Original Research Article

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Comparison between Dexmedetomidine and Midazolam for Postoperative Analgesia and Sedation in Mechanically Ventilated Patients

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Abstract

Context: Postoperative patients requiring mechanical ventilation in surgical ICU's require adequate sedation and analgesia in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in the ICU. The consequences of inadequate sedation and analgesia can be sustained, including self-removal of intraluminal tubes and vascular catheters, aggressive behavior by patients against care providers, and poor patient-ventilator synchrony. Oversedation can lead to prolonged duration of mechanical ventilation, more prolonged ICU, and hospital stays. *Aims:* To evaluate the effects of dexmedetomidine and midazolam for sedation in postoperative mechanically ventilated patients. *Study Design:* Arandomized prospective study. *Methods:* 100 patients aged above 18 years after major abdominal or pelvic surgeries requiring a minimum of 6 hours of artificial ventilation admitted to intensive care units were included as subjects, and they were randomly divided into two groups of fifty each. Group D received Dexmedetomidine, a loading dose of 2.5 μg/kg, and a maintenance dose of 0.5 μg/kg/hr, and Group M received Midazolam a loading dose of 0.05 mg/kg and a maintenance dose of 0.025 mg/kg/hr. Both groups were compared for the level of sedation using Ramsay sedation score, hemodynamic variables, safety profile. *Statistical analysis used:* Chi-square test and Student's unpaired *t*-test. *Results:* Ramsay sedation score was within the desired level (2–4) in both dexmedetomidine and midazolam group ($p > 0.05$). Patients who received dexmedetomidine infusion had significantly lower heart rates compared to patients who received midazolam infusion ($p < 0.00$), there were no significant differences in SBP, DBP, MAP and oxygen saturation between two groups. *Conclusion:* Dexmedetomidine and midazolam are safe sedative drugs for postoperative mechanically ventilated patients. Patients were easily aroused to cooperate without signs of irritation within the dexmedetomidine group.

Keywords: Dexmedetomidine; Midazolam; Mechanical ventilation.

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Introduction

The intensive care unit is an environment of high-level stress and discomfort for patients. The use of adequate sedation and analgesia is essential in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in ICU.[1] Intubated, mechanically ventilated patients in surgical ICU require sedation and analgesia to tolerate tracheal tube, artificial

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ventilation, to suppress cough and to prevent respiratory fighting during procedures such as bronchial suctioning, physiotherapy, and catheter placement.[2] The sedation of patients reduces stress response, provides anxiolysis, improves tolerance of ventilator support, and facilitates nursing care. However, the sedatives have adverse effects and have the potential to prolong mechanical ventilation and also increases health care cost.[3–4]

Dexmedetomidine is an α_2 adrenoreceptor agonist with a unique mechanism of action providing sedation and anxiolysis via receptors within the locus coeruleus, analgesia *via* receptors in the spinal cord and attenuation of stress response with no significant respiratory depression.[5] The recommended dose is an IV infusion bolus of 1 μg/kg body weight over a 10 minute period, followed by a continuous IV infusion of 0.2–0.7 μg/kg/hr. The maintenance dose is titrated until the sedation goal is reached. It has shown to inhibit CYP2 D6 *in vitro*, but the clinical significance of this inhibition is not well-established. Dexmedetomidine appears to have little potential for interactions with drugs metabolized by the cytochrome P450 system. Coadministration of Dexmedetomidine with sevoflurane, isoflurane, propofol, alfentanil, and midazolam may result in the enhancement of sedative, hypnotic or anesthetic effects.

Midazolam is selected as comparator medication owing to its frequent use for short-term sedation and is often identified as the most commonly used sedative in ICU. Gaba receptor agonist medication is the most commonly used sedatives for ICU patients; its preliminary evidence indicates dexmedetomidine advantages.[6] The sedative agents are commonly administered as boluses or by continuous infusion when required in an intensive care unit. However, the latter method of infusion is more common. It also ensures constant levels of sedation, thus reducing the chance of intermittent agitation. However, the studies have shown that continuous infusion is known to prolong the duration of mechanical ventilation and thus prolonging the duration of stay in ICU. The physician has to set the desired sedation score, and patients should be reevaluated regularly. This approach allows titration of the therapy and prevents the chances of over or under sedation.

The treating physician should understand that how much and for how long the sedation is given. The over and under sedation can have deleterious consequences in determining the patient outcome. Over sedation increases the prolonged ventilatory support and also duration of stay in ICU. Under sedation can result in hypercatabolism, immunosuppression, hypercoagulability, and increased sympathetic activity. Hemodynamic responses to measure sedation are unreliable in the critically ill patient, hence the need for formal sedation scoring. There are many clinical scoring systems to assess the depth of sedation in ICU; examples include the Ramsay sedation score, Addenbrookes, Bloomsbury scales, and Richmond Agitation Sedation Scale (RASS). In our study, we have used the Ramsay sedation score, shows in Table 1. The present study is being undertaken in a randomized single-blinded manner to evaluate sedative and analgesic properties, safety profile, cardiovascular responses, ventilation and extubation characteristics with dexmedetomidine compared to midazolam in postoperative mechanically ventilated patients.

Materials and Methods

A randomized prospective study was undertaken Intensive Care Unit Medical College Hospital. A total of 100 ASA 3, ASA 4, ASA 5 patients, aged 18 years and above, after major abdominal pelvic surgeries requiring a minimum of 6 hours of artificial ventilation were included in the study. Morbidly obese patients and patients with neurological deficits, local sepsis were excluded from the study.

About 100 patients who satisfied the inclusion and exclusion criteria were allocated randomly into two groups by using a random numbers table. Group D -Dexmedetomidine group received a loading dose 2.5 mcg/kg and a maintenance dose 0.5 mcg/kg/hr. Group M - Midazolam group received a loading dose 0.05 mg/kg and a maintenance dose 0.025 mg/kg/hr.

Anesthetic technique in the operating room was carried out with 0.5 mg/kg thiopentone, 3–4 mcg/kg fentanyl and vecuronium 0.05 mg/kg. Direct laryngoscopy and endotracheal intubation were done with appropriate endotracheal tubes, maintenance of anesthesia was provided with 33% O_2 + 66% N_2O + intermittent halothane+ intermittent positive pressure ventilation. Neuromuscular blockade was provided with vecuronium as required. At the end of the surgical procedure, the neuromuscular blockade was not reversed, and artificial ventilation was continued. After admission to ICU patients were randomized into either of one group, patients were connected to multiparameter, which records heart rate, noninvasive measurements of SBP, DBP, MAP, continuous ECG monitoring,

and O_2 saturation. Patients were immediately artificially ventilated with synchronized intermittent ventilation with pressure support mode. Sedatives used before study enrolment was discontinued prior to initiation of study drug. Each patient received a study drug after randomization. Optional loading doses(up to 2.5 mcg/kg dexmedetomidine or 0.05 mg/kg midazolam) was administered at the investigators discretion. The starting maintenance infusion dose of study drug was 0.5 mcg/kg/hr for dexmedetomidine and 0.025 mg/kg/hr for midazolam corresponding to the midpoint of allowable infusion dose range. Dosing of the study was adjusted by managing the clinical team based on sedation assessment performed with Ramsay Sedation Score (RSS), a minimum of every 1 hour for the first 6 hours, thereafter every 2 hours till extubation or up to 18 hours. No other sedatives or analgesics or muscle relaxants were allowed during the study period. Study drug infusion was stopped at the time of extubation in both the groups or after a maximum of 18 hours. The following parameters were assessed:

- Level of sedation was assessed by RSS initially every hour for 6 hours, thereafter every 2 hours till extubation or up to 18 hours;
- Hemodynamic parameters (HR, SBP, DBP, MAP, SpO_2);
- Duration of analgesia by pain assessment using Visual Analog Score (VAS);
- Duration of ICU stay;
- Side-effects.

Statistical analysis was done by Unpaired *t*-test, which was used to compare the mean levels between two groups and Chi-square test for categorical data.

Results

A randomized prospective study was conducted in order to evaluate the efficacy and safety of dexmedetomidine in comparison to midazolam in the management of analgesia and sedation for postoperative patients in surgical ICU. A total of 100 postoperative patients were divided randomly into two groups of 50 each. Group D received dexmedetomidine, and Group M received midazolam infusion. The results were obtained as follows:

The mean age of patients in Group D was 41.9 ± 12.4 years, and that of Group M was 41.1 ± 14 years. There was no statistically significant difference between the two groups with respect to age distribution (p = 0.768). In Group D there were 24 male and 26 female patients; in Group M there were 23 male and 27 female patients. There was no significant statistical difference in gender distribution between the two groups (p = 0.84). The mean weight of patients of Group D was 57.2 ± 13.5 kg, and that of Group M was 57.8 ± 12.2 kg. There was no statistically significant difference in the body weight between two groups (p = 0.8).

Shown in Table 1, mean Ramsay sedation score range from 2.3 to 3.5 in Group D, and 2.6 to 3.7 in Group M. sedation score was not statistically significant in two groups (p > 0.05), (Fig. 1).

Table 1: Ramsay sedation score

Score	Response
1	Anxious or Restless or Both
2	Cooperative, Oriented and Tranquil
3	Responds to Commands
4	Brisk Response to Stimulus
5	Sluggish Response to Stimulus
6	No Response to Stimulus

Mean heart rate ranged from 77–97 bpm in Group D and 89–93 bpm in Group M. Statistical evaluation showed a significant fall in heart rate (17 bpm) in Group D immediately after administration of dexmedetomidine, and the fall in heart rate was maintained throughout the study period which was statistically significant (p = 0.00), (Fig. 2).

Fig. 1: Sedation score comparison

Mean SBP ranged from 113.0–117.7 mm of Hg in Group D while in Group M ranged from 110.0–119.6 mm of Hg. Mean DBP ranged from 69.0–72.0 mm of Hg in Group D while in Group M ranged from 65.5–70.8 mm of Hg. Basal MAP ranged from 83.7–87.4 mm of Hg in Group D, whereas in Group M ranged from 80.7–85.7 mm of Hg. Oxygen saturation level ranged from 98.0–99.0% in Group D, whereas in Group M ranged from 98.1–99.1%, there was no statistically significant difference in SBP, DBP, MAP, and SpO_2 among two groups, (Figs. 3–5).

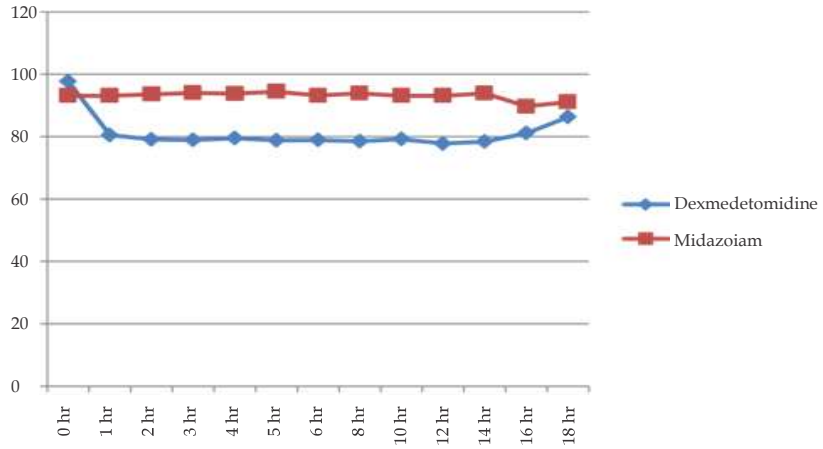

Fig. 2: Heart rate comparison.

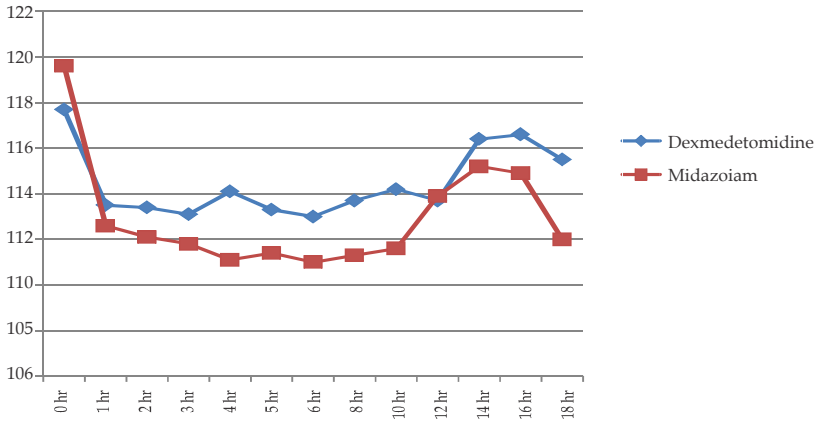

Fig. 3: SBP (Systolic Blood Pressure).

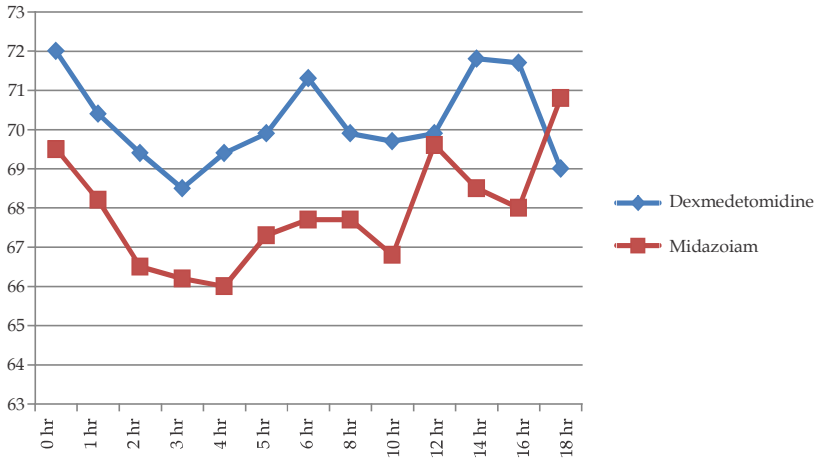

Fig. 4: DBP Comparison.

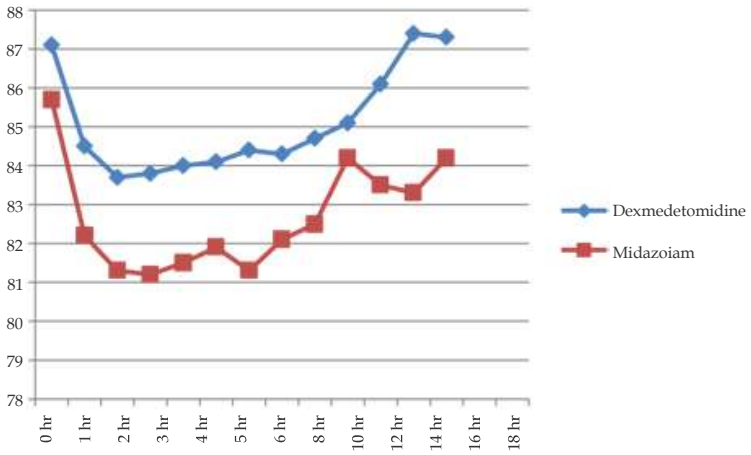

Fig. 5: MAP comparison.

Mean VAS score in Group D ranged from 2.2–3.1 after infusion of dexmedetomidine, whereas in Group M ranged from 2.0–4.0 after infusion of midazolam. There was no statistically significant difference in VAS among the two groups. Fig. 6. The mean ICU stay in Group D was 2.4 days, whereas in Group M was 2.6 days. There was no statistically significant difference in ICU stay among two groups (p = 0.22), (Fig. 7).

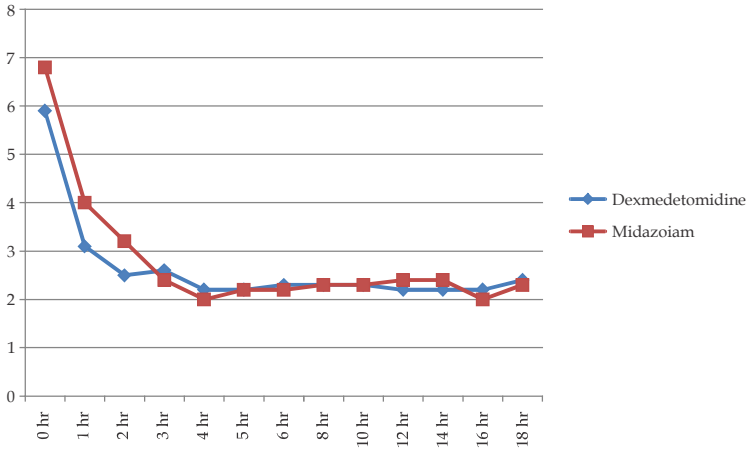

Fig. 6: VAS score comparison.

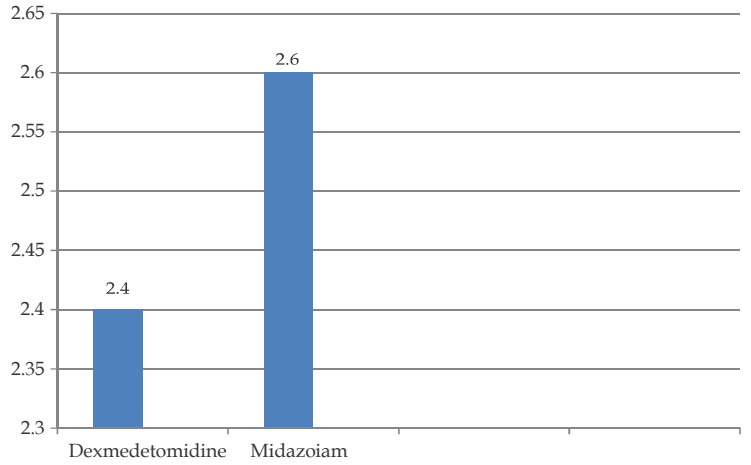

Fig. 7: Number of days of ICU Stay.

Discussion

Postoperative mechanically ventilated patients in surgical ICU require sedation and analgesia in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in the ICU.[1] Sedation helps in allaying the anxiety, increases tolerance to the endotracheal tubes, suppresses cough, and prevents respiratory fighting during intensive care procedures such as bronchial suctioning, physiotherapy, and catheter placement[2] and improves the outcomes of interventions in the Intensive care Unit.

The available literature has shown that sedative agent should have an action which is rapid in onset, should be effective at providing adequate sedation, allow rapid recovery after discontinuation, easy to administer, lack drug accumulation, have a few adverse effects and interact minimally with other drugs. The consequences of inadequate sedation and analgesia can be substantial, including self-removal of important intraluminal tubes and vascular catheters, aggressive behavior by patients against care providers, and poor patient-ventilator synchrony. Oversedation can lead to prolonged duration of mechanical ventilation, longer ICU and hospital stays, increased incidence of ventilator-associated pneumonia, and the inability of patients to communicate with health care providers or family members. The currently available sedatives include Propofol and benzodiazepines like Midazolam; both will provide adequate sedation, but they also produce many adverse effects. Benzodiazepines are anxiolytic and amnestic agents, but they can also cause paradoxical agitation in the elderly. Benzodiazepines are also associated with respiratory depression and the potential for the drug to accumulate, leading to aprolonged recovery period.

Midazolam is selected as the comparator medication owing to its frequent use for short-term sedation and is often identified as the sedative most commonly used in ICU. *Y*-Aminobutyric acid receptor agonist medications are the most commonly used sedatives for Intensive Care Unit (ICU) patients, yet preliminary evidence indicates that the α_2 agonist dexmedetomidine may have distinct advantages. Even after its beneficial effects, the midazolam has other outward effects, including restlessness, paradoxical reaction, cognitive impairment, amnesia, and respiratory depression.

Many newer sedatives are available in the market. Dexmedetomidine is one such newer sedative which is an α_2a adrenoreceptor agonist with a unique mechanism of action, providing sedation and anxiolysis via receptors within the locus coeruleus, a small nucleus present in the pons, analgesia *via* receptors in the spinal cord and attenuation of the stress response with no significant respiratory depression. Inaddition to sedation, dexmedetomidine provides analgesic effects, a lack of respiratory depression, sympatholytic blunting of the stress response, preservation of neutrophil function, and may establish a more natural sleep-like state. Dexmedetomidine is recently introduced in India (only in 2009) and available as 50 μg/0.5 ml, 100 μg/ml, 200 μg/2ml ampoules (Dexem, Themis Medicare Limited) and not many studies have been done using dexmedetomidine as a sedative in postoperative surgical ICUs.

Hence, the study was undertaken to evaluate the efficacy, hemodynamic variables, and safety profile of Dexmedetomidine as short-term sedative in comparison with most commonly used sedative Midazolam in postoperative mechanically ventilated patients. These studies are scant to prove the role of Dexmedetomidine as a sedative and analgesic in postsurgical patients in ICU. Hence, the study was undertaken to evaluate Dexmedetomidine as a sedative and analgesic in postsurgical patients in ICU. Hence, a randomized prospective study was conducted in order to evaluate the efficacy and safety of Dexmedetomidine in comparison to Midazolam in the management of analgesia and sedation for postoperative patients in surgical ICUs. A total of 100 postoperative patients were divided randomly into two groups of 50 each. Group D received Dexmedetomidine, and Group M received Midazolam infusion.

The mean age of the subjects in this study was 38.2 years in the Dexmedetomidine group and 39.1 years in the Midazolam group. About 52% in Group D and 54% in Group M were males. The mean weight of patients was 60.9 Kgs and 66.4 Kgs in Group D and Group M, respectively. There was no statistically significant difference with regards to mean age, weight, and sex. Hence, the two groups were comparable.

The mean sedation scores were ranged from 2.3 to 3.5 in Group D and 2.6 to 3.7 in Group M. There was no significant difference in Ramsay sedation score between Group D and Group M during the study period. In a similar study conducted by Jacobi J, Fraser GL et al.,[7] and Riker RR, Shehabi Y et al.,[5] dexmedetomidine produced equivalent sedation as Midazolam and the patients who have received Dexmedetomidine, despite artificial ventilation and intubation, were easily aroused to cooperate without showing irritation.

In the present study, there was significant bradycardia in the Dexmedetomidine group compared to the Midazolam group. There was a fall of 17 bpm after dexmedetomidine infusion, and the fall in heart rate was sustained throughout the study period and did not require any treatment. In a similar study, conducted by Vinit K Srivastava et al.[8] and Riker RR; Shehabi Y et al.,[5] heart rate showed a significant reduction in the dexmedetomidine group than in Midazolam group.

In the present study, visual analog scores were within the optimal range. VAS of 2–3 was achieved in both groups without using any other additive analgesia. In a similar study, conducted by McMurray et al.[9], and RM Venn et al.[10], they noted patients who received Midazolam infusions required significantly more analgesics than patients who received Dexmedetomidine infusions.

In the present study, there was no significant difference in length of ICU stay in both groups. In a similar study conducted by Stephen M; noted the recovery time and length of ICU stay were similar in both Dexmedetomidine and Midazolam groups.

Conclusion

The study was undertaken to evaluate the efficacy and safety of Dexmedetomidine compared to Midazolam as a short-term sedative in postoperative mechanically ventilated patients in surgical ICUs. Dexmedetomidine is a new alpha 2 agonist, which was as efficacious and had a safety profile similar to Midazolam.

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Conflicts of interest: Nil

Abbreviations

ICU	Intensive Care Unit
GABA	Gama Aminobutyric Acid
HR	Heart Rate
BP	Blood Pressure
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
MAP	Mean Arterial Pressure
SpO_2	Oxygen Saturation
mg	Milligram
μg	microgram
Kg	Kilogram
Hr/hrs	Hour/hours
RSS	Ramsay Sedation Score
bpm	Beats per minute
mm Hg	Millimeter of Mercury
ASA	American Society of Anesthesiologists
VAS	Visual Anolog Scale

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