Original Research Article

# A comparative study of dexmedetomidine propofol and midazolam with respect to changes in mean arterial pressure and $SpO_2$ after sedation at tertiary health care centre

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## Abstract

**Background:** Sedation is an important component of compassionate care in ICU patients to promote rest and sleep. The sedatives used most often include propofol and midazolam. These medications provide adequate sedation but also can cause oversedation. The α2 agonist dexmedetomidine have unique sedative properties 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, cardiovascular responses, ventilation and extubation characteristics, and patient perceptions of dexmedetomidine with those of the commonly used i.v. sedative agent propofol in the ICU. **Material and Methods:** Present study was a randomized. open label trial conducted in the ICU ppatients >18 years of age, who required immediate sedation as to permit the initiation and tolerance of mechanical ventilation. 30 patients each were randomly allocated to dexmedetomidine, propofol & midazolam group. **Results:** Male predominance was noted, in all groups (dexmedetomidine, propofol & midazolam), M:F ratio was 1.3 : 1. According to age distribution most common age group in dexmedetomidine, propofol & midazolam group was 31-45 years (40 %). At all times the difference in systolic blood pressure, diastolic blood pressure, $SpO_2$, mean arterial blood pressure among all the three groups calculated by ANOVA test was not statistically significant (P>0.05). 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. **Conclusion:** Dexmedetomidine provides hemodynamic stability and have no clinically important adverse effects on respiration in terms of mean $SpO_2$. Tracheal extubation was earlier in patients receiving dexmedetomidine and propofol than from midazolam.

**Keywords:** dexmedetomidine, propofol, midazolam, sedation, ICU patients.

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## INTRODUCTION

Patients admitted in intensive care units are exposed to a variety of noxious stimuli including pain after surgery, frequent venipuncture, and discomfort from the presence of an endotracheal tube. Sedation is an important component of compassionate care in these patients to promote rest and sleep.[1] Continuous sedation in the intensive care unit (ICU) is commonly used to control respiratory rate and anxiety and thus promote sleep and ultimately optimize care. Other goals of adequate sedation include optimizing safety for patients and caregivers, facilitating mechanical ventilation, reducing anxiety and delirium, inducing sleep, and, ultimately, providing

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comfort and safety.[2] The sedatives used most often include propofol and midazolam. These medications provide adequate sedation but also can cause oversedation. Oversedation 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.[3] Inadequate sedative techniques may adversely affect morbidity and even mortality in the intensive care unit (ICU), and the search for the ideal sedative agent continues. The ideal agent should satisfy the physician's desire for an effective, safe, titratable, cheap and rapidly acting drug that has both sedative and analgesic properties, and should also prevent anxieties and unpleasant memories for the patient.[4] The α2 agonist dexmedetomidine is a new sedative and analgesic agent which provides haemodynamic 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.[5] We therefore compared the sedative and analgesic properties, cardiovascular responses, ventilation and extubation characteristics, and patient perceptions of dexmedetomidine with those of the commonly used i.v. sedative agent propofol in the ICU.

## MATERIAL AND METHODS

Present study was a randomized. open label trial conducted in the ICU in Basaveshwar Teaching and General Hospital, Kalaburagi. Study duration was of 6 months. After approval from ethical committee and written informed consent of the patient, 90 patients were recruited for the study.

### Inclusion criteria

Patients >18 years of age, who required immediate sedation as to permit the initiation and tolerance of mechanical ventilation.

### Exclusion criteria

Known or suspected allergy or intolerance to dexmeditomedine, propofol or midazolam. Pregnancy, head injury, 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.

Assessment as to whether patients would require sedation for short term (<24 hr), medium term (>24 to <72 hr) or long term (>72hr) mechanical ventilation on admission to ICU was done. Patients stratified by predicted sedation time while receiving mechanical ventilation, were randomized and were entered into trial. Patient enrolled in the study were divided into three groups. There are 30 patients allocated for each group.

**GROUP 1:** Patient randomized 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 for each patient response to therapy.

**GROUP 2:** 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.

**GROUP 3:** 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.

The Ramsay sedation score was used to quantitate the desired degree of sedation, specified at the regular intervals and adjusted as the patient's condition (i.e. recovery or deterioration) dictated. 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. Complications which occurred as a result of patient's conditions, mechanical ventilation or infusion of sedative agent were recorded in all the three groups. All statistical analyses were performed using INSTAT for windows. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. 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).

## RESULTS

30 patients each were randomly allocated to dexmedetomidine, propofol and midazolam group. Male predominance was noted, in all groups (dexmedetomidine, propofol and midazolam). M:F Ration for Dexmedetomidine was 1.3 : 1, M : F ratio for propofol was 1.5: 1 and M: F ratio for midazolam was 1.4: 1. Total M:F ratio was 1.3 : 1. According to age distribution most common age group in dexmedetomidine, propofol and midazolam group was 31-45 years (40 %), 18-30 years (40 %) and 46-60 years (36 %) respectively. Mean ± SD in age group in dexmedetomidine, propofol and midazolam group was 37.03 ± 12.75 years, 36.7 ± 12.18 years and 37.9 ± 12.48 years respectively.

**Table 1:** Age Distribution

| Characteristic | Dexmedetomidine | | Propofol | | Midazolam | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| Male | 17 | 56 | 18 | 60 | 16 | 54 |
| Female | 13 | 44 | 12 | 40 | 14 | 46 |
| Age (Mean ± SD) (yrs) | 37.03 ± 12.75 | | 36.7 ± 12.18 | | 37.9 ± 12.48 | |

P value is calculated by one way analysis of variance (ANOVA). in all three groups in not statistically significant. (P > 0.05). At all times the difference is systolic blood pressure among all the three groups calculated by ANOVA test is not statistically significant (P > 0.05).

**Table 2:** Mean Changes in Systolic Blood Pressure

| Drugs | Baseline | During sedation | From stoppage of sedation to extubation | At extubation | From extubation to ICU discharge |
|---|---|---|---|---|---|
| Dexmedetomidine (Mean ± SD) | 132.7 ± 11.1 | 121.6 ± 8.61 | 125.8 ± 8.88 | 126.9 ± 9.47 | 119.8 ± 9.5 |
| Propofol (Mean ± SD) | 134.8 ± 11.5 | 118.8 ± 10.1 | 127.4 ± 10.09 | 128.2 ± 10.10 | 121.4 ± 9.26 |
| Midazolam (Mean ± SD) | 134.3 ± 15.2 | 123.6 ± 8.79 | 126.9 ± 9.74 | 128.4 ± 8.78 | 122.9 ± 9.17 |
| P value | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

At all times the difference is diastolic blood pressure among all the three groups calculated by ANOVA test is not statistically significant (P > 0.05).

**Table 3:** Mean Changes in Diastolic Blood Pressure

| | Baseline | During sedation | From stoppage of sedation to extubation | At extubation | From extubation to ICU discharge |
|---|---|---|---|---|---|
| Dexmedetomidine (Mean ± SD) | 77.87 ± 8.40 | 73.56 ± 7.40 | 74.89 ± 7.26 | 74.23 ± 6.96 | 76.22 ± 6.01 |
| Propofol (Mean ± SD) | 76.32 ± 7.56 | 70.75 ± 7.56 | 74.98 ± 6.47 | 73.23 ± 7.14 | 75.04 ± 6.90 |
| Midazolam (Mean ± SD) | 75.98 ± 8.03 | 73.99 ± 7.48 | 74.67 ± 6.95 | 75.33 ± 7.36 | 74.44 ± 6.09 |
| P value | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

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

**Table 4:** Mean Changes in Mean Blood Pressure

| Drugs | Baseline | During sedation | From stoppage of sedation to extubation | At extubation | From extubation to ICU discharge |
|---|---|---|---|---|---|
| Dexmedetomidine (Mean ± SD) | 96.21 ± 5.98 | 89.23 ± 6.11 | 89.78 ± 6.07 | 90.11 ± 7.46 | 89.98 ± 4.69 |
| Propofol (Mean ± SD) | 95.56 ± 6.85 | 86.86 ± 5.48 | 86.21 ± 4.38 | 87.73 ± 5.27 | 88.78 ± 5.69 |
| Midazolam (Mean ± SD) | 95.11 ± 7.91 | 90.99 ± 6.49 | 90.54 ± 6.17 | 90.11 ± 6.11 | 89.99 ± 5.42 |
| P value | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

At all times the difference in $SPO_2$, blood pressure among all the three groups calculated by ANOVA test is not statistically significant (P>0.05).

**Table 5:** Mean Changes in $SpO_2$

| Drugs | Baseline | During sedation | From stoppage of sedation to extubation | At extubation | From extubation to ICU discharge |
|---|---|---|---|---|---|
| Dexmedetomidine (Mean ± SD) | 98.33 ± 0.95 | 98.78 ± 0.68 | 98.21 ± 0.71 | 98.99 ± 0.64 | 98.11 ± 0.63 |
| Propofol (Mean ± SD) | 97.6 ± 1.08 | 98.21 ± 0.58 | 98.34 ± 0.66 | 98.22 ± 0.63 | 98.1 ± 0.63 |
| Midazolam (Mean ± SD) | 96.99 ± 0.93 | 97.1 ± 0.62 | 98.34 ± 0.63 | 98.21 ± 0.60 | 98.85 ± 0.66 |
| P value | >0.05 | >0.05 | >0.05 | >0.05 | >0.05 |

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. 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.

## DISCUSSION

The ideal sedative possesses a rapid onset of action, is convenient to administer and titrate, produces effective and reproducible sedation to the desired clinical goal and is free of hemodynamic, cardiac and respiratory side effects. The benzodiazepines used alone have modest hemodynamic effects. The predominant hemodynamic change is a slight reduction in arterial blood pressure, resulting from a decrease in systemic vascular resistance. The mechanism by which benzodiazepines maintain relatively stable hemodyamics involves the preservation of homeostatic reflex mechanisms, but there is evidence that the baroreflex is impaired by midazolam and diazepam. Midazolam causes a slightly larger decrease in arterial blood pressure than the other benzodiazepines, but the hypotensive effect is minimal and about the same as seen with thiopental.[3] Dexmedetomidine has been used in the intensive care for its sedative, anxiolytic, ad analgesic properties and does not produce respiratory depression due to its non-opioid mechanism of analgesia. Even at slower infusion rates, the increase in mean arterial pressure over the first 10 minutes was shown to be in the range of 7%, with a decrease in heart rate between 16% and 18%.[6] The mean arterial pressure and 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, ($p > 0.05$). Takrouri MS *et al.*,[7] concluded dexmedetomidine had sparing effect on the use of analgesics. The sedation quality is unique in that the patient is easily arousable. Bradycardia was observed in one patient who was treated effectively by stopping the infusion. Dexmedetomidine is useful sedative agent with analgesic properties which reduce the analgesic requirement of the patient. Kunisawa T[8] noted that dexmedetomidine undoubtedly is a useful sedative in the intensive care setting because it has a minimal effect on the respiratory system. Dexmedetomidine was administered at varying doses (0.1 – 2.5 μg/kg/hour) and durations up to 30 days. Dexmedetomidine seems to be an alternative to benzodiazepines or propofol for achieving sedation in adults because the incidences of delirium and coma associated with dexmedetomidine are lower than the corresponding incidences associated with benzodiazepines and propofol, although dexmedetomidine administration can cause mild adverse effects such as bradycardia. Reichert MG *et al.*,[9] compared dexmedetomidine and propofol as a sedative agent and noted no statistically significant differences were noted between the propofol and dexmedetomidine groups when assessing the outcomes of opioid requirements and the time to extubation. Generally, at propofol infusion rates greater than 30 μg/kg/mm, patients are amnesic.[10] Compared with midazolam when used to maintain sedation, propofol provides equal or better control and more rapid recovery. In mechanically ventilated patients, more rapid recovery translates to more rapid extubation when sedation is terminated. Propofol also has been used successfully in patient-controlled sedation. Propofol was rated better than midazolam when used by this technique, probably owing to its much more rapid onset and offset.[11] In present study during the sedation with dexmedetomidine, propofol and midazolam there was no significant effect on respiratory rate was noted ($p > 0.05$). Hoy SM *et al.*,[12] 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. It is not associated with respiratory depression. Arterial pressures were reduced in dexmedetomidine, propofol and midazolam sedation. The difference in arterial pressure between all the three groups during sedation was found to be statistically not significant ($p > 0.05$). Esko R. *et al.*[13] noted that propofol alone decreased mean arterial pressure and cardiac index; heart rate was increased. Myocardial blood flow and myocardial oxygen consumption were decreased by 26% and 31%, respectively. These result are in accordance with present study, where arterial pressure reduced during propofol sedation. Atkenhead AR *et al.*,[14] compared midazolam and propofol, they concluded that desired level of sedation was achieved easily in most patients in both groups. There were slight fails in arterial pressure, but there were no significant differences between the groups. Heart rate was lower in patients who received propofol. Ebert TJ, *et al.*[16] concluded that dexmedetomidine decreased catecholamines 45-76% and eliminated the norepinephrine increase. Catecholamine suppression persisted in subsequent infusions. The first two doses of dexmedetomidine increased sedation 38 and 65%, and lowered mean arterial pressure by 13%, but did not change central venous pressure or pulmonary artery pressure. Hogue CW Jr, *et al.*[17] concluded that plasma norepinephrine concentrations, blood pressure, heart rate, and some heart rate variability measures were lower after 1-hr infusion of dexmedetomidine. Thus the above mentioned studies shows that there is fall in blood pressure with dexmedetomidine, propofol and midazolam which is in accordance to present study.

## CONCLUSION

Thus 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 in terms of mean $SpO_2$. Tracheal extubation

was earlier in patients receiving dexmedetomidine and propofol than from midazolam.

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