Original Research Article

A Study of sedation with dexmedetomidine in comparison to propofol and midazolam with respect to tracheal extubation and length of stay in ICU

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Abstract

Background: Continuous sedation in the intensive care unit (ICU) is commonly used to control respiratory rate and anxiety and to promote sleep for an optimize care. 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. The sedatives used most often include propofol and midazolam. This study compares the effectiveness of dexmedetomidine for the sedation of patients admitted to our 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, SpO2 during and after sedation. **Material and Methods-** This study was randomized. open label trial conducted in the ICU in patients >18 yrs of age, who required immediate sedation as to permit the initiation and tolerance of mechanical ventilation. Patient enrolled in the study divided into three groups (dexmedetomidine, propofol and midazolam). 30 patients allocated for each group. **Results:** 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. Male predominance was noted, in all groups. A statistically significant difference was present among the groups During sedation, From stoppage of sedation of extubation and At extubation. There is no significant difference present among the groups in baseline pulse rate and from extubation to ICU discharge. **Conclusion:** Our study concludes 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. There was no significant difference in length of stay in ICU noted in all the three groups.

Keywords: IV sedation; Dexmedetomidine, Propofol; Midazolam; Time to tracheal extubation.

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INTRODUCTION

Continuous sedation in the intensive care unit (ICU) is commonly used to control respiratory rate and anxiety and to promote sleep for an 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 comfort and safety. Use of sedation is important to help achieve the right balance between sleep and wakefulness; the correct balance is essential for incorporating physical activity and patients cooperation in the plan of care. 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

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properties, and should also prevent anxieties and unpleasant memories for the patient. The sedatives used most often include propofol and midazolam. The α2 agonist dexmedetomidine is a new sedative and analgesic agent which has been used in ICU's for sedation up to 24h after surgery. Dexmedetomidine 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. This study compares the effectiveness of dexmedetomidine for the sedation of patients admitted to our 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, SpO2 during and after sedation.

MATERIAL AND METHODS

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

Eligibility Criteria

Inclusion criteria

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

Exclusion criteria

- Known or suspected allergy or intolerance to dexmeditomedine, propofol or midazolam.
- Pregnancy.
- Head injuzy
- 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.

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.

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. Patients receiving muscle relaxants and sedation were given a Ramsay sedation score of 6. 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 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 sedation scale to judge sedation level in critically ill patients.

Awake	Asleep
Anxious and / or agitated	Quiescent with brisk response to light glabellar tap or Loud auditory stimulus
Cooperative, oriented and tranquil	Sluggish response to light glabellar tap or loud auditory stimulus.
Response to command	No response

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. 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

Age (yrs)	Dexmedetomidine		Propofol		Midazolam	
	No	%	No	%	No	%
18-30	8	26	12	40	9	30
31-45	12	40	9	30	10	34
46-60	10	34	9	30	11	36
Mean ± SD (yrs)	37.03 ± 12.75		36.7 ± 12.18		37.9 ± 12.48	

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.

Table 2: Sex Distribution

Sex	Dexmedetomidine		Propofol		Midazolam	
	No	%	No	%	No	%
Male	17	56	18	60	16	54
Female	13	44	12	40	14	46
Total	30		30		30	

P value is calculated by one way analysis of variance (ANOVA). in all three groups in not statistically significant. (P > 0.05). A statistically significant difference was present among the groups During sedation, From stoppage of sedation of extubation and At extubation. There is no significant difference present among the groups in baseline pulse rate and from extubation to ICU discharge.

Table 3: Mean Changes in Pulse Rate

	Baseline	During sedation	From stoppage of sedation to extubation	At extubation	From extubation to ICU discharge
Dexmedetomidine (Mean ± SD)	92.00 ± 3.7	78.26 ± 4.97	83 ± 2.56	84.7 ± 2.27	89.21 ± 0.75
Propofol (Mean ± SD)	92.26 ± 3.55	85.66 ± 3.02	92.33 ± 1.74	94.23 ± 1.47	92.49 ± 0.84
Midazolam (Mean ± SD)	92.6 ± 3.64	84.93 ± 2.21	93.86 ± 1.814	94.4 ± 1.32	92.45 ± 0.85
P value	>0.05	<0.0001	<0.0001	<0.0001	>0.05

The difference in respiratory rate was not significant at baseline, during sedation, from stoppage of sedation to extubation and extubation to ICU discharge.

Table 4: Mean Changes in Respiratory Rate

Drugs	Baseline	During sedation	From stoppage of sedation to extubation	At extubation	From extubation to ICU discharge
Dexmedetomidine (Mean ± SD)	18.83 ± 1.36	13.93 ± 0.78	14.5 ± 0.5	14.46 ± 0.5	14.6 ± 0.56
Propofol (Mean ± SD)	18.46 ± 2.36	14 ± 0.83	14.56 ± 0.5	14.5 ± 0.5	14.5 ± 0.50
Midazolam (Mean ± SD)	18.56 ± 1.04	13.93 ± 0.78	14.53 ± 0.5	14.56 ± 0.5	14.53 ± 0.50
P value	>0.05	>0.05	>0.05	>0.05	>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 5: 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 dystolic blood pressure among all the three groups calculated by ANOVA test is not statistically significant (P > 0.05).

Table 6: 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 7: 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 8: 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

This study was considered to assess the efficacy of dexmedetomidine with propofol and midazolam, established IV 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 is used an ICU for sedation 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. The patients in this study were of gynaecological and obstetrical cases, emergency laprotomy cases, trauma cases, post operative routine cases, aspiration pneumonia cases, COPD cases. 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. Study done by Anger KE, et at[1] concluded that management of pain and sedation therapy is a vital component of optimizing patient outcomes. Reichert MG, Jones WA, et at[2] 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 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. In my 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.*[3] 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. Hall JE *et al.*[4] concluded that during sedation with dexmedetomidine and propofol there was hemodynamic variables (heart rate and mean arterial blood pressure), sedation, bispectral index score of sedation, ventilation (respiratory rate, O2 sat, and ETCO2), were determined during surgery and up to 95 min after surgery. lntraoperative sedation levels were targeted to achieve a bispectral index score of 70-80, Patient baseline cardio-respiratory variables were similar between groups. There were no differences between groups in psychomotor performance and respiratory rate during recovery. So this study also support our finding that dexmedetomidine and propofol not significantly affect respiratory rate during and after sedation in the period of recovery. Yahya Shehabi *et al.*[5] concluded that dexmedetomidine infusions (1) did not result in clinically significant respiratory depression, (2) decreased rather than increased the apnea/hypopnea index, and (3) exhibited some similarity with natural sleep.Esko Ruokonen, llkka Parviainen, *et al.*[6] concluded that in long-term sedation, dexmedetomidine is comparable to propofol/midazolam in maintaining sedation targets of RASS 0 to -3 but not suitable for deep sedation (RASS-4 or less). Dexmedetomidine had no effect on length of ICU stay. 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). There was no significant difference in time to ICU discharge in all the three groups. In this study chest complications (nosocomial pneumonia, barotraumas) 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.*[7] 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, Cukurova Z, et at[8] also noted that dexmedetomidine cause bradycardia. Prolonged sedation after cessation of sedation occurred most frequently with midazolam 11.34% than with propofol 3.11% and not seen in dexmedetomidine group. This finding in accordance with another study which authors found that patients receiving midazolam had a prolonged sedation time.[9] None of the complications were statistically significant.

CONCLUSION

Our study concludes 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. There was no significant difference in length of stay in ICU noted in all the three groups.

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