant in the unadjusted model

Conclusions

- In this study, fentanyl alone and conventional regimen were shown to be non-inferior in all models
  - Female gender was associated with a 50% reduction ventilator time – deserves further investigation.
  - ICU days and time-to-extubation are related to each other in this study
  - Substance abuse was shown to lengthen the time-to-extubation
- Mortality and re-intubation within 24 hours did not have any variables with a statistical difference or trend

Strengths

- Propensity scoring allowed the authors to match cases on multiple variables
- This allowed for a well-matched study and decreased confounders
- The first analgosedation trial that looked at time-to-extubation.

Limitations

- Retrospective study
  - Single Institutional Study
    - Tempered by propensity score
- Pilot study
  - Small sample
- Future studies
  - Multicenter observational study
  - Randomized control trial

References