A Comparative Study between Dexmedetomidine versus Midazolam for Sedation in Patients with Cardiogenic Pulmonary Edema in Intensive Care Unit

Thesis

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ABG	: Arterial blood gas
ACPE	: Acute cardiogenic pulmonary edema
ACV	: Assisted controlled ventilation
AHF	: Acute heart failure
ARF	: Acute respiratory failure
ASA	: American Society of Anesthesiologists
BiPAP	: Bilevel positive airway pressure
cAMP	: Cyclic adenosine monophosphate
CNS	: Central nervous system
COPD	: Chronic obstructive pulmonary disease
CPAP	: Continous positive airway pressure
ECG	: Electrocardiography
EPAP	: Expiratory positive airway pressure
ETT	: Endotracheal tube
FDA	: Food and drug administration
GABA	: Gammaaminobutyric acid
HR	: Heart rate
ICU	: The intensive care unit
IQR	: Inter quartile range
IPAP	: Inspiratory positive airway pressure
IPPV	: Intermittent positive pressure ventilation
IV	: intravenous
MAP	: Mean arterial blood pressures
NIV	: Non-invasive ventilation
NPPV	: Non-invasive positive pressure ventilation

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P Value	: Probability of error
PAV	: Proportional assisted ventilation
PEEP	: Positive end-expiratory pressure
PSV	: Pressure support ventilation
RASS	: Richmond Agitation–Sedation Scale
RR	: Respiratory rate
RSS	: Ramsay Sedation Scale
SAS	: Sedation-Agitation Scale
SD	: Standard deviation
SIMV	: Synchronized intermittent mandatory ventilation
ß	: Beta
TSH	: Thyroid stimulating hormone
VE	: Tidal volume
VPAP	: Variable positive airway pressure
VQ	: Ventilation perfusion
α	: Alpha
γ	: Gamma

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Introduction

Recently, non-invasive mechanical ventilation (NIV) has been increasingly used to manage hypoxemic acute cardiogenic pulmonary edema, avoiding endotracheal intubation and the additional risks of related complications by improving oxygenation, reducing the work required for breathing and increasing cardiac output ***(Gray et al., 2009).***

However, this procedure is associated with a high rate of failure, often due to patient agitation and refusal to continue the often uncomfortable sessions so providing sedation is an integral component to improve the patients' comfort to decrease rate of failure of non-invasive mechanical ventilation hence the need for endotracheal intubation and the additional risks of related complications ***(Clouzeau et al., 2010).***

The ideal sedative agent should allow for rapid modification of the sedation level by modifying the dose and should not have depressor effect on the cardiovascular or respiratory systems. It should have short duration without cumulative effects, allowing for rapid recovery of effective spontaneous respiration after interruption of its administration in patients undergoing mechanical ventilation ***(Paris and Tonner, 2005).***

Various agents (e.g., remifentanil, γ-aminobutyric acid (GABA) receptor agonists: including propofol and benzodiazepines such as midazolam) have been the most

commonly administered sedative drugs for ICU patients worldwide Despite the well-known hazards associated with prolonged use of GABA agonists, few studies of ICU sedation have compared these agents to other drug classes such as α_2-agonist: Dexmedetomidine (DEX) ***(Martin et al., 2006).***

Dexmedetomidine (DEX), an imidazol compound, a pharmacologically active dextro isomer of medetomidine that is a potent highly selective α_2 adrenergic receptor agonism. It has sedative, analgesic and anesthetic sparing effect, and sympatholytic properties. The central and peripheral sympatholytic action of (DEX) is mediated by α_2 adrenergic receptor and is manifested by dose-dependent decrease in arterial blood pressure, heart rate, cardiac output and norepinephrine release ***(Richa et al., 2008)***.

Midazolam is a short-acting drug in the benzodiazepine class used for treatment of acute seizures, moderate to severe insomnia, and for inducing sedation. It possesses profoundly potent anxiolytic, amnestic, hypnotic, anticonvulsant, skeletal muscle relaxant, and sedative properties. Like many other benzodiazepines, it has a rapid onset of action, high effectiveness and low toxicity level. The therapeutic as well as adverse effects of midazolam are due to its effects on the γ-aminobutyric acid (GABA) receptors. It enhances the effect of the neurotransmitter GABA on the GABA receptors ***(Barash et al., 2009).***

Midazolam was selected as the medication for comparison in this study owing to its frequent use for long-term sedation, and it was administered as a continuous infusion owing to its short half-life ***(Mayordomo-Colunga et al., 2009).***

Dexmedetomidine was selected as it has several unique properties including sedation, analgesic effects, and maintaining patient arousability. Patients are easily awakened to be assesed neurologically. Midazolam does not maintain arousability so it must be stopped before assessing patient for neurologic functions ***(Bradley, 2000).***

Aim of the Work

The present work was designed to compare the efficacy and safety of dexmedetomidine versus midazolam as a sedative agent in non-invasive mechanical ventilation (NIV), for management of hypoxemic acute cardiogenic pulmonary edema. With attention on the target range of sedation, failure rate and need for endotracheal intubation, hemodynamics and occurrence of adverse effects.

Chapter (1):

Sedation in the Intensive Care Units (ICU)

Sedation is the depression of a patient's awareness to the environment and reduction of response to external stimulation. Deep sedation is a depression of consciousness in which the patient can't be aroused but responds purposefully to repeated or painful stimuli. The patient may not be able to maintain airway reflexes or spontaneous ventilation, but cardiovascular function is preserved. The major goals of sedation are to improve the patient's perceptual experience during this physiologically and emotionally stressful period, secondarily; sedation reduces the physiologic stress response, cardiovascular response, facilitates the maintenance of circadian rhythms, and lessens delirium and agitation. The use of sedation is essential for the treatment of anxiety, pain, and agitation associated with mechanical ventilation in the patient with cardiogenic pulmonary edema ***(Schweickert and Kress, 2008).***

The primary objective of sedation is to allay anxiety, enhance patient comfort, promote sleep, and facilitate mechanical ventilation. The ideal level of sedation is one from which the patient can be easily aroused with maintenance of the normal sleep wake cycle. Assessing the degree of sedation and titration of the drug regimen is essential, as both over sedation and inadequate sedation are associated with significant complications. Complications of under sedation include severe

anxiety with delusional behavior, sympathetic over activity with increased myocardial oxygen consumption, self-injury, and intolerance to noninvasive mechanical ventilation. Over sedation is associated with significant morbidity including the need for prolonged endotracheal intubation with an increased risk of pulmonary complications, increased incidence of ventilator associated pneumonia, disorientation and delirium following emergence. Over sedation may mask significant neurological and neuromuscular complications. Ideally, patients should receive minimal sedation to achieve a state of "alertness and calm" ***(Treggiari et al., 2009).***

Acute cardiogenic pulmonary edema is a common medical emergency that accounts for up to 1 million hospital admissions for acute conditions per year in the United States. It is a leading cause of hospitalization, accounting for 6.5 million hospital days each year. In-hospital mortality from acute cardiogenic pulmonary edema is high (10 to 20%), especially when it is associated with acute myocardial infarction. Patients who do not have a response to initial therapy often require tracheal intubation and ventilation, with the associated potential for complications. Noninvasive methods of ventilation can avert tracheal intubation by improving oxygenation, reducing the work of breathing, and increasing cardiac output ***(Girou et al., 2003).***