ORIGINAL RESEARCH

Comparison of Propofol, Midazolam and Dexmedetomidine for sedation in patients under mechanical ventilation in Intensive Care Unit

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Received: 20 June, 2023 Accepted: 24 July, 2023

ABSTRACT

Aim: Dexmedetomidine provides hemodynamic stability and appears to have no clinically important adverse effects on respiration. Its sedative properties are unique in that it produces only mild cognitive impairment, allowing easy communication between health-care provider and patient in the ICU. We therefore compared the sedative and analgesic properties of dexmedetomidine with those of the commonly used I.V., sedative agent propofol and midazolam in the ICU.
Methods: 90 patients enrolled in the study divided into three groups. There are 30 patients allocated in each group. Patients in dexmedetomidine group received a loading dose of dexmedetomidine 0.5 to 1 mcg/kg over 10 minutes followed by a maintenance infusion of 0.1 to 1 mcg/kg/hr. The rate of the maintenance was subsequently titrated to achieve a target Ramsay sedation score that was specified for each patient. Patients in the propofol group received a loading dose of 0.5 to 1mg/kg then an infusion of 25 to 75 mcg/kg/min was adjusted to achieve the target Ramsay sedation score. Patients in midazolam group received an infusion of .012 to .024 mg/kg/hr adjusted to achieve the target Ramsay sedation score.
Results: The use of dexmedetomidine, propofol and midazolam for sedation in patients in the ICU was associated with reduced time to tracheal extubation for dexmedetomidine (7.4±1.85) hrs, for propofol (5.6±1.56) hrs compared to midazolam (16.9 ±15, 62) hrs, P value between dexmedetomidine and propofol group is > 0.05 which is statistically not significant.
Conclusion: Our study conclusively states that dexmedetomidine a new sedative analgesic agent is safe to be used in the ICU. Dexmedetomidine provides hemodynamic stability and have no clinically important adverse effects on respiration. Tracheal extubation was earlier in patients receiving dexmedetomidine and propofol than from midazolam.

Key words: Propofol, Midazolam, Dexmedetomidine, sedation, mechanical ventilation, Intensive Care Unit.

INTRODUCTION

In critically ill patients, pain and anxiety contribute to an already prominent sympathetic stress response that includes increased endogenous catecholamine activity, increased oxygen consumption, tachycardia and immuno suppression. Continuous sedation in the intensive care unit (ICU) is commonly used to control the respiratory rate and anxiety and thus promote sleep. The sedatives used most often include propofol and midazolam. Fulton et al[1] described that propofol possesses unique advantages over midazolam in short-term sedation. These medications provide adequate sedation but also can cause over sedation. Over sedation can lead to prolonged duration of mechanical ventilation, longer ICU and hospital stays, increased incidence of ventilator-associated pneumonia, and inability of patients to communicate with health care providers or family members. Under sedation is also harmful and can lead to anxiety, ventilatordysynchrony, dislodged equipment, delirium, increased oxygen consumption and hyperactivity. For decades, y-aminobutyric acid (GABA) receptor agonists (including propofol and benzodiazepines such as midazolam) have been the

most commonly administered sedative drugs for ICU patients worldwide .[2] Practice guidelines for providing sedation in the ICU have identified the need for well designed trials comparing the effectiveness of different sedative agents for important clinical outcomes.Newman et al[3] described that propofol infusion proved to be a useful and readily controllable sedative agent and discontinuation of the drug is followed by rapid recovery in most cases. The ideal agent should satisfy the physician's desire for an effective, safe, cheap and rapidly acting drug that has both sedative and analgesic properties, and should also prevent anxieties and unpleasant memories for the patient.The alpha2 against Dexmedetomidine is a new sedative and analgesic agent which has been licensed recently in the USA as ICU sedation for up to 24 h after surgery .[4] Dexmedetomidine provides hemodynamic stability and appears to have no clinically important adverse effects on respiration .Its sedative properties are unique in that it produces only mild cognitive impairment, allowing easy communication between healthcare provider and patient in the ICU.[5] We therefore compared the sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics and patient perceptions of Dexmedetomidine with those of the commonly used sedative agent like propofol and midazolam in the ICU.

PRIMARY OBJECTIVES

- To determine the safety and efficacy of new sedative and analgesic agent Dexmedetomidine.
- To determine whether sedation with Dexmedetomidine would lead to shorter time to tracheal extubation and length of stay in ICU than propofol and midazolam.

SECONDARY OBJECTIVES

- To monitor changes in heart rate, blood pressure, mean arterial pressure, SpO2 during and after sedation.
- To find out complications during and after sedation

METHOD

After obtaining written informed consent of the patient's attendant and approval from ethical committee for IEC number: - 767 on 04/06/2021, 90 patients irrespective of their genders were recruited for the study. This randomized open label trial was conducted in the Central ICU of a tertiary care Hospital from January 2021 to December 2022. Assessment as to whether patients would require sedation for short term (<24 hrs.), medium term (>24 to <72 hrs.) or long term >72hr) mechanical ventilation on admission to ICU were done. Patients were stratified by predicted sedation time while receiving mechanical ventilation, randomized and entered into the trial.

Patients of any gender

- Patients >18 yrs. of age
- Patients who require immediate sedation as to permit the initiation and tolerance of mechanical ventilation.

EXCLUSION CRITERIA

- Known or suspected allergy or intolerance to dexmedetomidine, propofol or midazolam.
- Pregnancy.
- Head injury
- Patient currently treated with or been treated with alpha-2 agonist and blockers.
- Status epilepticus.
- Coma due to cerebrovascular accidents or unknown etiology.
- Acute unstable angina.
- Acute myocardial infarction.

Patient enrolled in the study divided into three groups. There are 30 patients allocated for each group.

- Dexmedetomidine group**:** Patient randomized in dexmedetomidine group received a loading dose of 0.5 to 1 mcg/kg over 10 minutes followed by a maintenance infusion of 0.1 to 1 mcg/kg/hr. The rate of the maintenance was subsequently titrated to achieve a target Ramsay sedation score that was specified for each patient response to therapy.
- Propofol group**:** Patients randomized to the propofol group received a loading dose of 0.5 to 1mg/kg then an infusion of 25 to 75 mcg/kg/min was adjusted to achieve the target Ramsay sedation score. As for the propofol group in situations in which rapid control of sedation was required, an infusion bolus could be administered.
- Midazolam group**:** Patients randomized in midazolam group received an infusion of 0.012 to 0.024 mg/kg/hr adjusted to achieve the target Ramsay sedation score. Situations in which rapid control of sedation was required, an infusion bolus could be administered.Only tramadol 1mg/kg was given to patients of all the three groups as analgesic agent.

MEASUREMENT SCALES

The Ramsay sedation score was used to assess the desired degree of sedation, at the regular intervals and adjusted as the patient's condition (i.e., recovery or deterioration) dictated. Patients were maintained at Ramsay sedation score of >2 by adjustments to the sedative regimens MeasurementsThe Ramsay sedation score (target and actual) was recorded hourly for the first 72 hours or up to the time of discharge from ICU if this happened prior to 72 hours.

- Time to tracheal extubation, time to ICU discharge and requirements of reintubation were assessed.
- A record of vital signs was maintained every 20 minute for 40 minutes, then every 6 hour for 48

hours following extubation or until ICU discharge, whichever comes first.
- Decisions as to when a patient was ready for a trial of extubation or for discharge from the ICU were left to the attending intensivists.

Ramsay described Ramsay sedation scale to judge sedation level in critically ill patients.

RAMSAY'S SEDATION SCORE[6]

Awake:1-Anxious and / or agitated,2-Cooperative, oriented and tranquil,3-Response to command

Asleep:1-Quiescent with brisk response to light glabellar tap or Loud auditory stimulus,2-Sluggish response to light glabellar tap or loud auditory stimulus.3-No response.

Complications which occurred as a result of mechanical ventilation, patient's conditions or infusion of sedative agent were recorded in all the three groups.

Primary outcome measures

- The time from withdrawal of sedation until tracheal extubation and ICU discharge for each stratum were taken as the primary outcome measures.
- Data were collected for the duration of the patient ICU stay. ICU Length of stay was recorded as the time from admission to ICU until the patient was discharged.

Secondary outcome measures

- Hemodynamics (Changes in MAP, SBP, DBP, SpO_2, PR and RR) and complications were monitored.

STATISTICAL ANALYSIS

All Statistical analyses were performed using IBM SPSS 21.0 statistical software for this study. Data was expressed as either mean and standard deviation or numbers and percentages. All the data were compared with One way Analysis of Variance (ANOVA).This bar diagram shows the mean time (hours) from cessation of sedation to extubation for dexmedetomidine is 7.4 hours, for propofol is 5.6 hours and for midazolam is 16.9 hours. P-value of dexmedetomidine, propofol and midazolam group is <0.001, which is statistically significant.

RESULTS

There was no statistically significant difference in demographic parameters in any group (P >0.05).

Table-1: Mean Duration from cessation of sedation to extubation

	Dexmedetomidine	Propofol	Midazolam
Mean time(in Hours) from cessation of sedation to extubation	7.4	5.6	16.9

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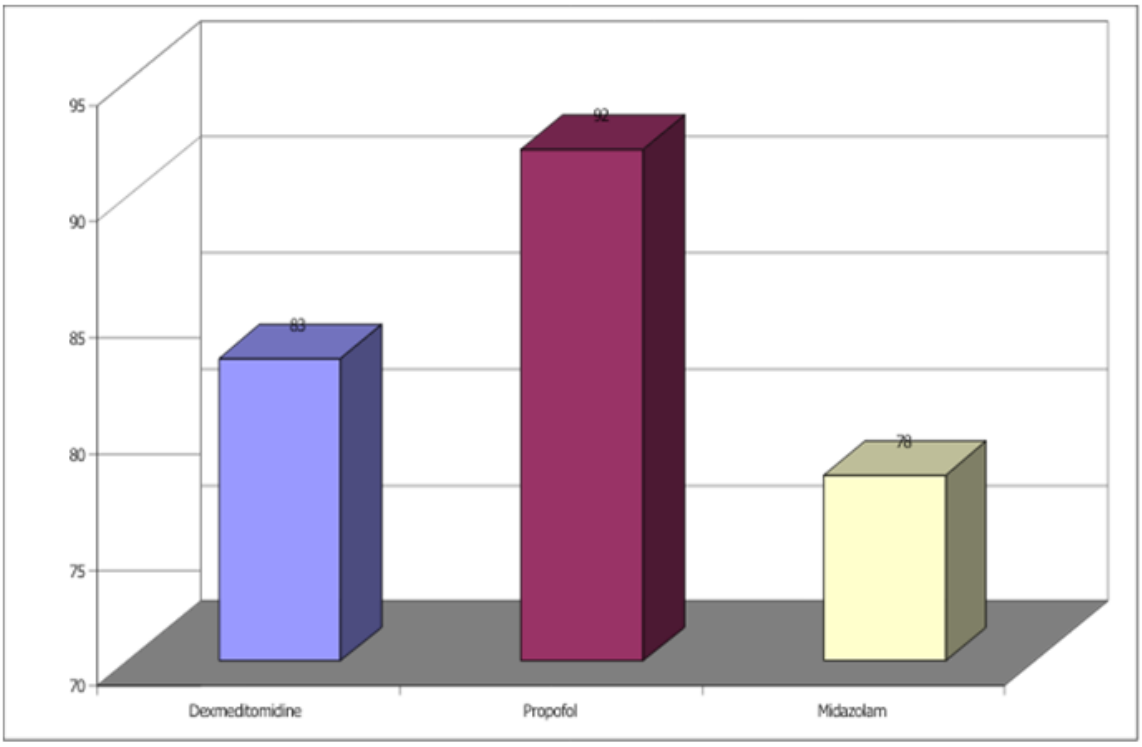
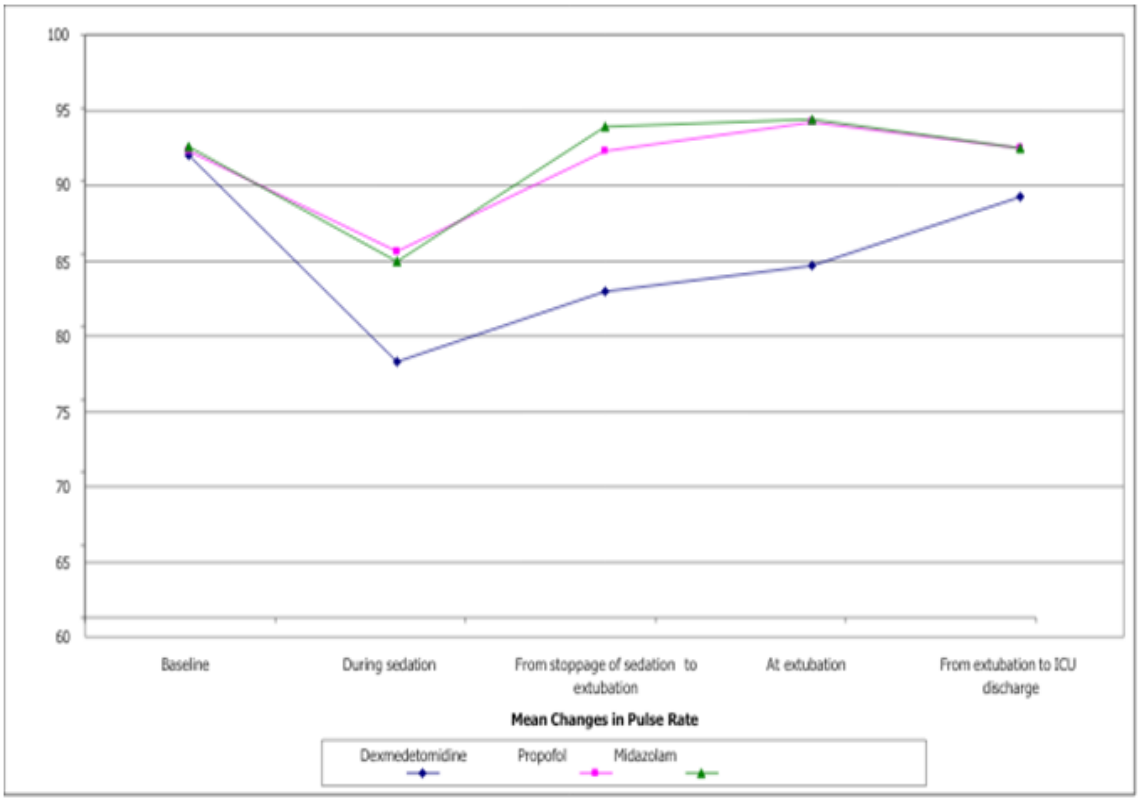
Figure-1: Mean Duration from cessation of sedation to ICU discharge



This bar diagram(figure 1) shows cessation of sedation to ICU discharge for dexmedetomidine its 83 hours for

propofol is 92 hours and for midazolam it is 78 hours. p value calculated by ANOVA test among all the three groups is > 0.05 which is statistically not significant.

Figure 2: Mean Changes in Pulse Rate



P value is calculated by one way analysis of variance (ANOVA). Baseline pulse rate in all three groups in not statistically significant. (P > 0.05).(figure 2)This table 2 shows the mean changes in respiratory rate in all groups. The difference in respiratory rate was not significant at baseline, during sedation, from stoppage of sedation to extubation and extubation to ICU discharge. Difference among the groups calculated by ANOVA test is not statistically significant (p>0.05).

Table-2: Mean Changes in Respiratory Rate (Breaths/Min)

	Baseline	During sedation	From stoppage of sedation to extubation	At extubation	From extubation to ICU discharge
Dexmedetomidine	18.83	13.93	14.5	14.46	14.6
SD	1.36	0.78	0.5	0.5	0.56
Propofol	18.46	14	14.56	14.5	14.5
SD	2.36	0.83	0.5	0.5	0.50
Midazolam	18.56	13.93	14.53	14.56	14.53
SD	1.04	0.78	0.5	0.5	0.50
P value	>0.05	>0.05	>0.05	>0.05	>0.05

Figure 3 shows mean changes in mean blood pressure in all the three groups. At all times difference in mean blood pressure among all the three groups calculated by ANOVA test is not statistically significant (P > 0.05).

Figure 3: Mean Changes in Mean Blood Pressure

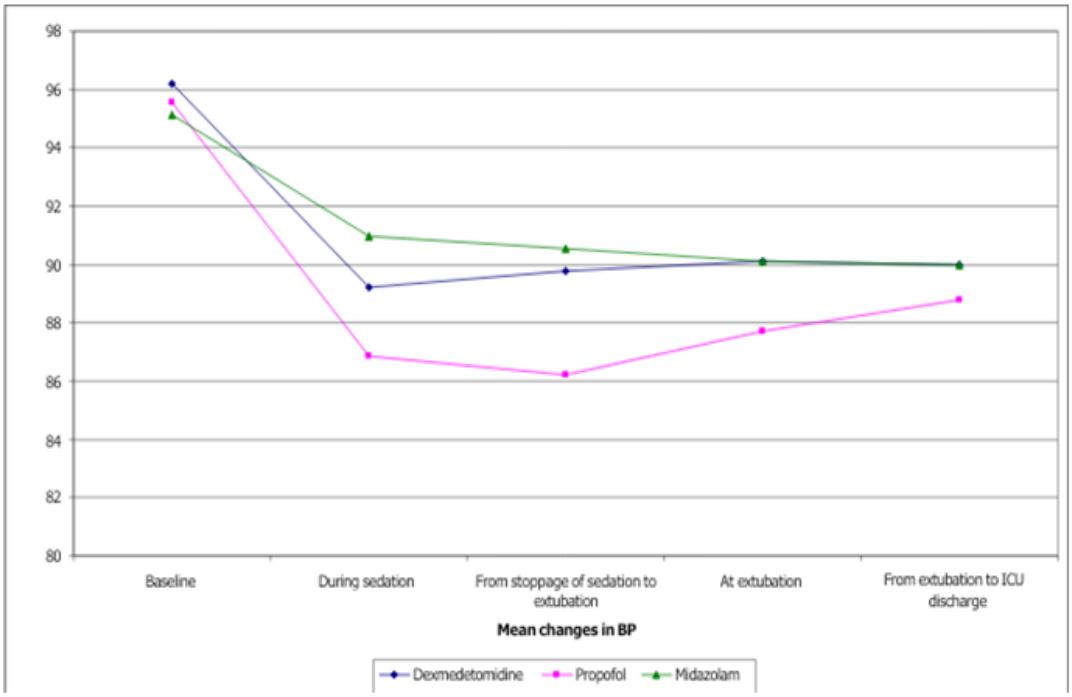


Table3: Major Complications (in %)

	Dexmedetomedine	Propofol	Midazolam
Chest Complications (Nosocomial Pneumonia, Barotraumas)	18	25.4	21
Ventricular Tachycardia	0	6.89	0
Bradycardia	7.5	0	0
Intravenous Line Sepsis	7.3	11.2	8.9
Prolonged Sedation	0	3.11	11.34
Hypotension	6.4	14.22	5

Table3 shows complications in all groups

DISCUSSION

This study was considered to assess the efficacy of a new drug dexmedetomidine with propofol and midazolam, established i.v sedative agent regularly used in ICU in terms of changes in vitals, duration of extubation ICU discharge and complications. The α2 agonist dexmedetomidine is a new sedative and analgesic agent which has been licensed recently in the USA as ICU sedation for up to 24 h after surgery. Dexmedetomidine provides hemodynamic stability and appears to have no clinically important adverse effects on respiration. Its sedative properties are unique in that it produces only mild cognitive impairment, allowing easy communication between health- care provider and patient in the ICU. We therefore compared the sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics, and patient perceptions of dexmedetomidine with those of the commonly used i.v. sedative agent propofol and midazolam in the ICU. Study done by Anger KE, et al[6] concluded that management of pain and sedation therapy is a vital component of optimizing patient outcomes; We sought to evaluate efficacy and safety outcomes between postoperative mechanically ventilated cardiac surgery patients receiving dexmedetomidine versus propofol therapy upon arrival to the intensive care unit (ICU). No differences in the ICU length of stay and duration of mechanical ventilation were seen between the propofol and dexmedetomidine groups, respectively. Reichert et al [7] concluded that no statistically significant differences were noted between the propofol and dexmedetomidine groups when assessing the outcomes of opioid requirements and the time to extubation. Christopher G. et al [8] concluded that among mechanically ventilated adults with sepsis who were being treated with recommended light-sedation approaches outcome in patients who received dexmedetomidine didn't differ from outcomes in those who received propofol. Above mentioned studies shows that no significant difference in the time to extubation after stoppage of sedation as this is also the finding of my study that there was no significant difference in the time to extubation. Richard et al [9] also support my outcome. In their study they found that the mean time from reduction of sedation to tracheal ex-tubation was shorter for propofol -treated

patients than for midazolam-treated patients (midazolam, 24.7 h [95% CI 14.5 to 35.0]; propofol 647 h [95% CI, 4.2 to 9.1) but not the time to ICU discharge (midazolam, 63.7 h [44.3 to 83.0]; propofol, 94.0 h [44.0 to 143.9]. Carrascoet al[10] concluded that propofol and midazolam were considered safe with respect to the induction of adverse reactions during their use in prolonged sedation. Recovery after interrupting sedation was significantly faster in patients treated with propofol than in those sedated with midazolam ($p < 0.05$). This study also supports my outcome that recovery of sedation and extubation is faster with propofol sedation than with midazolam. Weinbroum et al [11] resumption of spontaneous respiration was equally rapid. Recovery was faster after propofol ($P<0.02$), albeit with a higher degree of agitation. Amnesia was evident in all midazolam patients but in only a third of propofol patients. Both drugs afforded reliable, safe, and controllable long-term sedation in ICU patients and rapid weaning from mechanical ventilation. Midazolam depressed respiration, allowed better maintenance of sedation, and yielded complete amnesia at a lower cost, while propofol caused more cardiovascular depression during induction. Barrientos-Vega et al[12] in critically ill patients sedated with midazolam or propofol over prolonged periods, midazolam and propofol were equally effective as sedative agents. However, despite remarkable differences in the cost of sedation with these two agents, the economic profile is more favorable for propofol than for midazolam due to a shorter weaning time associated with propofol administration. Corbett et al [13] concluded that significant reduction in cost is associated with propofol use related to Intensive care unit stay and duration of mechanical ventilation for critically ill adult patients as compared to midazolam. So above studies dearly shows that propofol leads to earlier extubation than with midazolam which my study also supports.During sedation with dexmedetomidine, propofol and midazolam p value is <0.001 which is highly significant.So, it's clearly showed in my study that dexmedetomidine infusion leads to reduction in heart rate during sedation an it is statistically significant when compared with propofol and midazolam. Hemali et al[14] concluded that difference of mean hemodynamic parameters at different time interval in three drugs was not statistically significant. The heart rate of patients at 45 minutes interval remains lower in dexmedetomidine group as compared to propofol and midazolam group. Hoy SM et al[15] concluded that intravenous dexmedetomidine is generally well tolerated when utilized in mechanically ventilated patients in an intensive care setting and for procedural sedation in non-intubated patients. While dexmedetomidine is associated with hypotension and, bradycardia, both usually resolve without intervention.All of the above studies showing that dexmedetomidine infusion leads to reduction is heart rate which is in accordance to my study which also shows that patients receiving dexmedetomidine infusion having lower heart rates.The mean SpO_2 in all the three groups during sedation, from cessation of sedation to extubation at extubation and from extubation to ICU discharge, were comparable in dexmedetomidine, propofol and midazolam groups and there was statistically significant difference found, ($p> 0.05$).An-Min Hu, Xiong-Xiong Zhong et al [16] concluded that patients treated with dexmedetomidine had a reduced risk of mortality and it is preferred sedative in patients with or at risk for ARDS.

CONCLUSION

Dexmedetomidine provided satisfactory sedation in ICU. The mean time from cessation of sedation to tracheal extubation was shorter for dexmedetomidine and propofol treated patients than from midazolam treated patients.There was no significant difference in time to ICU discharge in all the three groups.

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