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Efficacy and Safety of Ketamine-Dexmedetomidine Versus Ketamine-Propofol for ICU Sedation: A Prospective Randomized Controlled Trial

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ABSTRACT

Objective: This study aimed to compare the efficacy and safety of ketamine-dexmedetomidine (KD) and ketamine-propofol (KP) infusions for sedation in postoperative mechanically ventilated patients.
Methods: This prospective, double-blind, randomized controlled study included 70 postoperative mechanically ventilated patients, aged 18-60 years, requiring intensive care unit (ICU) sedation for 12 to 24 hours. Participants were randomly allocated into two groups: KD (n=35) and KP (n=35). Ketamine was administered as a fixed bolus followed by a continuous infusion in both groups, while the co-administered sedative was titrated to achieve a target modified Richmond Agitation-Sedation Scale (mRASS) score of -1 to -3.
Results: Baseline demographic and clinical characteristics were similar between the two groups. The KP group achieved significantly deeper sedation than the KD group (-1.17±0.38 vs. -1.6±0.55, p<0.001). However, this absolute difference was modest (0.3-0.6 mRASS points), and both groups remained within the targeted light-to-moderate sedation range. The KD group demonstrated a significantly shorter duration of mechanical ventilation (21.18±2.3 vs. 23.48±2.55 hours, p<0.001), faster recovery (1.98±0.7 vs. 2.54±0.44 hours, p<0.001), and a shorter weaning duration (3.03±0.7 vs. 4.24±0.91 hours, p<0.001). Hemodynamic parameters remained stable and comparable between the groups.
Conclusion: Both regimens provided adequate sedation within clinically acceptable ranges. The KP regimen produced statistically deeper, though only modestly deeper, sedation. Conversely, the KD regimen was associated with comparatively lighter, more arousable sedation, a better early analgesic profile, and significantly faster recovery and ventilator weaning. Therefore, the choice of regimen should be individualized based on specific patient sedation goals, rather than assuming the general superiority of one combination over the other.

Keywords: Ketamine; Dexmedetomidine; Propofol; Mechanically ventilated patients; Sedation; Modified Richmond Agitation Sedation Scale

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Introduction

Sedation management in postoperative mechanically ventilated patients is a critical component of intensive care, aiming to balance patient comfort, safety, and optimal clinical outcomes [1]. The choice of sedative agents significantly impacts not only the quality of sedation but also analgesia, hemodynamic stability, the duration of mechanical ventilation, and the weaning process [2]. Commonly used sedatives include propofol, dexmedetomidine, and ketamine, each possessing distinct pharmacological profiles that present specific benefits and limitations in the critical care setting [3]. The combination of ketamine with either dexmedetomidine or propofol has been explored as a strategy to enhance sedation quality while potentially minimizing adverse effects; however, comparative evidence remains limited.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has emerged as a promising agent for continuous sedation in mechanically ventilated patients due to its analgesic properties and relative cardiovascular stability [4, 5]. Previous studies demonstrated that ketamine infusion facilitates adjunctive sedation and analgesia, often allowing for a reduction in the doses of other sedatives and analgesics, and is generally well tolerated with an acceptable adverse event profile [6, 7]. However, the psychotropic side effects of ketamine and its potential to induce agitation necessitate careful monitoring.

Dexmedetomidine, a selective α2-adrenergic receptor agonist, provides sedation characterized by cooperative arousability, minimal respiratory depression, and adjunctive analgesic effects [8]. It has been associated with improved neurological outcomes, such as a lower incidence of delirium compared to traditional benzodiazepines and propofol, although it carries the risks of hypotension and bradycardia [9, 10]. Propofol remains widely used due to its rapid onset and ease of titration. However, it can cause hypotension and respiratory depression, and prolonged infusions carry the risk of propofol infusion syndrome [11, 12].

The combination of ketamine with dexmedetomidine might synergistically combine the analgesic and cardiovascular benefits of ketamine with the sedative and delirium-sparing properties of dexmedetomidine, potentially improving both sedation quality and safety [13]. Conversely, combining ketamine with propofol may offer enhanced sedation through complementary mechanisms but could predispose patients to greater hemodynamic instability or prolonged ventilation [12]. Despite these theoretical considerations, robust evidence comparing these combinations in the postoperative mechanically ventilated setting remains scarce. The present trial was therefore designed to address this gap directly by comparing the two most frequently used ketamine-based combinations in this setting under a single standardized analgesic and monitoring protocol.

The primary objective of this study was to compare the efficacy and safety of intravenous KD versus KP infusions for sedation in postoperative mechanically ventilated patients. Specifically, the primary endpoint was to evaluate and compare the effectiveness of sedation, as measured by the modified Richmond Agitation-Sedation Scale (mRASS), between the two regimens in postoperative intensive care unit (ICU) patients undergoing mechanical ventilation.

Secondary objectives included: 1) comparing analgesic efficacy between the two protocols, evaluated via repeated pain assessments using the Nonverbal Pain Scale (NVPS) and the requirement for additional rescue analgesics; 2) evaluating safety through continuous monitoring of hemodynamic and respiratory parameters, including heart rate, blood pressure, mean arterial pressure, and peripheral oxygen saturation throughout the sedation period; and 3) assessing clinical recovery outcomes, including the total duration of mechanical ventilation, the time to recovery of full consciousness after sedation cessation, and the duration of the weaning process. Collectively, these objectives aimed to provide a comprehensive comparative assessment of the safety profile, analgesic efficacy, and clinical utility of each ketamine-based regimen in the postoperative ICU setting.

Materials and Methods

This prospective, randomized, parallel-group, controlled study was conducted at the Department of Anesthesiology and Critical Care on 70 patients, aged 18 to 60 years. Inclusion criteria comprised patients of either sex who required mechanical ventilation in the postoperative period for various surgical indications and required intensive care unit (ICU) sedation for up to 24 hours, provided that they had a core temperature <38 °C in the immediate postoperative period and were hemodynamically stable.

Exclusion criteria were as follows: age <18 years; pre-existing hypotension, bradycardia, or metabolic derangements; head injury or other neurological diseases; pregnancy; hepatic or renal insufficiency; intraoperative or postoperative hemodynamic instability necessitating inotropic support; requirement for neuromuscular blocking agents; and the use of epidural analgesia or any non-standardized analgesic regimen.

Eligible patients were randomly assigned in a 1:1 ratio to either the KD group (n=35) or the KP group (n=35) (Figure 1). Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes generated from a computerized random sequence by an investigator not involved in patient recruitment, care, outcome assessment, or analysis. Envelopes were opened only after eligibility was confirmed and informed consent was obtained.

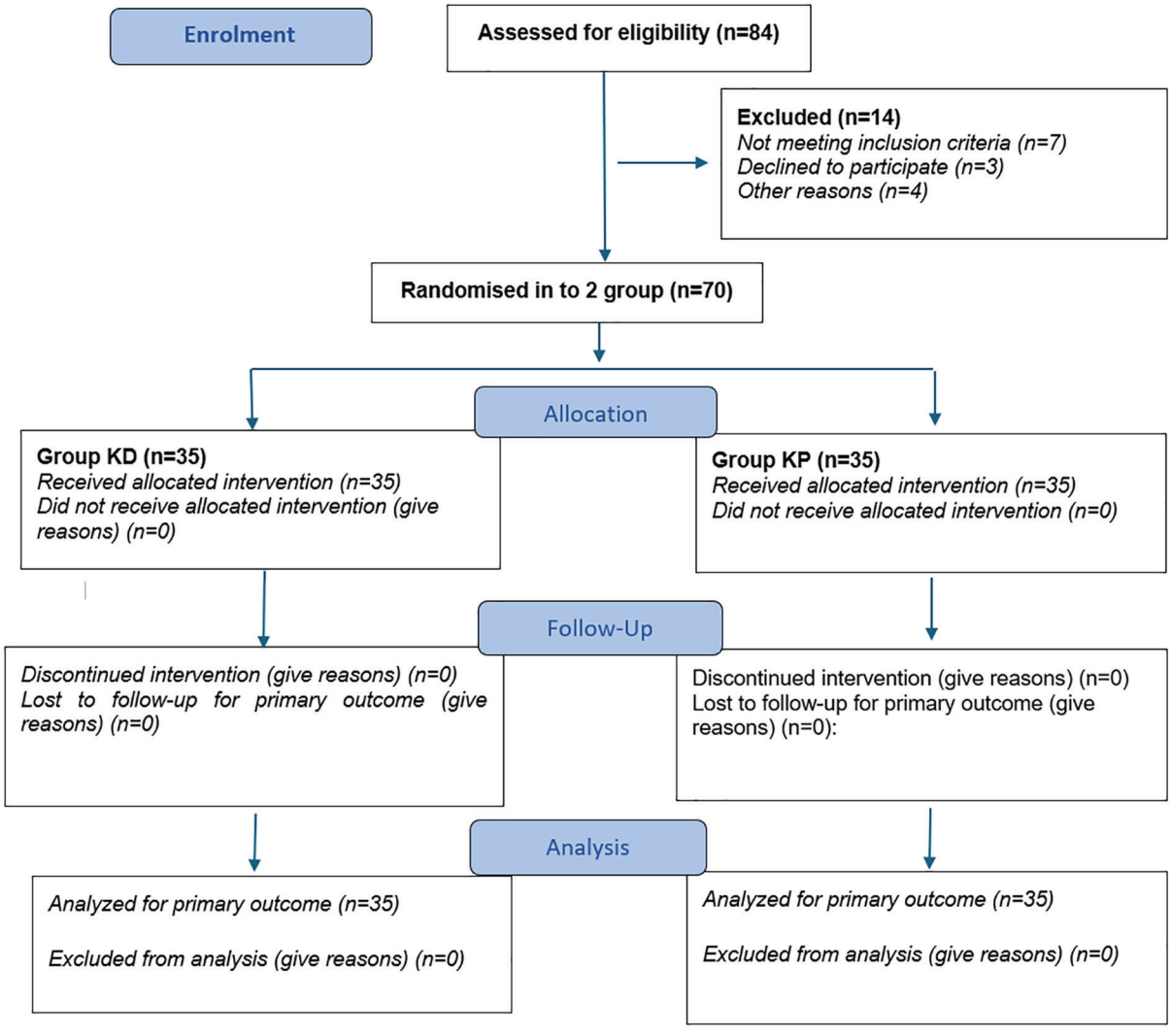


Fig. 1. The CONSORT flow diagram illustrates participant progress through the stages of the randomized trial, including enrolment, allocation, follow-up, and analysis, for the two study groups.

The patients were blinded to group allocation. The ICU nurse preparing and administering the drugs could not be blinded due to the distinct physical appearance of propofol. However, the data-recording nurse, a different trained ICU staff member, remained blinded to the assigned intervention. This was achieved by using identical infusion pumps, syringes, and tubing covered with adhesive tapes. The displays on the infusion pumps were also covered with opaque paper during data collection.

All participants were transferred directly from the operating room to the ICU. Patients who exhibited inadequate recovery of spontaneous respiration following general anesthesia attributable to residual neuromuscular blockade, prolonged anesthetic effects, or postoperative respiratory depression requiring continued ventilatory support, as well as patients undergoing prolonged surgical procedures, including those for gastrointestinal malignancies, gynecological malignancies, oral cavity, and mandibular carcinomas involving the airway, with high risk of postoperative airway edema requiring elective ventilation in the postoperative period, were included in the study. Furthermore, patients demonstrating inadequate respiratory effort following major surgical interventions, such as exploratory laparotomy, were included. Mechanical ventilation was provided via an endotracheal tube, initially utilizing volume-controlled ventilation. Progression to spontaneous breathing and subsequent weaning were guided by clinical judgment and institutional protocols.

To minimize variability in pain control, all patients received a standardized baseline analgesic regimen of intravenous tramadol 100 mg three times daily, consistent with the institutional standard for this patient subset. Rescue analgesia consisting of intravenous paracetamol 1 g or diclofenac 75 mg was administered if breakthrough pain was detected, defined as the NVPS score ≥2 [14]. Although primarily utilized for sedation, the ketamine infusions in both regimens also provided adjunctive analgesic effects. For sedation, all patients received an initial bolus dose of ketamine 1 mg/Kg intravenously, followed by a continuous intravenous infusion of ketamine at 0.25 mg/Kg/h at a fixed weight-based dose in both groups. In addition to ketamine infusion, dexmedetomidine was administered at 0.3–0.7 µg/kg/h in the KD group,

while propofol was administered at 25–50 µg/kg/min in the KP group. Both infusions were titrated in stepwise increments at 15–30-min intervals to achieve and maintain a target modified RASS score of −1 to −3, which is appropriate for postoperative patients undergoing early weaning [15].

Demographic and clinical data, including age, sex, and type of surgery, were recorded for all patients, along with ventilator settings. During the continuous infusion, observations were systematically recorded at 0, 1, 6, 12, and 24 hours. Hemodynamic variables, including heart rate, systolic and diastolic blood pressure, and mean arterial pressure, were monitored and recorded at each interval. Respiratory measures such as peripheral oxygen saturation (SpO_2) and fraction of inspired oxygen (FiO_2) were also documented. Sedation depth was evaluated using the mRASS at the same time points [15, 16].

Pain levels were assessed using the NVPS, which comprises five domains: facial expression; activity (movement); guarding; physiological I (heart rate, blood pressure, and respiratory rate); and physiological II (pupillary dilatation, diaphoresis, and flushing or pallor). Each domain was scored from 0 to 2, yielding a total score of 0 to 10 (0–2 indicating no significant pain, 3–6 moderate pain, and 7–10 severe pain), with acceptable inter-rater reliability [17, 18]. For the purposes of this study, the NVPS scores were categorized into three ordinal levels: 0 (score 0–2, absent pain), 1 (score 3–6, mild-to-moderate pain), and 2 (score 7–10, moderate-to-severe pain). Rescue analgesia was administered when the categorized score reached 2, and the requirement for rescue analgesia was documented [19]. Furthermore, patients were closely monitored for any complications or adverse drug reactions during the infusion period.

After stopping the infusion, additional parameters were collected to assess recovery and ventilatory outcomes. The total infusion duration was recorded for each patient. Weaning duration was defined as the time from the start of the spontaneous breathing trial (T3) to successful extubation (T4), although this measure did not apply to patients sedated for more than 24 hours. Recovery time was measured as the interval between infusion cessation (T1) and the return of full consciousness (T2), and this was documented for all eligible patients. Weaning was conducted according to a standardized institutional protocol. A spontaneous breathing trial (SBT) was initiated once all the defined criteria were met, and extubation following a successful SBT was performed by the treating intensivist. The decision to extubate was based on clinical grounds by the treating team and was not influenced by the study protocol. These data were utilized to evaluate both the effectiveness and safety of the sedative regimen in mechanically ventilated postoperative patients. Sample size estimation was conducted using R software (version 4.4.2). This calculation was based on the primary outcome of sedation depth, assessed by the mRASS, with parameters derived from a pilot study of 20 patients (10 per group) conducted at the same center during the two months preceding protocol finalization. These pilot participants met the same eligibility criteria, received the same sedation regimens under a similar monitoring protocol, and their data were not included in the main trial. In the pilot study, the KD group achieved a mean mRASS score of -2.10±1.10, while the KP group had a mean score of -0.80±SD 2.44. The mean difference between groups was 1.30, with a pooled SD of 1.89, yielding a standardized effect size (Cohen's d) of 0.69. Assuming a two-sided α of 0.05 and 80% statistical power, the required sample size was estimated at 34 subjects per group. To account for potential attrition, the sample size was increased to 35 subjects per group. The study was powered for the primary outcome of sedation depth, whereas the categorical analgesic outcomes (pain score distribution and rescue analgesia requirement) were considered secondary outcomes.

All statistical analyses were performed using R software (version 4.4.2). Normally distributed continuous variables were compared between the two groups using an independent-samples t-test (2 groups), and changes within groups over time were assessed using the paired t-test. Non-normally distributed continuous variables were compared using the Mann-Whitney U test and were presented as medians and interquartile ranges (IQRs). Categorical variables were compared using the Chi-square test or Fisher's exact test, with the latter used when the overall sample size was <20 or if the expected number in any one of the cells was <5. A $p<0.05$ was considered statistically significant. Between-group comparisons for the requirement of rescue analgesia and the distribution of NVPS categories at each follow-up time point (1, 6, 12 and 24 hours) were performed using Fisher's exact test due to small expected cell counts, and two-sided exact p values were reported. No adjustment was made for multiple comparisons, and these time-point analyses were therefore considered exploratory.

Results

A total of 70 postoperative mechanically ventilated ICU patients were included in this randomized controlled trial, with 35 patients allocated to the KD group and 35 to the KP group (Figure 1). Baseline demographic, ventilatory, and hemodynamic characteristics were comparable between the two groups, indicating adequate homogeneity prior to intervention. The mean age was 43.97±14.93 years in the KD group and 46.71±12.72 years in the KP group (p=0.411), while mean body weight was 68.71±7.99 Kg and 69.11±8 Kg, respectively (p=0.835). Sex distribution was also similar, with males comprising 60% of the KD group and 48.57%

of the KP group (p=0.337). Baseline ventilatory parameters, including tidal volume (415.71±29.83 mL in both groups), respiratory rate (14.17±0.89 vs. 14±0.69 breaths/min, p=0.370), PEEP (5.23±0.76 vs. 5.17±0.57 cmH_2O, p=0.742), FiO_2 (39.86±3.09 vs. 39.71±1.18, p=0.799), and SpO_2 (99±0.34 vs. 98.94±0.24, p=0.419), were comparable between groups. Baseline hemodynamic parameters were also similar, including heart rate (96.46±12.46 vs. 92.69±12.01 beats/min, p=0.202), systolic blood pressure (119.54±11.67 vs. 124.57±10.32 mmHg, p=0.060), diastolic blood pressure (71.63±9.01 vs. 74.94±8.86 mmHg, p=0.126), and mean arterial pressure (87.71±9.27 vs. 90.89±6.93 mmHg, p=0.100). Baseline sedation levels, assessed using the mRASS, were also comparable (-0.94±0.24 vs. -1.03±0.17, p=0.085). Both groups were therefore lightly sedated at baseline (mRASS approximately -1), which could be expected for patients transferred directly from the operating theatre with residual anesthetic effect, and this baseline provided the reference point against which the subsequent between-group differences in sedation depth should be interpreted. Baseline analgesic status was likewise comparable: the distribution of pain scores did not differ between groups (p=1.000), nor did the proportion of patients requiring rescue analgesia at baseline (8/35 in each group; p=1.000; Table 1).

The depth of sedation differed significantly between the two groups during follow-up. Patients receiving KP demonstrated deeper sedation than those receiving ketamine-dexmedetomidine. At 1 hour, the mean mRASS score was considerably higher in the KD group than in the KP group (-1.17±0.38 vs. -1.6±0.55, p<0.001). This difference persisted at 6 hours (-1.77±0.43 vs. -2.03±0.17, p=0.001) and 12 hours (-1.80±0.72 vs. -2.43±0.50, p<0.001). By 24 hours, the KP group achieved deeper sedation (mean mRASS -3.0) than the KD group (-2.0). However, since only three patients per group remained on sedative infusion at this time point, the 24-hour comparison was descriptive only, and no formal statistical inference was drawn (Figure 2). Both groups maintained sedation within a clinically acceptable moderate range, and their scores converged by 24 hours. Although statistically significant, the absolute difference in sedation depth was modest (around 0.3 to 0.6 points). Whether this difference conferred a meaningful clinical advantage depended on the need for deeper sedation, particularly when considering potential drawbacks such as delayed recovery and respiratory complications.

In contrast, analgesic effects clearly favored the KD regimen during the early postoperative periods. Patients in the KD group required numerically less rescue analgesia at 1 and 6 hours after surgery, with no rescue analgesics needed beyond 6 hours, whereas some patients in the KP group continued to require additional analgesia up to 6 hours (Table 2). Pain score patterns supported these observations, showing a higher proportion of patients remained pain-free with KD at 1, 6, and 12 hours, along with a distinct absence of moderate pain at later time points (Table 3). Formal statistical testing of these categorical variables was performed using Fisher's exact test. The requirement for rescue analgesia did not differ significantly at 1 hour (4/35 [11.4%] vs. 8/35 [22.9%], p=0.342) and approached but did not reach conventional significance at 6 hours (0/35 [0%] vs. 5/35 [14.3%], p=0.054).

Table 1. Baseline demographic and clinical characteristics of the study population

Variable		Group KD (n=35)	Group KP (n=35)	*p*-value
Male, n (%)		21 (60%)	17 (48.57%)	0.337
Female, n (%)		14(40%)	18 (51.43%)	0.337
Age, mean±SD		43.97±14.93	46.71±12.72	0.411
Tidal volume (mL, mean±SD)		415.71±29.83	417.43±23.81	0.791
RR, mean±SD		14.17±0.89	14±0.69	0.370
PEEP, mean±SD		5.23±0.76	5.17±0.57	0.742
FIO_2, mean±SD		39.86±3.09	39.71±1.18	0.799
SPO_2, mean±SD		99±0.34	98.94±0.24	0.419
Temperature (°F), mean±SD		98.43±0.45	98.55±0.48	0.254
Blood sugar (mg/dL), mean±SD		119.66±19.29	126.83±20.59	0.137
Weight (Kg), mean±SD		68.71±7.99	69.11±8	0.835
Modified RASS score, mean±SD		-0.94±0.24	-1.03±0.17	0.085
Heart rate, mean±SD		96.46±12.46	92.69±12.01	0.202
Systolic BP, mean±SD		119.54±11.67	124.57±10.32	0.060
Diastolic BP		71.63±9.01	74.94±8.86	0.126
Mean arterial Pressure, mean±SD		87.71±9.27	90.89±6.93	0.10
Pain Score, n (%)	0	22 (62.9%)	23 (65.70%)	1.000
	1	5 (14.28%)	4 (11.42%)	-
	2	8 (22.9%)	8 (22.9%)	-
Rescue analgesia, n (%)		8 (22.9 %)	8 (22.9 %)	1.000

RR:Respiratory rate; PEEP: Positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen; SpO_2: Peripheral Oxygen saturation; RASS: Richmond Agitation-Sedation Scale; BP: Blood pressure; MAP: Mean arterial pressure

Table 2. Comparison of rescue analgesia between study groups (n=70)

Rescue analgesia	Ketamine-dexmedetomidine (n=35)	Ketamine-propofol (n=35)	*p*-value
1 Hour	4 (11.4 %)	8 (22.9%)	0.342
6 Hour	0	5 (14.3%)	0.054
12 Hour	0	0	Not applicable
24 Hour	0	0	Not applicable

Table 3. Comparison of pain scores between study groups (n=70)

Time	Pain score	Ketamine-dexmedetomidine (n=35)	Ketamine-propofol (n=35)	*p*-value
1 Hour	0	31 (88.6%)	25 (71.4%)	0.129
	1	0 (0%)	2 (5.7 %)	
	2	4 (11.4%)	8 (22.9%)	
6 Hours	0	34 (97.14%)	27 (77.14 %)	0.018
	1	1 (2.86%)	3 (8.57 %)	
	2	0 (0 %)	5 (14.28 %)	
12 Hours	0	34 (97.14%)	28 (80 %)	0.055
	1	1 (2.86%)	7 (20%)	
24 Hours	0	3 (100%)	3 (100%)	1.000

Table 4. Comparison of Clinical Parameters (n=70)

Parameter	Ketamine-dexmedetomidine (n=35) (mean±SD)	Ketamine-propofol (n=35) (mean±SD)	*p*-value
Duration of ventilation required (hours)	21.18±2.3	23.48±2.55	<0.001
Total duration of infusion	17.97±2.87	18.97±2.98	0.155
Recovery time (T2-T1)	1.98±0.7	2.54±0.44	<0.001
Duration of weaning (T4-T3)	3.03±0.7	4.24±0.91	<0.001

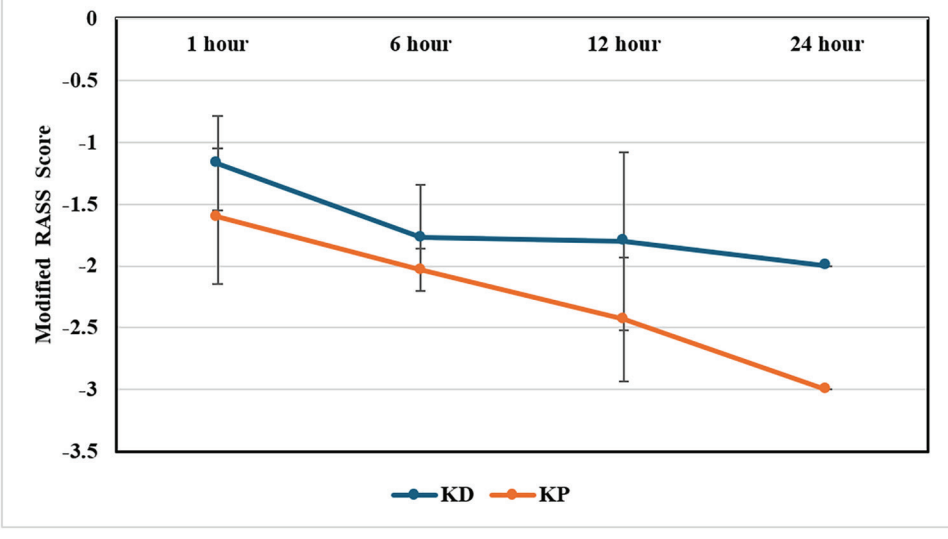


Figure 2. The figure shows the comparison of mean modified Richmond Agitation-Sedation Scale (RASS) scores between the ketamine-dexmedetomidine (KD) and ketamine-propofol (KP) groups at different follow-up time intervals (1, 6, 12, and 24 hours) in postoperative mechanically ventilated patients (n=70). Mean modified RASS scores are presented with error bars representing standard deviation. Both groups demonstrated progressive sedation over the observation period. However, the ketamine-propofol group consistently exhibited lower (more negative) RASS scores than the ketamine-dexmedetomidine group, indicating comparatively deeper sedation at later follow-up intervals. KD: Ketamine-dexmedetomidine; KP: Ketamine-propofol; RASS: Richmond Agitation-Sedation Scale.

No patient in either group required rescue analgesia at 12 or 24 hours (Table 2). The distribution of NVPS categories differed significantly between groups at 6 hours (p=0.018) but not at 1 hour (p=0.129) or at 12 hours (p=0.055) and was identical at 24 hours, when all six remaining patients were pain-free (p=1.000; Table 3). Taken together, these results indicated a consistent directional advantage for KD in early analgesia that attained statistical significance only at the 6-hour assessment. Since the trial was powered for sedation depth rather than for these categorical analgesic endpoints, and no correction was applied for multiple time points, these findings should be interpreted as exploratory and hypothesis-generating.

Clinical recovery parameters were significantly improved in the KD group. The duration of mechanical ventilation was shorter in the KD group than the KP group (21.18±2.3 hours vs. 23.48±2.55 hours, $p<0.001$). Recovery time was also significantly reduced (1.98±0.7 vs. 2.54±0.44 hours, $p<0.001$). Similarly, the duration of weaning from mechanical ventilation was shorter in the KD group than in the KP group (3.03±0.7 hours vs. 4.24±0.91 hours, $p<0.001$). Although the total duration of infusion did not differ significantly between groups (17.97±2.87 vs. 18.97±2.98 hours, $p=0.155$), these benefits likely reflected more favorable pharmacodynamic effects rather than shorter drug exposure (Table 4). Clinically, reductions in ventilation and weaning time are important as they might lower risks associated with prolonged ventilation, enable earlier mobilization and neurological evaluation, and improve ICU resource allocation.

Hemodynamic parameters remained stable and comparable between the two study groups throughout the follow-up period. SpO_2 remained consistently high (≈99%) in both groups at all time points, with no statistically significant differences. Similarly, heart rate values did not differ significantly between the KD and KP groups during the observation period ($p>0.05$). Systolic and diastolic blood pressure measurements were also comparable between groups at all time points, indicating similar cardiovascular responses to both sedation regimens. Mean arterial pressure remained stable and indicated no significant intergroup differences throughout the study (Table S1).

By 24 hours postoperatively, both treatment groups showed comparable analgesia and sedation, with all patients achieving satisfactory pain control and similar sedation levels. Overall, while KP was associated with statistically deeper sedation, KD demonstrated a more advantageous clinical profile characterized by superior early analgesia, a reduced need for additional analgesics, and markedly better recovery and ventilatory outcomes without compromising hemodynamic stability. This finding indicated that within this clinical context, the primary benefits of KD lay more in analgesic efficacy and recovery enhancement rather than in sedation depth alone.

Discussion

Adequate sedation and analgesia are essential components in the management of surgical patients requiring ventilatory support in the ICU. The ideal sedative regimen should ensure optimal patient comfort, facilitate ventilator synchrony, maintain hemodynamic stability, provide adequate analgesia, and allow early recovery to enable timely weaning from mechanical ventilation. In the present study, the efficacy and safety of two ketamine-based sedation regimens (KD and KP) were evaluated in postoperative mechanically ventilated patients. The findings demonstrated that both regimens were effective in achieving satisfactory sedation with acceptable safety profiles, and no adverse effects were observed in either of the regimens. However, notable differences were observed in sedation depth, analgesic efficacy, and recovery characteristics.

The baseline demographic and clinical characteristics were comparable between the two groups, indicating that the study cohorts were well matched and minimizing the likelihood of confounding factors influencing the observed outcomes. Age distribution, sex proportion, ventilatory parameters, baseline hemodynamic variables, and baseline sedation scores did not differ significantly between groups. This comparability strengthened the internal validity of the study and supported the conclusion that the differences observed in clinical outcomes were primarily attributable to the sedation regimens administered.

The comparison of sedation levels revealed that patients receiving the KP combination achieved deeper sedation than those receiving KD. Mean mRASS scores were significantly lower in the KP group at 1, 6, and 12 hours following initiation of sedation. Propofol is a potent sedative-hypnotic agent that enhances inhibitory neurotransmission through γ-aminobutyric acid (GABA) receptor modulation, resulting in rapid onset and profound sedation [11, 20]. This pharmacodynamic profile likely contributed to the deeper sedation observed in the KP group. In contrast, dexmedetomidine produces sedation through selective α2-adrenergic receptor agonism in the locus coeruleus, resulting in a more cooperative and arousable form of sedation [21, 22]. Although the KD regimen produced relatively lighter sedation levels, the achieved sedation scores remained within the clinically acceptable target range for mechanically ventilated ICU patients, suggesting that both regimens were effective in maintaining adequate sedation [23]. The present findings extend those of Mogahd *et al.,* who compared the same two ketamine-based combinations for sedation in post-coronary artery grafting patients [15].

The clinical significance of the observed difference in sedation depth warrants explicit consideration. Although the between-group difference in mean mRASS was statistically significant at 1, 6, and 12 hours, its magnitude of approximately 0.3 to 0.6 points on an ordinal scale spanning +4 to -5 was small. A difference of this size did not move patients between sedation categories, and both groups remained within the light-to-moderate sedation range (mRASS -1 to -3) recommended for mechanically ventilated adults [24]. The clinical significance of such a difference depends entirely on the therapeutic goal. Where deeper sedation is the goal, for example in severe ventilator desynchrony, refractory hypoxemia, or raised intracranial pressure, the greater sedative potency of the KP combination might be advantageous.

Where the target is a calm, arousable, and cooperative patient who can participate in neurological assessment and progress rapidly to weaning, the lighter and more readily reversible sedation produced by KD is the more appropriate target. Therefore, the present findings did not favor any one regimen in particular setting, demonstrating that both regimens provided better sedation in absolute terms, positioning patients at slightly different points within an acceptable sedation range.

Analgesic efficacy favored the KD regimen, although on formal testing, the difference reached statistical significance only at the 6-hour assessment. A consistently higher proportion of patients in the KD group remained pain-free during the first 6 hours of observation compared with the KP group, and this difference was statistically significant at 6 hours while showing the same direction of effect, without reaching significance, at 1 hour and 12 hours. These findings were consistent with the pharmacological characteristics of dexmedetomidine, which exerts intrinsic analgesic and opioid-sparing effects through the modulation of nociceptive transmission within the central nervous system [25]. The synergistic interaction between dexmedetomidine and ketamine likely enhanced analgesic efficacy by combining NMDA receptor antagonism with α2-adrenergic-mediated inhibition of nociceptive signaling [13]. Correspondingly, the requirement for rescue analgesia was numerically lower in the KD group throughout the early postoperative phase, although this difference did not reach statistical significance at either 1 hour or 6 hours. The analgesic advantage of the KD combination should therefore be described as consistent in direction and significant at a single time point, rather than as uniformly established across the observation period, and warrants confirmation in a trial powered specifically for analgesic endpoints.

Hemodynamic stability is a critical consideration when selecting sedative agents for ICU patients. Both sedation regimens demonstrated comparable hemodynamic profiles, with no statistically significant differences in heart rate, systolic blood pressure, diastolic blood pressure, or mean arterial pressure during the observation period. These findings highlighted the relative cardiovascular stability associated with ketamine-based combinations. Ketamine possesses sympathomimetic properties that could offset the hypotensive effects commonly associated with sedative agents such as propofol and dexmedetomidine [3, 26]. As a result, the balanced pharmacodynamic interaction between ketamine and the co-administered sedative likely contributed to the stable hemodynamic parameters observed in both groups.

Similarly, respiratory parameters remained stable throughout the study period. Oxygen saturation values did not differ significantly between the two groups at any follow-up time point. The maintenance of adequate oxygenation indicated that both sedation strategies were safe with respect to respiratory function. Unlike many conventional sedatives, dexmedetomidine has minimal respiratory depressant effects, and ketamine preserves airway reflexes and respiratory drive, which together might explain the favorable respiratory safety profile observed in the present study [8, 27].

An important clinical finding of this study was the difference in recovery characteristics between the two regimens. Patients receiving KD experienced significantly shorter durations of mechanical ventilation, faster recovery times, and shorter weaning periods than those receiving KP. These findings might be explained by the pharmacological properties of dexmedetomidine-induced sedation, which allowed patients to remain easily arousable and cooperative without significant respiratory depression [28, 29]. This facilitates neurological assessment and promotes earlier readiness for ventilator weaning. In contrast, deeper sedation associated with propofol-based regimens might delay awakening and prolong the process of ventilator liberation [30].

The reduced duration of mechanical ventilation and shorter weaning time observed in the KD group have important clinical implications [31]. Prolonged mechanical ventilation is associated with an increased risk of ventilator-associated pneumonia, ICU delirium, and longer ICU stay [24, 32]. Therefore, sedation strategies that facilitate early recovery and rapid ventilator weaning might contribute to improved overall patient outcomes. The results of this study suggested that the KD combination might offer advantages in this regard [3].

Two additional considerations are relevant to the clinical implementation of these findings but were not addressed in the present study. The first is cost. Dexmedetomidine has a substantially higher acquisition cost per unit than propofol. However, no formal cost analysis was performed, given the relatively short sedation periods in this study. Nevertheless, in resource-constrained settings, the additional cost might outweigh the modest recovery benefits observed with dexmedetomidine. The second is delirium. Although dexmedetomidine has been reported to reduce the incidence compared with benzodiazepines [24], demonstrating a similar benefit over propofol remains limited and inconclusive [33]. Delirium was not evaluated in the present study, representing an additional limitation. Future prospective comparisons of these two sedation regimens should therefore incorporate systematic delirium assessment.

Despite the strengths of this study, certain limitations should be acknowledged. The sample size was relatively small, which might limit the external validity of the findings. Additionally, the study was conducted at a single center, and institutional variations in sedation protocols might influence outcomes. The exclusion of patients

requiring neuromuscular blocking agents was methodologically necessary; nonetheless, it also excluded patients with severe respiratory failure or refractory hypoxemia. Therefore, the present findings should not be extrapolated to that population. The use of tramadol as the standardized baseline analgesic introduced pharmacogenetic variability in analgesic response through CYP2D6 polymorphism [34]. The availability of diclofenac as a second-line rescue agent carried recognized renal and cardiovascular risk in critically ill patients, notwithstanding that its use was restricted and that patients with renal impairment or hemodynamic instability were excluded by protocol. The trial was powered for sedation depth and not for the categorical analgesic endpoints, which were analyzed without correction for multiple time points and are therefore exploratory. Only three patients per group remained on sedation at 24 hours. Therefore, the 24-hour observations are descriptive rather than inferential. Sedation-related cost, delirium, long-term neurocognitive outcome, and ICU length of stay were not evaluated and warrant further investigation. Future multi-center randomized studies with larger patient populations and extended follow-up periods would provide more comprehensive evidence regarding the optimal sedation strategy for mechanically ventilated ICU patients.

The findings of this study demonstrated that both KD and KP combinations were effective and safe sedation regimens for postoperative mechanically ventilated patients in the ICU. Notably, the KD regimen was associated with lighter, more arousable sedation, a better early analgesic profile, and more favorable recovery characteristics, along with significantly shorter durations of mechanical ventilation, recovery, and ventilator weaning. However, KP produced statistically deeper, though only modestly deeper, sedation.

Importantly, these benefits were achieved without compromising hemodynamic or respiratory stability, which remained comparable between the two groups. Collectively, these results indicated that the ketamine dexmedetomidine combination might offer a clinically advantageous sedation strategy for the management of postoperative mechanically ventilated ICU patients. The choice between the two regimens should nevertheless be individualized according to the patient characteristics and the clinical goal of sedation. KP might be preferred when deeper sedation is intentionally required, whereas KD might be more appropriate when the priorities are maintaining a calm, arousable state, providing effective early analgesia, and facilitating prompt liberation from mechanical ventilation. Based on the findings of the present study, the search for an optimal sedative combination suitable for all postoperative ICU patients remains ongoing.

Declaration

Ethics Approval and Consent to Participate: This study was approved by the Institutional Ethics Committee (EC/NEW/INST/2022/HR/0189; No.BREC/24/389) and was registered prospectively with the Clinical Trial Registry of India (Registration no.: CTRI/2025/04/085026, date 17th April 2025, accessible at http://ctri.nic.in/). This study was completed without any conflict of interest for 8 months, from May 2025 to December 2025. The procedure was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Declaration of Helsinki (2013 and the International Council for Harmonization Good Clinical Practice (ICH-GCP E6(R2) guidelines [35]. The patient attendants provided written informed consent to participate in the study and allowed the use of their data for research and educational purposes.

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Table 1. Values are presented as mean±standard deviation (SD) for continuous variables and number (percentage) for categorical variables. No statistically significant differences were observed between the ketamine-dexmedetomidine (KD) and ketamine–propofol (KP) groups at baseline ($p>0.05$), indicating comparable pre-intervention characteristics. RR:Respiratory rate; PEEP: Positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen; SpO_2: Peripheral Oxygen saturation; RASS: Richmond Agitation-Sedation Scale; BP: Blood pressure; MAP: Mean arterial pressure

Table 2. Values are presented as numbers (percentages) of patients requiring rescue analgesia at each follow-up time point. Comparisons between the ketamine-dexmedetomidine and ketamine-propofol groups were performed using the Chi square test or Fisher's exact test, as appropriate. Since expected cell counts were small at every time point, two-sided Fisher's exact test was used throughout. Exact p values were 0.342 at 1 hour and 0.054 at 6 hours; no patient in either group required rescue analgesia at 12 or 24 hours; thus, no test was applicable at those time points.

Table 3. Data are presented as numbers (percentages) of patients in each pain score category across follow-up time points. The ketamine-dexmedetomidine group demonstrated a higher proportion of patients with a pain score of 0 during the early postoperative period than the ketamine–propofol group, indicating better analgesic control. Between-group comparisons of the pain score distribution were performed using two-sided Fisher's exact test: $p=0.129$ at 1 hour, $p=0.018$ at 6 hours, $p=0.055$ at 12 hours, and $p=1.000$ at 24 hours. Sample size at 24 hours: n=3 in each group.

Table 4. Values are expressed as mean±standard deviation (SD). Between-group comparisons were performed using independent samples t-tests. The ketamine–dexmedetomidine group demonstrated significantly shorter durations of ventilation, recovery time (T2–T1), and duration of weaning (T4–T3) than the ketamine–propofol group, while the total duration of infusion did not differ significantly. Statistical significance was set at $p<0.05$.

Table S1. Values are expressed as mean±standard deviation for continuous variables and number (percentage) for categorical variables. Comparisons between the ketamine–dexmedetomidine and ketamine-propofol groups were performed at predefined follow-up intervals (1, 6, 12, and 24 hours). $p<0.05$ was considered statistically significant.

Table S2. Values are expressed as mean±standard deviation (SD). Between-group comparisons were performed using independent samples t-tests. Statistical significance was set at $p<0.05$. The t-test could not be computed at 24 h because the standard deviation in both groups was 0. mRASS: Modified Richmond Agitation-Sedation Scale.

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