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Adverse effects of fentanyl/midazolam among patients of intensive care unit (ICU): a narrative review

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ABSTRACT

Patients of intensive care unit (ICU) have a complicated condition due to disease, comorbid, and other risk factors. Some ICU patients need to get an invasive process to reduce pain, anxiety, and support their condition. During an invasive process, including mechanical ventilation which causes pain or anxiety, the patient is given sedative and analgesic agents to support the procedure and reduce the patient's pain and anxiety. However, the use of fentanyl/midazolam has the potential to cause adverse effects, for instance, hypotension, hypoxia, and delirium in several ICU patients. Several risk factors that can lead to adverse effects are aging, obesity, underlying cardiac disease, and the amount of dosage. Therefore, it is essential to recognize the risk factors and monitor the use of fentanyl/midazolam to prevent the worsening condition of patients.

ABSTRAK

Pasien di ICU memiliki kondisi yang kompleks dikarenakan penyakit, komorbid, atau faktor risiko lainnya. Beberapa pasien ICU memerlukan proses invasif untuk mengurangi rasa nyeri, cemas, dan menunjang kondisi klinis dari pasien. Selama proses invasif, termasuk di dalamnya yaitu penggunaan ventilasi mekanik yang dapat menyebabkan nyeri dan cemas, pasien mendapatkan agen sedatif dan analgesik untuk menunjang prosedur invasif tersebut dan mengurangi rasa nyeri dan cemas dari pasien. Namun, penggunaan fentanil/midazolam memiliki potensi menyebabkan kejadian yang tidak diinginkan seperti hipotensi, bradikardia, hipoksia, dan delirium. Beberapa faktor risiko yang dapat menimbulkan kejadian yang tidak diinginkan seperti usia lanjut, obesitas, dan memiliki komorbid penyakit jantung. Oleh karena itu, penting untuk dapat mengidentifikasi faktor risiko, melakukan monitor penggunaan fentanil/midazolam untuk mencegah perburukan kondisi pasien.

INTRODUCTION

The condition of patients in the intensive care unit (ICU) is generally vulnerable and unstable, and their clinical conditions are complex.[1] The most common conditions of instability in the intensive care unit are decreased consciousness and respiratory failure. Respiratory failure is the condition of an inability of the respiratory system to meet the patient's oxygen, ventilation, or metabolic needs.[2] Mechanical ventilation is one of the invasive ways to treat patients with respiratory failure.[3]

Patients in the ICU usually use short-acting analgesics and sedative agents while using mechanical ventilation or other invasive procedures indicated to improve the synchrony of mechanical ventilation, relieve discomfort, and decrease the overall work of breathing

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of patient.[4] Since the use of mechanical ventilation and other invasive procedures in critical care settings is common, it is important to monitor the use of analgesics and sedatives since they may have the potential for adverse drug reactions. Therefore, it requires monitoring of safety and the potential for sedation-related adverse events in patients.[5]

The prevalence of adverse drug reactions (ADRs) was 4.5 to 34.1% in adult intensive care units, and the range from 74.3 to 90% are predictable.[6] It is hoped that efforts to identify potential and actual adverse effects can become a method for achieving optimal therapy targets for patients. The most common sedation-related adverse events are hypoxia, apnea, hemodynamic fluctuations, vomiting, and hypotension, while severe adverse events are rare.[7]

Apnea conditions were found to be higher in patients given a combination of midazolam and opioids, while hypotension was reported to be higher in patients given propofol and midazolam combined with opioids.[7] The frequency of sedation-related adverse events can be said to be small enough to have the potential to cause significant morbidity, however, the presence of minor and moderate sedation-related adverse events can be used as an indicator to increase safety in the use of sedative and analgesic agents.[5]

The condition of ICU patients is critical and requires complex treatment or therapy, which requires close monitoring. One of the monitoring measures that can be carried out is the safety of therapy. Safety aspects are important to monitor, for example, identifying potential adverse effects or actual adverse effects to prevent patients from experiencing worsening conditions. This review article attempts to explore the prevalence, risk factors, and identify adverse effects of fentanyl/midazolam in patients as information and considerations for health practitioners in providing optimized pharmacotherapy in critical care settings.

METHOD

In this study, we performed a narrative review of the literature to assess the ADRs from the use of fentanyl/midazolam compared to other sedative in patients who requires mechanical ventilation or other procedural sedation. This article's review explored previous research results from PubMed as literature resources. The search strategy uses the keywords adverse effects, fentanyl, midazolam, and ICU patients. All articles included start from the last 10 yr.

RESULTS

TABLE 1. Summary of adverse effects of fentanyl/midazolam in ICU patients

Author	Study design	Population	Result
Lee *et al.*[8]	Double blind, parallel, randomized controlled trial	Patients between 2 mo and 18 yr of age with mechanical ventilation	*Adverse effects*: 2 cases of hypotension in fentanyl/midazolam and midazolam alone were detected. However, coma and ileus, the most common adverse reaction from fentanyl, did not occur. Fentanyl combined with midazolam is safe rather than midazolam monotherapy. *Comorbidities*: Cardiovascular disease, gastrointestinal disease, hemato-oncologic disease, immunologic disease, pulmonary disease.
Okumura *et al.*[9]	Randomized controlled trial	Patients aged 20 – 64 yr who scheduled for dental surgery	*Adverse effects*: 4 patients with hypotension in dexmedetomidine + midazolam group and 1 patient with hypotension in dexmedetomidine + fentanyl/midazolam. 5 patients had residual intraoperative memory in dexmedetomidine + midazolam and dexmedetomidine + fentanyl/midazolam. Adverse effects occur in the post-operative. *Comorbidities*: Hypertension, DM, depression, and epilepsy.
Selvaraj *et al.*[10]	Randomized controlled study, double blind	Patients from 18 and 70 yr of age with documented narrow complex tachycardia and no pre-excitation	*Adverse effects*: Transient hypotension and hypoxia occur in one patient in the fentanyl/midazolam group. Adverse events occur during electrophysiology and ablation of supraventricular tachycardia. *Comorbidities*: Supraventricular tachycardia
Liu *et al.*[11]	Prospective randomized controlled trial, single center	Patient in SICU who requiring mechanical ventilation with sedation	*Adverse effects*: Delirium occurs in three groups (p= 0.014; 22.9% for the remifentanil/midazolam group, 40% in the fentanyl/midazolam group, and 57.1% from midazolam group). Remifentanil has reduced delirium significantly (p= 0.007). The duration of monitoring delirium is conducted until the patient is discharged from the ICU. *Comorbidities*: Abdominal, vascular, orthopedic, genitourinary.
Gulla *et al.*[12]	Randomized controlled trial	Pediatric patients in PICU of a tertiary care teaching hospital	*Adverse effects*: persistent bradycardia occurs in 4 children in dexmedetomidine group, while in midazolam group, none of the patient had bradycardia. Hemodynamic stability, assessed by vasoactive inotropic score, was not different between the group of midazolam and dexmedetomidine. Adverse effects occur during patients require mechanical ventilation. *Comorbidities*: Pneumonia, gastrointestinal sepsis, and sepsis.

DISCUSSION

Fentanyl is one of the opioid drugs that have sedation and analgesic effects. The mechanism of fentanyl is the activation of a Mu-selective opioid agonist. Therefore, it will lead to localization in the brain within specialized neuroanatomical structures, and the control of emotions and pain. The dose of fentanyl for anaesthesia adjunct is 2–50 μg/kg/dose IV for a single dose and in patients with patient-controlled analgesia is 10–20 μg IV every 6 to 20 min as needed.[13] One of the most frequent analgesia and sedatives that are used in patients with mechanical ventilation is the combination of fentanyl and midazolam.

Midazolam is used for hypnosis and

anxiolysis during general anesthesia, in patients requiring mechanical ventilation, and treatment for seizures. The mechanism of midazolam is associated with the accumulation of GABA and binding to the benzodiazepine receptors. Almost the indication that midazolam for example sedation, anxiolysis, anterograde amnesia, and anticonvulsant effect are related to the mechanism of action through GABA. Midazolam is metabolized by hepatic CYP450 and glucuronide conjugation. For the intravenous sedation, the dose is titrated from 0.05 to 0.15 mg/kg.[14]

The use of a combination of analgesia and sedation refers to the recommendation from clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU called analgosedation. The meaning of analgosedation is 'either analgesia-first sedation (analgesic usually opioid) is used before a sedative to reach the sedative goal or analgesia-based sedation (analgesic usually opioid) is used instead of sedative to reach the sedative goal.[15] One example of analgosedation is the use of a combination of fentanyl/midazolam in ICU patients, especially with mechanical ventilation.

Some multifactor conditions lead to adverse effects of fentanyl/midazolam. Patients who are elderly and receive high-dose sedatives/analgesics are prone to have adverse reactions to fentanyl/midazolam. Moreover, obesity and hypoalbuminemia are the conditions that can become the risk factors for adverse effects from fentanyl/midazolam, since it can cause drug accumulation in adipose tissue and can lead to prolonged effect of midazolam.[16] Furthermore, the hypotension was observed in patients who have underlying cardiac conditions while receiving fentanyl/midazolam.[17]

The safety of midazolam and fentanyl/midazolam for sedation therapy is evaluated in mechanically ventilated patient children. The adverse effects that occur are hypotension. Two patients have hypotension in each group receiving midazolam and the other group receiving fentanyl/midazolam. Meanwhile, ileus, coma, and mortality didn't occur among the adverse reactions that were evaluated in this study.[8] The safety of the sedations, including adverse effects, was also evaluated in pediatric oncology patients divided into midazolam/fentanyl and midazolam/ketamine groups. Patients who received midazolam/fentanyl had lower incidences of vomiting ($p = 0.033$) but experienced more pain ($p = 0.008$). Overall tolerable side effects were comparable in both groups.

There are several mechanisms of opioid-induced hypotension. The first mechanism is neurologic, the pathway of administration of μ-agonists directly into the central nervous system can produce hypotension and bradycardia. Another mechanism is by cardiac pathway, fentanyl can decrease the contractility of myocardial. Moreover, in the hormonal mechanism, histamine can be stimulated for release by fentanyl. Hypotension potentially occurs in the administration of fentanyl due to cardiovascular instability that is caused by the opioid mechanism in the central nervous system by neurologic and cardiac pathway.[18] The adverse effects that occur with rapid intravenous midazolam administration are hypotension tachycardia and infusion syndrome, and respiratory distress, which can occur in the high dose of use.[14] The complete mechanism of midazolam can potentially lead to hypotension may be caused by vasodilatation related to the level of extravascular prostanoids and calcium.[19]

In addition, the study reported persistent bradycardia occurs in 4 children in the dexmedetomidine group, while in the midazolam group, none of the patients had bradycardia.[12] This result isn't linear with the mechanism of midazolam inducing predominance of sympathetic activity, leading to decreased heart rate and

blood pressure.[20] However, it can be generalized since other factors can affect the hemodynamic profile of patients while using midazolam.

The safety of dexmedetomidine/ midazolam and dexmedetomidine/ midazolam/ fentanyl are evaluated. Hypotension occurs in four patients from the dexmedetomidine/ midazolam group and one patient from dexmedetomidine/midazolam/ fentanyl.[9] Patients during ablation of supraventricular tachycardia also get evaluated, the hypotension occurs in one patient who receives intermittent doses of midazolam and fentanyl.[10] Another potential adverse effect that can occur in patients receiving sedation is delirium. The group of patients who receive remifentanil/midazolam has a lower occurrence of delirium (p = 0.007) compared with the fentanyl/midazolam and midazolam group. Fentanyl has the potential effect of prolonging the awakening time. Therefore, remifentanil has less potential to have an adverse effect, delirium.[11]

Another potential adverse effects that occur in ICU patients who receive midazolam is delirium. The mechanism of midazolam which can overstimulate the cortical GABA system and then reduce corticostriatal glutamatergic tone and impair the action of the thalamus, also inhibits the central nervous system in high doses and can cause confusion.[21] The mechanism of the drug, duration of use, and risk factors in patients who require fentanyl/midazolam can lead to potential adverse effects in patients in ICU who have unstable conditions. Therefore, monitoring efficacy and safety is crucial in patients who receive sedation to prevent their condition from worsening.

CONCLUSION

Several ADRs that occur in patients who receive fentanyl/midazolam are hypotension, hypoxia, and delirium. Some risk factors increase the potential ADR, for instance, aging, obesity, underlying cardiac disease, and the amount of dose of fentanyl/midazolam. Monitoring potential ADRs and identifying the risk factors can assist physicians in making choices, ensuring that patients receive safe and effective drugs.

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