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ORIGINAL RESEARCH **INTENSIVE CARE**

Comparison of dexmedetomidine and midazolam in reducing agitation in the ICU patients using the Richmond Agitation Sedation Scale (RASS) and Bispectral Index (BIS)

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ABSTRACT

Background & objective: Agitation is a frequent and serious complication in ICU patients undergoing mechanical ventilation (MV). It may be due to many causes, the most important being incomplete paralysis and inadequate sedation. Intensivists have used a variety of different options to prevent agitation. This study compared dexmedetomidine and midazolam in reducing agitation using the Richmond Agitation Sedation Scale (RASS) and Bispectral Index (BIS), and assessed sedation quality and hemodynamic effects.

Methods: A double-blind randomized clinical trial was conducted on 28 ICU patients who were on MV. The patients were divided into two groups: either to receive an infusion of dexmedetomidine (0.4 µg/kg/hr) or midazolam (0.04 mg/kg/hr) following a standardized loading dose. RASS, BIS, and hemodynamic parameters were recorded at baseline, 4, 8, and 24 hours, and compared in two groups.

Results: At 8 and 24 hours, agitation occurred in 28.6% of midazolam patients versus 14.3% and 7.1% in the dexmedetomidine group ($P < 0.05$). BIS and RASS were strongly correlated ($r > 0.8$, $P < 0.001$). Dexmedetomidine significantly reduced heart rate and mean arterial pressure without adverse effects.

Conclusion: Dexmedetomidine is more effective than midazolam in reducing agitation, offering better sedation quality with stable hemodynamics. BIS complements RASS in guiding sedation in ICU settings.

Abbreviations: BIS: Bispectral Index, ICU: Intensive Care Unit, MAP: mean arterial pressure, RASS: Richmond Agitation Sedation Scale,

Keyword: Agitation; Bispectral Index; Dexmedetomidine; Intensive Care Units, Midazolam; Richmond Agitation Sedation Scale; Sedation

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1. INTRODUCTION

Critically ill patients admitted to the Intensive Care Unit (ICU) often require mechanical ventilation and invasive interventions, which can trigger pain, anxiety, dyspnea, and agitation. Agitation, especially emergence agitation or delirium, is a frequent complication that compromises patient safety by increasing the risk of self-extubation, catheter dislodgement, and even barotrauma due to excessive respiratory effort. The World Health Organization reported a rising burden of critical illnesses globally, with up to 24.6 ICU admissions per 100,000 population. In Indonesia, local hospital data such as that from RSUP H. Adam Malik Medan highlight the growing volume of ICU admissions, underscoring the clinical relevance of effective sedation strategies in this population.

Midazolam, a short-acting benzodiazepine that acts on GABA-A receptors, has been widely used in ICU sedation for its anxiolytic, hypnotic, and amnestic effects. However, its use has been associated with a significant incidence of agitation and delirium. Recent studies have suggested that dexmedetomidine, a selective α2-adrenergic agonist, may offer superior outcomes by mimicking natural sleep, providing lighter sedation, and preserving respiratory function. For instance, Garg et al. (2022) demonstrated that dexmedetomidine significantly reduced emergence agitation by up to 89.5%, while Shehabi et al. (2020)[2] showed a reduction in agitation from 77% to 13% after dexmedetomidine infusion (Hariharan & Garg, 2017;[1] Nath et al., 2015;[3] Shehabi et al., 2021).[2] Additionally, the incidence of agitation was found to be significantly lower with dexmedetomidine (7.6%) compared to placebo (18.5%).[4]

Despite increasing evidence supporting dexmedetomidine, current literature has yet to comprehensively compare both agents using validated clinical and neurophysiological monitoring tools such as the Richmond Agitation Sedation Scale (RASS) and the Bispectral Index (BIS). While RASS is widely accepted as a reliable clinical scale, BIS provides an objective EEG-based numerical measure of sedation depth. Meta-analyses by Heavner et al. (2023) support a strong correlation between BIS and RASS, but few studies have directly compared how these two sedatives perform when evaluated through both instruments simultaneously in ICU settings.[5]

This study aimed to fill that gap by evaluating and comparing the incidence of agitation in ICU patients receiving dexmedetomidine versus midazolam, using both RASS and BIS as outcome measures. Through a randomized, double-blind clinical design, the study not only examines the clinical effectiveness of these agents but also investigates the concordance between subjective and objective measures of sedation. By integrating these tools, this research aspires to contribute to the refinement of ICU sedation protocols, optimize patient safety, and enhance outcomes for critically ill patients requiring mechanical ventilation.

2. METHODOLOGY

This study employed a randomized, double-blind, clinical trial design to compare the incidence of agitation in critically ill patients treated with dexmedetomidine versus midazolam in the Intensive Care Unit (ICU). The primary outcomes were assessed using both the Richmond Agitation Sedation Scale (RASS) and Bispectral Index (BIS) to evaluate The study population consisted of adult patients admitted to the ICU at our hospitals between February 2025 and the completion of sampling. Eligible participants were intubated, critically ill patients aged 18 years or older. Patients were excluded if they had received other sedatives, were pregnant or breastfeeding, had unstable angina or acute myocardial infarction, had severe cardiac dysfunction (left ventricular ejection fraction <30%, bradycardia <50 bpm, or advanced heart block), had recently undergone brain surgery, or were under neuromuscular blockade. A total of 28 participants were included, randomized equally into two intervention groups using a computerized randomization tool.

Two sedative agents were administered: midazolam at a continuous infusion dose of 0.04 mg/kg/hour and dexmedetomidine at 0.4 µg/kg/hour following a loading dose of 1 µg/kg over 10 minutes. The depth of sedation and agitation levels were measured at four time points: baseline (T0), 4 hours (T1), 8 hours (T2), and 24 hours (T3) post-intervention. The RASS assessment was conducted first, followed by BIS monitoring using standard EEG electrode placement procedures on the forehead and temporal region. Demographic data, hemodynamic parameters, and clinical characteristics were also recorded during the study period.

Data were collected by trained personnel under double-blind conditions, where both the administering clinicians and outcome assessors were unaware of group allocation. The study received prior ethical approval from the Health Research Ethics Committee of the XXX and the participating hospitals.

2.1. Data analysis

Statistical analysis was conducted using SPSS. Descriptive statistics summarized baseline characteristics. The Chi-square test was used to compare the incidence of agitation between groups. Correlation between RASS and BIS scores was evaluated using

Table 1: Comparative demographic data in the two groups

Characteristics	Midazolam (n = 14)	Dexmedetomidine (n = 14)	P-value	Total (n = 28)
Gender				
• Female	5 (41.7)	7 (50)	0.44	12 (42.9)
• Male	9 (64.3)	7 (50)		16 (57.1)
Age (year)	53.28 ± 14.36	46.35 ± 17.71	0.03	49.82 ± 16.21
Education level				
• No school	1 (7.1)	1 (7.1)	0.02	2 (7.1)
• Elementary School	0	2 (14.3)		2 (7.1)
• JHS	1 (7.1)	6 (42.9)		7 (25)
• SHS	5 (35.7)	5 (35.7)		10 (35.7)
• Bachelor	7 (50)	0		7 (25)

Data presented as n (%) or mean ± SD; P < 0.05 considered as significant

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Table 2: Comparison of the incidence of agitation in the two groups

Characteristics	Midazolam	Dexmedetomidine	*Relative risk*	P-value
RASS T0				
Agitation	14 (100)	14 (100)		-
No Agitation	0	0		
RASS T1				
Agitation	0	0		-
No Agitation	14 (100)	14 (100)		
RASS T2				
Agitation	4 (28.6)	2 (14.3)	2	0.003
No Agitation	10 (71.4)	12 (85.7)		
RASS T3				
Agitation	4 (28.6)	1 (7.1)	4	0.002
No Agitation	10 (71.4)	13 (92.9)		

T0: pre-intervention; T1: 4 hours post-intervention; T2: 8 hours post-intervention; T3: 24 hours post-intervention; RASS- Richmond Agitation Sedation Scale; P < 0.05 considered as significant

Pearson's correlation coefficient. A p-value of less than 0.05 was considered statistically significant. The relative risk for agitation was also calculated to determine the comparative effectiveness of the two sedatives.

3. RESULTS

The study involved 28 critically ill patients divided equally into two intervention groups receiving either dexmedetomidine or midazolam. The demographic characteristics showed that the majority of participants were male (57.1%), with a higher male proportion in the midazolam group (64.3%) compared to dexmedetomidine (50%). The mean age in the midazolam group was 53.2 ± 14.3 years and 46.3 ± 17.7 years in the dexmedetomidine group, with a statistically significant difference (P = 0.03). Educational level varied, with most patients in the dexmedetomidine group having junior high school education, whereas in the midazolam group, university-level education was more common, also indicating a statistically significant difference (P = 0.02).

In terms of agitation as assessed by the RASS score, both groups showed no agitation at baseline and at 4 hours post-intervention. However, at 8 hours (T2), 28.6% of the midazolam group showed signs of agitation compared to 14.3% in the dexmedetomidine group. At 24 hours (T3), agitation persisted in 28.6% of midazolam patients and dropped to 7.1% in the dexmedetomidine group. The relative risk of agitation at 24 hours was 4 times higher in the midazolam group (P = 0.002), indicating a statistically significant difference.

Correlations between RASS and BIS scores were also examined. In the midazolam group, RASS and BIS values at all four time points (T0 to T3) showed strong positive correlations (r ranging from 0.81 to 0.97; P < 0.001). Similarly, the dexmedetomidine group demonstrated strong correlations between RASS and BIS (r = 0.87 to 0.93; P < 0.001), validating the consistency between clinical sedation scoring and objective EEG-based sedation assessment.

Hemodynamic parameters showed varied patterns. In both groups, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) remained within normal limits across all time points. However, dexmedetomidine was associated with significantly lower diastolic blood pressure at 4 and 8 hours (P = 0.03) and significantly lower MAP at 8 and 24 hours (P = 0.01 and 0.02, respectively). Heart rate was

Table 3: Relationship of RASS to BISS in the Midazolam Group

Midazolam Group	RASS	BIS	r	P-value
T0	1.7 ± 0.4	79.1 ± 6.2	0.81	0.001
T1	-3.5 ± 0.6	50.1 ± 8.4	0.94	0.001
T2	-1 ± 1.8	59.7 ± 12.1	0.95	0.001
T3	-0.6 ± 1.4	64 ± 11.9	0.97	0.001

T0: pre-intervention; T1: 4 hours post-intervention; T2: 8 hours post-intervention; T3: 24 hours post-intervention; RASS- Richmond Agitation Sedation Scale; BIS-Bispectral Index; P < 0.05 considered as significant

Table 4: Relationship of RASS to BISS in the Dexmedetomidine Group

Dexmedetomidine Group	RASS	BIS	r	P-value
T0	1.7 ± 0.4	81 ± 6.2	0.87	0.001
T1	-3.2 ± 0.5	52.2 ± 8.2	0.91	0.001
T2	-0.6 ± 1.1	68.1 ± 7.4	0.93	0.001
T3	-0.5 ± 0.7	68.7 ± 6.6	0.92	0.001

T0: pre-intervention; T1: 4 hours post-intervention; T2: 8 hours post-intervention; T3: 24 hours post-intervention; RASS- Richmond Agitation Sedation Scale; BIS-Bispectral Index; P < 0.05 considered as significant

also significantly lower in the dexmedetomidine group at all time points except baseline ($P < 0.05$). Despite these changes, no incidents of hypotension or bradycardia were observed, suggesting hemodynamic effects remained within a clinically acceptable range.

4. DISCUSSION

This study demonstrates that dexmedetomidine is more effective than midazolam in reducing agitation in critically ill patients within the ICU setting. The findings show a significant reduction in agitation at 8 and 24 hours post-intervention in the dexmedetomidine group, confirming its superior sedative profile under conditions requiring light to moderate sedation. This supports existing evidence in the literature, including the systematic review by Wen et al., (2023), which reported a significantly lower risk of delirium and agitation in patients sedated with dexmedetomidine compared to midazolam (RR 0.63; 95% CI 0.50–0.81; P = 0.0002).[6] Likewise, Kawazoe et al., (2017) found better-controlled sedation with dexmedetomidine, along with reduced mortality and ventilator dependence.[7]

The results further indicate that dexmedetomidine not only reduces the incidence of agitation but does so while maintaining adequate sedation depth. The strong correlation between RASS and BIS observed in both groups reinforces the validity of BIS as a reliable monitoring tool for sedation levels, aligning with findings from Heavner et al., (2022) and Barbato et al., (2017), which suggest BIS scores correlate well with clinical sedation scales such as RASS, RSS, and SAS in ICU patients.[5,6] These findings support the growing adoption of BIS in critical care for real-time sedation titration and minimization of over- or under-sedation, ultimately improving ICU outcomes.[7,8]

In terms of hemodynamic effects, the dexmedetomidine group demonstrated significantly lower diastolic pressure, MAP, and heart rate compared to midazolam. These effects are attributed to the sympatholytic and vagomimetic actions of α2-adrenergic agonists (Weerink et al., 2017).[9] While dexmedetomidine carries a known risk of bradycardia and hypotension, none of the patients in the current study experienced clinically significant adverse cardiovascular events. The hemodynamic differences were tolerable, as previously reported by Nath et al., (2015) and Xu et al., (2018), who observed similar profiles with minimal need for vasoactive support.[3,10] This makes dexmedetomidine suitable even for critically ill populations, provided that careful monitoring is ensured.

The agitation observed in the midazolam group at later time points may be partially explained by the disruption of REM sleep and increased risk of emergence delirium associated with benzodiazepines. Midazolam's sedative effect is mediated via GABAA receptor modulation, which influences sleep architecture by shortening REM phases and increasing stage 2 non-REM sleep (Aggarwal et al., 2020; Engelborghs et al., 2008; Pereira et al., 2020; Reves et al., 1985).[11-14] This alteration may predispose ICU patients—especially those under mechanical ventilation—to heightened vulnerability for agitation when the sedative effect begins to wear off.

Dexmedetomidine, in contrast, provides a sedative state that closely mimics natural sleep by targeting the locus coeruleus, a key nucleus in regulating physiological sleep.[13,15] This may explain the more stable sedation profile and lower incidence of agitation in the dexmedetomidine group. Notably, the study by Su et al., (2016) also demonstrated a protective role of dexmedetomidine against postoperative delirium in elderly patients, supporting the hypothesis that natural sleep patterns are critical for mental stability during ICU stays.[16]

Table 5: Comparative hemodynamic data in the groups

Parameter	Time	Midazolam	Dexmedetomidine	P-value
Systolic Blood Pressure (mmHg)	T0	120.3 ± 23.1	120 ± 14.9	0.12
	T1	118.3 ± 15.8	116.2 ± 9.1	0.83
	T2	120.7 ± 14.3	113.5 ± 8.7	0.13
	T3	116.1 ± 14.5	115.1 ± 9.5	0.22
Diastolic Blood Pressure (mmHg)	T0	78.3 ± 15.3	71.1 ± 7.2	0.12
	T1	74.2 ± 15.3	66.4 ± 8.1	0.03
	T2	73.4 ± 9.8	66.3 ± 7.1	0.03
	T3	73.7 ± 9.4	67.6 ± 6.8	0.06
Mean Arterial Pressure (mmHg)	T0	90.6 ± 14.3	87.2 ± 8.1	0.44
	T1	88.7 ± 10.4	82.6 ± 7.3	0.08
	T2	89 ± 8.9	81.7 ± 5.9	0.01
	T3	87.4 ± 9.8	83.1 ±7.1	0.02
Pulse Rate (beats/min)	T0	110.2 ± 13.1	100.2 ± 13.8	0.06
	T1	89.8 ± 11.5	77.4 ± 8.1	0.003
	T2	95.9 ± 12.2	83.2 ± 15.9	0.02
	T3	95.9 ± 8.4	83 ± 12.3	0.003

T0: pre-intervention; T1: 4 hours post-intervention; T2: 8 hours post-intervention; T3: 24 hours post-intervention; P < 0.05 considered as significant

While both agents successfully maintained sedation levels within target ranges (as evidenced by consistent RASS and BIS scores), the quality of sedation and patient comfort appears to be enhanced with dexmedetomidine. Furthermore, the results highlight the importance of using both clinical and objective measures—RASS and BIS—in tandem for a comprehensive sedation assessment. This combination can help overcome the subjective limitations of clinical scales and provide more consistent titration guidance in complex ICU environments.

5. LIMITATIONS

Nevertheless, this study is not without limitations. The observation period was limited to 24 hours, which may not fully capture the longer-term trends in agitation or delirium. Additionally, the dosing regimens, midazolam at 0.04 mg/kg/hr and dexmedetomidine at 0.4 µg/kg/hr, reflect relatively low maintenance doses, potentially influencing the sedation depth and agitation onset beyond the initial monitoring period. Other factors that influence agitation, such as pain levels, ventilator settings, electrolyte imbalance, or oxygenation status, were not assessed in this study and could act as confounding variables. Future studies with extended observation windows, higher or titratable dosing, and more comprehensive physiologic monitoring are warranted.

6. CONCLUSION

Dexmedetomidine was more effective than midazolam in reducing agitation among ICU patients, particularly at 8 and 24 hours after administration. Strong correlations between RASS and BIS in both groups support BIS as a valid objective tool for monitoring sedation. Despite hemodynamic differences, both agents were well tolerated without significant adverse events. These findings support the use of dexmedetomidine and BIS monitoring to optimize sedation strategies in critically ill patients.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Conflict of interest

All authors declare that there was no conflict of interest.

9. Funding

The study utilized the hospital resources only.

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11. Authors' contribution

MIA conceived and designed the study, conducted research, provided research materials, collected and organized data, also analyzed and interpreted data.

MIA, DWW, BLS, and ASW wrote the initial and final draft of the article and provided logistical support.

DWW and BLS as a supervisor. All authors have critically reviewed and approved the final draft and are responsible for the manuscript's content and similarity index.

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