

## The Effect of Midazolam Sedation on Agitation Incidence in Post-Operative Patients Who Are Intubated in the ICU of RS Adam Malik Medan

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### ABSTRACT

**Background:** Agitation in critically ill patients is a phenomenon that can endanger patient safety and assistance during treatment in the intensive care unit (ICU). It is characterized by increased motor and mental activity that manifests as inappropriate behavior, disorganized thoughts, and loss of self-control over actions.

**Objective:** Evaluating the effect of midazolam sedation on the incidence of agitation in post-operative intubated patients in the ICU at RS Adam Malik, Medan.

**Methods:** This is a retrospective analytical study with a cross-sectional using a scoring approach to determine the relationship between midazolam use and agitation in postoperative patients intubated in the ICU after surgery at RS Adam Malik, Medan. The subject selection technique used was non-probability sampling with a consecutive sampling method, where 115 subjects were needed. Bivariate analysis for numeric variables used the Independent T-test if the data was normally distributed, or the Mann-Whitney U test if the data was not normally distributed. The results of the analysis were said to be significant if  $p < 0.05$ , with a confidence level of 95%.

**Result:** The results of the study the dose of midazolam given to postoperative patients intubated in the ICU of RS Adam Malik, Medan had a minimum dose of 0.017 mg/kg/hour, a maximum of 0.031 mg/kg/hour and an average of 0.023 mg/kg/hour which was related to the incidence of patient agitation during the ICU obtained a significant relationship  $p < 0.05$ .

**Conclusion:** The effect of midazolam sedation on the incidence of agitation in postoperative patients who were intubated in the ICU of RS Adam Malik, Medan, patients who experienced agitation had a statistically significant difference in the dose of midazolam. And there were side effects of agitation in the form of release of invasive instruments/devices, such as endotracheal tubes, in patients who did not receive sufficient sedation.

**Keywords:** agitation; ICU; intubated; midazolam; postoperative

## INTRODUCTION

Agitation in critically ill patients, particularly in the intensive care unit (ICU), can jeopardize patient safety and worsen their condition. It is characterized by increased motor and mental activity, leading to inappropriate behaviors and loss of self-control.<sup>1</sup> This can obscure diagnoses, delay treatment onset, and increase morbidity and mortality. The causes of agitation are multifactorial, involving underlying medical conditions that can worsen organ dysfunction. Agitation increases the risk of self-extubation, injury, and other complications, leading to prolonged hospital and ICU stays, longer mechanical ventilation, higher mortality rates, and increased healthcare costs.<sup>2</sup>

Postoperative agitation is also a common issue that can result in injury, self-extubation, catheter removal, and interfere with recovery. Research shows that the incidence of postoperative agitation in adults ranges from 4.7% to 22.2%, with otolaryngologic and ophthalmologic procedures increasing the risk. Medications such as propofol, midazolam, ketamine, and alpha-2 agonists are used to prevent agitation, but they may cause side effects such as drowsiness, delayed recovery, and nausea. Midazolam, widely used as a sedative, can cause prolonged sedation and delayed recovery. Studies on midazolam's effectiveness in preventing postoperative agitation show mixed results. Some studies indicate positive effects when midazolam is administered intravenously, but it is ineffective when given orally. A meta-analysis concluded that midazolam does not provide significant prophylaxis against postoperative agitation.<sup>3,4</sup>

Other research suggests that midazolam use may increase the risk of postoperative agitation by up to nine times compared to patients not receiving premedication. Therefore, further research is needed to evaluate the benefits of using midazolam to manage agitation in intubated postoperative patients.<sup>4-7</sup>

## METHOD

This study is a retrospective analytical research with a cross-sectional design, using a scoring approach to determine the relationship between the use of midazolam and the occurrence of agitation in intubated postoperative patients. The target population in this study includes all postoperative intubated patients in the ICU of RS Adam Malik, Medan, whose data are complete in the medical records, from January 2023 to January 2024. Meanwhile, the study sample consists of patients who meet the inclusion criteria and receive continuous sedation therapy with midazolam postoperatively at the hospital.

## RESULTS

This study was conducted at several hospitals, including RS Adam Malik, Medan, Medan General Hospital, and Putri Hijau Hospital in Medan. A total of 36 samples that met the inclusion criteria were divided into two groups: one group received a scalp block with 0.5% ropivacaine, and the other group was administered intravenous dexmedetomidine.

The average age of the patients is  $51.61 \pm 10.04$  years, with a normal data distribution ( $p > 0.05$ ). The median body weight is 58 kg with a non-normal data distribution ( $p < 0.05$ ), and the average height is  $161.56 \pm 2.78$  cm with a normal data distribution ( $p > 0.05$ ). In terms of

gender, males are more dominant, with 60 subjects (52.2%) compared to females, with 55 subjects (47.8%). Regarding the type of surgery, the majority of patients who remained intubated postoperatively were those who underwent digestive surgery, with 78 patients (67.8%), followed by oncology surgery with 20 patients (17.4%), neurosurgery with 12 patients (10.4%), plastic surgery with 2 patients (1.7%), and obstetrics and gynecology surgery with 3 patients (2.6%). All patients (100%) underwent surgery with general anesthesia (GA). The average duration of surgery was  $5.42 \pm 0.88$  hours, with a normal data distribution ( $p > 0.05$ ). The average initial mean arterial pressure (MAP) upon admission was  $85.84 \pm 13.4$ , with a normal data distribution ( $p > 0.05$ ). The initial heart rate upon admission had a median of 88 bpm with a non-normal data distribution ( $p < 0.05$ ). The average MAP after 2 hours of monitoring was  $87.53 \pm 13.7$ , with a normal data distribution ( $p > 0.05$ ). The heart rate after 2 hours of monitoring had a median of 90 bpm with a non-normal data distribution ( $p < 0.05$ ). (Table 1)

The mean MAP was  $85.84 \pm 12.28$ , and the mean heart rate was  $89.35 \pm 12.28$ , both showing a normal data distribution with a  $p$ -value  $> 0.05$ . After one hour of monitoring in the ICU, the mean MAP increased to  $87.53 \pm 13.73$ , and the mean heart rate increased to  $92.16 \pm 10.94$ , both also displaying a normal data distribution with a  $p$ -value  $> 0.05$ . A paired T-test comparing the initial measurements to those after one hour in the ICU revealed a  $p$ -value  $< 0.05$ , indicating a significant increase in MAP and heart rate during the first hour of ICU care. (Table 2)

The study found that the minimum midazolam dose was 0.017 mg/kg/hour, the maximum dose was 0.031 mg/kg/hour, and the median dose was 0.024 mg/kg/hour. The data were not normally distributed as the  $p$ -value was  $< 0.05$ . (Table 3)

The agitation level according to gender shows that 31 male patients (51.7%) out of 60 total male patients experienced agitation. For female patients, 24 patients (43.6%) out of 55 total female patients experienced agitation. There was no significant difference between male and female patients, with a  $p$ -value  $> 0.05$ . (Table 4)

The agitation level according to the type of surgery shows that 37 patients (47.4%) out of 78 total digestive surgery patients experienced agitation. For oncology surgery, 8 patients (40%) out of 20 total patients experienced agitation. For neurosurgery, 6 patients (50%) out of 10 total patients experienced agitation. For plastic surgery, 2 patients (100%) out of 2 total patients experienced agitation. For obstetrics and gynecology (Obsgyn), 2 patients (66.7%) out of 3 total patients experienced agitation. There was no significant difference between the types of surgery, with a  $p$ -value  $< 0.05$ . (Table 5)

The average duration of surgery in patients who experienced agitation was  $5.6 \pm 0.123$  hours, while the duration of surgery in patients who did not experience agitation was 5.26 hours, with  $p < 0.05$ , indicating statistical significance. (Table 6)

The average dose for post-operative patients experiencing agitation is  $0.0227 \pm 0.004$  mg/kg/hour, while patients who did not experience agitation had an average dose of  $0.0247 \pm 0.003$

mg/kg/hour. The Mann-Whitney test results indicate a significant effect of midazolam sedation on the occurrence of agitation in patients. (Table 7)

**Table 1.** Patient demographic characteristics

Variables	Results	p-value*
Age	$51.61 \pm 10.04$ years	0.2
Body weight	58 (45-82) kg	0.001
Height	$161.56 \pm 2.78$ cm	0.09
Gender		
Male	60 (52.2%)	
Female	55 (47.8%)	
Type of surgery		
Digestive	78 (67.8%)	
Oncology	20 (17.4%)	
Spinal surgery	12 (10.4%)	
Plastic surgery	2 (1.7%)	
Obstetrics and gynecology	3 (2.6%)	
Type of anesthesia		
General anesthesia (GA)	115 (100%)	
Duration of surgery	$5.42 \pm 0.88$ hours	0.2
Initial MAP upon admission	$85.84 \pm 13.4$	0.092
Initial HR upon admission	88 (70-110) bpm	0.024
MAP after 2 hours of monitoring	$87.53 \pm 13.7$	0.085
HR after 2 hours of monitoring	90 (71-120) bpm	0.001

\*Normality Test using the Kolmogorov-Smirnov method

**Table 2.** Clinical characteristics of postoperative intubated patients in the ICU

Variable	Initial measurement	2 hours in the ICU	p-value
MAP	$85.84 \pm 13.47$	$87.53 \pm 13.73$	0.0001*
HR	88 (70–110)	90 (71–120)	0.0001**

\*Paired T-test; \*\* Wilcoxon Test

**Table 3.** The average dose of midazolam administered to post-operative intubated patients in the ICU

Variable	Minimum	Maximum	Median	p-value
Midazolam Dose (mg/kg/hour)	0.017	0.031	0,024	0.001

\*Test: Kolmogorov-Smirnov

**Table 4.** Agitation levels of patients based on gender

Gender	Agitation	No agitation	Total	p-value*
Male	31 (51.7%)	29 (48.3%)	60	0.39
Female	24 (43.6%)	31 (56.4%)	55	
Total	55	60	115	

\*Uji Chi Square

**Table 5.** Comparison of differences in changes in inflammatory responses: CRP, NLR, and PLR between the two groups

Surgery type	Agitation	No agitation	Total	p-value
Digestive	37 (47.4%)	41 (52.6%)	78	0.53
Oncology	8 (40%)	12 (60%)	20	
Neurosurgery	6 (50%)	6 (50%)	10	
Plastic surgery	2 (100%)	0 (0%)	2	
Obgyn	2 (66.7%)	1 (33.3%)	3	
Total	55	60	115	

\*chi square

**Table 6.** Patient agitation level based on surgery duration

	Agitation	No agitation	p-value
Surgery duration	5.60 ± 0.123 hour	5.26 ± 0.106 hour	0.04

\*Unpaired T-test

**Table 7.** The effect of midazolam sedation on agitation events in postoperative patients who are intubated in the ICU

Event	N	Mean ± Deviation standard	p-value
Agitation	55	0.0227 ± 0.004	0.047
No agitation	60	0.0247 ± 0.003	

\*Mann-Whitney Test

## DISCUSSION

The study highlights the clinical characteristics of postoperative intubated patients in the ICU, focusing on hemodynamic parameters, emergence agitation (EA), and the administration of sedatives, particularly midazolam. Patients in the ICU showed an average mean arterial pressure (MAP) of 85.84 mmHg and a heart rate of 89.35 beats/min.<sup>8</sup> There was a notable increase in MAP and heart rate upon ICU admission and within the first hour, aligning with previous findings indicating higher heart rate and MAP in postoperative patients receiving midazolam.<sup>9</sup>

Midazolam, a benzodiazepine, demonstrated a short half-life (1.5–3 hours) and dose-dependent effects ranging from anxiolysis to hypnosis and retrograde amnesia. It acts by binding to gamma-aminobutyric acid-A (GABA-A) receptors, enhancing inhibitory neurotransmitter activity in the central

nervous system. The average dosage administered was 0.023 mg/kg/hour, with ranges between 0.017–0.031 mg/kg/hour. Despite its benefits, including preventing EA and controlling autonomic responses, prolonged or high doses of midazolam may increase the risks of delirium and respiratory depression.<sup>10</sup>

Emergence agitation, characterized by psychomotor agitation, delusions, and disorientation, is a common postoperative complication. In this study, the EA incidence was 47.8%. Risk factors include long surgical duration, insufficient sedation or analgesia, and pain. Agitation was linked to complications such as self-extubation, hypoxia, and increased morbidity. Effective management of EA involves appropriate sedation protocols, analgesia, and non-pharmacological measures to ensure patient comfort and safety.<sup>11</sup>

Comparative studies revealed that midazolam effectively reduces EA, especially at doses of 0.05–0.1 mg/kg given before the end of surgery. However, the efficacy varies, with higher doses reducing severe agitation but potentially delaying recovery. Other sedatives, including dexmedetomidine and propofol, were also effective in reducing EA but showed varying side effects. In pediatric patients, lower doses of midazolam reduced EA incidence but were less effective against severe cases.<sup>12-14</sup>

The study emphasizes optimizing sedation practices and pain management to minimize agitation and improve outcomes in postoperative intubated patients. Proper documentation of initial bolus administration and adherence to recommended dosages are crucial in achieving effective sedation and preventing complications.<sup>14,15</sup>

## CONCLUSION

The demographic characteristics of postoperative intubated patients in the ICU at RS Adam Malik, Medan, showed an average age of  $51.61 \pm 10.04$  years. Male patients were predominant, accounting for 52.2%, and most underwent digestive surgery (72.2%). The median body weight was 58 kg, with an average surgery duration of  $5.42 \pm 0.88$  hours. All patients received general anesthesia (GA) during their procedures.

The clinical characteristics revealed an average mean arterial pressure (MAP) of  $85.84 \pm 13.47$  mmHg and a heart rate of  $89.35 \pm 12.28$  beats/min at ICU admission, with further increases observed during the two-hour ICU observation period (MAP  $90.01 \pm 12.15$  mmHg and heart rate  $101.35 \pm 14.11$  beats/min). No cases of barotrauma were recorded, but five patients experienced

unintentional extubation of their endotracheal tubes while in the ICU.

The midazolam dosage administered to these patients ranged from a minimum of 0.017 mg/kg/hour to a maximum of 0.031 mg/kg/hour, with an average dose of 0.023 mg/kg/hour.

The incidence of agitation among postoperative intubated patients in the ICU was 47.8%. Patients who experienced agitation received an average midazolam dose of 0.022 mg/kg/hour, while those without agitation received an average dose of 0.024 mg/kg/hour. This difference was statistically significant. Insufficient sedation was associated with agitation-related complications, such as the dislodgement of invasive devices, including endotracheal tubes.

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