Section : Anaesthesiogy

Original Research Article

A COMPARATIVE STUDY OF DEXMEDETOMIDINE AND MIDAZOLAM FOR SEDATION IN PATIENTS ON MECHANICAL VENTILATION IN ICU

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Abstract

Background: The use of non-benzodiazepine sedatives over benzodiazepines, is now advocated in light of recent evidences, in order to improve outcome of the patients in ICU sedation. However, very few studies in the literature have compared these two most commonly used ICU Sedation agents. In present study we aim to assess and compare the efficacy of dexmedetomidine and midazolam for sedation in critically ill patients admitted in ICU. **Materials and Methods:** A Prospective Randomized Comparative Study including adult patients of age >18 to <65 years with a sample size of 90 of either sex admitted to the ICU requiring mechanical ventilation in ICU. **Result:** Out of 90 a total of 4 patients were excluded from the study due to non-survival up to 24 hrs while one cases was excluded from dexmedetomidine group due to discontinuation of drug, as it caused severe bradycardia and hypotension. So final analysis was done on 85 cases, 43 in dexmedetomidine group and 42 in midazolam group. Both the groups were comparable with regards to pulse rate, SBP, DBP, O_2 saturation at baseline and also throughout the follow up duration of 24 hours ($p>0.05$). **Conclusion:** Extubation was possible significantly earlier in cases managed by dexmedetomidine as compared to midazolam (3.34 vs 5.52 hrs; $p<0.01$). Incidence of delirium was significantly higher in cases managed by midazolam as compared to dexmedetomidine (50% vs 25.6%; $p<0.01$).

INTRODUCTION

The ICU environments are filled with uncomfortable procedures both invasive and non-invasive which may include, but are not limited to endotracheal intubation, central venous catheterisation, change in positioning and physical restraints. Also, ICU is a noisy atmosphere which aggravates anxiety in a conscious patient.[1] Clinical outcome of the patients can be worsened by ICU related stress and anxiety; and prevention of exposure to this can help enhancement of outcome.[2]

Mechanical ventilation, invasive and non-invasive interventions, pain, anxiety are the major external and internal stimuli that may lead to patient discomfort, anxiety and agitation in intensive care unit(ICU). Inadequate sedation and analgesia cause unnecessary sympathetic activation, hence leading to negative impact on the outcome of a critically ill patient.[3] In mechanically ventilated patients, inadequate sedation can cause patient ventilator asynchrony.[4] Hence, the international guidelines recommend routine use of sedative drug to reach and sustain optimal level of comfort to prevent these stressful effects.[5] Therefore sedation and analgesia are the integral part of management of critically ill patients in ICU. Sedation is the process of relieving anxiety and establishing a state of calm. This process may include general supportive measures (like frequent communication with patients and families), and drug therapy. The drugs used most often for sedation in ICUs are benzodiazepines (midazolam and lorazepam), propofol, dexmedetomidine, haloperidol etc.

Midazolam and Dexmedetomidine are most commonly used sedatives in ICU.

Midazolam is a short acting GABA agonist benzodiazepine, which has been used for many years, as one of the ICU sedative drugs.[6,7] It has rapid recovery and minimum respiratory and hemodynamic depression. Repeated dosing and continuous infusion in ICU can lead to prolong sedation and delayed recovery.[8] Because of their

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well known adverse effects associated with prolong use, the paradigm is now changing towards use of non-benzodiazepine drugs for ICU sedation.

Dexmedetomidine is alpha 2 adrenergic receptor agonist, which acts in the central nervous system producing sedative, anxiolytic, and sympatholytic effects with minimum heamodynamic and respiratory depression. In contrast to benzodiazepines, dexmedetomidine also has analgesic action, that acts via spinal cord receptor and thereby deceasing the need for opioid analgesia. The use of non-benzodiazepine sedatives over benzodiazepines, is now advocated in light of recent evidences, in order to improve outcome of the patients in mechanical ventilation.[9] So we conducted this study to assess and compare the efficacy of Dexmedetomidine and midazolam for sedation in critically ill patients admitted in ICU, as guided by RASS and study the various hemodynamic responses to administration of Dexmedetomidine and compare them with those of Midazolam.

MATERIALS AND METHODS

A Prospective Randomized Comparative Study was conducted in Department of Anaesthesiology and Critical Care, Dr. Sushila Tiwari Government Hospital, Haldwani, Uttarakhand. A sample size of 90 patients was taken for a study duration of 18 months.

Inclusion Criteria

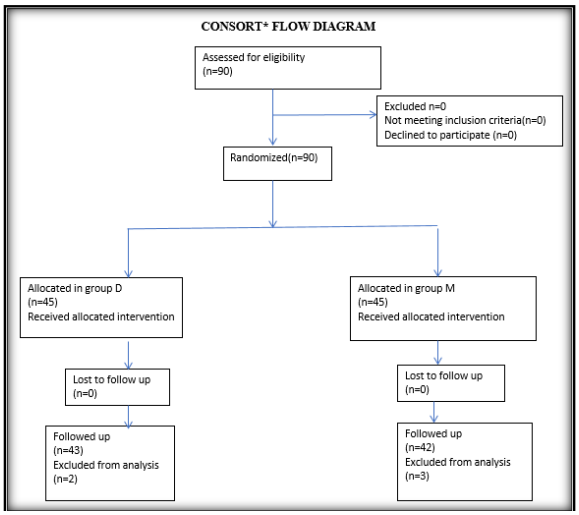
1. Both genders
2. Patients >18 and <65 years of age.
3. Patients with need of mechanical ventilation

Exclusion Criteria

1. Patients who are hemodynamically unstable – bradycardia (heart rate<50bpm) or hypotension (mean arterial pressure <60 mm hg) despite appropriate intravenous volume replacement and vasopressors.
2. Patients with neurological disease and active seizures.
3. Patients with acute myocardial ischemia, second- and third-degree heart block etc.
4. Diabetic patients with uncontrolled blood sugar level.
5. Morbidly obese patients.
6. Patients under 18 years and over 65 years of age.
7. Known allergy to the drug.
8. Pregnancy
9. Patients with chronic liver disease.
10. Patients on chronic opioid therapy or use of alpha 2 agonists or antagonist 24 hours prior to admission.

A Prospective Randomized Comparative Study was commenced after approval from the institutional ethical committee. After taking written informed consent from the accompanying attendants, 90 patients of age >18 to <65 years of either sex admitted to the ICU requiring mechanical ventilation were selected for the study and randomly divided into two groups using computer generated random numbers table: Demedetomidine group (group D) and Midazolam group (group M). A detailed history and complete physical examination was done for all the patients.Group D received Dexmedetomidine infusion started with a bolus of 1micrograms/kg within 10 mins and then 0.1 to 0.6 micrograms/kg/hr as infusion. Group M received Midazolam infusion started with a bolus of 0.05 mg/kg within 1 to 5 minutes followed by continuous infusion with the dose of 1 to 2 mg/hr as per need. The rate of the maintenance infusion was adjusted to achieve the target RASS score of 0 to -3. Both groups are monitored for period of 24 hours.

Patients in either group not adequately sedated received Fentanyl 0.5 to 1 micrograms/kg intravenously as the rescue drug for agitation.



*Consolidated Standards of Reporting Trial 2010

RESULTS

Table 1: Distribution of cases as per study drug

Group	N
Dexmedetomidine (D)	45
Midazolam (M)	45

Present study included 90 critically ill patients, admitted in ICU and requiring mechanical ventilation. The patients were allocated using table of random numbers into two groups for receiving different drugs for sedation:

- GROUP D: received Dexmedetomidine
- GROUP M: received Midazolam

A total of 4 patients were excluded from the study due to non-survival up to 24 hrs (1 in Dexmedetomidine and 3 in midazolam group) while one cases was excluded from dexmedetomidine group due to discontinuation of drug, as it caused severe bradycardia and hypotension. So final analysis was done on 85 cases, 43 in dexmedetomidine group and 42 in midazolam group.

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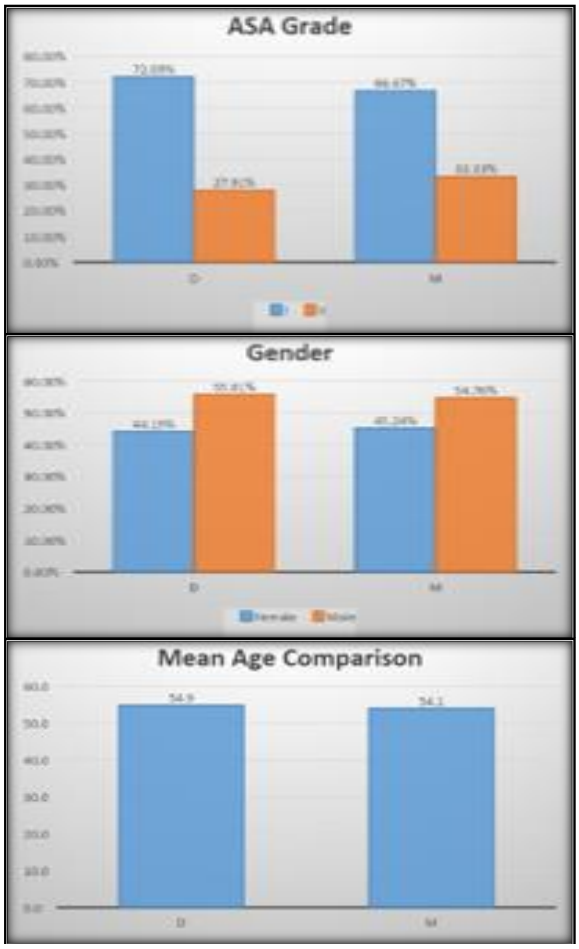
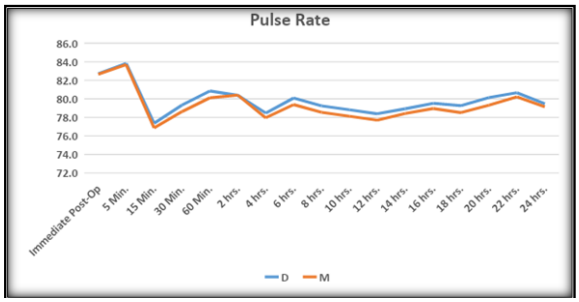
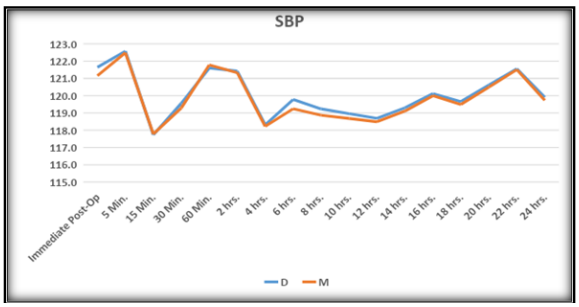
Mean age of the cases was 54.5 years with no difference between study groups (p-0.53).
Out of the total 90 cases studied, 55.29% were males and 44.71% were females. Both the groups were comparable with regards to gender distribution (p-1.0).
A total of 68.9% were in ASA grade I while 31.1% were in ASA grade II. Both the groups were comparable with regards to ASA grade distribution (p-1.0).



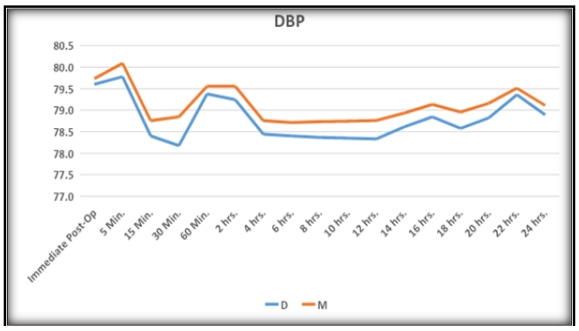
Both the groups were comparable with regards to pulse rate at baseline and also throughout the follow up duration of 24 hours (p>0.05).



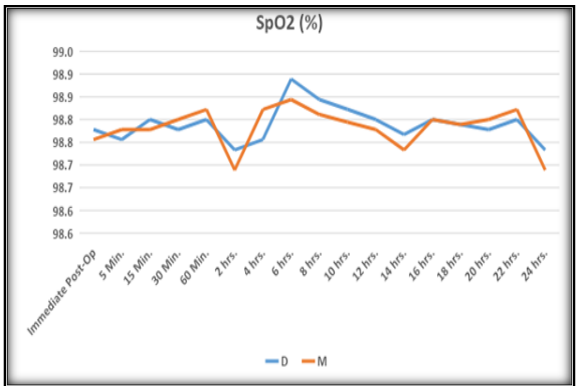
Both the groups were comparable with regards to systolic blood pressure at baseline and also throughout the follow up duration of 24 hours (p>0.05).



Both the groups were comparable with regards to diastolic blood pressure at baseline and also throughout the follow up duration of 24 hours (p>0.05).



Both the groups were comparable with regards to oxygen saturation at baseline and also throughout the follow up duration of 24 hours (p>0.05).



The rate of the maintenance infusion was adjusted to achieve the target RASS score of 0 to -3. Mean time spent in RASS range was 80% in cases of dexmedetomidine group while it was 75.1% in cases of midazolam group respectively (p-0.26).
Extubation was possible significantly earlier in cases managed by dexmedetomidine as compared to midazolam (3.34 vs 5.52 hrs; p<0.01).
Patients in either group not adequately sedated received Fentanyl 0.5 to 1 micrograms/kg intravenously. Additional sedatives were required in 34.88% cases in dexmedetomidine group as compared to 52.38% cases of midazolam group (p-0.12).

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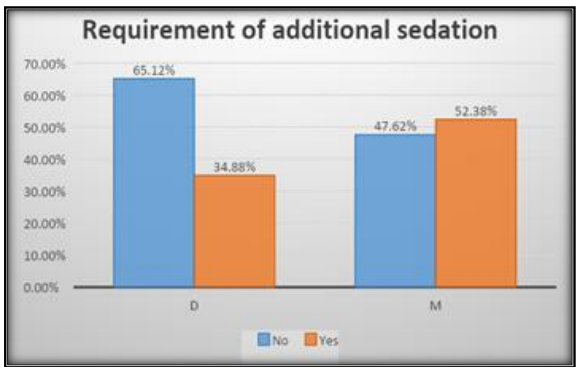
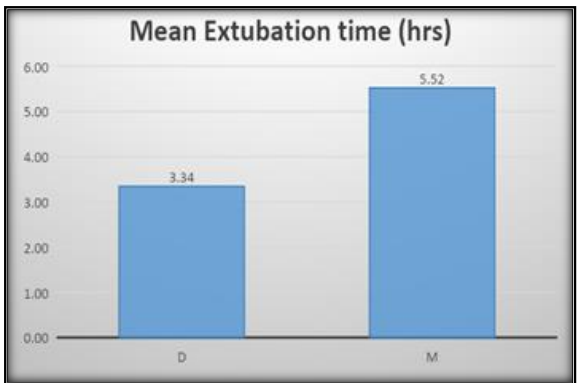
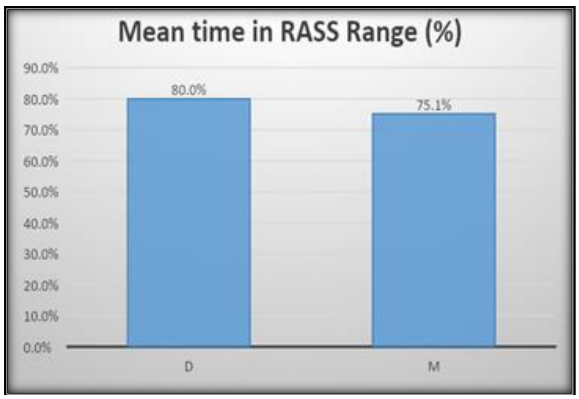
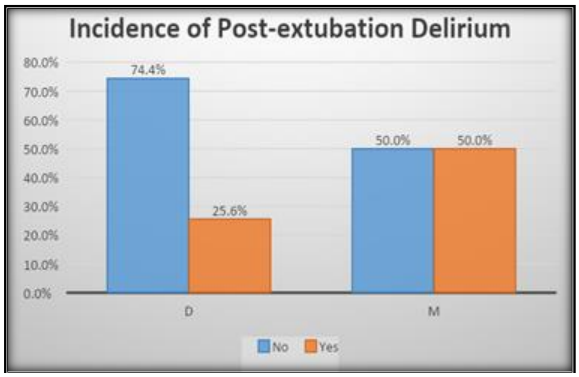


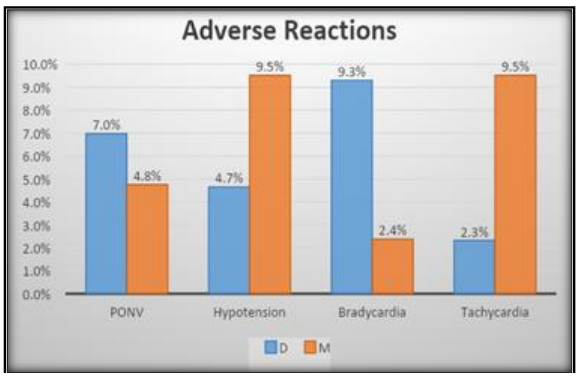




Both dexmedetomidine and midazolam groups were comparable (p>0.05) with regards of incidence of adverse reactions like PONV (7% vs 4.8%), hypotension (4.7% vs 9.5%) bradycardia (9.3% vs 2.4%) and tachycardia (2.3% vs 9.5%).

Incidence of delirium was significantly higher in cases managed by midazolam as compared to dexmedetomidine (50% vs 25.6%; p<0.01).





DISCUSSION

Present study included 90 critically ill patients, admitted in ICU and requiring mechanical ventilation. The patients were allocated using table of random numbers into two groups (45 each) for receiving different drugs for sedation: GROUP D: received Dexmedetomidine, and; GROUP M: received Midazolam. A total of 4 patients were excluded from the study due to non-survival up to 24 hrs (1 in Dexmedetomidine and 3 in midazolam group) while one cases was excluded from dexmedetomidine group due to discontinuation of drug, as it caused severe bradycardia and hypotension. So final analysis was done on 85 cases, 43 in dexmedetomidine group and 42 in midazolam group.

Mean age of the cases was 54.5 years with 55.29% males and 44.71% females.

A total of 69.41% were in ASA grade I while 30.59% were in ASA grade II. Both the groups were comparable with regards to demography and ASA grade distribution (p>0.05).

Sedation Characteristics

In present study, we adjusted the rate of maintenance infusion to achieve the target Richmond Agitation Sedation Scale (RASS) score between 0 to -3. Mean time spent in RASS range was 80% in cases of dexmedetomidine group while it was 75.1% in cases of midazolam group respectively (p-0.26). Additional sedatives were required in 35.6% cases in dexmedetomidine group as compared to 55.6% cases of midazolam group (p-0.09).

Ruokonen E et al,[10] compared dexmedetomidine (DEX) with standard care (SC, either propofol or midazolam) for long-term sedation. Target Richmond agitation-sedation score (RASS) was reached a median of 64% (DEX) and 63% (SC) of the sedation time (ns). The study suggests that in long-term sedation, DEX is comparable to SC in maintaining sedation targets of RASS 0 to -3. Richard R. Riker et al,[11] compared the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients. There was no difference in percentage of time within the target RASS range (77.3% for dexmedetomidine group vs 75.1% for midazolam

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group; difference, 2.2% [95% confidence interval {CI}, -3.2% to 7.5%]; P = 0.18).

Extubation Time

Extubation was possible significantly earlier in cases managed by dexmedetomidine as compared to midazolam (3.34 vs 5.52 hrs; p<0.01).

Chaudhari A et al,[12] study observed that mean duration of extubation after cessation of sedation was faster with dexmedetomidine group than midazolam group (33.27±11.37 minutes vs 49.43±5.58 minutes). Manoj Tripathi et al,[13] observed a significant difference in the time of extubation between Group D (21 ± 6.44 h) and Group M (30.4 ± 10.62 h; p= 0.008), which was in accordance with our results.

Adverse Reactions & Delirium

Both the groups were comparable with regards to hemodynamic parameters like pulse rate and blood pressure at baseline and also throughout the follow up duration of 24 hours (p>0.05). The study groups were comparable (p>0.05) with regards of incidence of adverse reactions like PONV (7% vs 4.8%), hypotension (4.7% vs 9.5%) bradycardia (9.3% vs 2.4%) and tachycardia (2.3% vs 9.5%). Incidence of post-extubation delirium was significantly higher in cases managed by midazolam as compared to dexmedetomidine (50% vs 25.6%; p<0.01).

Results by Yousry El-Saied Rizk et al,[14] showed that dexmedetomidine provides hemodynamic stability and has no clinically important adverse effects on respiration also provide less number of patients suffering from delirium. Rajbanshi LR et al,[15] study observed that patients treated with dexmedetomidine had less incidence of ICU delirium (odds ratio=2.669, P=0.029). ICU morbidity and mortality was comparable between the groups.

Thus, to summarize, present study conclude that Dexmedetomidine provides comparable sedation to midazolam with no clinically remarkable adverse effects on blood pressure or respiration. Incidence of post-extubation delirium was also lower with dexmedetomidine. Tracheal extubation was earlier in patients receiving dexmedetomidine, aiding in faster recovery.

CONCLUSION

We thus conclude that Dexmedetomidine is a safe and effective drug to be used for sedation in ICU patients. Dexmedetomidine provides comparable sedation to midazolam and has no clinically remarkable adverse effects on blood pressure or respiration. Incidence of delirium was also lower with dexmedetomidine as compared to midazolam. Tracheal extubation was earlier in patients receiving dexmedetomidine than receiving midazolam, leading to lesser ICU stay and faster recovery. Present study thus recommend use of Dexmedetomidine as a drug of choice for ICU Sedation.

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