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Dr. Mohammed Ali
Assistant Professor, Department of Anaesthesiology, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Correspondence
Dr. Mohammed Ali
Assistant Professor, Department of Anaesthesiology, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

A Study On comparison of dexmedetomidine, Propofol and Midazolam for Sedation in Surgical Icu

Dr. Mohammed Ali

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Abstract
Introduction: This study compares the efficiency of dexmedetomidine for the sedation of patients admitted to surgical intensive care unit (ICU) with propofol and midazolam in respect to tracheal extubation and length of stay in ICU. And to study changes in heart rate, mean arterial pressure, SpO_2 during and after sedation.
Methodology: 60 patients randomized into 3 groups of 20 to receive either dexmedetomidine, propofol or midazolam drug. The dexmedetomidine group loading dose was 0.5 to 1 µg/kg over 10 minutes, followed by maintenance infusion at 0.1 to 1 µg/kg/hr. The propofol group received a loading dose of 0.5 to 1 mg/kg followed by an infusion of 25 to 75 mcg/kg/min. The midazolam group received an infusion of 0.012 to 0.024 mg/kg/hr. Respiratory rate, heart rate, blood pressure, Ramsay sedation score, tramadol need, saturation, time to extubation, duration in ICU were monitored and recorded all through the ICU stay.
Results: Hypotension occurred in 6.4% patients in dexmedetomidine group, 14.22% in propofol group and 5% in midazolam group. Bradycardia occurred in 7.5% patients receiving dexmedetomidine at the time of loading of drug. During sedation mean pulse rate in dexmedetomidine group was 77.54±9.34, in propofol group 89.34±10.1 and for midazolam group 90.23±10.7. Time to tracheal extubation was less for dexmedetomidine group (7.4±1.85 hrs) and for propofol (5.6±1.56 hrs) compared to midazolam (16.9±15.62 hrs).
Conclusion: Dexmedetomidine is a satisfactory agent for sedation in ICU. Dexmedetomidine provides hemodynamic stability and have no clinically important adverse effects on respiration. The mean time from cessation of sedation to tracheal extubation was shorter for dexmedetomidine and propofol treated patients than from midazolam treated patients.

Keywords: Anaesthesia; Dexmedetomidine, Propofol; Midazolam; SBP; DBP; Heart rate; Respiratory rate; SpO_2; Time to tracheal extubation

Introduction
Patients admitted to the surgical Intensive Care Unit (ICU) are usually in need of invasive and uncomfortable interventions such as mechanical ventilation. To reduce anxiety, increase tolerance, and improve outcomes of such interventions, sedation is common practice [1] Conventionally, sedative agents administered in the ICU are gamma-aminobutyric receptor agonists which include the benzodiazepines (usually midazolam) and propofol. Optimum sedation is vital in striking a balance between providing pain relief and maintaining patient calm while preventing over-sedation and unnecessarily lengthy ICU stays [2]. Many protocols advise daily sedation interruptions to assess the level of sedative in the patient and to avoid over-sedation. Due to limitation of subjective sedation scales to assess ICU sedation, over-sedation and under sedation are the major challenges in the ICU management.
The sedatives used most often include propofol and midazolam. 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 [3]. Under sedation is also harmful and can lead to anxiety, ventilator dysynchrony, dislodged equipment, delirium, increased oxygen consumption and hyperactivity. Making the distinction between too much sedation and not enough sedation can sometimes be difficult when propofol and midazolam is used [4].
Commonly used agents include benzodiazepines, propofol, short acting opioids like remifentanil and dexmedetomidine. Although opioids are useful for treatment of postoperative pain, they alone cannot be appropriate for treatment of postoperative pain,

They alone cannot be appropriate for sedation for postoperative mechanically ventilated patients [3]. Dexmedetomidine an α-2 adrenoceptor agonist capable of producing sedation, anxiolysis and analgesia without respiratory depression. These properties make it potentially useful for short duration postoperative ventilation like; neurosurgical patients requiring delayed extubation [4].

This study was undertaken to compare 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 in the ICU like propofol and midazolam.

Aims and 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.
- Changes in heart rate, blood pressure, mean arterial pressure, SpO_2 during and after sedation.
- Complications during and after sedation.

Materials and Methods

Trial Design

After approval from ethical committee and written informed consent from the patients, 60 patients of both gender were recruited for the study. This study was a randomized prospective trial conducted in the surgical ICU of Shadan Institute of Medical Sciences. The ICU has 24-hour coverage by resident house staff. Assessment as to whether patients would require sedation for short term (<24 hrs.), medium term (>24 to <72 hrs.) or long term >72 hrs.) 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.

Eligibility Criteria Inclusion criteria

- Patients of either gender.
- Patients >18 yrs. of age.
- Patients who require immediate sedations so 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.
- Patient currently treated with or been treated with alpha-2 agonist or antagonist.
- Status epilepticus.
- Coma due to cerebrovascular accidents or unknown etiology.
- Acute unstable angina.
- Acute myocardial infarction.

Material used

- Injection dexmedetomidine
- Injection propofol
- Injection midazolam

Method

Patient enrolled in the study were divided into three groups and 20 patients were 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.

Group 2: Patients randomized to the propofol group received a loading dose of 0.5 to 1 mg/kg then an infusion of 25 to 75 mcg/kg/min was adjusted to achieve the target Ramsay sedation score.

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.

Measurement Scales

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. Patients were maintained at Ramsay sedation score of >2 by adjustments to the sedative regimens.

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

Ramsay sedation score

Awake

- Anxious and / or agitated.
- Cooperative, oriented and tranquil.
- Response to command only.

Asleep

- Quiescent with brisk response to light glabellar tap or Loud auditory stimulus.
- Sluggish response to light glabellar tap or loud auditory stimulus.
- No response to stimulus.

Measurements

The 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 occurred prior to 72 hours. After 72 hours, it was recorded as the patient's condition or infusion rate was altered. Time to tracheal extubation, time to ICU discharge and requirements of reintubation were recorded. A record of vital signs was maintained every 20 minute for first 24 hours, then every 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 intensivist. Complications which occurred as a result of patient's conditions, mechanical ventilation 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 was taken as the primary outcome measures. The situations in which patients required multiple independent periods of sedation or reintubation due to alterations in their disease processes, the first period of sedation accompanied by tracheal extubation was utilized for data collection surrounding this event. 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.

Statistical analysis

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

Table 1: Age Distribution

Age (yrs)	Dexmedetomidine		Propofol		Midazolam	
	No	%	No	%	No	%
18-30	5	25	8	40	7	35
31-45	9	45	6	30	8	40
46-60	6	30	6	30	5	35
Mean	37.03		36.7		37.9	
SD	12.75		12.18		12.48	

This table shows distribution of patients according to age in all groups. The mean and standard deviation of age in all groups have been demonstrated.

- There was no statistically significant difference in age distribution in any group (P >0.05).

Table 2: Sex Distribution

Sex	Dexmedetomidine		Propofol		Midazolam	
	No	%	No	%	No	%
Male	12	60	9	45	08	40
Female	8	40	11	55	12	60
Total	20		20		20	

This table shows sex distribution of patients in all the groups.

- There was no significant difference in sex distribution in any group (P > 0.05).

Table 3: Weight Distribution

Weight (kg)	Dexmedetomidine		Propofol		Midazolam	
	No	%	No	%	No	%
35-54	5	25	5	25	8	40
55-74	10	50	9	45	6	30
75-95	5	25	6	30	6	30
Mean	64.56		64.3		62.2	
SD	13.02		15.7		14.11	
Total	20		20		20	

This table shows distribution of patients according to weight in all age groups.
The mean & SD of weight in all age groups have been demonstrated.

- There was no significant difference in weight distribution in any age group (P > 0.05).

Table 4: Mean Changes in Heart Rate

	Baseline	During sedation	From stoppage of sedation to extubation	At extubation	From extubation to ICU discharge
Dexmedetomidine	90.00	76.26	82	83.5	88.20
SD	3.5	4.87	2.76	2.37	0.65
Propofol	91.26	84.76	93.33	95.33	93.39
SD	4.55	4.02	1.74	1.47	.84
Midazolam	93.6	83.93	92.86	93.4	91.45
SD	3.64	2.21	1.81	1.32	0.85
P value	>0.05	<0.0001	<0.0001	<0.0001	>0.05

This table shows the Mean change in Heart Rate and SD during various events compared to the baseline Heart 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).
- During sedation: p value during sedation is < 0.001 means statistically significant difference is present among the groups
- From stoppage of sedation of extubation: p value is < 0.001 means statistically significant difference is present among the groups.
- At extubation: p value is < 0.001 means statistically significant difference is present among the groups.
- From extubation to ICU discharge: p value is > 0.05 means there is no significant difference present among the groups.

Table 5: Mean Changes in Respiratory Rate

	Baseline	During sedation	From stoppage of sedation to extubation	At extubation	From extubation to ICU discharge
Dexmedetomidine	17.83	12.93	13.5	14.36	14.6
SD	1.36	0.78	0.5	0.5	0.56
Propofol	17.46	14	13.56	14.5	14.5
SD	2.36	0.83	0.5	0.5	0.50
Midazolam	17.56	12.93	13.53	14.46	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

This table shows the mean changes in respiratory rate and SD during various events compared to the baseline in all groups

- Difference among the groups calculated by ANOVA test is not statistically significant (p>0.05).

Table 6: Mean Changes in Systolic Blood Pressure

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

This is table shows the mean changes in systolic blood pressure in dexmedetomidine, propofol and midazolam group.

- 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 7: Mean Changes in Diastolic Blood Pressure

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

This table shows mean changes in diastolic blood pressure in dexmedetomidine, propofol and midazolam group.

- 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 8: Mean Changes in Mean Blood Pressure

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

This table 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).

Table 9: Mean Changes in SpO_2

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

This table shows mean changes in SPO_2 dexmedetomidine, propofol and midazolam group.

- At all times the difference in SpO_2 among all the three groups calculated by ANOVA test is not statistically significant (P>0.05).
- ❖ Mean time (h) from cessation of sedation to extubation for dexmedetomidine is 7.4 h, for propofol is 5.6 h and for midazolam is 16.9 h. P value of dexmedetomidine, propofol, and midazolam group is <0.001, which is statistically significant.
- ❖ Mean time (h) from cessation of sedation to ICU discharge for dexmedetomidine its 83 h for propofol is

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

Discussion

The alpha-2 agonist dexmedetomidine is a new sedative and analgesic agent which has been licensed recently as ICU sedation for up to 24 hrs 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 [5-6].

This study was considered to assess the efficacy of a new drug dexmedetomidine with established i.v. sedative agents (i.e. propofol and midazolam) regularly used in ICU in terms of changes in vitals, time to extubation, ICU discharge and complications.

The patients in this study were of gynaecological and obstetrical cases, emergency laparotomy cases, trauma cases and post-operative routine cases.

The groups were studied and compared with respect to

- Duration of sedation / ICU length of stay.
- Changes in cardiovascular and respiratory status.
- Any complications.

On analyzing the demographic data, the three groups were statistically comparable with respect to age, sex and weight.

In this trail, 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) compared to midazolam (16.9±15.62) hrs. P value between dexmedetomidine and propofol group is > 0.05 which is statistically not significant. P value between dexmedetomidine and midazolam group is <0.001 which is highly significant. P value between propofol and midazolam group is <0.00l which is patients on dexmedetomidine and propofol having shorter extubation times than with the midazolam. Study done by Anger KE et at (2010)**[7]** concluded that management of pain and sedation therapy is a vital component of optimizing patient outcomes and 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 MG, Jones WA, *et at* (2011) [8] 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. Above mentioned both studies show that no significant difference in the time to extubation after stoppage of sedation as this is also the finding of this study that there was no significant difference in the time to extubation. Atikenhead AR, Willats SM, Parke G *et al* (1989) [9] concluded that desired level of sedation was achieved easily in most patients in both groups. There were slight falls in arterial pressure, but there were no significant differences between the groups. Heart rate was lower in patients who received propofol. When the infusion was discontinued, there was less variability, in recovery of consciousness in patients who had received propofol. In a subgroup of patients, weaning from mechanical ventilation was achieved significantly faster after discontinuation of propofol than of midazolam. Grounds RM *et al* **[10]** concluded that propofol infusion allowed rapid and accurate control of the level, of sedation which was satisfactory for longer than with midazolam, Patients given propofol recovered significantly more rapidly from their sedation once they had fulfilled the criteria for weaning from artificial ventilation and as a result spent a significantly shorter time on a ventilator. There were no serious complications in either group. This study is in accordance the present study in which significant difference is present in weaning the patient from mechanical ventilator after stoppage of sedation. Midazolam took longer time in weaning. Grounds RM, Lalor JM, Lum1ey J, Royston D, Morgan M (1987) [10] also support the outcome. In their study they found that the mean time from reduction of sedation to tracheal extubation was shorter for propofol treated patients than for midazolam treated patients but not the time to ICU discharge.

Carrasco G, Molina R *et al* (1993) [11] concluded that propofol and midazolam were considered safe with respect to the incidents 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 the outcome of this study that recovery of sedation and extubation is faster with propofol sedation than with midazolam. Weinbroum AA *et al* (1997) [12] resumption of spontaneous respiration was equally rapid. Recovery was faster after propofol (P<0.05), 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.

In this study patients receiving dexmedetomidine have significantly lower heart rate compare to propofol and midazolam. During sedation mean pulse rate in dexmedetomidine group was 77.54±9.34, in propofol group 89.34±10.1 and for midazolam group 90.23± 10.7.

During sedation with dexmedetomidine, propofol and midazolam p value is <0.001 which is highly significant. Thus, it's clearly evident in this study that dexmedetomidine infusion leads to reduction in heart rate during sedation and it is statistically significant when compared with propofol and midazolam. Hoy SM, Keating GM (2011)**[13]** concluded that while dexmedetomidine is associated with hypotension and, bradycardia, both usually resolve without intervention. Eren G, Cukurova Z, *et al* (2011) [14] concluded that dexmedetomidine was as effective as higher doses of midazolam in sedation. In addition, propofol has no direct effect on SA node activity or intraatrial conduction; therefore, it does not directly induce bradyarrhythmias. The above mentioned study shows that there is no direct significant effect of propofol on heart rate as in this study also patients receiving propofol did not show any significant effect on heart rate compared to the baseline.

In this study during the sedation with dexmedetomidine,

propofol and midazolam there was no significant effect on respiratory rate (p> 0.05). Hoy SM *et al* [13] 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 and it is not associated with respiratory depression.

Complications

In this study chest complications (nosocomial pneumonia, barotrauma) were the most common complication noted. 18% patients in dexmedetomidine groups, 25.4% patients in propofol group, 21% patients in midazolam group had chest complications. These findings were in accordance to Goodman NW *et al* [15] who studied the ventilatory effects of propofol infusion and concluded that it leads to more chest complications.

Bradycardia occurred in 7.5% patients receiving dexmedetomidine and the time of loading of the drug. This finding was in accordance with Eren G *et al* (2011) [16] who showed that dexmedetomidine causes bradycardia.

Intravenous line sepsis occurs more frequently with propofol 11.2% as compared to midazolam 8.9% and dexmedetomidine 7.3%. Cole DC *et al* (2015) [17] corroborate the findings with the present study.

Prolonged sedation after cessation of sedation occurred most frequently with midazolam 11.34% than with propofol 3.11% and not seen in dexmedetomidine group. Hypotension occurred 14.22% in propofol group, 6.4% in dexmedetomidine group and 5% in midazolam group.

None of the complications were statistically significant.

Conclusion

The present study was carried out in post-operative mechanically ventilated patients in the surgical ICU. Study had 60 patients, 20 in dexmedetomidine group, 20 in propofol group and 20 in midazolam group.

In this prospective randomized study following conclusions were drawn:

1. Dexmedetomidine is a satisfactory agent for sedation in ICU.
2. The mean time from cessation of sedation to tracheal extubation was shorter for dexmedetomidine and propofol treated patients than from midazolam treated patients.
3. There was no significant difference in time to ICU discharge in all the three groups.
4. There was no significant difference between the groups for age, sex, weight, baseline heart rate, blood pressure, respiratory rate.
5. There was significant difference in the heart rate of the patients during sedation. Lower heart rate was seen in dexmedetomidine receiving patients.
6. Blood pressure and respiratory rate were lower in dexmedetomidine and propofol group though it's not statistically significant.

Thus, this study conclusively states that dexmedetomidine a new sedative analgesic agent is safe to be used in the surgical 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.

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Conflict of Interest

None

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