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. 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. Pharmacotherapy including analgesics, sedatives, and antipsychotics are considered the standard of care to optimize patient safety and comfort during MV. 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. 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. However, use of a multidisciplinary care team and an ICU-specific sedation and analgesia
protocol can limit morbidity and mortality defined above. 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. These affects include increased mortality and morbidity. Patients who experience delirium have increased ICU and hospital LOS, which are associated with an increase in cost to the health system.

The majority of patients in the ICU, who experience pain, will experience pain recall after transferring out of the ICU. 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. 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). 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.

**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.\(^\text{17}\) According to some evidence, adequate pain control is vital and potentially achieved with little to no sedative administration.\(^\text{16}\) 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 succioning, wound dressings, and prevention of adverse events such as self-extubation.\(^\text{18}\) Patients may experience anxiety from the events surrounding an ICU admission secondary to an inability to communicate and/or sleep deprivation.\(^\text{2,16-20}\) 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).\(^\text{19}\) However, this practice has been challenged by recent literature stating that less sedation may reduce the risk of PTSD.\(^\text{20}\)
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).\textsuperscript{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.\textsuperscript{25,26}

Benzodiazepines are extensively used sedatives in the ICU and exert their effect by binding to the gamma-aminobutyric acid receptor (GABA) complex.\textsuperscript{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.\textsuperscript{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. The effects of accumulation may be reduced by providing a daily drug holiday and maintaining the lowest infusion dose that produces satisfactory sedation. Benzodiazepines have been shown to increase the risk of delirium in approximately 70% of mechanically ventilated patients. 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.

Dexmedetomidine (Precedex©) is a centrally acting alpha-2 agonist. Dexmedetomidine promotes anxiolysis and sedation; however, it does not cause respiratory depression. 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.

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. One published multi-centered study compared Remifentanil with a “conventional regimen”. 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 propofol 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.\textsuperscript{16}
Table 1. Exposure of Medication Combination in the Rozendaal, FW et al.\textsuperscript{16}

<table>
<thead>
<tr>
<th>Drug, %</th>
<th>Conventional Sedation &amp; Analgesia, %\textsuperscript{*} n = 109</th>
<th>Remifentanil n = 96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic Meds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>58%</td>
<td>-</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>38%</td>
<td>-</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Sedation Meds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>81%</td>
<td>-</td>
</tr>
<tr>
<td>Propofol</td>
<td>46%</td>
<td>65%</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>7%</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{*}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\textsuperscript{16}

<table>
<thead>
<tr>
<th>Ventilator Outcomes</th>
<th>Conventional Sedation &amp; Analgesia n = 109</th>
<th>Remifentanil n = 96</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of MV (mean days) + (95% CI)</td>
<td>5.1 (3.5, 6.7)</td>
<td>3.9 (2.6, 5.2)</td>
<td>0.025</td>
</tr>
<tr>
<td>Weaning time (mean hours) + (95% CI)</td>
<td>24.8 (21.4, 28.1)</td>
<td>5.9 (0.8, 11)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
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

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator days</td>
<td>Time (days) spent on the mechanical ventilator</td>
</tr>
<tr>
<td>ICU days</td>
<td>Time spent admitted to the ICU</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>Patients who died in the ICU</td>
</tr>
<tr>
<td>Re-intubation within 24 hours</td>
<td>Patients placed back on the ventilator ≤ 24 hours from extubation</td>
</tr>
</tbody>
</table>

Table 5. Analytical Strategy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time-to-extubation</td>
<td>Kaplan Meier &amp; Cox Proportional Hazard Model</td>
</tr>
<tr>
<td>ICU days</td>
<td>Linear Regression</td>
</tr>
<tr>
<td>ICU mortality</td>
<td>Logistic Regression</td>
</tr>
<tr>
<td>Re-intubation within 24 hours</td>
<td>Logistic Regression</td>
</tr>
</tbody>
</table>

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.\textsuperscript{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.
LOS = \( \beta_0 + \beta_1 \times \text{age} + \beta_2 \times \text{Psychiatric history} + \beta_3 \times \text{Study group} + \beta_4 \times \text{Race} \\
+ \beta_5 \times \text{Substance abuse history} + \beta_6 \times \text{Source of payment} + \beta_7 \\
\times \text{number of admissions in past year} + \beta_8 \times \text{Gender} + \beta_9 \times \text{Re} \\
- \text{intubation within 24 hours} + \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.
\[
\text{logit} \left( \frac{\text{mortality: Yes}}{\text{No}} \right) = \beta_0 + \beta_1 \times \text{age} + \beta_2 \times \text{Psychiatric history} + \beta_3 \times \text{Study group} + \beta_4 \\
\times \text{Race} + \beta_5 \times \text{Substance abuse history} + \beta_6 \times \text{Source of payment} + \beta_7 \\
\times \text{number of admissions in past year} + \beta_8 \times \text{Gender} + \beta_9 \times \text{Re} \\
- \text{intubation within 24 hours} + \beta_{10} \times \text{BMI Groups}
\]

**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.
\[
\text{logit} \left( \frac{\text{Yes}}{\text{No}} \right) \\
= \hat{\beta}_0 + \hat{\beta}_1 \times \text{age} + \hat{\beta}_2 \times \text{Psychiatric history} + \hat{\beta}_3 \times \text{Study group} + \hat{\beta}_4 \\
\times \text{Race} + \hat{\beta}_5 \times \text{Substance abuse history} + \hat{\beta}_6 \times \text{Source of payment} + \hat{\beta}_7 \\
\times \text{number of admissions in past year} + \hat{\beta}_8 \times \text{Gender} + \hat{\beta}_9 \times \text{ICU los} \\
+ \hat{\beta}_{10} \times \text{BMI Groups}
\]
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 [± Standard deviation (SD)] or percentages were reported between the two groups: age FA 62.5 ± 13.9 vs. CR 65.2 ± 14.3 (p =0.382), gender FA 65% were male vs. CR 48.% male (p = 0.127), ICU days FA 10.6 ± 11.6 vs. CR 13.5 ± 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 ± 1.2 FA and 1.1 ± 1.3 (p = 0.095). The only difference between the two groups was a reduction in ventilator days – the primary outcome measure 5.7± 4.7 FA and 8.3± 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

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

*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**

![Kaplan Meier Graph](image)
**Figure 6. Cox Proportional Hazard Model**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard (Referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fentanyl alone</td>
<td>0.70 (0.47, 1.18)</td>
<td>0.99 (0.60, 1.63)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (Referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.92 (0.57, 1.48)</td>
<td>0.60 (0.32, 0.98)</td>
</tr>
<tr>
<td><strong>Substance Abuse</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (Referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.70 (0.36, 1.24)</td>
<td>0.60 (0.26, 0.96)</td>
</tr>
<tr>
<td><strong>ICU length of stay</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.90 (0.83, 0.93)</td>
<td>0.90 (0.82, 0.92)</td>
</tr>
<tr>
<td><strong>Insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (Referent)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>0.90 (0.33, 2.33)</td>
<td>2.00 (0.70, 5.75)</td>
</tr>
<tr>
<td>Public</td>
<td>0.70 (0.47, 1.18)</td>
<td>0.99 (0.60, 1.68)</td>
</tr>
</tbody>
</table>

Standard Treatment is Fentanyl Plus
UHR refers to Hazard Ratios derived from univariate Cox Regression Models
AHR refers to Hazard Ratios derived from multivariable Cox Regression Models
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>
<thead>
<tr>
<th>Parameter</th>
<th>Ref Category</th>
<th>Unadjusted Model (Univariate Statistics)</th>
<th>Adjusted Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Parameter Estimate</td>
<td>95% Confidence Limits</td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td>17.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>0.0</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.2</td>
<td>-0.4</td>
</tr>
<tr>
<td>Number of hosp visits in the last year</td>
<td>Other</td>
<td>-1.3</td>
<td>-3.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-0.7</td>
<td>-2.7</td>
</tr>
<tr>
<td>Insurance Private</td>
<td>Other</td>
<td>4.1</td>
<td>-6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.3</td>
<td>-2.9</td>
</tr>
<tr>
<td>Insurance Public</td>
<td>Other</td>
<td>5.4</td>
<td>-3.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>CR</td>
<td>-2.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-2.6</td>
<td>-7.8</td>
</tr>
<tr>
<td>Female</td>
<td>Male</td>
<td>-5.6</td>
<td>-10.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-7.1</td>
<td>-12.2</td>
</tr>
<tr>
<td>Re-intubation within 24 hours (Y/N)</td>
<td>No</td>
<td>9.4</td>
<td>2.5</td>
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<td></td>
<td></td>
<td>7.0</td>
<td>-0.4</td>
</tr>
<tr>
<td>Substance Abuse (Y/N)</td>
<td>No</td>
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<td>-8.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3.1</td>
<td>-11.0</td>
</tr>
<tr>
<td>Psychiatric history (Y/N)</td>
<td>No</td>
<td>5.4</td>
<td>-11.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-3.2</td>
<td>-9.7</td>
</tr>
<tr>
<td>Race Other vs. White</td>
<td>White</td>
<td>0.3</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.9</td>
<td>-6.1</td>
</tr>
<tr>
<td>BMIC Obese</td>
<td>Normal</td>
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<td>-3.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.7</td>
<td>-3.8</td>
</tr>
<tr>
<td>BMIC Overweight</td>
<td>Normal</td>
<td>1.1</td>
<td>-5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.6</td>
<td>-6.3</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Effect</th>
<th>Ref</th>
<th>Unadjusted Model (Univariate Statistics)</th>
<th>Adjusted Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Odds Ratio</td>
<td>95% Confidence Limits</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>ICU length of Stay</td>
<td>1.0</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>insurance Private vs. Other</td>
<td>Other</td>
<td>2.5</td>
<td>0.3</td>
</tr>
<tr>
<td>insurance Public vs. Other</td>
<td>Other</td>
<td>2.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Conventional regimen vs. Fentanyl</td>
<td>Fentanyl</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Race Other vs White</td>
<td>White</td>
<td>0.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Psychiatric History (Y/N)</td>
<td>No</td>
<td>1.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Substance Abuse (Y/N)</td>
<td>No</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI Obese vs. Normal</td>
<td>Normal</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>BMI Overweight vs. Normal</td>
<td>Normal</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Number of hosp visits in the last year</td>
<td></td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Risk of Re-Intubation within 24 hours of Extubation**

This model was used to assess the relative risks of being re-intubated within twenty-four hours 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>
<thead>
<tr>
<th>Table 9. Relative Risk of Re-intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effect</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>ICU length of Stay</td>
</tr>
<tr>
<td>insurance Private vs. Other</td>
</tr>
<tr>
<td>insurance Public vs. Other</td>
</tr>
<tr>
<td>Gender Female</td>
</tr>
<tr>
<td>Conventional regimen vs. Fentanyl</td>
</tr>
<tr>
<td>Psychiatric History (Y/N)</td>
</tr>
<tr>
<td>Race Other vs White</td>
</tr>
<tr>
<td>BMI Obese vs. Normal</td>
</tr>
<tr>
<td>BMI Overweight vs. Normal</td>
</tr>
<tr>
<td>Substance Abuse (Y/N)</td>
</tr>
<tr>
<td>Number of hospitalizations in the past year</td>
</tr>
</tbody>
</table>
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\textsuperscript{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)\textsuperscript{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.
REFERENCES


Appendices

KU IRB Approval Letter

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 ryan3@kumc.edu

Sincerely,

Jamie Ryan, BA
Office of Compliance
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 exceeded 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 blood volumes. Although the physical risks may be very low, consideration should also be given to needle phobia 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 for pathogenic organisms which could be deemed potentially sensitive should be carefully reviewed. Such studies 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) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared 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 other than research purposes (such as medical treatment or diagnosis).

Research utilizing retrospectively or prospectively collected, routine medical record information or leftover specimens collected at the time of clinical care would qualify if the information is NOT considered sensitive and 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 study 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 IRB must ensure that appropriate safeguards are in place to prevent any potential harm that may be associated with a breach of confidentiality.

EXAMPLE: If the subject is asked to verbally describe his or her working conditions in a sweatshop, and his or her voice could be recognized, appropriate mechanisms should be used to disguise the subject's voice to prevent 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, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or qualitative assurance methodologies.

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

EXAMPLE: The results of a study involving standardized IQ scores of a particular ethnic group correlated with their socioeconomic status and the educational levels of their parents may be stigmatizing. This would be particularly true if confidentiality were breached. Although this research fits the expedited category, the potential 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

Date of Review
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

Acknowledgements

- Committee Members
  - Douglas D Bradham, Dr.P.H - Chair
  - Philip Twumasi-Ankrah, PhD
  - Jim Haan MD, FACS

Origins of mechanical ventilation

We are mainstreamed into medicine began with positive pressure ventilation

- Negative pressure ventilators
  - "Iron lung" - first used in England in the 1920s
  - Used extensively during polio epidemics 1940s - 1950s

- Positive pressure ventilators
  - Bias flow ventilation first used at Massachusetts General Hospital in 1955
  - Now the mainstay of mechanical ventilation

Mechanical Ventilation Today

Reasons for intubation

- Acute respiratory support
- Intubation disorder
- Cough
- Procedural
- Airway
- Inability to protect airway
- Drug overdose
- Head injury

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
**Patient Flow**

**Mechanical Ventilation**

- **Epidemiology**
  - 2005, discharge records from 6 states
  - Represented 25% of the US population
  - 6.5 million hospital visits
  - 190,000 patients received mechanical ventilation (MV)

**In-Hospital Incidence/Mortality 2005**

**National Significance**

<table>
<thead>
<tr>
<th>Variable</th>
<th>2005 National Estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total JHS population</td>
<td>710,267</td>
</tr>
<tr>
<td>Total MV hospitalizations</td>
<td>710,267</td>
</tr>
<tr>
<td>Incidence per 1,000 population</td>
<td>7.7</td>
</tr>
<tr>
<td>Total hospital deaths with MV</td>
<td>379,413</td>
</tr>
<tr>
<td>Deaths per 1,000 population exposed</td>
<td>1.8</td>
</tr>
<tr>
<td>Total hospital costs for MV patients</td>
<td>$12.2 billion</td>
</tr>
</tbody>
</table>

**ICU Costs/Outcomes**

- **2000-2005**
  - Annual ICU costs 56-62 million
  - 13.4% of hospital costs
  - 4.1% of national health expenditures
  - 0.00% 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

**SEDATION AND ANALGESIA**
“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.”

— Tom Girard on the implications of the ABC trial
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)

Deep vs. Light Sedation of ICU Patients

Pre-PAD Guidelines

Post-PAD Guidelines

Analgesedation

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

Analgesedation

• 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

Purpose of Study

• To determine if analgesedation fentanyl alone (FA), compared to conventional sedation 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.
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, lorazepam, propofol, or desflurane 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
  - Opioid PLC
  - Pulmonology consult
  - IRB approved (9/12/2013, 9/26/2013)
  - University of Kansas School of Medicine – Wichita Human Subjects Committee
  - Via Christi Health Institutional Review Board

Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria (Fentanyl)</th>
<th>Exclusion Criteria (Fentanyl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Fentanyl use for pain and sedation</td>
<td>- No fentanyl use for pain and sedation</td>
</tr>
<tr>
<td>- Mechanical ventilation</td>
<td>- No mechanical ventilation</td>
</tr>
<tr>
<td>- Administration via CVC or nasal route between 2/1/2010 and 5/31/2013</td>
<td>- Administration via other routes</td>
</tr>
<tr>
<td>- Prescribed use for clinical purposes</td>
<td>- Prescribed use for non-clinical purposes</td>
</tr>
<tr>
<td>- Residence in ICU</td>
<td>- Residence outside ICU</td>
</tr>
</tbody>
</table>

Case Matching by Propensity

- Defined
  - An individual conditional probability of being assigned to the intervention or control given the complete set of all information about the individual
- Purpose
  - To reduce the number of confounders between the two groups and achieve balance, in an observational study
- Matching variables
  - APACHE II score
  - Admission diagnosis
  - Reason for intubation
Study Outcome Variables

- **Primary** – time to exudation
  - Duration (days) from intubation to exudation within 20 days from ICU admission
  - Censoring
    - Death
    - Exudation
    - Transfer to another institution
    - 20 days

- **Secondary**
  - ICU length of stay (days)
  - Hospital mortality (1= Y/N)
  - Re-intubation within 24 hours (1= Y/N)

Study Period Time Frames & Primary Outcome

Structure of the Analytical Strategy – Covariates

Covariates

- Study group
- Age
- Gender
- Race
- Non-White
- Heart attack (CAD)
- Other coronary artery disease
- Diabetes
- Kerns index ≤ 4
- Insufficiency
- BUN ≥ 20
- Creatinine ≥ 2.5 ≤ 10
- OAB ≤ 10
- Insurance
- Public
- Private
- Medicaid or Managed care insurers
- No
- 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
- Secondary Outcomes
  - ICU days
  - Linear regression
  - ICU mortality
  - Logistic regression
  - Re-intubation within 24 hours
    - Logistic regression

Demographics, by Study Group

<table>
<thead>
<tr>
<th>Study group</th>
<th>Fentanyl Alone (N = 70)</th>
<th>Conventional Regime (N = 135)</th>
<th>Total (N = 205)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Median [IQR]</td>
<td>65.7 [50.2, 76.9]</td>
<td>65.5 [54.3, 76.9]</td>
<td>65.7 [54.3, 76.9]</td>
<td>0.23</td>
</tr>
<tr>
<td>Gender, Female (%)</td>
<td>36.5</td>
<td>38.1</td>
<td>37.5</td>
<td>0.63</td>
</tr>
<tr>
<td>Admissions Diagnosis*</td>
<td>1/74</td>
<td>1/77</td>
<td>1/76.5</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>17 (24.3)</td>
<td>30 (22.2)</td>
<td>47 (23.9)</td>
<td>0.29</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>13 (18.6)</td>
<td>27 (20.0)</td>
<td>40 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8 (11.5)</td>
<td>11 (8.2)</td>
<td>19 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Other Admissions</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Acute Renal Failure</td>
<td>2 (2.9)</td>
<td>4 (2.9)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>3 (4.3)</td>
<td>5 (3.7)</td>
<td>8 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>1 (1.4)</td>
<td>2 (1.5)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Severe Infectious</td>
<td>1 (1.4)</td>
<td>2 (1.5)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (21.4)</td>
<td>24 (17.6)</td>
<td>39 (19.1)</td>
<td></td>
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<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>9 (12.9)</td>
<td>18 (13.4)</td>
<td>27 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>8 (11.5)</td>
<td>11 (8.2)</td>
<td>19 (9.3)</td>
<td></td>
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<tr>
<td>Cardiopulmonary Injury</td>
<td>10 (14.3)</td>
<td>15 (11.1)</td>
<td>25 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.3)</td>
<td>6 (4.4)</td>
<td>9 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg), Mean ± SD</td>
<td>80.6 ± 10.7</td>
<td>81.3 ± 11.1</td>
<td>81.0 ± 10.6</td>
<td>0.36</td>
</tr>
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</table>

Demographics, by Study Group (cont’d.)

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</tr>
<tr>
<td>Acute Renal Failure</td>
<td>2 (2.9)</td>
<td>4 (2.9)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Diabetic Nephropathy</td>
<td>3 (4.3)</td>
<td>5 (3.7)</td>
<td>8 (3.9)</td>
<td></td>
</tr>
<tr>
<td>Respiratory Failure</td>
<td>1 (1.4)</td>
<td>2 (1.5)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Severe Infectious</td>
<td>1 (1.4)</td>
<td>2 (1.5)</td>
<td>3 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>15 (21.4)</td>
<td>24 (17.6)</td>
<td>39 (19.1)</td>
<td></td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>9 (12.9)</td>
<td>18 (13.4)</td>
<td>27 (13.2)</td>
<td></td>
</tr>
<tr>
<td>Overdose</td>
<td>8 (11.5)</td>
<td>11 (8.2)</td>
<td>19 (9.3)</td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary Injury</td>
<td>10 (14.3)</td>
<td>15 (11.1)</td>
<td>25 (12.2)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (4.3)</td>
<td>6 (4.4)</td>
<td>9 (4.4)</td>
<td></td>
</tr>
<tr>
<td>Weight (kg), Mean ± SD</td>
<td>80.6 ± 10.7</td>
<td>81.3 ± 11.1</td>
<td>81.0 ± 10.6</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Hypotheses

- Primary
  - Infants 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 reintubations within 24 hours as compared to the conventional regimen.

KM Time-to-Extubation (days)
Cox Proportional Hazard Model

- Significant variables
  - ICU days HR: 0.9 (p < 0.001)
  - Female HR: 0.5 (p = 0.003)
  - Substance abuse HR: 0.5 (p = 0.038)
- FA and CR were similar in the time-to-extubation HR: 0.9 (p = 0.99)
- ICU days and ventilator time have been shown to be highly correlated
- Being female and no history of substance abuse reduced the time-to-extubation by 50%

ICU – Length of Stay

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Gender</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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 -0.5, p < 0.001)
- Patients who were reintubated within 24 hours had a significantly longer length of stay in the unadjusted model (Parameter estimate 0.9, p < 0.001)
- Not among the patients who failed 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 -0.5, p value < 0.001)

ICU Mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unadjusted</th>
<th>Unadjusted + Gender</th>
<th>Unadjusted + Gender + Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Gender</td>
<td>0.5</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

Re-intubation within 24 Hours

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total</th>
<th>(1)</th>
<th>(2)</th>
<th>(3)</th>
<th>(4)</th>
<th>(5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Midazolam</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ketaconazole</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Sedative</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-intubations</td>
<td>1.3</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Mortality and Re-intubation within 24 Hours

- Fentanyl alone was a factor for mortality and re-intubation within 24 hours.
- Logistic regression was used to calculate the odds ratio for each drug after adjusting for mortality.
- Age and BMI were adjusted and odds ratio was adjusted for mortality.
- Other variables showed a trend towards significance.

The limit analysis was used to calculate the odds, offering a statistically significant difference in re-intubation.

This model only included patients re-intubated within 24 hours.

The final model included all patients re-intubated within 24 hours.

Conclusions

- In this study, fentanyl alone and conventional regimens were shown to be non-inferior in all models.
- Female gender was associated with a 50% reduction in re-intubation 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 analgesia study and extubation 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 controlled trial

References