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Original Article

Correlation between Fentanyl and Midazolam Doses with Pain and Delirium at Haji Adam Malik Medan Central General Hospital

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ABSTRACT

Introduction: Pain is generally known as the fifth vital sign. It can trigger a stress response and stimulate adrenergic-sympathetic activity, causing tachycardia and hypertension and increasing oxygen consumption. Delirium is an acute disturbance of consciousness in the form of inattention, disorganized thoughts, and perceptual disturbances that change in a short time. Undiagnosed pain and delirium can lead to increased infection rates, prolonged mechanical ventilation, hemodynamic compromise, delirium, and compromised immunity.
Objective: To determine the relationship between pain and delirium in intubated patients in the ICU of Haji Adam Malik Hospital using CPOT to assess pain and CAM ICU to assess delirium.
Methods: This study used a cross-sectional observational analytic design with a quantitative approach. This study was conducted to determine the relationship between pain and delirium using the CPOT and CAM ICU scales in patients who were intubated at Haji Adam Malik General Hospital Medan during January 2023-February 2023.
Results: The relationship between pain and delirium had a p-value of 0.001, a significant relationship because p-value was< 0.05%.
Conclusion: There is a significant relationship between pain and delirium (p = 0.001).

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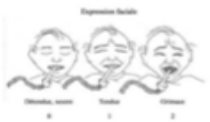
GRAPHICALABSTRACT

Indicator	Score		Description
Facial expression 	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening
	Grimacing	2	All above facial movements plus eyelid tightly closed, patient may bite ETT or clench teeth
Body movements	Absence of Movements	0	Does not move at all
	Protection	1	Slow, cautious movements, touching or rubbing pain site
	Restlessness / Agitation	2	pulling at lines, attempting to sit up, thrashing limbs, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients) **OR** - - - - - - - - - - - - - - - - **Vocalisation (extubated patients)**	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but Tolerating	1	Coughing, alarms activated but stop spontaneously
	Fighting ventilator	2	Asynchrony, blocking ventilation, alarms frequently activated
	Talking in normal tone or no sound	0	Talking normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying, sobbing	2	Crying out, sobbing
Muscle Tension Evaluation by passive flexion and extension of upper limbs when patient is at rest OR When patient is being turned	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements
TOTAL		**__/8**	**A PAIN SCORE 3-8 INDICATES PAIN**

Introduction

Stone tablets were used by ancient civilizations to document their observations of pain and the methods they employed for its treatment. These included applying pressure, heat, water, and sunlight. In the early stages of human development, pain was often associated with malevolence, sorcery, and supernatural entities. Alleviating pain was entrusted to skilled individuals such as sorcerers, shamans, priests, and priestesses, who relied on the use of herbs, rituals, and ceremonial practices as means of treatment. The ancient Greeks and Romans were the pioneers in developing a theory of sensation, proposing that the perception of pain is produced by the brain and nervous system. However, it was during the Middle Ages and the Renaissance, specifically in the 1400s and 1500s, when evidence supporting these theories started to accumulate. Notably, Leonardo da Vinci and his contemporaries concluded that the brain played a vital role in sensation. Da Vinci also contributed to the concept that the spinal cord transmits sensations to the brain. During the 17th and 18th centuries, philosophers were fascinated by the exploration of the human body and the senses. One notable example occurred in 1664 when Rene Descartes, a French philosopher, outlined what is currently recognized as a pain pathway.

Descartes explained the process of how fiery particles, upon contact with the foot, traveled to the brain, leading to the sensation of pain. This comparison of pain to the sound of a ringing bell further enhanced understanding in the field. Pain is generally known as the fifth vital sign and is a signal of decreased physiological function in most organs of the body [1]. Pain is a subjective sensation that varies greatly among individuals. What may cause excessive pain for one person may not produce the same level of discomfort for another.

Throughout the history, people have sought a common understanding of pain and have searched for objective scales or indexes to accurately measure this sensation. Severe pain triggers the stress response and stimulates adrenergic-sympathetic activity, causing tachycardia and hypertension. It also increases oxygen consumption in the heart muscle and can cause ischemia of the heart muscle in certain patients [2].

Some pains can be easily identified by their cause and can be effectively treated by addressing the underlying wounds or injuries. However, there are certain types of pain that do not have a clearly identifiable or apparent reason. Different types of pain may not have any readily apparent injuries or wounds that require treatment. In some cases, this particular kind of pain can persist even after the initial injuries have fully healed. Regrettably, studying pain can be challenging for two main reasons: it is difficult to conduct tests that cause pain in a research setting, and designing experiments related to pain without infringing upon ethical principles and human rights is also arduous. Due to this fact, current tests that cause pain (such as the hot plate test and tail flick test) exclusively employ animals as test subjects or concentrate on the connection between an existing pain condition and particular movements (for example, the back pain-inducing test evaluates the pain condition while performing actions like lying supine, rolling over, and sitting up).

Pain in patients with critical conditions can manifest as anxiety and delirium, which are often not handled properly and can cause psychological sequelae such as post-traumatic stress disorder. Systemic manifestations of pain include systemic inflammatory response syndrome, hyperglycemia, immunosuppression, difficult wound healing, hypercoagulability, and increased catabolism. This leads to an increase in length of stay in the intensive care unit or hospital and mortality [1-3].

Materials and Methods

This study used a cross-sectional observational analytic design with a quantitative approach. This study was conducted to assess the relationship between pain assessment and delirium using the CPOT and CAM ICU scales in patients who were intubated at Central General Hospital Haji Adam Malik Medan Medan during January 2023-February 2023. The research was conducted in the ICU Room of the Haji Adam Malik General Hospital in Medan after graduating from ethical clearance, and a number of research subjects were met. The research subjects were patients who were treated in the ICU of Central General Hospital Haji Adam Malik Medan from January 2023 to February 2023 based on the inclusion and exclusion criteria. The inclusion criteria in this study were intubated adult patients (>18 years old) who were treated in the ICU of Central General Hospital Haji Adam Malik Medan. Exclusion criteria in this study were vegetative patients and patients or families of patients who refused to participate in the study. Brain death, patients had a large sample size. 95 patients were needed from January to March 2023 at the ICU of Central General Hospital Haji Adam Malik Medan.

The data that has been collected is then analyzed using statistical software (Microsoft® Excel 2019 and IBM SPSS 26.0) and displayed in table form. For categorical data (nominal) it is presented in frequency and percentage statistics, while for numerical data (ordinal, interval) it is presented in mean + standard deviation for normally distributed data.

For data that is not normally distributed, it presented in the form of median values (the minimum and the maximum values).

Table 1: Characteristics of intubated patient subjects in the ICU of Central General Hospital Haji Adam Malik Medan

Characteristics	n (%)
Age (years) 18-35 36-46 >46	17 (17.9) 13 (13.7) 65 (68.4)
Sex Man Woman	55 (57.9) 40 (42.1)
Length of Stays (days) 0-7 7-14 >14	21 (22.1) 74 (77.9) -
Dose Fentanyl + midazolam (ml/hour) 18 mcg+0.9 mg /hour 24 mcg+1.2 mg /hour 30mcg+1.5 mg/hour	- 36 (34.7) 56 (47.7) 3 (17.9)
Pain No Pain Pain	20 (21.1) 75 (78.9)
Delirium No Delirium Delirum	50 (52.6) 45 (47.4)

Table 2: Correlation between fentanyl dose and pain

Fentanyl and Midazolam Dosage (ml/hour)	Pain (%)	No Pain (%)	Total n (%)	*P*-value
Dose A	30 (83.3%)	6 (16.7%)	36 (100.0%)	0.012
Dose B	45 (80.4%)	11 (19.6%)	56 (100.0%)	
Dose C	0 (0.0%)	3 (100.0%)	3 (100.0%)	

To determine the relationship between pain and delirium and the relationship between confounding factors and pain and delirium using the chi-square test.

Results and Discussion

This study aims to determine the relationship between pain and delirium in intubated patients in the ICU of Central General Hospital Haji Adam Malik, as well as the demographics and characteristics of the sample and patient studied. In this study, 95 study samples were obtained that met the inclusion criteria, but were not included in the exclusion criteria category.

Characteristics of the subjects according to age, sex, length of stay, dose of fentanyl, pain, and delirium are indicated Table 1.

In Table 1, the highest number of patients with an age range > 46 years was 65 people (68.4%). Regarding gender characteristics, there were more male patients, 55 (57.9%), compared to 40 female patients (42.1%). The largest percentage of patients treated with a length of stay of 7-14 days (77.9%) was 74 people. For presentation, the dose of fentanyl plus midazolam used at a dose of 24 mcg + 1.2 mg/hour was the highest figure (56 people), amounting to 47.7%. Of the 95 patients, 20 people felt no pain (20.1%) and 75 people (78.9%) felt pain; 50 people (52.6%) did not have delirium, while 45 people (47.4%) had delirium. Of the 36 people who received fentanyl doses of Dose A (18 mcg + 0.9 mcg/hour), 30 people (83.3%) felt pain. Of the 56 people who received fentanyl doses of Dose B (24 mcg plus 1.2 mcg/hour), 45 (80.4%) felt pain. Meanwhile, for the fentanyl dose of Dose C (30 mcg + 1.5 mcg/hour), no patient felt pain. A significance value was obtained using the chi-square test (*P*-

value = 0.012), which means that there was a significant relationship between fentanyl dosage and pain (Table 2).

For fentanyl and midazolam doses of Dose A (18 mcg+0.9 mcg/hour), 20 patients, or 55.6%, experienced delirium. Meanwhile, for fentanyl and midazolam doses of Dose B (24 mcg + 1.2 mg/hour), 24 patients, or 42.9%, experienced delirium. Patients who experienced delirium at a dose of Dose C (30 mcg + 1.5 mg/hour) were 1 person, or 33.3%. A significance value was obtained using the chi-square test (*P*-value = 0.500), which means there is no significant relationship between the doses of fentanyl and midazolam and delirium (Table 3). Table 4 indicates that there is no correlation between the combined doses of fentanyl and midazolam on pain and sedation.

The diagnosis of delirium in patients treated in the ICU uses the Confusion Assessment Method-Intensive Care Unit (CAM-ICU), which has been widely used and is the standard for diagnosing delirium in the world with a sensitivity of 94% and a specificity of 90% to 95% [4, 5]. The main goal of delirium treatment is to determine and treat the trigger and predisposing factors. To prevent pain and anxiety from developing into delirium and agitation, critical patients in the ICU need to be given analgesics and sedatives. In addition to sedative drugs, patients still need other treatments to protect themselves and ICU staff, namely by using safety devices such as bed railings, hands tied with soft straps, or bodies tied with soft straps to the bed. Besides that, in delirium or critical patients, CPOT can be used as a tool to detect pain [6, 7].

This CPOT was developed by Gelinas et al. in France and, not long after, translated and validated in various countries for use. This assessment tool was developed to detect pain in critically ill patients [8]. This study aims to determine the relationship between pain and delirium in intubated patients in the ICU of Central General Hospital Haji Adam Malik. In addition to the general objectives, this study also has specific objectives, including knowing the characteristics of intubated patients, the degree of pain using CPOT in intubated patients, the degree of delirium using the CAM-ICU, the characteristics of the use of fentanyl analgesics, the characteristics of length of stay, and the relationship between fentanyl dose and pain.

Fentanyl dose with delirium, relationship of confounding factors with pain, and confounding factors with delirium in intubated patients in the ICU, Central General Hospital Haji Adam Malik Medan We need to know. Delirium is caused by a variety of stressors, including infection, inflammation, drug toxicity, and metabolic disorders, all of which lead to an acute cerebral stress response as well as a pain response. Pain has a similar effect, acutely provoking catecholamine release and a pro-inflammatory sympathetic response in the short term, in contrast to chronic pain, which can lead to dysfunction of the cortisol system and prolonged inflammatory cytokine activity. So it is possible that discomfort or pain, whether acute or chronic, can also cause similar stress reactions that can trigger delirium, although no studies have examined this, thus making the causal relationship between pain and delirium very complex and possibly bidirectional [9, 10].

The cholinergic system may be the main link in this condition. Decreased central cholinergic activity is the final common pathway in the development of delirium symptoms, but the cholinergic system also has an important role in pain modulation, so this might be explained by the fact that delirium patients may experience impaired pain modulation [11, 12]. The results of this study showed that there was a significant difference in the average CPOT score between the non-delirium and delirium groups on fentanyl doses, where the relationship between pain and delirium has a *P*-value of 0.001, which is considered to have a significant relationship. While the relationship between fentanyl dose and pain in intubated patients has a *P*-value of 0.012, which is considered to have a significant relationship while the relationship between the doses of fentanyl and midazolam between delirium and no delirium had no significant relationship because the P-value was > 0.05% [13-15].

Table 3: Association between fentanyl and midazolam doses and delirium

Fentanyl 300 mcg and Midazolam 15 mg (ml/hour)	Delirium n (%)	No Delirium n (%)	Total n (%)	*P*-value
Dose A	20 (55.6%)	16 (44.4%)	36 (100.0%)	0.500
Dose B	24 (42.9%)	32 (57.1%)	56 (100.0%)	
Dose C	1 (33.3%)	2 (66.7%)	3 (100.0%)	

Table 4: Correlation between fentanyl and midazolam doses with pain and delirium

Fentanyl Dose	Pearson's correlation coefficient	*P*-value
Pain	0.045	0.012*
Delirium	0.301	0.500

Note: Pearson's correlation coefficient; P-value < 0.05 is significant

The results of this study found that there was a significant relationship between pain and delirium. According to Sampson, EL, West, E., and Fischer, pain can trigger pain impulses that are transmitted to neuron cells that are in the anterior lateral horn. Partly to the anterior horn of the spinal cord, which will increase the sympathetic autonomic nervous system so that it can increase the effect on cardiovascular respiratory, gastrointestinal, urinary, and endocrine hormones, namely catecholamines. Catecholamines are neurotransmitters such as dopamine, epinephrine, and noradrenaline that are released during a stress response in the body. When a stress response occurs in the body, it triggers the sympathetic nervous system and the adrenal glands to release stress hormones such as cortisol. Prolonged exposure to catecholamines can create negative psychological and physical outcomes, which can reduce certain neurotransmitters that affect mood, creating negative feedback between emotions and physiology. Chronic pain can also cause dysfunction of the cortisol system and prolonged inflammatory cytokine activity, which can increase delirium. According to research in 2014, pain can trigger tissue damage, which will increase inflammatory mediators [16, 17]. In this study, the relationship between the doses of fentanyl and midazolam, which had a delirium effect at a dose of 18 mcg + 0.9 mg/hour in 20 patients, was 55.6%; at a dose of 24 mcg + 1.2 mg/hour, it was 24 or 42.9%; and at a dose of 30 mcg + 1.5 mg/hour for 1 patient, 33.3%, resulting in a *P*-value of 0.500, which means that there is no significant relationship between the doses of fentanyl and midazolam and delirium. In All study in 2021, the study examined the effect of midazolam on delirium. Midazolam is still often used for sedation because of its limited effect on hemodynamics and short half-life. Clinical practice guidelines explain the use of midazolam and its relationship with delirium in pain-less patients.

Based on the common use of midazolam to sedate patients admitted to the intensive care unit (ICU), the relationship between midazolam administration within 24 hours Assessment of delirium and incidence of delirium in patients in the ICU assessed the outcome of delirium risk treated with midazolam infusion within 24 hours. Before the delirium diagnosis was determined, delirium was diagnosed in 28.28% of patients, and patients taking midazolam within 24 hours were more likely to develop delirium. Moreover, the data show that midazolam is associated with several adverse outcomes, including an increased risk of death and length of ICU stay. However, there is no significant association between treatment with midazolam and length of stay [18-20].

Conclusion

In the end, this study aims to determine the relationship between pain and delirium in intubated patients at H. Adam Malik Hospital in Medan. According to the dose of fentanyl, 36 people (47.7%) received 18 mcg+0.9 mcg/hour, 56 people (34.7%) received 24 mcg+1.2 mcg/hour, and 30 mcg+1.5 mcg/hour people

(17.6%). There is a significant relationship between fentanyl dosage and pain (*P*-value = 0.012). Patients who received fentanyl doses of 18 mcg + 0.9 mcg/hour experienced the most pain: 30 people (83.3%). There was no significant relationship between fentanyl and midazolam doses and delirium (P-value = 0.500). Patients who received a dose of fentanyl and midazolam (18 mcg + 0.9 mg/hour) experienced the most delirium, namely 20 patients or 55.6%.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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